A population-based linkage of administrative data sources to investigate associations between assisted reproductive technology and cancer risk in Great Britain

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Signed declaration

‘I, Caroline Williams confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.’

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Abstract

Introduction:

Exposure of women to supra-physiological hormone levels and exposure of early embryos to artificial environments could increase cancer risks in women who have had assisted reproductive technology (ART) and children born after ART. This study aims to investigate possible associations by linking routinely collected data.

Methods:

Records of 255,786 ART treated women and 106, 013 ART conceived children in Great Britain (1991-2010) were linked to national registries of England & Wales and of Scotland, and the National Register of Childhood Tumours to obtain cancer outcome status. Observed cancers were compared against age and sex specific expectation, based on national rates. Analyses were stratified for potential moderating, mediating and confounding factors; 95% confidence-intervals, 2-sided P-values and trends were calculated assuming a Poisson distribution.

Results:

In 2,257,789 person-years of observation in ART treated women with an average follow-up of 8.8 years, no increased risk of corpus uteri (SIR-1.12; 95%CI 0.95-1.30), or invasive breast (SIR-0.96; 0.2-1.00) cancer was detected. An increased risk of ovarian cancer (SIR-1·39; 1·26-1·53), both invasive (SIR-1·40; 1·24-1·58) and borderline (SIR-1·36; 1·15-1·60) was limited to women with endometriosis, nulliparity, or both. There was no increased risk of ovarian tumours in women treated for only male factor or unexplained infertility. In 700,705 person-years of observation in ART conceived children with an average follow-up of 6.6 years, no overall increased risk of childhood cancer was found (SIR-0.98; 0.81-1.19). An excess of hepatoblastoma (SIR-3.64; 1.34-7.93), was likely mediated by low-birthweight (Birthweight<2500g SIR-10.29; 3.34-24.02).

Conclusion:

Routinely collected national data, linked to investigate cancer outcomes after ART, were largely reassuring, although some specific increases were detected. There was no convincing evidence relating increased risks to ART procedures *per se*. Average follow-up was 8.8 years for women and 6.6 years for children, therefore longer follow-up is required to confirm impact on lifetime risks.

Impact Statement:

This thesis has already had a considerable impact. The results regarding cancer in women after assisted conception were published in the British Medical Journal. In 2019, this paper was on the required reading list for re-certification in the subspecialty of 'Reproductive Endocrinology and Infertility' by the American Board of Obstetrics & Gynaecology, meaning all assisted reproduction specialists in USA have read it. Thus, thousands of clinicians, (over 1,700 in the USA alone), have been able to use our results, (in conjunction with other studies), to council millions of service users about the potential risks of developing cancer after assisted reproduction.

The results of the childhood cancer section of this thesis were published in the New England Journal of Medicine. This study was selected by '*Faculty Opinions*' as a recommended paper, rated as exceptional. It won awards at two international conferences, and has been presented at service user engagement events, including by the Progress Educational Trust (February 2021). Therefore, it was possible to convey these, largely reassuring, results to a very wide audience of service users, clinicians, and researchers. The results of this study were largely in accordance with results of two other similar, large studies, published shortly afterwards. In combination, this work is able to provide relatively strong evidence that the risks of childhood cancer does not appear to be raised in individuals born after assisted reproduction. Whilst further work is needed, particularly to look at longer term risks as this population enters adolescence and adulthood, this represents an important advance in knowledge, which is of significance to thousands of service users and clinicians.

There have also been unintended impacts of this thesis. The link between endometriosis and ovarian cancer well was known prior to this thesis. However, as this study was very large, it provided more evidence to support this association, which has since been quantified further.

This thesis has also led to quality improvements in several datasets. The HFEA database was extensively cleaned and validated, removing data errors which could have led to inaccurate

future conclusions. Errors in the NHS-Central Registry and National cancer database registries were also identified and corrected during this study.

This project has also led to advances in the way HFEA, and NHS-Digital datasets are used. Whilst working with the NHS-Digital team, I discovered a novel way to use maternal data to 'backfill' the significant amounts of missing HFEA data relating to offspring, (using maternal datasets in the NHS-Digital registry, linking these to ONS birth records and then using the original data set data to identify the offspring of interest). Not only has this improved the HFEA dataset for future research use, but it has also highlighted a previously unused method for linkage of mother and child in NHS databases, when child identifiable details are scant.

PhD Supervisors

- **Principal Supervisor** - Professor Alastair Sutcliffe, UCL Great Ormond Street Institute of Child Health
- **Subsidiary supervisor-** Dr Beverley Botting, UCL Great Ormond Street Institute of Child Health

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Acknowledgements & the roles of others in this work

- ## Supervisors

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- ## Collaborators

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- **National Registry Childhood Tumours staff**

  I would like to acknowledge and thank the NRCT staff, particularly Tim Vincent, who prepared NRCT data for export to the HFEA.

- **NHS-Digital**

  I would like to acknowledge and thank NHS-Digital staff, especially James Grey, whom I worked closely with on the linkage phase of the Women's arm of the project. He provided great communication and knowledge of the NHS-Digital registry. He enabled me to be in charge of and direct data linkage, despite not being on site, by directing all queries to me.

- **National Records for Scotland (NRS)**

  I would similarly like to acknowledge and thank NRS staff, especially Gail Turner, who did a similar job to James Grey in Scotland. Gail provided great communication and knowledge of the NRS dataset, which is subtly different to the NHS equivalent. She also enabled me to lead the linkage phase in Scotland remotely, again discussing all queries directly with me.

- **National Institute for Health Research (NIHR) & Cancer Research UK (CRUK)**

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Study Publications

- ***Williams CL***, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, Bunch KJ, Murphy MFG, Sutcliffe AG. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2-million-person years of observation. British Medical Journal. 2018; 362:k2644[1]
- ***Williams CL***, Bunch KJ, Murphy MFG, Stiller CA, Botting BJ, Wallace WH, Davies MC, Sutcliffe AG. Cancer risk in children born after donor ART. *Human Reproduction*. 2018; 33 (1): 140-146[2]
- ***Williams CL***, Bunch KJ, Stiller CA, Murphy MF, Botting BJ, Wallace WH, et al. Cancer risk among children born after assisted conception. *The New England journal of medicine*. 2013; 369(19): 1819-27[3]

Prizes & Honours

- ***Williams CL***- 'Three-minute thesis' 2017 – UCL grand finalist having won two preliminary rounds at the Great Ormond Street, Institute of Child Health & School of Life & Medical Sciences.
- ***Williams CL***. 'Cancer Risk among Children Born after Assisted Conception' N Engl J Med 2013; 369:1819-27201. ***Lorber Prize, 2014, RCPCH.*** http://www.rcpch.ac.uk/what-we-do/fellowships-and-prizes/lorber-prize/lorber-prize-0
- ***Williams CL***. 'Cancer risk in children born after assisted conception'. **Clinical Science Award for oral presentation, ESHRE annual conference 2013.**
- ***Williams CL***. 'Systematic review and meta-analysis of cancer risk in children born after assisted reproduction'. ***Dr Michael Blacow Memorial Prize, 2011, RCPCH***. http://www.rcpch.ac.uk/what-we-do/fellowships-and-prizes/dr-michael-blacow-memorial-prize/dr-michael-blacow-memorial-prize

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Common Abbreviations

ART- *Assisted reproductive technology or assisted reproductive therapy*

IVF- *In-Vitro Fertilisation*

ICSI- *Intra-cytoplasmic Sperm Injection*

PGD- *Pre-implantation Genetic Diagnosis*

IVM- *In-Vitro Maturation*

IUI- *Intrauterine Insemination*

FSH- *Follicle Stimulating Hormones*

LH- *Luteinising Hormones*

ET- *Embryo transfer*

FET- *Frozen Embryo transfer*

GnRH- *Gonadotrophin Releasing Hormones*

hCG- *Human Chorionic Gonadotrophin*

OHSS- *Ovarian Hyper Stimulation Syndrome*

HFEA- *Human Fertilisation & Embryology Authority*

NRCT- *National Registry of Childhood Tumours*

NHS- *National Health Service*

NRS- *National Records for Scotland*

UMN- *Unique Member Number*

SIR- *Standardised Incidence Ratio*

AER- *Absolute Excess Risk*

CI- *Confidence Interval*

Definition of assisted reproductive technology

For the purposes of this thesis, assisted reproductive technology (ART; also referred to as assisted reproduction and assisted conception) will be defined using the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and World Health Organization (WHO) definition as 'all treatment or procedures that include the in-vitro handling of both human oocytes and sperm or of embryos, for the purpose of establishing a pregnancy'[4] . Therefore, this includes *in vitro* fertilisation (IVF), intra-cytoplasmic sperm injection (ICSI), and related micromanipulation techniques but does not include Intrauterine Insemination (IUI).

Please note much of this work was undertaken between September 2011 and September 2017. One of the two literature reviews (looking at childhood cancer) was undertaken in 2011 and 2012, before the main body of that part of the thesis was started in 2012/2013. The second literature review was undertaken in 2014. The references are therefore generally contemporaneous to this period but have been updated when scientifically appropriate. Comparison with more recently published work is made in the discussion.

Introduction

Assisted reproductive technology (ART) is one of the most important medical breakthroughs of the last century and offers hope to the approximately 10% of couples who struggle to conceive[5,6]. The number and proportion of children born after assisted reproduction is rising annually. There have already been over 8 million births after Assisted Reproductive Technologies (ART) worldwide and with falling fertility rates in some countries, this is likely to rise[7]. In 1992, at the start of this study period, one in every 333 children born in the UK was conceived using assisted reproduction, by the end of our study period in 2010, this figure was one in every 50 children[8].

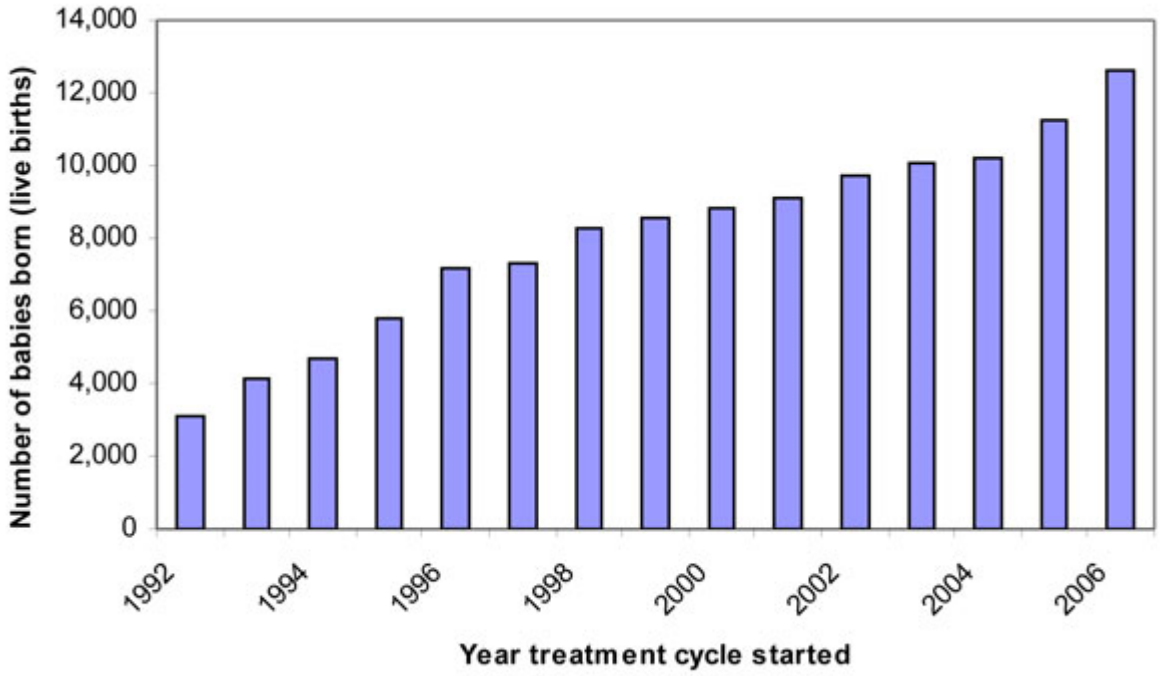


Figure 1. *The number of children born after ART in the UK annually in this study period. This figure is based on data received from the Human Fertilisation & Embryology Authority[9].*

Assisted reproductive techniques have developed rapidly since the birth of the first *in-vitro* fertilised (IVF) conceived infant, Louise Brown, in 1978. Whilst the development and use of these techniques has progressed rapidly, the same cannot be said for research into the safety outcomes of such treatments. The reason for this is not clear; however a contributing factor may

be that ART providers are not usually responsible for providing care after fertility treatment and often have little direct contact with the family after the initial treatment period. This makes collection of follow-up data difficult. In addition, some of the potential adverse outcomes are rare events and therefore very large cohorts are required to comprehensively investigate risk.

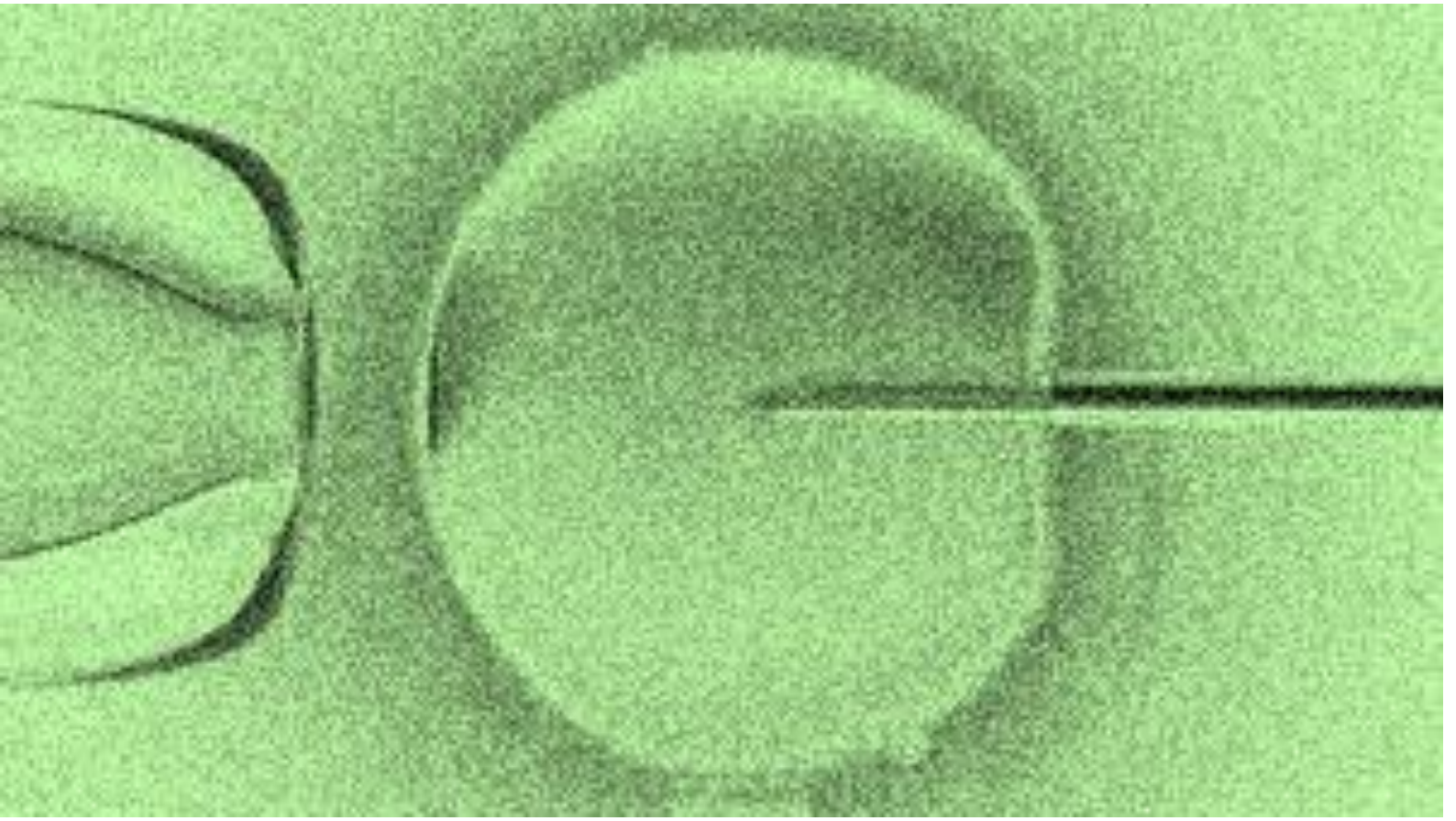
Cancer, in both women who have had assisted reproduction and children born after assisted reproduction, is one such potential outcome not adequately investigated to date. This study aimed to make use of an unprecedented opportunity to investigate cancer risk in these populations in Great Britain. A change in the Human Fertilisation & Embryology Authority (HFEA) act, 2009, allowed researchers limited access, for the first time, to identifiable information on all assisted conceptions in the UK since 1991. The number of both women and children developing cancer after ART in Great Britain was ascertained by linking data from the HFEA registry to:

- **NHS-Digital Central Registry & National Records for Scotland (NRS)** (recording all cancers and deaths in the population of England, Wales & Scotland) to identify women who have had ART and subsequently developed cancer.
- **The National Registry of Childhood Tumours (NRCT)** (a large population- based childhood cancer registry covering England, Wales, and Scotland during the study period) to identify children conceived after ART who have subsequently developed cancer.

The numbers of cancers recorded in these cohorts has been compared with expected numbers, based on annual age-specific national incidence rates. Where possible and where data are available, potential confounding, moderating and mediating variables have been considered.

Findings reported in this thesis and in related publications[1-3] are important to families who have used assisted reproduction or are considering using assisted reproduction, to clinicians, public health bodies and the general public.

Chapter 1- Background



History of assisted reproduction

The first attempts at *in-vitro* fertilisation (IVF) of mammalian eggs occurred in 1878 by a Viennese embryologist named Schenk. It took a complete century of experiment and investigation into *in-vitro* techniques before the birth of the first human after *IVF* in 1978, when Louise Brown was born in Oldham, UK[10]. Other important developments followed soon after including the first human pregnancy using a cryopreserved and thawed embryo in 1983[11], the first human pregnancy after preimplantation genetic diagnosis (PGD) in 1990[12] and invention of intracytoplasmic sperm injection (ICSI) in 1992[13]. These sentinel events and others in the early history of assisted reproduction are displayed on the timeline in *figure 2*. Further developments include the first birth after in-vitro maturation (IVM) of oocytes, followed by IVF, in 1994[14] and extended embryo culture (to 5 day blastocysts)[15,16].

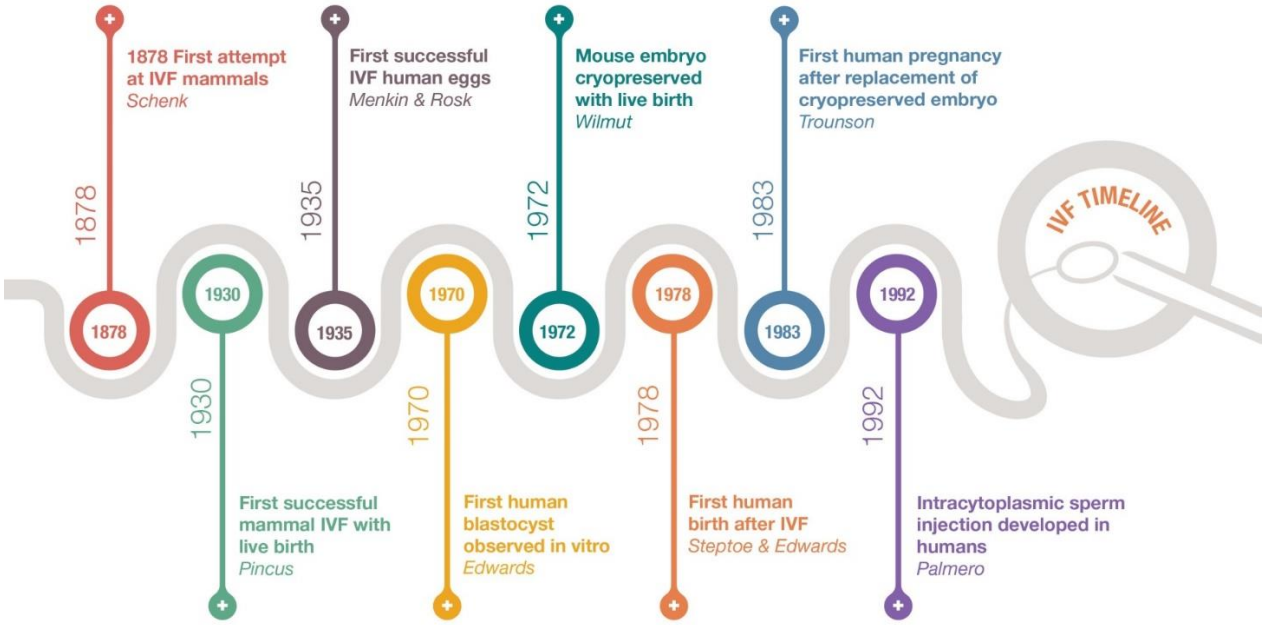


Figure 2. *Timeline of a number of sentinel events in the development of in-vitro fertilisation (IVF)*

Overview of assisted reproduction treatments

Most women who have assisted reproduction are exposed to a variety of different medications during their treatment. Simulated cycles, which accounted for 99.1% of all cycles in the UK in 2010[17], generally involve ovarian stimulation with exogenous hormones to promote multifollicular growth and simultaneous suppression of endogenous follicle-stimulating hormone (FSH) & luteinizing hormone (LH). Oocytes undergo final maturation, (usually in-vivo, unless in-vitro maturation is being used), and ovulation is then triggered. Eggs are then surgically retrieved and fertilised in an *in-vitro* environment. Standard IVF involves mixing sperm and eggs in the *in-vitro* environment; ICSI involves directly injecting a single sperm into a retrieved mature oocyte. Resulting embryos are then matured for a varying length of time and replaced in the uterus during embryo transfer (ET). During cleavage embryo transfer, an embryo is transferred after 2-3 days in the IVF laboratory; blastocyst embryo transfer involves maturing the embryo in an in-vitro environment, typically for 5 days, until trophoblast (outer cell layer) and embryoblast (inner cell mass) layers have formed.

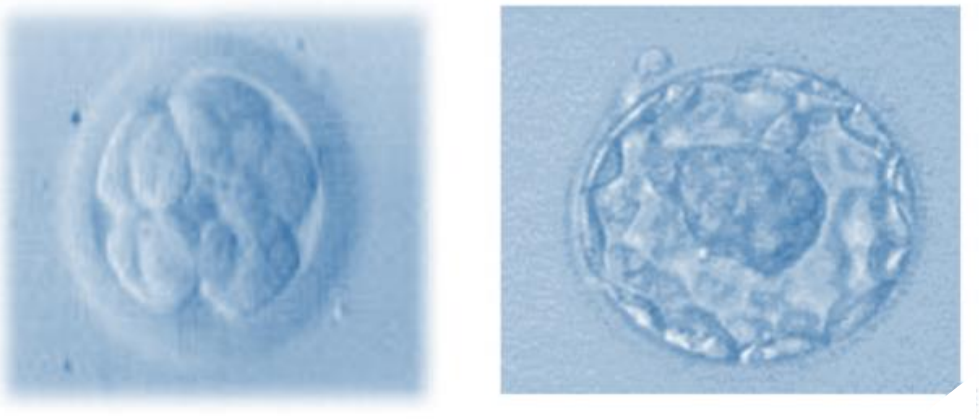


Figure 3. *Cleavage stage embryo (day 2-3) Left; Blastocyst stage embryo (day 5) Right.*

Un-stimulated or 'natural cycles' involve collection of a smaller number of oocytes, usually one or two, which have been stimulated by endogenous hormones as part of the normal menstrual cycle. Fertilisation, embryo maturation and embryo transfer techniques are equivalent between stimulated and non-stimulated assisted reproduction cycles.

Assisted reproduction treatments during study period

This study includes data collected over a period of 19 years from 1991 to 2010. During this period there were a number of advances in assisted reproduction leading to better success rates. Most such advances in this period were in assisted reproduction laboratories and include the development of pre-implantation genetic diagnosis (PGD)[12], ICSI[13], *in-vitro* maturation [of ova] (IVM)[14] and blastocyst culture[15]. ICSI and blastocyst culture were widely adopted throughout the UK during the study period. PGD and IVM were also used during the study period, however, given that they were designed for specific and relatively rare indications; they have been less widely used, particularly during the study period. Ovarian stimulation regimens as part of assisted reproduction cycles were relatively constant in the UK throughout the study period.

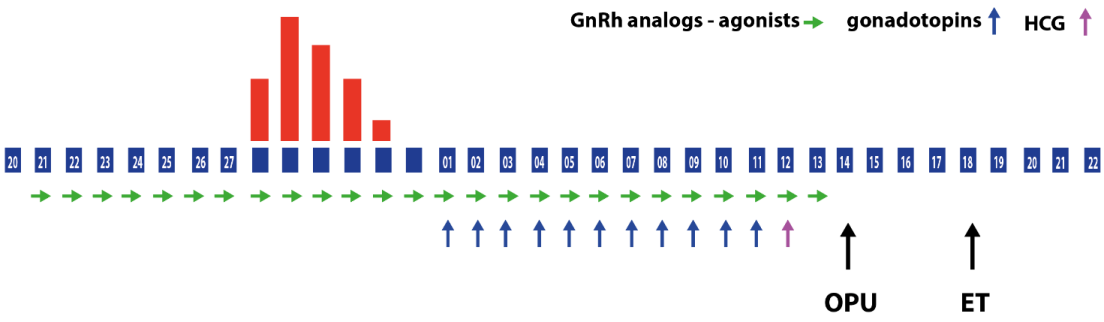


Figure 4*. 'Standard' stimulation protocol used in assisted reproduction during study period. OPU- ovarian pick up or egg retrieval; ET embryo transfer.*

A typical 'standard' stimulation protocol during the study period includes: -

- **Gonadotropin-releasing hormone (GnRH) agonists (or analogues) used for down-regulation or suppression of endogenous gonadotrophins (Follicle-Stimulating Hormone (FSH) and Luteinising Hormone (LH)).**

  GnRH agonists are typically given from day 21 of the menstrual cycle in order to suppress endogenous production of FSH & LH and work by down-regulating GnRH receptors as they have both a greater affinity for GnRH receptors than endogenous GNRH and a much longer half-life[18]. Therefore their sustained use leads to a reduction and then suppression of the release of FSH & LH[18]. Use of GnRH agonists was standard by 1991 and not replaced by GnRH antagonists as standard treatment for down-regulating endogenous gonadotrophins until after the study period.

- **Gonadotrophin injections used for ovarian stimulation**

  Exogenous gonadotropins are typically started on day one or two of the next cycle in order to stimulate follicle development.

  Clomiphene citrate was also used for ovarian stimulation in the pioneering years of assisted reproduction treatment, but this was uncommon in the UK by the start of the study period.

- **Human chorionic gonadotrophin (hCG) used for triggering ovulation**

  Once an adequate number of mature sized follicles have developed (to 13-20mm), hCG is given for the final maturation of the developing oocytes. Oocyte retrieval occurs around 36 hours after the administration of hCG.

  Whilst purified, then highly purified urinary preparations of both gonadotrophins and hCG were initially used, followed by recombinant preparations in later years, these are essentially equivalent.

- **Progesterone support used to thicken endometrial lining and maintain pregnancy.**

Class of drug	Examples	Side effects, as recorded by the British National Formulary[19] &/or the HFEA[20]
Gonadotropins	Recombinant FSH LH; Follitropin α Follintrophin β Lutropin α Human menopausal gonadotrophins; Menotrophin (FSH & LH), Urofollitrophin (FSH)	Ovarian hyper-stimulation syndrome (OHSS), allergic reactions, skin reactions, increased risk of multiple pregnancy and miscarriage, GI disturbance, head ache, joint pain, fever, thromboembolism (rare)
Human Chorionic gonadotropin (HCG)	Recombinant Choriogonadotrophin α	Nausea, vomiting, abdominal pain, headache, OHSS
GnRH agonists / analogues	Buserelin Goserelin Nafarelin	Headaches, nausea, vomiting, hot flushes, night sweats, headaches, vaginal dryness, mood swings, changes in breast size, acne, sore muscles.
Progesterone	Cyclogest Gestone Utrogestan	Nausea, vomiting, swollen breasts.
Clomiphene Citrate *(not in standard use during study period)*		Hot flushes, mood swings, nausea, breast tenderness, insomnia, increased urination, heavy periods, acne, weight gain, multiple pregnancy
GnRH antagonists *(not in standard use during study period)*	Cetrorelix Ganirelix	Nausea, headaches, malaise, hypersensitivity reactions (rare)

Table 1. *Recorded side effects of drugs commonly used in assisted reproduction and fertility treatment.*

Known adverse maternal outcomes of assisted reproduction

There are a number of known maternal complications of assisted reproduction, including those relating to multiple pregnancy, ovarian hyper-stimulation syndrome (OHSS), risk of thromboembolism, risk of ectopic pregnancy, and side effects of medications (*Table 1*).

Multiple pregnancy rates are higher in assisted conceptions compared to spontaneous conceptions; 20.6% of all births after assisted reproduction were multiple births the UK in 2010[21] compared to 1.6% in the general population in the same year[22]. This is a source of significant maternal morbidity and mortality as multiple pregnancies are associated with higher rates of pre-eclampsia, gestational diabetes, preterm delivery, cholestasis, dermatoses of pregnancy, anaemia, and hyperemesis gravidarum[22,23]. Thankfully, rates of multiple pregnancy after assisted conception have decreased in the years after the study period [21,24], (from 24% in 2009 to 11% in 2017 in the UK[24]), due, at least in part, to the steady increase in the proportion of elective single embryo transfers in the UK as well as across most parts of Europe[21].

	Singleton Pregnancy	**Twin Pregnancy**	**Triplet Pregnancy**	**Quadruplet Pregnancy**
Pre-eclampsia	6	10-12	25-60	>60
Gestational Diabetes	3	5-8	7	>10
All Pre-term labour	15	40	75	>95
Delivery < 37/40	10	50	92	>95
Delivery < 32/40	2	8	26	>95

***Table 2**. Incidence (%) of major maternal complications in pregnancies after assisted conception by different pluralities, over the study period. [23]*

Mild OHSS is estimated to occur in around 15%-30% of all assisted conception cycles[25,26] whilst moderate and severe forms occur in 1-6% of all cycles[25-27]. In women considered high risk for OHSS because of young age, low body mass index, polycystic ovary syndrome (PCOS), and particularly women with high levels of anti-mullerian hormone, moderate or severe OHSS may occur in up to 20% of treatment cycles[28]. Mild OHSS results in fluid accumulation and weight gain but more severe forms can result in oliguria, ascites, pulmonary oedema, thromboembolism and even death[26]. As well increased maternal morbidity and mortality, OHSS can also increases the risk to resulting pregnancies by increased risks of still birth, low birth weight and pre-term birth[29]. Therefore, all women undergoing ovarian stimulation, particularly those at high risk, are closely monitored[26]. Prevention strategies such as using GnRH antagonists, altering the ovulation trigger, (by reducing hCG dose or using GnRH agonists as the trigger), and increasing use of frozen embryo transfer, are much more common now than they were during the study period[26].

There is also some evidence that women who have assisted reproduction are at increased risk of pulmonary and venous thromboembolism compared to age matched controls who deliver during the same calendar period (aHR 1.77; 95%CI 1.41-2.23; adjusted for parity, multiple births, smoking, maternal age)[30]. This excess risk was particularly prominent in the first trimester (aHR 4.05; 95%CI 2.54-6.46; additionally adjusted for BMI)[30].

Pre-eclampsia is also more common in assisted conception pregnancies (OR 1.63; 95%CI 1.53-1.74), as is prolonged rupture of membranes, placental abruption and placenta previa; shown in singleton and multiple assisted conception pregnancies[31]. Pre-eclampsia appears to be particularly associated with frozen embryo transfers, possibly related to the absence of the corpus luteum[32]. Interventions such as caesarean sections and induction of labour were also found to be more common in assisted conception pregnancies[31,33].

Cancer risk in women after assisted conception

In addition to the above recognised maternal risks of assisted reproductive technology treatments, there are theoretical reasons why women who have assisted reproduction may have increased risks of specific types of cancer. These relate to both the assisted reproduction treatments and to the background characteristics of women who choose to have assisted conception.

In most assisted reproduction cycles, stimulation of multiple follicles by exogenous gonadotropins results in a significant rise in oestradiol (E2) levels. The mean peak oestradiol level in a standard stimulated ART cycle is 3000pg/ml (range: 1000- 4000 pg/ml)[34]. This is 4 times larger than the mean peak level in an un-stimulated cycle (750pg/ml, range: 315-1800 pg/ml)[34]. Excess oestradiol exposure has been implicated in the development of ovarian, breast, and corpus uterine cancer, amongst other cancers[35]. Oestrogens are both *mitogens*, increasing the probability of mutations due to an increased rate of mitosis, and *mutagens*, directly inducing DNA damage[35]. Gonadotrophins have similarly been associated with carcinogenesis, particularly in relation to ovarian cancer[36,37]; these may act directly or through stimulation of ovarian steroidogenesis[36,38,39]. Recently it has been suggested that gonadotrophins may induce migration and invasion in ovarian cancer, but not proliferation of ovarian cancer lines[37].

Ovarian punctures may also be implicated in ovarian carcinogenesis. Incessant ovulation is postulated to cause structural changes to the ovary which may stimulate cancer development either by formation of pre-malignant epithelial inclusion cysts at ovulation or by a proliferation of epithelial cells to repair the defect in the ovary surface post- ovulation[38,40,41]. The correlation between increasing number of life-time ovulations and higher risk of ovarian cancer supports this hypothesis[38]. It is postulated that assisted reproduction, which generally involves multiple iatrogenic ovarian punctures, could similarly increase risks of ovarian cancer[42].

Women who choose to have assisted conception may be at higher risk of breast, endometrial and ovarian cancer, irrespective of fertility treatment. For example, women who have assisted conception are less likely to have children than the generally population, thus also less likely to have breast fed a child and are more likely to have endometriosis than the general population, all three are risk factors for ovarian cancer[43-48] (*Table 3*).

Women with high body mass index (BMI) are more likely to develop ovarian cancer than those with normal body mass index[48]. However, it is not completely clear how the average BMI of women undergoing assisted conception compares to population averages in the UK. High body mass index is associated with reduced fertility[49], however, in the UK women with BMI over 30 are less likely to be accepted for fertility treatment, and certainly NHS funded fertility treatment[50]. In addition, some studies suggest that women who have assisted conception are more likely to exercise regularly than the general population[51].

Risk factors for breast cancer associated with infertility are likely to have a more complex effect (*Table 3*). Women having assisted reproduction are more likely to give birth to their first child at an older age, which is known to increase the risk of breast cancer[52], but are less likely to have a late age at menopause, another risk factor for breast cancer[53]. The situation is made more complex as a number of relevant risk factors for breast cancer have a non-linear relationship with risk. For example, pregnancy increases the risk of breast cancer transiently postpartum, but subsequent pregnancies decreases risk[54,55]. High body mass index reduces pre-menopausal risk, but increases post-menopausal risk[48,56].

Cancer	Known risk factors related to hormonal exposure/ infertility	References
Ovarian	Low parity Breastfeeding (reduces risk) Oral contraceptives (reduces risk) Hormone replacement therapy High body mass index Endometriosis	43-48,57
Breast Cancer	Parity- *pregnancy increases risk transiently, subsequent pregnancy reduces risk* Older age at first pregnancy Breastfeeding (reduces risk) Hormone replacement therapy Oral contraceptives Late age at menopause Body mass index- postmenopausal	48,52-60
Endometrial/ Corpus Uterine	Hormone replacement therapy (oestrogen only) Low parity Early menarche Late age at menopause Obesity Polycystic ovary syndrome (PCOS) Oral contraceptives (reduces risk) Endometrial polyps	48,61-67

Table 3*. Known hormonally related risk factors for specific cancers.*

In recent years, PGD for BRCA mutations has been developed. This may increase the proportion of women with related mutations undergoing assisted conception and therefore be another reason why women undergoing assisted conception are at higher risk of breast and ovarian cancer. However, such PGD techniques were developed after the study period.

Literature review investigating cancer risk in women after assisted conception

A literature review was undertaken to assess published evidence investigating the risk of breast, endometrial/ corpus uteri and ovarian cancer in women who have had assisted conception before work on this component of the thesis began on 20.11.2014. This was updated on 13.2.2017.

Review question: 'Are women who have assisted reproduction at higher risk of breast, endometrial/ corpus uteri and ovarian cancer than the general population and/ or untreated women diagnosed with fertility problems?'

PICO style inclusion criteria:

Population/ intervention: This review considered studies including women undergoing assisted reproductive technologies defined as 'All treatments or procedures that include the *in vitro* handling of human oocytes and sperm or embryos for the purpose of establishing pregnancy[4]. Studies including women having hormonal stimulation NOT part of assisted conception not specifically sought, but where found were considered separately.

Comparison: Cohort studies and systematic reviews comparing risk of cancer, (specifically of the breast, endometrium/ corpus uteri or ovary), in women undergoing assisted conception to either the general population or specific sub-fertile populations were sought.

Outcome: The outcomes considered will be doctor diagnosed breast, endometrial, corpus uteri or ovarian cancer (including both invasive and borderline ovarian cancer).

Review methods: Searches of MEDLINE and EMBASE were carried out using multiple combinations and variations of keywords 'Neoplasm', ' Cancer', 'Assisted Reproductive Techniques', '*in-vitro* fertilization'. No restrictions were used. This search was carried out on 20.11.2014 and updated on 13.2.2017. Full search criteria are available in *appendix 1.* An additional hand search of bibliographies of selected studies and review articles was carried out. All relevant cohort studies and systematic reviews were identified and reviewed independently by two authors. A meta-analysis was not undertaken as part of this systematic review, given that several recent, relevant, high quality meta-analyses were identified through the systematic review.

Results: 6,377 articles were cited by Pubmed, 11,705 by Embase. Article titles were scanned and primary research articles and systematic reviews in the related study area identified for further investigation. 372 abstracts were selected for review. Using the above PICO criteria, 13 cohort studies and three systematic reviews were identified. Repeating this search on 13.2.2017 identified two additional cohort studies and two additional systematic reviews. Details of these studies, including numbers of exposed women, number of cancers, follow-up details and results are incorporated in *table 4*.

Conclusions: Studies investigating breast cancer risks in women who underwent assisted reproduction are inconsistent[42,68-76]. Although some studies have shown an increased risk of breast cancer in women after assisted reproduction[75], most studies do not suggest an overall increased risk [68,70-74,76-78]. A number of studies have suggested possible increased risk within subgroups of treated women including those treated at younger ages[69,78], with multiple cycles[70] and with Progesterone[79]. Despite the fact that breast cancer is the most common cancer in women, most studies have relatively few events, largely due to small study size.

Most studies investigating endometrial cancer risk in ART treated populations have not found a significant increased risk in exposed populations[71-73,76,77]. However, most studies provide very

imprecise estimates due to small sample size and few events[71-73,77]. One study suggested an increased risk of endometrial cancer associated with exposure to Gonadotrophins, commonly used as part of ART[80]. Largely, studies comparing risks in ART treated populations to the general population, without taking into account important confounders such as nulliparity and PCOS have tended to find higher, all be it non-significant risks, compared to studies which do take into account such factors.

Early cohort studies investigating fertility drugs used alone suggested an increased risk of ovarian cancer[81]. Recent studies investigating their use as part of assisted reproduction tend to be more reassuring[42,72,82,83]. Recent systematic reviews have suggested that studies which are at high risk of bias due to lack of adjustment for potentially important confounders, such as nulliparity and endometriosis, are more likely to show an increased risk of invasive ovarian cancer than those studies who are able to take these potential confounding variables into account[42,84]. They also note the small size and few events in many studies and call for further large population based studies, taking potential confounding variables into account[42,84]. Very few studies have investigated risks of borderline ovarian cancers in women exposed to ART[73,83,85]. Some[83,85], but not all[73] have found an increase in borderline tumours.

Study Details & Exposed cohort (n)	Cancers in exposed				F/U	Results				Comments
	Breast	Corpus Uteri	Ovarian			Breast	Corpus Uteri	Ovarian		
			I/V	B/L				I/V	B/L	
Venn 1995[86] ***Lancet*** **AUS N= 5,564**	34	?	6		(1-15yrs)	ART vs sub-fertile aRR 1.11 (0.56-2.20)	ART & Infertile vs Gen Pop SIR 2.84 (1.18-6.81)	ART vs infertile aRR 1.45 (0.28-7.55)		• Short follow-up • Few cases
Venn 1999[71] ***Lancet*** **AUS N=20,656**	143	12	13		7 years (1-21)	SIR 0.91 (0.74-1.13)	SIR 1.09 (0.45-2.61)	SIR 0.95 (0.73-1.23)		• Transient ↑BC & CUC 1st 12mths • ↑OC & CUC unexplained infertility
Dor 2002[77] ***Fert Ster*** **ISR N=5026**	11	2	1		3.5 years	SIR 0.69 (0.46-1.66)	SIR 2.25 (0.25-8.11)	Not significant		• Small study • Imprecise estimates
Lerner- Geva[87] 2003 ***Int J gyn ca*** **ISR N=1082**	21 cases of any cancer type				6.5 years	SIR 1.91 (1.18-2.91) When first 12 month excluded SIR 1.46 (0.83-2.36)				• Small study • Individual cancers not considered
Kallen 2005[31] ***BJOG*** **SWE N=12,186**	37	-	24 ?12 invasive		-	OR 0.76 (0.54-1.06)	-	OR 2.08 (1.15-3.76)		• Parous women
Kristiansson 2007[88] ***HR*** **SWE N=8716**	24	1	3	?8	6.2 years	aRR 0.93 (0.58-1.43)	Too small			• Parous women
Jensen 2007[79] ***Can Epi Bio*** **DNK N=165/395/98/13**	156	-	-		8.8 years	aRR 1.20 (0.82-1.78) Gonadotrophin aRR 0.94 (0.73-1.12) hCG aRR 1.28 (0.75-2.19) GnRH aRR 3.36 (1.60-7.07) Progesterone		-		• Analysis by drugs used • Comparison to infertile women mainly treated with other drugs • Small numbers

Study Details & Exposed cohort (n)	Cancers in exposed				F/U	Results				Comments
	Breast	Corpus Uteri	Ovarian			Breast	Corpus Uteri		Ovarian		
			I/V	B/L					I/V	B/L
Pappo 2008[70] ***Ann Surg Onc*** **ISR N=3,375**	35	-	-		8.1 years	SIR 1.4 (0.98-1.96)	-		-		• >40yrs 1st Rx SIR 1.9; 0.97-3.30 • >3 cycles SIR 2.0; 1.15-3.27
Jensen 2009 ***BMJ***[89] **Am J Epi**[80] **DNK N=184 gonada N=413 hCG N=110 GnRH**	-	55	90		16 years	-	aRR 2.21 (1.08-4.50) Gonadotrop. aRR 1.36 (0.83-2.23) hCG aRR 1.09 (0.47-2.52) GnRH		aRR 0.83 (0.50-1.37) Gonadotrop. aRR 0.89 (0.62-1.29) hCG aRR 0.80 (0.42-1.51) GnRH		• Analysis by drug • Comparison to infertile women mainly treated with other drugs • Small numbers exposed
Kallen 2011[74] ***HR*** **SWE N=24058**	95	5	57		8.3 years	aOR 0.76 (0.62-0.94)	Too small		aOR 2.09 (1.39–3.12)		• Parous women • First cancers presented here
Van Leeuwen 2011[83] ***HR*** **NLD N=19146**	-	-	30	31	14.7yrs	-	-	SIR 1.35 (0.91-1.92) IVF vs Gen pop SIR 1.24 (0.64-2.17) Sub-fertile vs Gen pop	SIR 1.93 (1.31-2.73) IVF vs Gen pop SIR 0.67 (0.18-1.71) Sub-fertile vs Gen pop		• Considering Ovarian tumours, Borderline & Invasive • Compares to gen pop & sub-fertile group • OC ↑after 15 years SIR-3.54; 1.6-6.7 • Small numbers in sub-analyses

Study Details & Exposed cohort (n)	Cancers in exposed				F/U	Results				Comments
	Breast	Corpus Uteri	Ovarian			Breast	Corpus Uteri	Ovarian		
			I/V	B/L				I/V	B/L	
Yli-Kuha 2012[73] ***HR*** **FIN N=9175**	55	4	9	4	7.75yrs	OR 0.93 (0.62–1.40)	OR 2.0 (0.37–10.9)	OR 2.57 (0.69 – 9.63)	OR 1.68 (0.31– 9.27)	• Possible healthy cohort effect (breast cancer) • Sub-groups and confounders not investigated
Stewart 2012[78] ***Fert Ster*** **AUS N=7381**	148	-	-	-	16yrs	HR 1.10 (0.88–1.36)	-	-		• Compares to sub-fertile cohort • ↑risk if 24yrs at 1st Rx aHR 1.56; 1.0–2.4
Brinton 2013[72] ***Fert Ster*** **ISR N=67608**	140	15	21		8.1yrs	aHR 0.90 0.71-1.15)	aHR 1.56 (0.63–3.86)	aHR 1.58 (0.75-3.29)		• Compared to sub-fertile cohort • Adjusted for age at entry, BMI, smoking, parity at exit, and socio-economic status.
Stewart 2013 (a)[85] ***Gyne Oncol*** **AUS N=7544**	-	-	-	17	16.9yrs	-	-	-	aHR 2.46 (1.20, 5.04)	• Parous women (HR 0.89; 0.43–1.88) • Endometriosis (HR 0.31; 0.04–2.29)
Stewart 2013 (b)[82] ***Gyne Oncol*** **AUS N=7548**	-	-	16	-	17 yrs.	-	-	Parous women HR- 1.01 (0.35-2.90) All HR-1.36 (0.71-2.62)	-	• Investigates invasive ovarian cancer • Small study, few events • Imprecise estimates
Reigstad 2014[75] ***Int J of Can*** **NOR N=16,626**	138	-	-	-	16yrs	aHR1.20 (1.01–1.42)	-	-		• Parous women • Excludes cancer before Rx aHR 1.17 (0.98-1.40) • F/U >10yrs aHR 1.35 (1.07–1.71)

Study Details & Exposed cohort (n)	Cancers in exposed				F/U	Results				Comments
	Breast	Corpus Uteri	Ovarian			Breast	Corpus Uteri	Ovarian		
			I/V	B/L				I/V	B/L	
Luke 2015[76] ***Fert ster*** **USA** **N=113,226** **53859 no prior ART**	404	49	48		4.87 yrs.	SIR 0.83 0.75-0.91	SIR 0.76 0.57-1.01	SIR 1.18 0.87-1.56		• Compares to the general pop • No change with parity, no. cycles, cumulative dose or cycle outcome

Table 4. *Cohort studies investigating cancer risk in women after assisted conception identified through systematic review. Shaded rows indicate that data overlaps with subsequent included studies*

Study & Exposed	Cases			Results			Comments
	Breast	Corpus Uteri	Ovarian	Breast	Corpus Uteri	Ovarian	
Siristatidis 2013[84] ***Hum Reprod Update*** **N=109,969**	-	18	76	-	RR 2.04 (1.22-3.43) vs Gen Pop RR 0.45 (0.18-1.14) vs Subfertile	RR 1.50 (1.17-1.92) vs Gen Pop RR 1.26 (0.62-2.5) vs Subfertile	• When confounding effect of infertility removed, ART does not increase risks of studied cancers
Rizzuto 2013 [42] ***Cochrane*** **N= 182,972**	• No convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment. • There may be an increased risk of borderline ovarian tumours in sub-fertile women treated with IVF. • Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias, due to retrospective study design, lack of accounting for potential confounding and estimates based on a small number of cases. • More studies at low risk of bias are needed						
Sergentaini 2014[69] ***Hum Reprod Update*** **N=69,814+**	576	-	-	RR 0.91 (0.74-1.11) vs gen pop RR 1.02 (0.88-1.18) vs sub-fertile	-	-	• Parous women: RR- 0.86 (0.73-1.01) • <30yrs first treatment RR- 1.64 (0.96-2.80)
Gennari 2015[68] ***Breast Cancer Res Tr*** **N=207914 (not all ART)**	2,347	-	-	RR 0.96 (0.80–1.14) ART only	-	-	• Breast cancer after fertility treatment • ART treated women were a subgroup • Clomiphene treatment: - RR- 1.26 (1.06 to 1.50)

Study & Exposed	Cases			Results			Comments
	Breast	Corpus Uteri	Ovarian	Breast	Corpus Uteri	Ovarian	
Saso 2015[90] ***Eur J Obstet Gyn R B*** **N=103,758 (not all had ART)**	-	83 IVF 137 All	-	-	All OR 0.78 (0.39-1.57) IVF OR 0.38 (0.30-0.47)	-	• Includes ALL uterine cancers inc. cervical • Breast cancer after fertility treatment • ART treated women were a subgroup • Potential bias as IVF treatment often not started until after cervical cancer screening complete.
Skalkiddou 2017[91] ***Cochrane DB syst rev***	• Includes all fertility treatments. Includes most important drugs used in ART, but doesn't specifically state if they were used as part of ART • Concludes that robust conclusions cannot be drawn regarding exposure to gonadotrophins in relation to uterine cancers due to very low quality evidence with high risk of bias, and small numbers of studies.						

Table 5. *Systematic reviews and meta-analyses investigating cancer risk in women after assisted conception.*

Known outcomes of children born after assisted reproduction

General Health Outcomes

Multiple birth is the most well documented risk of assisted reproduction. The multiple birth rate in the UK is more than 13 times higher in deliveries after assisted reproduction than after spontaneous conception[22]. In recent years the multiple birth rate has declined, due to the steadily increasing use of elective single embryo transfer in the UK[21]. HFEA data suggest that in 2019, only 6% of all births after assisted conception are multiple births; this has decreased from 25% in 2008[92].

Multiple pregnancies, regardless of their mode of conception, are known to be associated with adverse outcomes including preterm birth, low birth weight, neonatal mortality, disability amongst survivors and congenital malformations (the latter largely related to monozygotic high order pregnancies)[93-98]. It remains unclear, however, if peri-natal outcome in multiple birth after ART, is better or worse compared with similar high order spontaneously conceived pregnancies[99-101].

In addition, after adjusting for maternal age and parity, singletons born after ART have been shown to have significantly higher risks of the following compared to children born after spontaneous conception (SC):

- Preterm delivery[33,102,103 104]
- Low birth weight[33,103]
- Very low birth weight[33,103]
- Being small for gestational age [33,103]
- Peri-natal mortality[33,105]
- Congenital malformations[105-107]
    - An approximate 30% increase has been shown

    - Some data suggests a significant increase in children born after ICSI and not IVF[106]
- Imprinting syndromes[108-110]
    - Such as Beckwith-Wiedemann syndrome (BWS) and Angelman syndrome (AS)

However, the proportion of such adverse outcomes in both singleton and multiple ART births have declined in recent years[101,107]. Reasons for this are unclear, but include a gradual change in ART patient characteristics and refinement of clinical and laboratory ART techniques[101,107].

Uncertainly exists regarding the long-term physical health of children conceived after ART compared to spontaneously conceived children. Literature suggest that children born after ART may have minor, yet statistically significant increased blood pressure, and therefore possible adverse cardio-metabolic outcomes[111-113].

Neurodevelopmental outcome in children born after ART has largely been shown to be similar to children born after spontaneous conception[114-116], though small differences, unlikely to be of clinical significance have been seen in academic performance[115], including in children born after specific types of ART[117].

There is, however, evidence to suggest poorer neurological health. Several large cohort studies with good follow up periods reported an increased risk of cerebral palsy in singletons born after ART[118-120]. A recent systematic review suggested this may be more than two-fold higher than general population rates[121]. There is also some evidence that children born after ART have an increased risk of epilepsy, compared to spontaneously conceived children[122-124]. Both of these adverse outcomes may be related to multiple births, low birth weight, prematurity, to parental sub-fertility or other unknown factors[119,122].

Assisted Reproductive Techniques or Sub-Fertility?

Whether adverse outcomes in ART conceived children are caused by assisted reproductive technologies themselves, underlying sub fertility or by a combination of these, is a key question in ART outcome research. Romundstad et al. attempted to address this question with regard to adverse perinatal outcome in singletons by using data from population based registries to compare children born after ART with their spontaneously conceived siblings (n=2204 per group)[125]. When the groups as a whole were compared (i.e. all children born after assisted conception vs. all spontaneously conceived children), the children born after assisted conception had significantly lower birth weight, shorter duration of gestation and increased risk of being small for gestational age. However, when the same comparisons were made using paired analysis between siblings, these differences disappeared. Average birth weight was only 9 g less in the ART group (95% CI -18g - +36g), gestational age only 0.6 days shorter (95% CI -0.5 - +1.7) and the risk of being small for gestation was similar between groups (OR 0.9 (95% CI 0.62-1.57))[125]. However the study may have been limited as it is possible some of the spontaneously conceived siblings might have been conceived as an indirect result of fertility treatments[126]. Debate continues to surround the question of causation and further research is warranted.

It is also unclear if the increased incidence of imprinting disorders in children born after ART is related to the genetic or epigenetic predisposition of sub fertile couples and/or to the interference that specific aspects of ART may have on epigenetic reprogramming during gametogenesis and early embryonic development. Evidence supporting the possibility of an increase in incidence of epigenetic aberrations in children born after ART has prompted concerns that these children may be at higher risk of cancer than children born after spontaneous conception.

Cancer risk in children born after assisted reproduction

Assisted reproduction involves exposing gametes and embryos to hormonal stimulation in supra-physiological levels, to culture media and to physical stress. This happens within the same timeframe as epigenetic reprograming of the pre-implantation embryo, which are extremely sensitive to stress. Adaptations in foetal epigenetic patterns may occur as a result. Altered epigenetic patterns have previously been found in human assisted conception embryos[127,128], cord blood and placenta[129,130]. As noted above, several authors have reported unexpectedly high numbers of children born after ART with imprinting disorders[108-110]. This is largely due to epigenetic defects; specifically, aberrant DNA methylation leading to altered gene expression[110,131,132]. These findings are supported by similar outcomes in animal models[133-135]. Accumulating evidence suggests an influence on the epigenome of embryo culture, ovarian hyper-stimulation, embryo transfer and exposure to light, resulting in imprinting disorders, among other potential effects[136,137].

Epigenetic mechanisms are known to play a role in human carcinogenesis as part of imprinting disorders[138], *and independently* of such syndromes[139,140]. Some imprinting disorders, including subsets of Beckwith-Wiedemann syndrome, are known to be associated with specific childhood tumors such as Wilms' tumours, neuroblastoma, hepatoblastoma and rhabdomyosarcoma[141-144]. However, there is accumulating evidence that global hypomethylation and hypermethylation of tumor-suppressor genes play significant roles in human tumours in individuals *without* imprinting disorders[139,145-147]. Evidence suggests that epigenetic abnormalities may play a role in the development of a variety of different types of childhood cancer including acute lymphoblastic leukaemia[148], neuroblastoma[149], sarcoma[150], germ cell tumours[151] and retinoblastoma[146,152]. It is therefore possible that processes involved in ART, may lead to epigenetic modification of DNA, potentially resulting in the development of cancer in the offspring[153].

Literature review investigating cancer risk in children born after assisted conception[154]

A systematic review was undertaken to evaluate epidemiological evidence investigating this possible risk. Where appropriate, data has been combined into meta-analyses.

Review question: *'Are children born after assisted conception at higher risk of cancer than spontaneously conceived children?'*

PICO style inclusion criteria:

Population/ intervention: This review includes studies of children born after assisted reproductive technologies. This is defined as 'All treatments or procedures that include the *in-vitro* handling of human oocytes and sperm or embryos for the purpose of establishing pregnancy'[4] including but not limited to IVF, ICSI, and gamete/embryo cryopreservation. It does not include assisted/artificial insemination. Studies including children born after maternal hormonal stimulation but not ART were also sought but not included in the meta-analysis.

Comparison: Studies comparing cancer risk in children born after ART, to risk in children born after spontaneous conception were sought. Studies that included a comparison group of children born after spontaneous conception to previously sub-fertile mothers were considered to be particularly useful.

Outcome: The outcomes considered were any site-specific cancer or cancer as a whole*.

Cancer must be physician diagnosed

* Cancer defined as an abnormal growth of cells that tend to proliferate in an uncontrolled way and, in some cases, to metastasize.

Literature review methods: Searches of MEDLINE and EMBASE were carried out on 21.10.2010, with a further update at the official start of this study (3.11.2011) using multiple combinations and variations of keywords 'Neoplasm', 'Cancer', 'Assisted Reproductive Techniques', '*in-vitro* fertilization'. Full search criteria are available in *appendix 1.* An additional hand search of bibliographies of selected studies and review articles was carried out. All relevant identified studies were reviewed independently by two authors. Studies were classified according to design. Cohort studies were quality assessed by two reviewers prior to inclusion in the meta-analysis. High quality studies were those that were population based and identified cases using validated registries. Pooled odds ratios were calculated for combined data from selected studies, comparing observed and expected cases of childhood cancer. 'R' release 2.11 was used for statistical analysis.

Results: From over 4300 results, 60 relevant primary articles were identified, (21 cohort studies, 11 case-control studies and 28 case reports/ series). Of the 28 case reports, 4 did not included data on children born after assisted conception[155-157]. The remaining 24 reports described cancers in 28 children born after ART.

Cancer Type	No. of cancers reported
Renal Tumours[158-163]	6
Retinoblastoma[164-168]	5
Neuroblastoma[169-172]	5
Brain Tumours[173-177]	5
Hepatoblastoma[160-162,178]	4
Teratoma[179-181]	3
Leukaemia[175]	1

Table 6*. Case reports of cancer occurring in children born after assisted conception*

Of the 11 case-control studies, 10 included children born after maternal hormonal treatment and or maternal investigation for infertility but not ART or ART status was not clear[182-191]. One investigated CNS tumours only and found no increased risk associated with ART[192].

Of the 21 cohort studies, 8 contained data which was then included in a subsequent study and were thus excluded[118,193-198]. Two were excluded as they related to cancer in children born exclusively or predominantly after maternal non-ART fertility treatment, and there was no way to differentiate between such children and children born after ART[199,200]. The remaining 11 cohort studies were included in the meta-analysis[201-211]. The overall combined Odds ratio was 1.43 (95% Confidence interval 1.14-1.72).

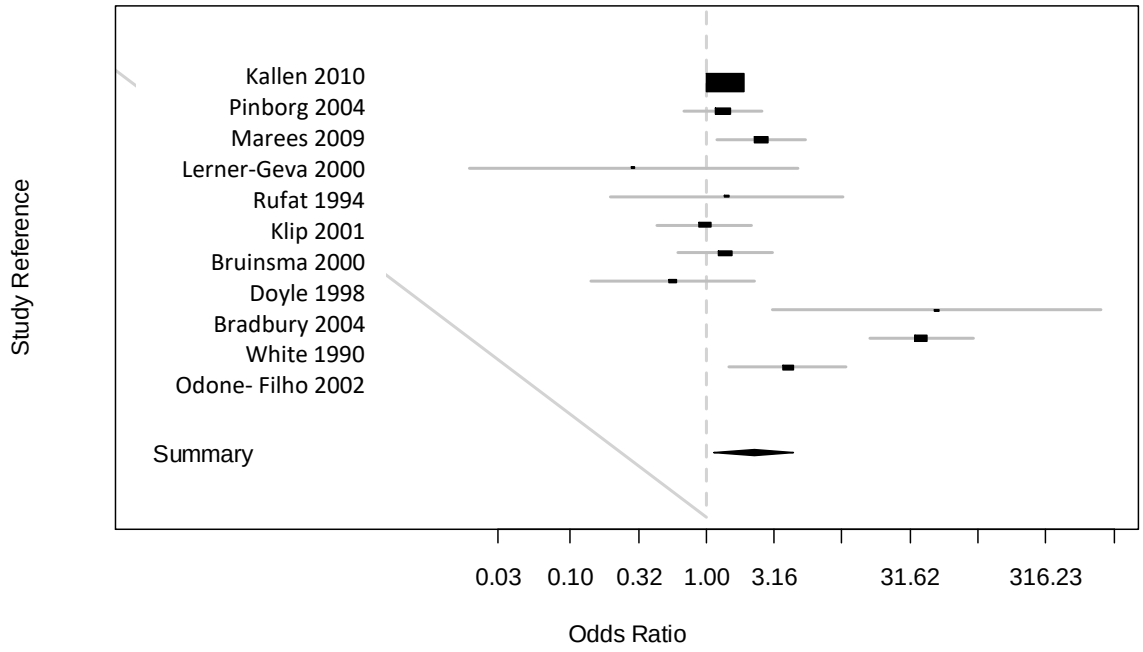


Figure 5. *Forrest plot & meta-analysis of cohort studies investigating cancer risk in children born after ART compared to spontaneously conceived children.*

When restricted to higher quality, registry based studies[201-208,211] (OR= 1.32; 95% CI 1.09-1.55).

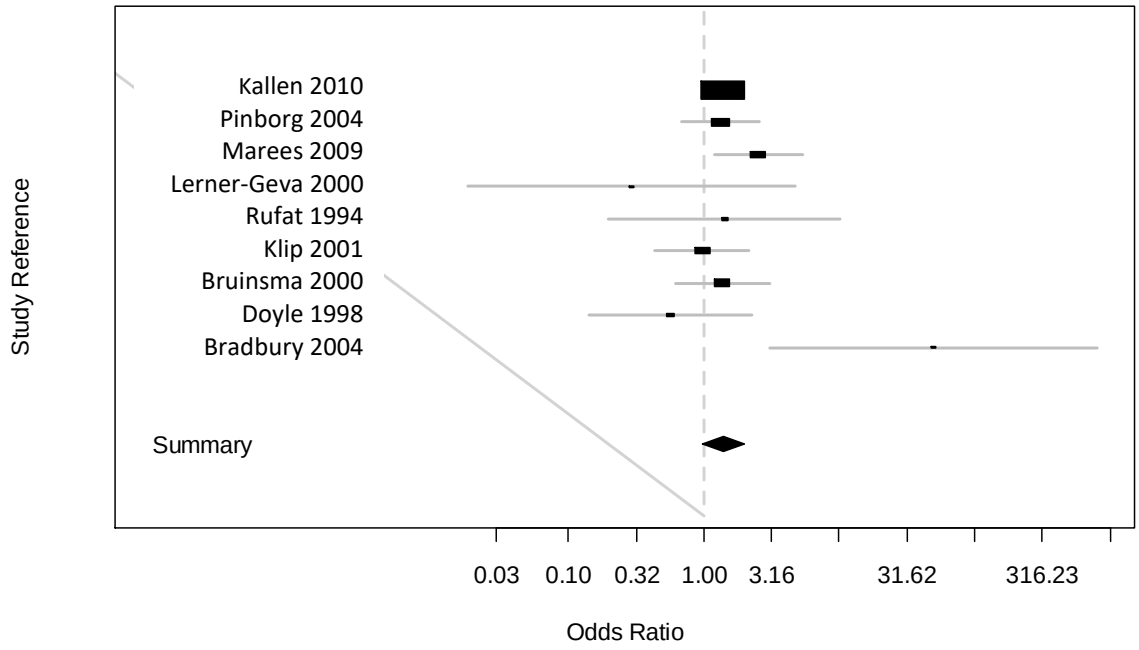


***Figure 6**. Forrest plot & meta-analysis including 9 registry-based cohort studies investigating cancer risk in children born after ART compared to spontaneously conceived children.*

Further analyses restricted to studies including ‘all cancers’ (OR= 1.31; 95% CI 1.05 -1.63).

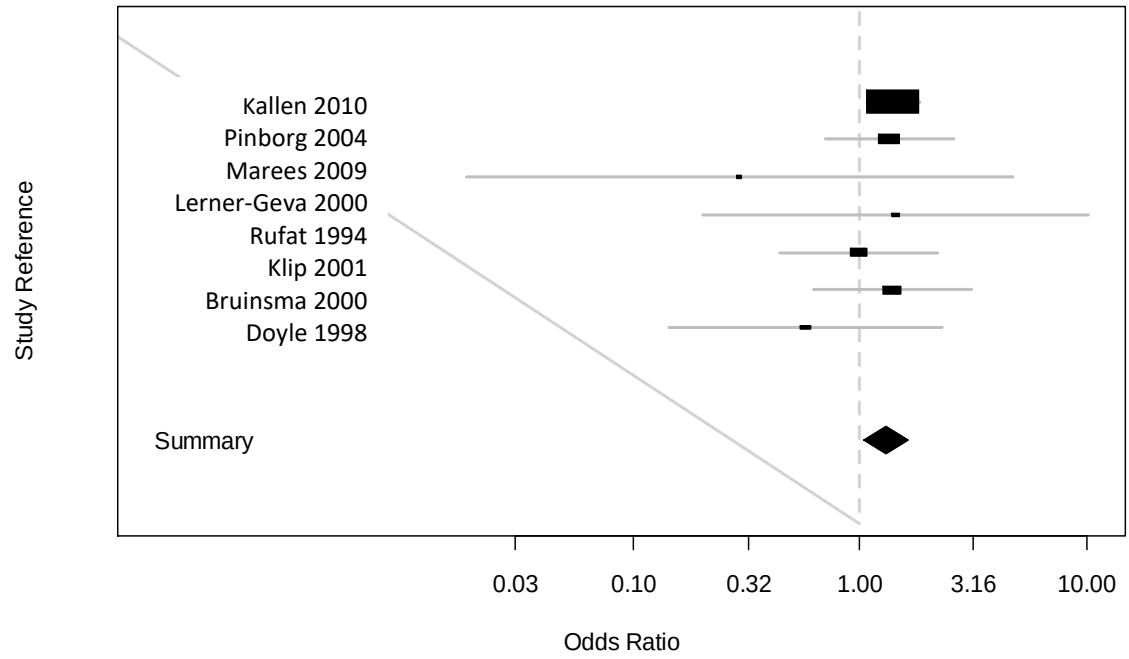


Figure 7. *Forrest plot & meta-analysis of 7 high quality, population & registry-based cohort studies investigating risk of ‘all cancer’ as a whole, in children born after ART compared to spontaneously conceived children.*

Publication bias was not deemed to be a large influence on the results of this systematic review and meta-analysis.

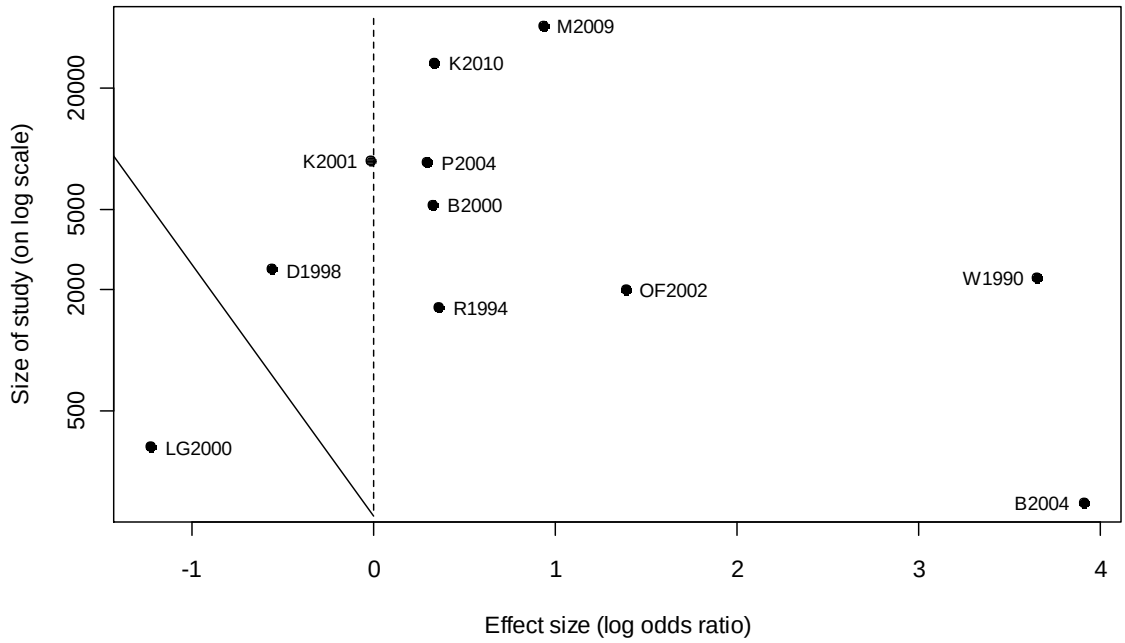


Figure 8. *Funnel plot of cohort studies included in the above meta-analyses.*

Conclusion: The results suggested a small increased risk of childhood cancer after assisted conception. At the time of undertaking, it was concluded that additional larger population-based studies were warranted to confirm this and to investigate risk of specific cancers. Should these further studies have similar findings, underlying mechanisms also warrant investigation. Comprehensive, reliable data in this area are essential for pre-treatment counseling of couples wishing to undergo ART, for facilitating early diagnosis and for the broader public health.

Specific Cancers

Specific cancers noted, by the above included epidemiological studies, to occur at increased risk in children born after ART include, acute lymphoblastic leukemia [201], tumors of the eye, including retinoblastoma[197,201,203], neuroblastoma [209]. The Dutch group who originally reported the possible increase in risk of retinoblastoma in children born after ART[197], found no increased risk in the later study period[203].

Since this literature review was undertaken, there have been several further studies published investigating cancer risk in children born after assisted conception. As these were largely published after the linkage and analysis stage of this section of this thesis was undertaken, (2011-2013), these studies are considered further in *Chapter 6; Discussion.*

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Kallen[201] 2010 SWE	All cancer & Site Specific Categories	Retrospective population-based record linkage using registry data 1982- 2005 (Cancer 2006)	Exposed 26,692 Control 2,417,878	Swedish cancer registry rates applied with adjustment for year of birth Further adjustments made no difference to results, thus not done	Up to 23 years	All- 53 / 38 (O/E) OR 1.42 (CI 1.09-1.87) Haem-18/12.3 (O/E) CNS-15/8.1 Retino-2/1.25 LCH-6 /1	Increased risk of all cancer Increased risk haem cancers, mainly ALL
Pinborg[202] 2004b DNK	All & specific cancers	Retrospective population-based record linkage 1995-2000 (Cancer 2001)	Exposed 8,602	N/A	Minimum one year	9/ 6.7 Expected number calculated by Raimondi[212] OR 1.34 (CI 0.7-2.58)	Cancers included; ALL Hepato-blastoma
Marees[203] 2009 NLD	Retino-blastoma only	Retrospective population-based cohort-(non-registry linkage) Questionnaires & medical notes Diagnosis 1995-2007	Expected exposed cases n=162	Expected rates calculated using population estimates	6.1yrs median	Total study period 7/2.76 (O/E) RR 2.54 (CI 1.02-5.23) 2002-2007 2/1.55 (O/E) RR1.29 (CI 0.16-4.66)	Increased risk not seen in expanded study period, only in original study period covered by Moll et al[197]

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Klip[205] 2001 NLD	All cancer	Retrospective cohort study- Questionaries' 1980-1995	IVF & related techniques 9484 Parents had IVF- 8711 Spont. conception to sub-fertile mothers 4214	Expected rates were calculated using Netherland's cancer registry for the periods 1990-1997 & Eindhoven cancer registry up to 1990	6.0 years mean 4.6 years exposed cohort	6/6.1 (O/E) IVF only SIR 1.0 (CI 0.4-2.1)	
White[209] 1990 AUS	All Cancer	1979-1987	614	Not calculated by study but by Raimondi [212]		3 ART/0.13	
Bruinsma [206] 2000 AUS	All cancers	Retrospective population-based record linkage 1979-1995	5249	Applying Victorian age-specific population-based incidence from 1992-1995	3yr 9 months	6/4.33 SIR 1.39 (CI 0.62-3.09)	
Doyle[207] 1998 GBR	All cancers	Population based registry linkage 1978-1991	2507	Application of national cancer registration rates age and year	8.6 yrs. (mean)	2/3.5 SIR 0.57 (CI 0.07-2.06)	

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Bradbury [208] 2004 GBR	Retino-blastoma	Registry based cohort-GP research database	176	Not calculated		0/0	
Lerner-Geva[211] 2000 ISR	All cancers	Retrospective population-based record linkage 1981-1994	332	Application of general population-based rates of same time period		0/1.7	
Odone-Filho[210] 2002 BRA	All cancers	Local population-based cohort 1996-2000 (Not registry or linkage based	2000	Application of population-based rates	Max 4yrs	4/1	
Rufat[204] 1994 FRA	All cancers	Retrospective local cohort study-Questionaries'	1411	Not calculated	Min 1 yr.	1/0.7	
Bergh[193] 1999	All cancer	Retrospective population	Exposed	Swedish cancer registry rates applied with	Up to 13 years	4 / 3.6	Data overlaps with

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
SWE		based record linkage 1982- 1995	5,856 Control Gen pop 1,505724	adjustment for year of birth			Kallen[201] 2010
Ericson[194] 2002 SWE	All cancer	Retrospective population-based record linkage 1984-1997	Exposed9 056 General Pop 1,417116	Swedish cancer registry rates applied with adjustment for year of birth, maternal age, parity, known period of involuntary childlessness	Up to 13 years	11 /12.5	Data overlaps with Kallen[201] 2010
Kallen[195] 2005 SWE	All cancer & Specific categories	Retrospective population-based record linkage 1982-2001 (Cancer 2002)	16 280	Swedish cancer registry rates applied with adjustment for	Up to 19 years	29/21.4	Data overlaps with Kallen[201] 2010

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Pinborg[196] 2004a DNK	All cancers & site specific Twin only study	Retrospective population-based record linkage- Twins only 1995-2000	Exposed Twins 3,393 Twins General pop 10,239	N/A	Minimum one year	0 11 in control group P=0.076	Same ART data as Pinborg[202] 2004b
Pinborg[198] 2010 DNK	All Cancers Considering FET as main exposure	Retrospective population-based cohort (National hospital discharge register) 1995-2007	Exposed FET 957 Exposed Fresh IVF 10,329 Control 4,800	Sub-group of interest was FET.		1 FET 5 Non FET 1 Non ART	Data likely to overlap significantly with PInborg 2004b, (smaller no. exposed cases), data focussed on FET.
Lidegaard [118] 2005 DNK	Only included cancers associated with imprinting diseases	Retrospective population-based cohort 1995-2001 (NB- national hospital discharge register used)	6 052 IVF 442 349 non-IVF (? ICSI etc. in the non-IVF group?) Singleton only	Expected rates not calculated	4.1 IVF 4.5 non- IVF	0 /72	Significant overlap with Pinborg 2004b Focus is imprinting diseases therefore cancer case assentation not exhaustive

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Moll[197] 2003 NLD	Retino-blastoma only	Retrospective population-based cohort-(non-registry linkage) 1995-2001 (Cancer 2002)		Expected rates calculated using population-based estimates	Min one year	5/0.69	Data overlaps with Marees 2008
Klip 2002 NLD Reprint in Evidence-based Obstetrics & Gynecol. (2002) 4, 140 -141	All cancer	Retrospective cohort study-Questionaries' 1980-1995	IVF & related techniques 9484 Parents had IVF- 8711 Spont. conception to sub-fertile mothers 4214	Expected rates were calculated using Netherland's cancer registry for the periods 1990-1997 & Eindhoven cancer registry up to 1990	6.0 years mean 4.6 years exposed cohort	6/6.1 (O/E) IVF only SIR 1.0 (CI 0.4-2.1)	Data identical to Klip 2001. Reprint & Commentary in Evidence-based Obstetrics & Gynecol. (2002) 4, 140 -141
Brinton[199] 2004 DNK	All cancers & site-specific cancer	Retrospective Pop based record linkage 1963-1996 Children born after fertility treatment	51 063 (16 786 prior to maternal infertility)	Danish cancer registry rates applied adjustment for age, sex and calendar specific incidence rates	10.1 years (mean)	51/44.7 (O/E) SIR 1.14 (CI 0.4-1.6) Leuk 18/13.9 Lymph 4/3.6 CNS 12/12	Includes children born after fertility drugs and not necessarily ART (with no distinction between them).

Study Details	Outcome	Design	Cohort Numbers	Expected Calculation	Follow Up	Outcome	Comment
Hargreave 2009[200] DNK	All cancers & site-specific cancer	Retrospective population based record linkage 1963-1998	69 391	Danish cancer registry rates applied		Overall SIR 1.22 (1.07-1.37) Leuk SIR 1.49 (CI 1.15-1.90) CNS SIR 1.20 (CI 0.93-1.53)	Includes children born after fertility treatment and not necessarily ART (with no distinction between them).

Table 7*. Cohort studies investigating cancer risk in children born after assisted conception identified through systematic review. Shaded rows indicate that study not included in meta-analysis*

Chapter Summary & Study Rationale

There are comprehensive theoretical reasons why women who have assisted reproductive treatments *may* be at greater risk of specific cancer types, particularly of the breast, ovary, and endometrium/ corpus uteri. There have been several studies attempting to investigate these risks, however they have produced somewhat inconsistent results, potentially because of their small size, few exposed cases and the lack of consideration of potential confounding factors.

Similarly, there are also sound theoretical reasons why children born after assisted conception may be at higher risk of childhood cancer. Relatively few studies have attempted to investigate these potential risks and have similarly been limited by small sample size and few events, given the rarity of childhood cancer.

Despite these potential and largely unquantified risks, the use of assisted reproduction has increased worldwide. Due to changes in the law regarding the recoding of assisted reproduction cycles in the UK, (detailed further in chapters 2 and 4), it is now possible for the first time, to gain access to a large cohort of women who have had ART and to a large cohort children born after ART, in Britain.

Therefore, this study aims to investigate cancer risks in women who have had, and children born after ART in Great Britain.

Study aims

Primary Aims:

1. To investigate if women treated with hormonal therapies as part of assisted reproduction are at increased risk of cancer as a whole and site-specific cancers over the decade after their treatment.

2. To investigate if children, born after assisted reproduction are at increased risk of cancer as a whole and site-specific cancer, over their early childhood.

Secondary Aims:

Cancer in Women after ART

1. To investigate effect of duration and age at exogenous hormone exposure in women.

2. To investigate if different types of sub fertility are associated with different types of cancer.

Cancer in Children after ART

1. To investigate if different types of assisted reproduction are associated with differing childhood cancer risk (for example comparing fresh and cryopreserved embryo replacement cycles).

2. To investigate if different types of parental sub-fertility are associated with different types of childhood cancer.

Hypotheses

At the time these studies were carried out, there was genuine equipoise for all research questions this study addressed. The below hypotheses were based on theoretical mechanisms and relevant studies published to date.

Cancer in women after ART

- Women who have had hormonal treatment as part of assisted reproduction have an increased risk of cancer compared to women who have not had such treatment.
- Ovarian, breast, and endometrial cancers are the site-specific cancers most likely to be increased in this population, potentially related to excess oestrogen exposure and multiple ovarian punctures.
- Increased risks may be accounted for by confounding factors such as parity, anovulation, and endometriosis.

Cancer in children after ART

- Children born after assisted reproduction have an increased cancer risk compared to children born after spontaneous conception.
- The site-specific cancers most likely to be increased are Leukaemia, Retinoblastoma, and cancers associated with imprinting disorders such as Neuroblastoma and Wilms' tumours.

Chapter 2 – Cancer risk in women after assisted reproduction; Data sources & study methods

The Human Fertilisation & Embryology Authority (HFEA) database

The HFEA is an 'arm's length body' of the department of health and acts independently on behalf the United Kingdom government. It was set up and is governed by UK legislation, initially in 1990[213], and updated in 2008[214]. Its main purpose is the regulation of assisted reproductive techniques in the UK (England, Wales, Scotland & Northern Ireland) through licensing, monitoring, and inspecting fertility clinics. However, as part of its regulatory functions, the HFEA is legally mandated to collect specific information about all assisted conception cycles in the UK since 1991, including details of infertility cause, parity (up to completion of an individual's last treatment cycle), age at first treatment, some treatment details, and some details of resulting births. As HFEA registration of all ART cycles carried out within the UK is a mandatory legal requirement, the resulting HFEA dataset is assumed to be close to 100% complete.

Due to a change in the HFEA legislation Act[214], effective of 6th April 2010, it is now possible to have limited access to identifiable records of assisted conceptions in the UK from 1991 onwards, subject to ethical approval. Specific consent is not needed for the use of HFEA data on treatment cycles carried out prior to 1st of October 2009 (subject to approval under section 251, UK National Health Service Legislation Act 2006[215]), however patients are able to retrospectively withdraw their consent for research use of their data. From 1st of October 2009, prospective consent has been sought for HFEA data to be used for research. Unfortunately, the proportion of couples giving prospective consent varies nationally and has been as low as 30% in some regions (*Personal communication*; Dr Melanie Davies, Consultant in fertility medicine and external advisor to the HFEA Scientific and Clinical advisory board, from 2009 to present day).

The HFEA database included 302,487 records of women documented as having had ART in the United Kingdom between 1st January 1991 and 31st December 2010 and as having data available for research.

For the period 1st January 1991 to 30th September 2009, the database population represents 99.9% of the at-risk or source population as 290 of 294,903 (0.1%) women retrospectively removed consent for their data to be used prior to this study starting.

There are 5,762 women recorded on the HFEA database as having had their first assisted reproduction cycle in the period 1st January 2010 to 31st December 2010 and as having given consent for their data to be used for research. Unfortunately, after discussions with the HFEA, they were not able to provide accurate figures for the at-risk source population for this period, (i.e. *all* women who had ART in the UK for the first time between 1st January 2010 and 31st December 2010). However, a reasonable estimate of this population is 25,500 women. This has been estimated, assuming that the steady annual increase in women having their first ART cycle which occurred between 2004 and 2009 continued at approximately the same rate (see figure 9 and table 8). Using this rough estimate, the number of records available for research pertaining to ART cycles performed in 2010 (n=5,762) represents approximately 22.5% of all ART cycles undertaken that year.

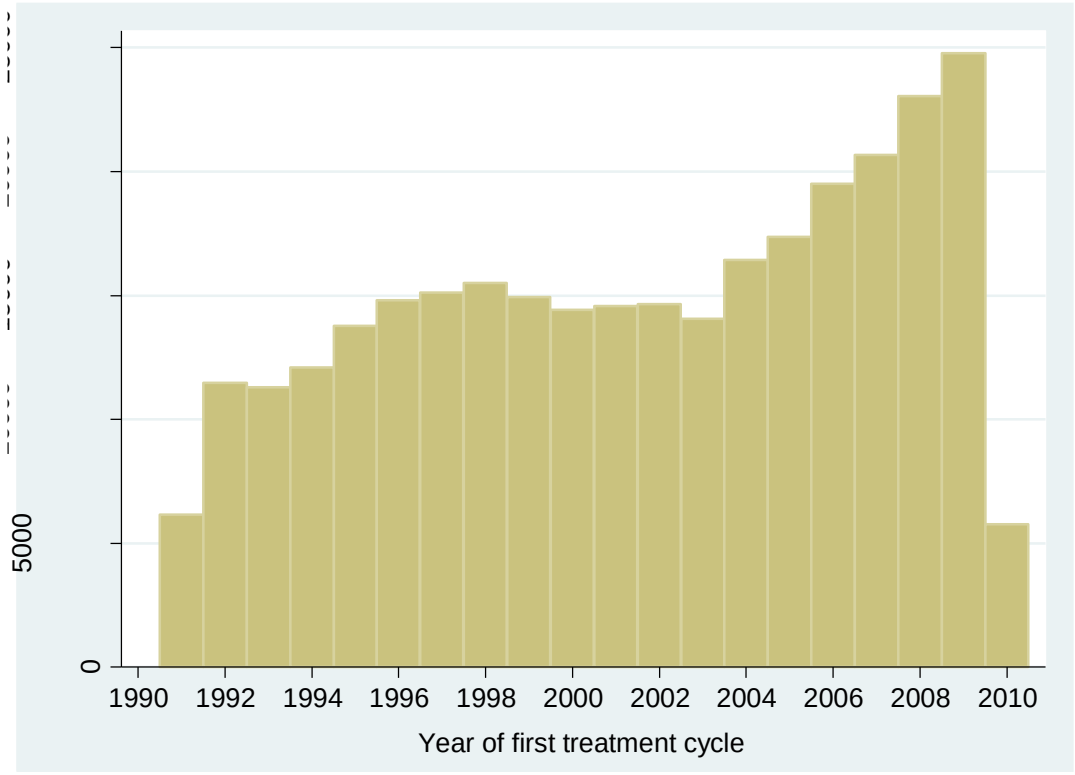


Figure 9. *Number of women who had ART 1991-2010, where data available for research (HFEA data-base population), by year at first treatment.* [1]

First treatment year	Frequency	%	Cumulative %
1991	6, 145	2.03	2.03
1992	11, 472	3.80	5.83
1993	11, 294	3.74	9.57
1994	12,096	4.00	13.57
1995	13,780	4.56	18.13
1996	14,797	4.90	23.03
1997	15,106	5.00	28.03
1998	15,502	5.13	33.15
1999	14,926	4.94	38.09
2000	14,413	4.77	42.86
2001	14,581	4.83	47.69
2002	14,646	4.85	52.54
2003	14,071	4.66	57.19
2004	16,431	5.44	62.63
2005	17,360	5.74	68.37
2006	19,511	6.46	74.83
2007	20,662	6.84	81.67
2008	23,037	7.62	89.29
2009	24,783	8.20	97.49
2010	5,762	1.91	99.40
Treatment year unrecorded	2,112	0.60	100.00
Total	302,487	100	

Table 8. *Women who had ART 1991-2010, where data was available for research (HFEA data-base population), by year of first treatment[1].*

Variables collected by the HFEA during the study period are recorded in the HFEA data capture sheet, provided by the HFEA in 2009 in *appendix 2*. As discussed below and in table 10, the completeness and data quality of each data item varies significantly. Data have been manually entered onto the HFEA system over the 19 year study period, with regular data audits. Given the HFEA's primary regulatory role, data audits and quality assurance procedures have traditionally been focused on patient identifiable variables. This has resulted in reliable identifiable variables for our cohort, as can be seen from HFEA reported data in table 9.

Identifiable Variable	% of records with probable valid entry
Mother's Surname	100%
Mother's Forename	100%
Mother's Surname at Birth	46.3%
Mother's Forename at Birth	3.0%
Mother's Date of Birth	100%
Mother's Town or District of Birth	56.5%
Mother's Country of Birth	58.2%
Treatment Cycle Start Date	100%
Treatment Centre No/ Name	100%

Table 9. *Completeness of HFEA cohort identifiable variables, as reported by the HFEA at study start.*

Whilst data audits have not focused on non-identifiable variables, the HFEA database is a dynamic system, in that it continually receives updated information from fertility clinics, from cycle outcomes, further cycles and specific corrections. This results in continuous data quality updates. In addition, the HFEA undertook a large scale record update, in December 2010, prior to record transfer, to ensure that all treatment cycles each individual woman received were correctly assigned to that specific woman.

The available HFEA variables are generally either reported by the individual fertility clinics directly or self-reported and completed forms passed to the HFEA through the treating fertility clinic. Sources for individual variables are detailed with other HFEA Meta-data for successfully linked records, *table 10*.

HFEA data item	Freq. potential valid data	Details	Data Source	% Complete
Date of Birth	255,786		Clinic reported	100
Ethnic group	46,107	30 potential responses	Self-reported	18·0
Start date of first treatment cycle	255,786	Year of each treatment cycle recorded. Year mid-point used to calculate person-years at risk.	Clinic reported	100
Start date of last treatment cycle	255,786		Clinic reported	100
Age at first treatment	255,786	Categorised: - <25 yrs.- 5,671 25-29 yrs.- 39,932 30-34 yrs.- 92,788 35-39 yrs.- 85,868 40-44 yrs.- 28,174 45+yrs – 3,353	Derived, first treatment cycle date minus date of woman's birth	100
Broad Cause of infertility	244,286	Female- 70,293 Male- 84,871 Both- 41,365 Unexplained- 47,757	Clinic reported	95·5
Endometriosis	255,786	Yes- 18,630 No- 237,156	Clinic reported	100
Tubal disease	255,786	Yes- 66,370 No- 189,416	Clinic reported	100
Ovulatory disorder	255,786	Yes- 36,016 No- 219,770	Clinic reported	100
Male factor infertility	255,786	Any: - Yes-126,236 No-129,550 Specific: Sperm concentration: - Yes- 18,679, No-237,107 Sperm morphology: - Yes-10,586, No-245,200 Sperm motility: - Yes-9,263, No-246,523 Sperm immune issue: - Yes-2,493, No-253,293	Clinic reported	100
Primary Female infertility	255,576	Yes-113,918 No- 141,658	Clinic reported	99·9
Secondary Female Infertility	255,786	Yes-86,322 No-169,464	Clinic reported	100
Primary Male Infertility	255,786	Yes-117,207 No-138,579	Clinic reported	100
Secondary Male Infertility	255,786	Yes-80,843 No-174,943	Clinic reported	100
Primary Couple infertility	255,786	Yes-139,272 No-116,514	Clinic reported	100

HFEA data item	Freq. potential valid data	Details	Data Source	% Complete
Secondary Couple infertility	255,786	Yes-58,584 No-197,202	Clinic reported	100
Duration of infertility	206,304	<2yrs- 17,194 2-3yrs- 67,529 4-5yrs- 56,203 6-7yrs- 29,946 8-9yrs - 15,394 >=10yrs -20,038	Self-reported	80·6
Number of Treatment cycles	255,778	Natural cycle only-9,781 Stimulated cycles- 1- 131,670 2- 63,842 3-4- 41,224 5+ - 9,261	Clinic reported	99·9
Type of ART treatment	255,177	IVF only- 150,700 ICSI/ Unspecified micromanip- 76, 596 IVF & ICSI- 27,881	Clinic reported	99·8
Treatment centre	255,786	Treatment centre was the only geographical variable available	Clinic reported	100
Number of Pregnancies by end of last treatment cycle	255,377	0- 82,747 1- 94,836 2-3- 63,821 4-5- 11,246 6+ 2,727	Derived variable: Self -reported pregnancies at start of last treatment cycle* plus HFEA rec ART preg from last cycle.	99·8
Years since last pregnancy	121,698	Variable contains a number of values which are likely to be age at last pregnancy.	Self-reported	47·6
Age at last pregnancy	121,698	Median- 31·7 yrs. IQR 35·5-27·7 yrs.	Self-reported	47·6
Number of live births by end of last treatment cycle	255,701	0- 129,217 1- 96,839 2-3- 27,593 4+ 2,052	Derived variable: Self -reported births at start of last treatment cycle* plus HFEA rec ART birth from last cycle.	99·9
Multiple births	255,786	Yes- 29,366 No- 29,366	Clinic reported	100
ART birth recorded by HFEA	255,786	Yes- 105,183 No-150,183	Clinic reported	100

Table 10. *HFEA Meta-data relating to women who have had assisted conception in Great Britain from 1991-2010 and who are included in analysis (chapter 3). *Self-reported previous pregnancies and births were validated against HFEA recorded previous cycle outcomes.* [1]

NHS-Digital Central Registry (medical register information service; MRIS)

The *NHS-Digital* medical register, records all individuals who are born in England or Wales, die in England or Wales or who have registered with an NHS general practitioner in England & Wales. It holds the following information: -

- Demographics including: -
    - Names: forename(s); surname(s); previous name(s)
    - Date of Birth
    - NHS-number
    - Postcode & Previous recorded postcodes
- Exits from the register: -
    - Embarkations out of England & Wales
    - Deaths:
        - It is a legal requirement that deaths are registered within 5 days in England & Wales.
        - ONS death registrations are then updated on the NHS medical register on a monthly basis. NHS-Digital standard is to include reported deaths within 21 days of date of death. This is longer when inquests are on-going.
- Re-entries to the register: -
    - If a cohort member moves from England/ Wales to Scotland, they appear on the Scottish NHS central register as a re-entry and provided there is no discrepancy in dates, are treated as having continuous study follow-up.

- Cancer related clinical information.
    - For each individual distinct cancer diagnosis a cohort member may receive from a registered medical practitioner, data includes: -
        - Cancer diagnosis date
        - Cancer topography code (ICD9/ ICD10)
        - Cancer morphology (ICD-O-2/ICD-O-3)
        - Cancer behavior (ICD-O-2/ICD-O-3)

If NHS-Digital are provided with identifying demographic details for cohort members, they can provide a service whereby cohort members are identified on the medical register and 'flagged'. Their current status with regards to cancer and exits from the register can then be reported to researchers. 'Flagging' a patient allows future status to be reported to the researcher as soon as it is recorded on the register.

Unfortunately, due to legal specification by the HFEA act 2008[214], this study is not permitted to permanently 'flag' cohort members on national medical registries. Instead it permits linkage for current status, followed by repeated linkage in the future to inform long-term outcomes.

Cancer registrations on NHS-Digital central registry

Cancer outcomes recorded on the NHS-Digital medical register during the years covered by this study were collated by the Office for National Statistics (ONS) from multiple sources including:

- National Cancer Registration and Analysis Service (NCRS) in England
    - Collating data from all individual cancer registries in England
- Welsh Cancer Intelligence & Surveillance Unit (WCISU)
- Hospital episode statistics
- National clinical audit data

Data quality and completeness of NHS-digital cancer registrations

Once cancer registrations are received they are validated using extensive validation procedures including the compatibility of site and histology data. Registry validation procedures are closely based on international standards[216].

Cancer registration is described as a 'dynamic process'[217] as data files remain open for modification, should more accurate information become available later. Occasionally, completely new incident cases are added to the central registry after ONS have reported incident cancers to the NHS-Digital central registry. Over a 41-year period (1971-2011) including the study period (1991-2011), the difference between contemporaneous cancer incidence (reported within 12 months of diagnosis) and that reported longer than 12 months after diagnosis was less than 5%[217] (*Figure 10*).

This study uses cancer outcome data for cohort members relating to cancer diagnoses from cohort entry until 28th March 2011, as reported by 28th March 2012. Therefore 'late' cancer registrations relating to 2011 and possibly to 2010 may be a potential source of bias but 'late'

registrations relating to early cohort years are highly likely to have been included in the study outcome data. As of March 2014, the proportion of 'late' cancer registrations for diagnoses in 2011 is estimated at 0.47%[217], all of which will be unrecorded by this study. The proportion of 'late' cancer registrations relating to cancer diagnoses in 2010 is estimated as 3.47%, an unknown proportion of which will be unrecorded by this study (although it would not be unreasonable to assume that the majority of late registrations would be recorded within 24 months of cancer diagnosis date and therefore included in this study for cancer diagnoses in 2010).

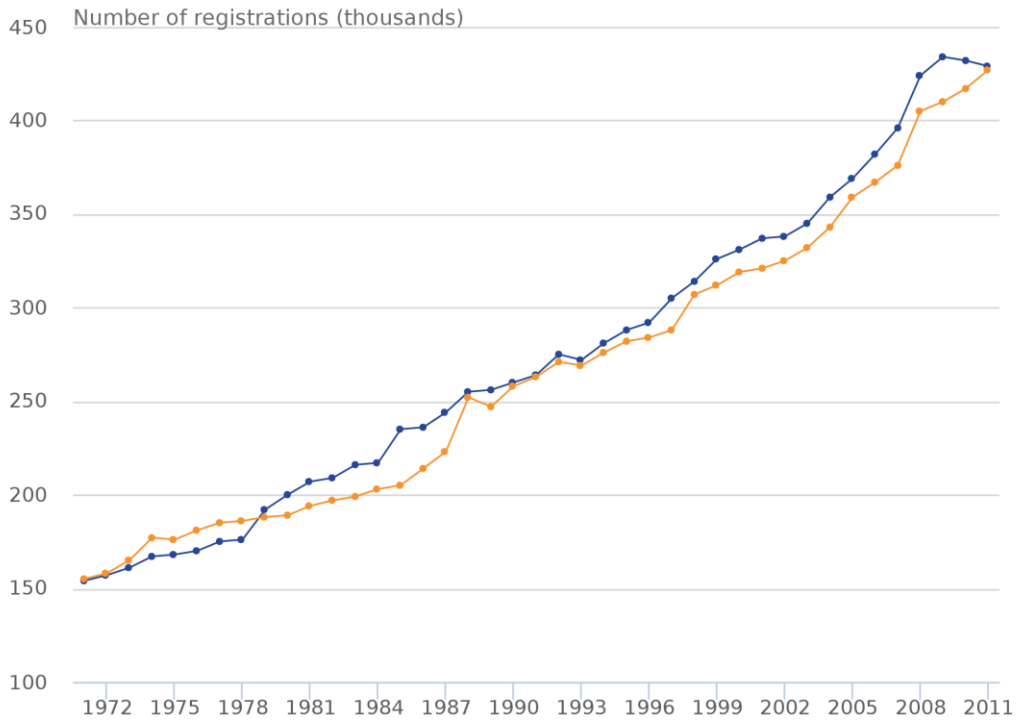


***Figure 10**. Cancer registrations within & beyond 12 months of cancer diagnosis date (Orange= cancer registrations received within 12 months of diagnosis; Blue= cancer registrations received 12 months or more after cancer diagnosis; as of March 2014) [217].*

National Records of Scotland (NRS), NHS central register

The Scottish NHS central register is held by National Records of Scotland, the Scottish equivalent of NHS-Digital and is a similar, smaller, dataset to the NHS-Digital central registry for England & Wales described above. There are strong links between the two organisations and they worked in parallel on this linkage project; communicating regularly where cohort members have moved between England/ Wales and Scotland to provide continuous follow-up for cohort members if they remain within England, Wales and Scotland.

The Scottish central medical register contains basic demographic details of everyone who was born in Scotland, died in Scotland and anyone who is (or has been) on the list of a general medical practitioner in Scotland. It holds: -

- Demographics including: -
    - Names: forename(s); surname(s); previous name(s)
    - Date of Birth
    - NHS-number
    - Community health index number (an additional unique identifying variable)
    - Postcode & Previous recorded postcodes
- Exits from the register: -
    - Embarkations out of Scotland
    - Deaths:
        - It is a legal requirement that deaths are registered within 8 days in Scotland.
        - Death registrations are then updated on the Scottish central medical register on a monthly basis.
- Re-entries to the register
    - If a cohort member moves from Scotland to England/ Wales, they appear on the *NHS-Digital* central register as a re-entry and provided there is no discrepancy in dates, are treated as having continuous study follow-up.

- Cancer related clinical information. For each individual distinct cancer diagnosis a cohort member may receive from a registered medical practitioner, data includes: -
    - Cancer diagnosis date
    - Cancer topography code (ICD9/ ICD10)
    - Cancer morphology (ICD-O-2/ICD-O-3)
    - Cancer behavior (ICD-O-2/ICD-O-3)

NRS provides a similar 'flagging' service to NHS-Digital, providing current status with regards to cancer and/ or death. Unfortunately, as above, this study does not have permission to permanently 'flag' cohort members, but can undertake linkage to establish current status.

Cancer registrations on the Scottish NHS central register

Since 1997 cancer outcomes recorded on the Scottish NHS central register have been collated by the Scottish Cancer Registry via Scottish Open Cancer Registration And Tumour Enumeration System (SOCRATES)[218]. SOCRATES receives cancer notifications from a variety of sources including: -

- NHS hospital systems including: -
    - Discharges
    - Radiotherapy records
    - Oncology records
    - Haematology records
    - Pathology records
- Prospective audit datasets
- The General Register Office for Scotland
- Paper records from private hospitals

Prior to the formation of SOCRATES in 1997, the Scottish NHS central register cancer registration data were collated from 5 individual regional cancer registries in Scotland[218].

Data quality and completeness of Scottish cancer registrations

Cancer registrations are validated using extensive validation procedures including using routine indicators, computer validation and ad hoc studies of data accuracy and completeness of ascertainment[218]. Registry validation procedures are closely based on international standards[216] and also include data exchange with specialist registries. A recent study comparing ascertainment of incident breast cancer by the Scottish cancer registry system with that collected by 5 independent breast cancer trials reported 98% ascertainment, although they also report a 0.3% misclassification of invasive breast cancer as carcinoma in situ[219].

Linkage methods: Background

Data linkage or record linkage can be defined as "a process of pairing records from two files and trying to select the pairs that belong to the same entity"[220]. Two commonly used methods of data linkage are: -

- Deterministic linkage
- Probabilistic linkage

Deterministic linkage generates links based on one or a number of identifiers, which are the identical between datasets and are unique to the particular individual or entity. Deterministic linkage may be appropriate when a unique identifier is present in both datasets, (for example NHS number)[220].

Probabilistic linkage is often used when a unique identifier is not available in both data sets. It involves the matching of a wider range of partially identifying information, which are not necessarily unique. A weight is assigned (using a standard formula) to each potential match based on how closely the two variables in question agree between the two databases. Researchers can then set a threshold below which they will not consider a match[220]. Indeed probabilistic linkage can be used to enhance deterministic record linkage algorithms and has been shown to reduce error when linking health service data in the UK[221].

Different data linkage methods were used in the two different sections of this thesis (investigating cancer in women who have had ART and investigating childhood cancer in individuals born after ART). This is because of the differing identifying variables available for each cohort, (as provided by the HFEA), the quality and completeness of those fields and practical considerations such as standard practices at the different sites where linkages were undertaken.

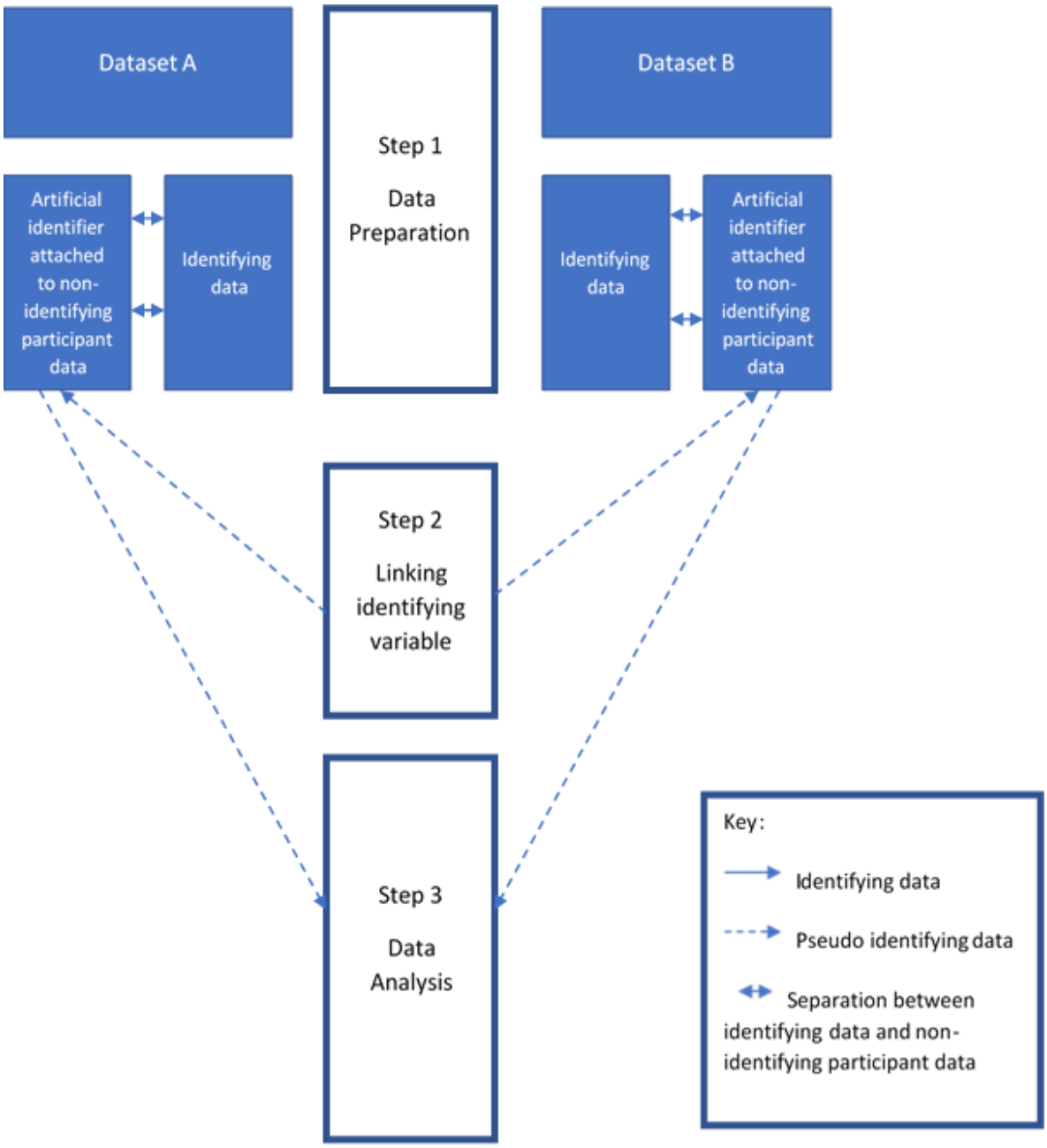


Figure 11. *Typical data linkage pathway, illustrating the separation principle. Adapted from Gilbert et al.* [222].

The linkage pathways used in this study follow the separation principle, whereby identifiable data and exposure/ outcome data are separated at the start of a project. This ensures that bias is not introduced in the linkage, as individuals who are undertaking linkage do not have access to exposure data at that time. It also ensures patient confidentiality as at no point do researchers, or indeed anyone working on the project, have access to both identifiable and outcome data.

However, as recent guidance has suggested[222], this could potentially also lead to bias as information about source data and linkage quality and completeness is often not shared between individuals undertaking different steps of the linkage pathway. There are two main types of linkage error[222,223]: -

- False matches
    - When individuals are matched to incorrect records which do not relate to them.
- Missed matches
    - When records are not correctly identified as relating to the same individual.

[220,222,223]

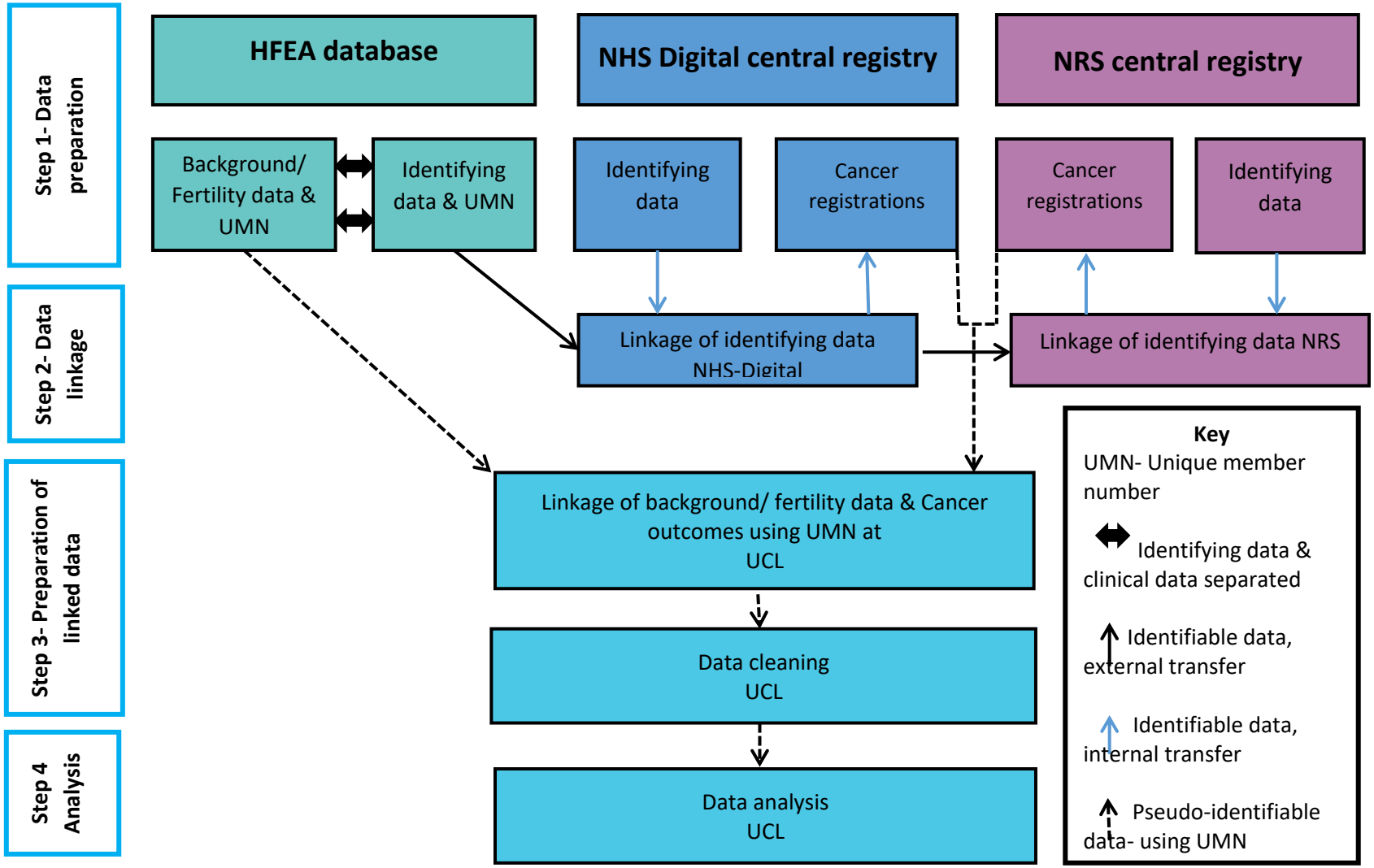
Causes of linkage errors include: -

1) Identifiers entered incorrectly
2) Individuals sharing identifiers
3) Different identifiers used across different data sets or across time for the same person

[220,222,223]

This study has attempted to address potential sources of linkage error related to each of these causes.

Linkage methods: Linkage pathway



As detailed in *figure 12*, the separation principle was used for linkage in this section of the thesis. This was done to comply with data protection principles of handling personal data fairly, safely and securely according to an individual's data protection rights.

Linkage methods: Data preparation (Step 1)

The HFEA updated their records just prior to data transfer, ensuring all data (identifiable and non-identifiable) were up to date according to the information held by the HFEA. This process was specifically introduced to reduce the risk of linkage errors due to incorrectly entered identifiable data.

A unique member number (UMN) for each individual woman was then attached to every record relating to that woman. Identifying data were then separated from background and fertility data, ensuring that the same UMNs were kept attached to both the identifying data and the corresponding background fertility data relating to the same women.

NHS Digital and NRS central registries keep identifiable data and cancer registrations up to date as a matter of routine. As above, cancer registrations are reasonably complete 12 months after cancer diagnosis. Although identifying data and cancer registrations are kept on the same database, when viewing identifiable data, cancer registration status is not visible unless specifically requesting such data. Only separated data (either identifiable data with UMN ***OR*** clinical data with UMN, but **never both together**) were transferred between organisations in order to comply with data protection principles.

Identifiable data and corresponding UMNs relating to 302, 487 individual women, treated with ART in the United Kingdom were then securely transferred from the HFEA, using NHS-Digital's 'data depot' system (the NHS's secure data transfer system).

Linkage specification (Step 2)

NHS-Digital (England & Wales)

NHS- Digital initially employed automatic deterministic linkage, using: -

a) Forename

b) Surname

c) 2 of 3 parts of date of birth matching

If more than one match was found, no match was accepted, even if one of the automatic matches was complete. This was in order to reduce false-match linkage errors due to individuals sharing identifiers. HFEA records with more than one automatic match to NHS-Digital records were additionally manually matched. HFEA records where no match was found were also then manually matched. Manual matching utilised: -

a) Forename (including partial versions)

b) Surname (including partial versions)

c) Date of birth

d) All other recorded names

e) Place of birth

f) Treatment centre & Cycle date

All other recorded names were used in order to reduce linkage errors resulting from individuals being recorded using different identifiers on different databases. Place of birth and treatment centre (used in combination with treatment cycle dates) were used as additional validating variables, allowing further differentiation of two or more potential matches based on broad geographical location. Unfortunately, more detailed geographical variables were not available for cohort members.

HFEA records which remained unmatched at the end of the linkage process at NHS-Digital and records where an HFEA record was linked to an NHS-Digital record, but subsequently recorded as embarking to Scotland, were then securely transferred to NRS.

National Records of Scotland (NRS)

NRS initially utilized automatic deterministic linkage using:-

a) Forename

b) Surname

c) 3 of 3 parts of date of birth matching

Again, if more than one automatic match was found, no match was accepted. HFEA records with more than one match to NRS records were then manually matched along with HFEA records where no match was found. Manual matching at NRS utilised the same additional variables as at NHS-Digital.

Linkage quality control

At the request of, and in conjunction with the author of this study, NHS-Digital undertook a quality assurance exercise to test the specificity of the automatic matching algorithm used.

1) A batch of records was matched using the automatic matching algorithm used by NHS-Digital (*Algorithm A*).
2) The same batch of records was then automatically matched using forename, surname and all three parts of date of birth correct (*Algorithm B*).
3) A manual operator match was then performed on the same batch of records (*Manual*, treated as the gold standard).

The results of the three above matches were then compared. If all three of the above linkage methods resulted in linkage of the same two records, this was taken as a confirmed match.

If comparison of the three linkage methods resulted in any of the below situations, further investigation was undertaken, using all available variables from all databases: -

- *Algorithm A* and *Manual* both matched the same HFEA record to the same NHS digital record, but *Algorithm B* did not produce a match.
- *Algorithm B* and *Manual* both matched the same HFEA records to the same NHS digital records, but *Algorithm A* did not produce a match.
- Both *Algorithm A* and *Algorithm B* matched the same record to a different NHS digital record.

The results showed zero false positive matches out of 4239 matches using *Algorithm A* and nine false positive matches using *Algorithm B*.

Algorithm A – 0/4239 false positive matches

Algorithm B – 9/4239 false positive matches

This gives assurance that automatic linkage at NHS-Digital (which covered the majority of linked records in this study), resulted in a very low false positive match rate (<0.02%). Although NRS were not able to use algorithm A, instead using algorithm B, their automatic linkage false positive rate was also likely to be very low (<0.2%). 7.4% of all records successfully matched during this study were matched automatically at NRS (n=19,751; see *table 11*).

Manual matching was undertaken by a small team (4 individuals, all experienced in record linkage), at NHS-Digital, led by James Grey. Internal daily meetings were held to discuss match quality and precision. Weekly meetings were held between the study author and NHS-Digital team to discuss linkage specification and quality, as well as the general linkage progress. More frequent correspondence by email and phone occurred between weekly meetings.

Manual matching at NRS was also done by a small team, experienced in data linkage (2 individuals). This team was led by Gail Turner and again regular internal quality assurance

meetings were held alongside fortnightly meetings with the study author. More frequent correspondence by email and phone occurred between fortnightly meetings.

Once HFEA records were successfully linked, cancer outcomes and details of exits from the registers relating to linked individuals were then accessed. UMNs and outcome information were then separated from identifiable data. Pseudo-anonymous outcome data (including UMN) was then securely transferred to UCL using 'data depot'.

Linkage outcomes (Step 2)

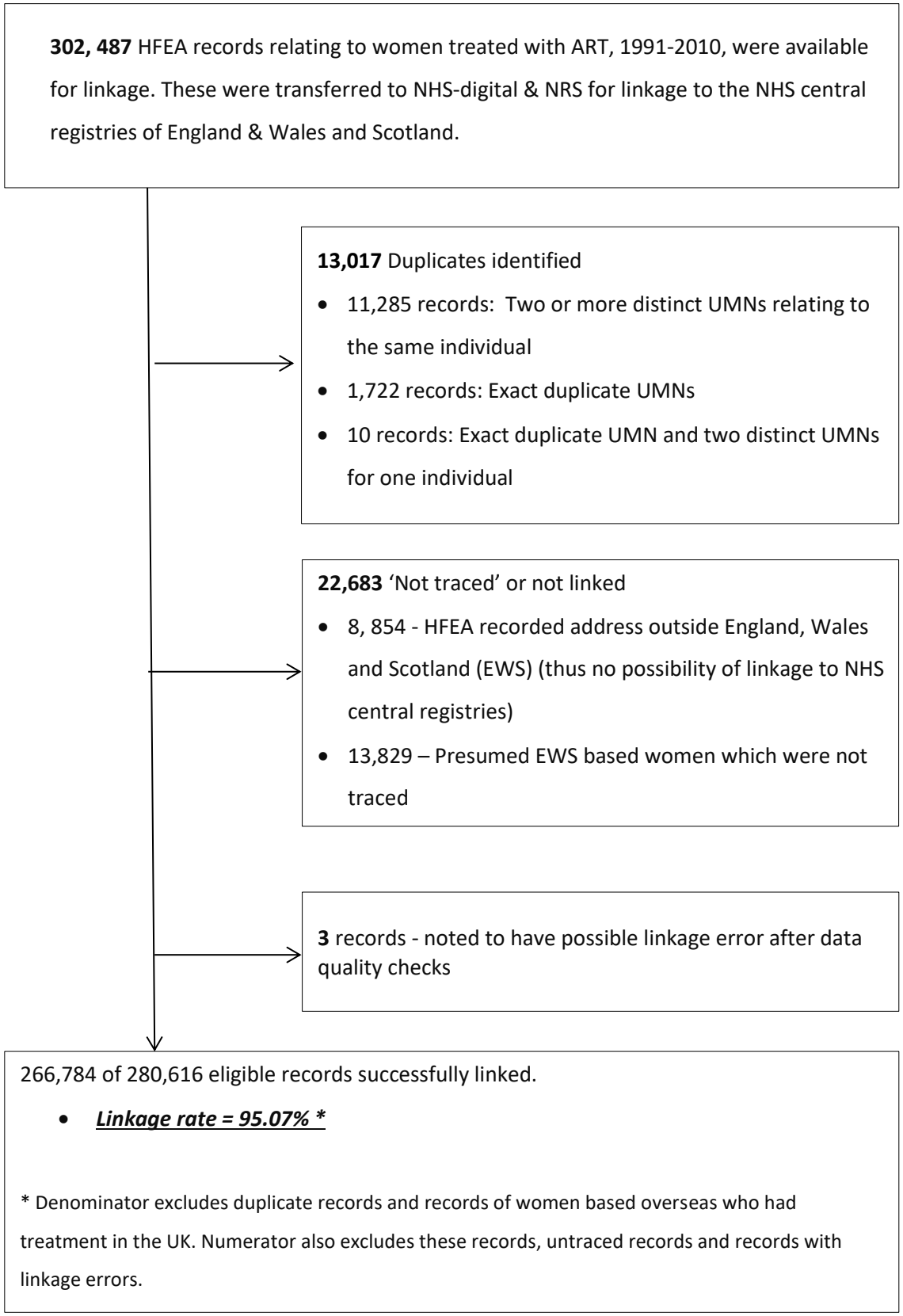


Figure 13. *Data linkage results for the section of this thesis investigating cancer risk in women after ART* [1]

Duplicates

As indicated in *figure 13*, 13,017* HFEA duplicate records were identified by the linkage process and excluded from the study.

There were 8,660 individuals who were assigned two different UMNs (with HFEA records containing identical identifying information; thus 8660 duplicate records). There were 986 individuals who were assigned three different UMNs (thus 1972 duplicate records), 167 individuals who were assigned four different UMNs (thus 501 duplicate records), 29 individuals who were assigned 5 different UMNs (116 duplicate records), 6 individuals who were assigned 6 different UMNs (thus 30 duplicate records) and one individual records with 7 different UMNs (thus 6 duplicate records).

There were 1,722 circumstances where the same HFEA record, containing the same UMN and same identifying information was included twice in the data transferred from the HFEA to NHS-Digital (thus 1,722 duplicate records). There were 5 circumstances were an individual was assigned two different UMNs, and one of those records was exactly duplicated (thus 10 duplicate records).

* Initially reported as 13,025 but 8 UMNs were found to have been reported as duplicates in error- see data cleaning below.

‘Not traced’- including those residing outside of England, Wales and Scotland

There were 22,683 HFEA records where neither NHS-Digital nor NRS were able to trace the individual on their central registries. [†]

These records were taken back to the HFEA for further investigation. 8, 854 of the 22,683 unmatched records were identified as relating to women who were not likely to appear on central registries for England & Wales or Scotland. This was based on area level address (country, region or town) ***and*** place of birth, as recorded by the HFEA, ***both*** being outside of England, Wales & Scotland. 3,183 of these women were recorded as both being born and currently residing in Northern Ireland.

3,796 women whose records were unmatched were recorded as having had assisted reproductive treatment in a fertility clinic in Northern Ireland. Whilst relatively unlikely, it is still possible that some of these women could potentially be linked to the NHS central registry, for example if they had travelled to Northern Ireland from their home in England, Wales or Scotland for treatment. These records were therefore not excluded on the basis of treatment centre being in Northern Ireland alone (though many of these were excluded on the basis of being born in and currently residing in Northern Ireland, as above).

This study does not include linkage to the NHS central registry of Northern Ireland, which would have been preferable to enable this study to estimate population risks for the whole of the United Kingdom. This option was explored at the outset of this project, however the linkage systems for the NHS central registry of Northern Ireland is not well developed and it was felt that such linkage may have introduced unacceptable linkage errors.

[†] Initially reported as 22,707 but 24 records were found to have actually been traced- see data cleaning below.

Summary of Successful Matches

	Matched in England & Wales	Matched in Scotland	Total
Matched by Automatic Deterministic Linkage	172,607	19,751	192,358
Matched by Manual Linkage	72,561	1,868	74,429
Total	245,168	21,619	**266,787**

***Table 11**. Summary of successful matches by automatic vs. manual matching, including those matched by NHS-Digital (in England & Wales) and by NRS (In Scotland).*

As detailed in figure 13 above, three of these matches, initially considered successful, were subsequently identified as potential linkage errors during data cleaning processes. Therefore these three records were subsequently excluded. Circumstances of each linkage error is detailed in the following subsection.

Data Cleaning (Step 3)

Merging HFEA/ NHS-Digital/ NRS data

Pseudo-anonymised HFEA data, containing non-identifying demographic and clinical fertility data plus unique member number (UMN), were securely transferred from the HFEA to UCL. The HFEA file was constructed with a single line per treatment cycle. Data were initially consolidated to produce a single line per individual. 1,727 Genuine duplicates, where exact duplicate UMNs were present and contained exactly replicated background/ fertility data were dropped from the file leaving 300,760 HFEA records relating to women who had ART 1991-2010 in the UK. This corresponds to the number of exact duplicates found in the sister file, containing UMN and identifiable data, during the linkage process.

Pseudo-anonymised outcome data, containing cancer, death and embarkation data plus unique member number (UMN), were securely transferred from the NHS-Digital and NRS to UCL. Data were in a variety of different files and were consolidated; ensuring data from multiple sources (e.g. NHS-Digital vs NRS) relating to a single individual were combined using UMN. This file contained outcome data relating to 266, 787 women.

All data were received in excel format, and imported into STATA, version 12[224], for all but the most basic data cleaning/ data consolidation. HFEA data and NHS-Digital/ NRS outcome data were then merged: -

1. 266, 787 records successfully merged
2. 33,973 records contained only HFEA data ('master data only')
3. 0 records contained only NHS-Digital/ NRS data ('using data only')

22,707 records reported as 'not traced' by NHS-Digital/ NRS were then highlighted in the merged file to ensure that they were genuinely all 'not traced'. 24 records marked as 'not traced'

appeared to contain both background and outcome data. In 15 cases, records had been reported as having not been traced by one of NHS-Digital or NRS but had been traced by the other. The remaining 9 records had been initially reported to UCL as having not been traced by NHS-Digital, but included outcome data reported by NHS-Digital. All 24 records were manually 're-matched' (using manual matching criteria described above) at NHS-Digital/ NRS, according to where outcome data was reported from. For all 24 records, data linkages were validated and confirmed as containing the correct outcome data. Therefore all 24 records were retained in the analysis file. The 15 records reported as 'not traced' by one agency and successfully linked by the other represent communication errors between NHS-Digital and NRS. The UMNs of the 9 records initially reported as 'not traced' and then whose outcome data were reported by the same agency were included in the 'not traced' file in error.

Two or more UMNs reported by NHS-Digital and/ or NRS as relating to a single individual were then investigated in the merged file. In 34 records, where UMNs were reported as duplicates (and thus should have no outcome data attached), outcome data were observed. These were investigated: -

- On 26 occasions, outcome data were attached to the duplicate UMNs reported by NHS-Digital/ NRS as having no outcome data, and not to the duplicate UMN reported to contain outcome data.
    - These 26 records represent simple errors by NHS-Digital as to which duplicate record contained the outcome data.
- In 8 cases, different outcome data were contained in reportedly duplicate UMNs.
    - NHS-digital manual 're-match' of these cases showed that these 8 records did in fact relate to different individuals and were included in the duplicate file in error.

Therefore all 34 records were retained in the analysis file.

On initial analysis of the merged data file, 241 records were noted as having UMNs assigned by the HFEA (and thus included in the HFEA data file) and as having NHS-Digital/ NRS outcome data and thus their records had merged correctly in the step above. However, the HFEA background and fertility data was completely blank for these 241 records. It was confirmed by the HFEA that although these women had undergone ART in the UK 1991-2010, no background or fertility data was held by the HFEA relating to these women. Therefore, in retrospect, these records should not have been included in the original data transfer from the HFEA to NHS-Digital, and were excluded from the analysis file.

Cleaning background and fertility variables (HFEA variables)

Date of Birth: Whilst the exact date of birth was available to NHS-Digital/ NRS for linkage purposes, data of birth of cohort members provided by the HFEA in the analysis dataset was a date randomised with 3 days of the true date of birth. This was done to comply with data protection procedures and ethical regulations, whilst ensuring that accurate time at risk was quantifiable for each cohort member. One record containing an invalid date of birth (01/01/1900), was considered to have missing date of birth.

Date of first Treatment: The years in which women were recorded as having had ART, as reported by individual treating clinics to the HFEA, were included in a single variable received from the HFEA. This was a string variable of all recorded treatment years, (e.g. 1998, 1999, 2001 etc.). These were then separated into multiple variables, the mid-point of the first recorded treatment year taken as the date of first treatment. Unfortunately the HFEA do not collect any further detailed information about treatment dates. All records with date of first treatment available contained dates between 1991-2010.

Date of last treatment: This was the mid-point of the last recorded treatment year. All records with date of last treatment available contained dates between 1991-2010. A further validation

of this field was performed comparing year of last treatment to 'Registration form year' provided by the HFEA containing the year of the last HFEA registration. There were no additional discrepancies identified using this validation.

1,678 records had no treatment dates available and were excluded as time at risk was not calculable.

Age at first treatment (derived field): Date of first treatment cycle, minus age at first treatment.

- 51 records generated an age at first treatment <16 years of age. For these records date of birth and date of first treatment were considered missing.
    - These records and the above single record with date of birth 01/01/1900 were excluded as time at risk and/ or age during time at risk was not calculable.
- Age at first treatment was then grouped:
    - <25
    - 25-29
    - 30-34
    - 35-39
    - 40-44
    - 45+

Ethnicity: This self-reported variable contained 30 potential responses. Records marked as "NULL" or "Not stated" or " " were marked as missing but no further data validation was possible for this variable. Ethnicity was only 18% complete for linked records (*Table 10*).

Duration of Infertility: The majority of records with non-missing data in this self-reported field contained an apparently valid integer relating to the number of years of infertility. However, in a small number of cases an actual year was recorded (e.g.1997), relating to the year in which an

infertility diagnosis was made. This was converted to number of years of infertility by subtracting this year from year of last treatment. For records where the duration of infertility exceeded the age at first treatment, duration of infertility was considered missing (n=10). More precise validation was not possible as some women had recorded their duration of infertility as their age. It is not possible to decipher an individual women's intention behind this; for example some may have done this as they had never been pregnant, some may have done this if they had a congenital condition which caused their infertility, and some for other reasons.

- Duration of infertility was then grouped:
    - <2yrs
    - 2-3yrs
    - 4-5yrs
    - 6-7yrs
    - 8-9yrs
    - >=10yrs
    - Unrecorded

Broad Cause of Infertility/ Endometriosis/ Tubal Disease/ Ovulatory disorder/ Male factor infertility: These fields are reported directly from the treating ART clinic to the HFEA. These fields were used to validate each other. All records with endometriosis/ tubal disease/ ovulatory disorder had either female factor infertility or male and female factor infertility recorded as the broad cause of infertility and vice versa. All records with a specific male factor (e.g. sperm count etc.- see *table 10*) had male factor or male and female factor infertility recorded as the broad cause of infertility and vice versa. Those who had unexplained infertility recorded as the broad cause of infertility did not have a specific cause of infertility (e.g. endometriosis or sperm count) recorded.

Type of ART treatment: This field was a string variable, reported directly from the treating clinic to the HFEA detailing the treatment used during each cycle. Therefore each woman may have multiple different forms of ART recorded within this variable. Each individual was categorised as having had: -

- IVF only
- IVF & ICSI/ Unspecified Micromanipulation
- Unknown/ unspecified ART [4]

Number of Cycles: This field, reported by the treating clinic to the HFEA, was recorded as a string variable in the form of natural vs stimulated cycles (e.g. 1 vs 3 for women who had one natural cycle and three stimulated cycles). This field was recoded into number of stimulated cycles. For women who had at least one recorded natural cycle and no stimulated cycles, they were categorised as having no stimulated cycles. For all women with at least one stimulated cycle recorded, regardless of the number of natural cycles, this number was categorised as:

- 1
- 2
- 3-4
- 5+
- Unrecorded

Numbers of cycles were validated against treatment years. No individuals had more treatment years recorded than number of cycles (excluding those with 0 stimulated cycles i.e. natural cycle only). No individuals had three more treatment cycles than the number of treatment years (assuming that having more than 3 stimulated cycles within a single treatment year is not possible). In fact most women had one treatment cycle per calendar year, but three was used as a cut off in this instance as this was treated as the theoretical maximum possible number of stimulated cycles in a year.

Number of Pregnancies by end of last treatment cycle (derived field): This variable was derived using self-reported pregnancies immediately prior to last treatment cycle ***plus*** HFEA reported ART pregnancy resulting from the last treatment cycle. This derived field was validated against self-reported pregnancies from previous HFEA registration forms and HFEA reported ART pregnancies from previous treatment cycles.

Number of live births by end of last treatment cycle (derived field): This variable was derived using self-reported live births immediately prior to last treatment cycle ***plus*** any HFEA reported ART live birth resulting from the last treatment cycle. This derived field was validated against self-reported live births from previous HFEA registration forms and HFEA reported ART live births from previous treatment cycles.

Initially, validation of the above two derived variables produced multiple discrepancies, with whole sections of the dataset presenting inconsistencies between pregnancies/ live births reported at last treatment cycle registration and those reported at earlier treatment cycle registrations. Investigation of this uncovered a coding error when data were extracted from the original dataset in step 1 of the linkage pathway. Further investigation of this error showed this was limited to the variables number of previous self-reported pregnancies and live births (from all cycle registrations). No other variables were affected. Once these variables were re-extracted from the original HFEA dataset, the variables, 'Number of Pregnancies by end of last treatment cycle' & 'Number of live births by end of last treatment cycle' were recalculated as detailed above.

Further difficulties arose when calculating these fields. An old version of the version of the HFEA data collection form contained two sections for previous pregnancies and two for previous live births. These sections were designed so that women who were having ART filled in one section only and women having donor insemination (DI) filled in the other section only. However, many

women misunderstood this and completed both sections (n=6,384). Where the total pregnancies and total live births given for both sections were the same, it was assumed that the information had just been duplicated (i.e. the women had filled in the same information twice in error). This assumption was validated using the same data from previous registrations. For 56 records, data was different in the ART and DI sections. After discussion with supervisors of this study, these variables were marked as missing.

Number of pregnancies (at end of last treatment) was grouped as: -

- 0
- 1
- 2-3
- 4-5
- 6+
- Unknown

Very high numbers of pregnancies were reported by 8 women, with a range of ages at first treatment. After discussion with supervisors of this study, individuals reporting 20 or more pregnancies were marked as having this field missing (n=8).

Number of live births (at end of last treatment) was grouped as initially: -

- 0
- 1
- 2-3
- 4+

The 2-3 and 4+ groups were later consolidated to improve the power in analyses using this variable. Very high numbers of live births were reported by 9 women. For all 9, gravida was much lower. Although these may have represented multiple live births, after discussion with supervisors of this study, individuals reporting 9 or more live births were marked as having this field missing (n=9).

Years since last pregnancy: Self-reported field. This field contained a variety of different outcomes, some were a number of years and others were an actual year (e.g. 1997). In the latter situation, the given year was used in conjunction with the last treatment cycle date (a proxy for when the information was given) to generate a number of years since last pregnancy. Date of birth was then used to estimate the age at last pregnancy, if this was an invalid figure (for example if the women was less than 13 years of age at last pregnancy), the field was considered as having missing data (n=455).

Age at last pregnancy: Self-reported field. Age of less than 13 years at last pregnancy were marked as missing. For records where this was given in the form of a year, this was used in conjunction with the last treatment cycle date (a proxy for when the information was given) and date of birth, to generate age at last pregnancy.

Cleaning outcome variables (NHS-Digital/ NRS data)

Fact of cancer diagnosis, deaths, record cancellation, embarkation from the UK, embarkation to another UK region included in the study (e.g. from England/ Wales to Scotland or vice versa) and embarkation to Northern Ireland were reported by NHS-Digital/ NRS as different types of events. Thus women had multiple events each with a different date of event recorded.

Event dates were recoded into date format, ensuring each event contained a valid date. A number of invalid dates were present resulting from outcome data being transferred from NHS-Digital/ NRS in different formats (e.g. 01.01.1991 and 01/01/1991) these were corrected by referring back to original NHS-Digital/ NRS data files manually.

For each cancer event, cancer diagnosis date, cancer topography code (ICD9/ ICD10), cancer morphology (ICD-O-2/ICD-O-3) and cancer behavior (ICD-O-2/ICD-O-3) were reported, where data were available. This study did not analyze second cancer events or cancer events occurring before the date of their first ART cycle.

17,951 first cancer events were identified (this included malignant events/ carcinoma in situ and carcinoma of uncertain behaviour of any topography).

8,904 cohort members had a cancer diagnosis in years preceding their date of first treatment and where therefore excluded from further analysis (*figure 14*).

Individuals who had a cancer diagnosis in the same year as first treatment year were not excluded as it was not possible to distinguish between those who had ART after their cancer diagnosis and those who had ART prior to their cancer diagnosis date within that year (n=677); these individuals were excluded in sensitivity analyses for specific cancers; *see below and chapter 3*).

Cancer topography: For 47 records, a cancer event was reported with a cancer diagnosis date but no topography, morphology, or behaviour data. All 47 records were re-traced, and their data scrutinised at NHS-Digital. Unfortunately, no further information was found to aid categorisation in any of these 47 cancer events. All these records were marked as having had a cancer diagnosis. Their study exit date /end of time at risk was set as their date at cancer diagnosis (*see below for details*). Given the lack of further information, none of these events were included in any analyses of specific cancers.

In 36 cases the topography site referred to a secondary cancer (ICD10 codes C77*, C78* and C79*). Further investigation revealed the topography of the primary cancer site in three cases. All three of these primary cancers occurred within three months of the secondary cancer diagnosis (one related to a case of breast cancer, the two others were cases of melanoma). Therefore, the case of breast cancer was included in breast cancer analyses. The remaining 33 cases were marked as having had a cancer diagnosis, and thus their study end date marked as their date of cancer diagnosis, but not included in any of the site-specific analyses.

One individual was recorded as having a cancer not compatible with their gender (a testicular cancer recorded in a woman). This was investigated at NHS-Digital and at the National Cancer Registration and Analysis Service (NCRAS) where the cancer was originally reported from. This was identified as a linkage error at NCRAS, the cancer being assigned to the wrong individual on their system. The linkage made at NHS-Digital was verified as correct. Therefore, the individual woman was not excluded from the study, but this cancer event was removed from the merged dataset. The records of NCRAS & NHS-Digital were appropriately amended.

Study entry/ exit

Study entry date was set as the date of first treatment, estimated as mid-point of first treatment year as exact dates were not available.

Study end date (point at which individuals were censored from the study) was set as the earliest of: -

- Date of first cancer
- Date of death
- Date of embarkation from England/ Wales/ Scotland
- Study end date (28.03.2011)

Study entry/ exit dates were validated using all recorded event dates.

- 122 individuals were recorded as embarking from England, Wales, and Scotland before the date of their first treatment (*figure 14*).
    - These individuals were excluded from the analysis.
    - It is likely that these women had once lived in England, Wales or Scotland and had returned for fertility treatment but had not re-registered with a general medical practitioner (and were likely only temporary residents at the time of ART).
- In three cases, validation using event data revealed probable linkage errors.
    - One record reported a death in 2003, but a child born after ART in 2006. This case was not a straight forward linkage error relating only to the linkage undertaken for this study, but a linkage error in the NHS-Digital central registry as a further posting was reported by NHS-Digital in 2008. The case was excluded from the study and NHS-Digital data amended.
    - One record reported a death 9 years before the date of first treatment.
    - One record reported a death 7 years before date of first treatment, (treatment resulted in a live birth).
    - All three records were excluded from analysis *(figures 13 and 14*).

- 386 patients had a cancer diagnosis in the first 6 months of their first treatment year.
    - As date of first treatment was estimated as mid-point of first treatment year, this resulted in a cancer being recorded before treatment. As it was not possible to determine if the cancer occurred immediately before the first or immediately after it, study entry date was set to the 1st of January of the first treatment year, in order to include these patients in the analysis.
- 26 records had additional discrepancies between study entry and exit dates
    - 6 individuals were recorded as having died within the first 6 months of the same calendar year as first treatment.
        - As date of first treatment was estimated as mid-point of first treatment year, this resulted in a death being recorded before treatment.
        - However it is possible (and probable) that for these individuals, they had treatment within the first 6 months of the recorded first treatment year and died shortly afterwards.
        - Therefore these records were retained for analysis and study entry date altered to the 1st of January in the year of first treatment.
    - 20 individuals embarked from England, Wales and Scotland within the first 6 months of the same calendar year as first treatment.
        - As date of first treatment was estimated as mid-point of first treatment year, this resulted in embarkation being recorded before treatment.
        - However it is possible (and probable) that for these individuals, they had treatment within the first 6 months of the recorded first treatment year and embarked shortly afterwards.
        - Therefore these records were retained for analysis and study entry date altered to the 1st of January in the year of first treatment.

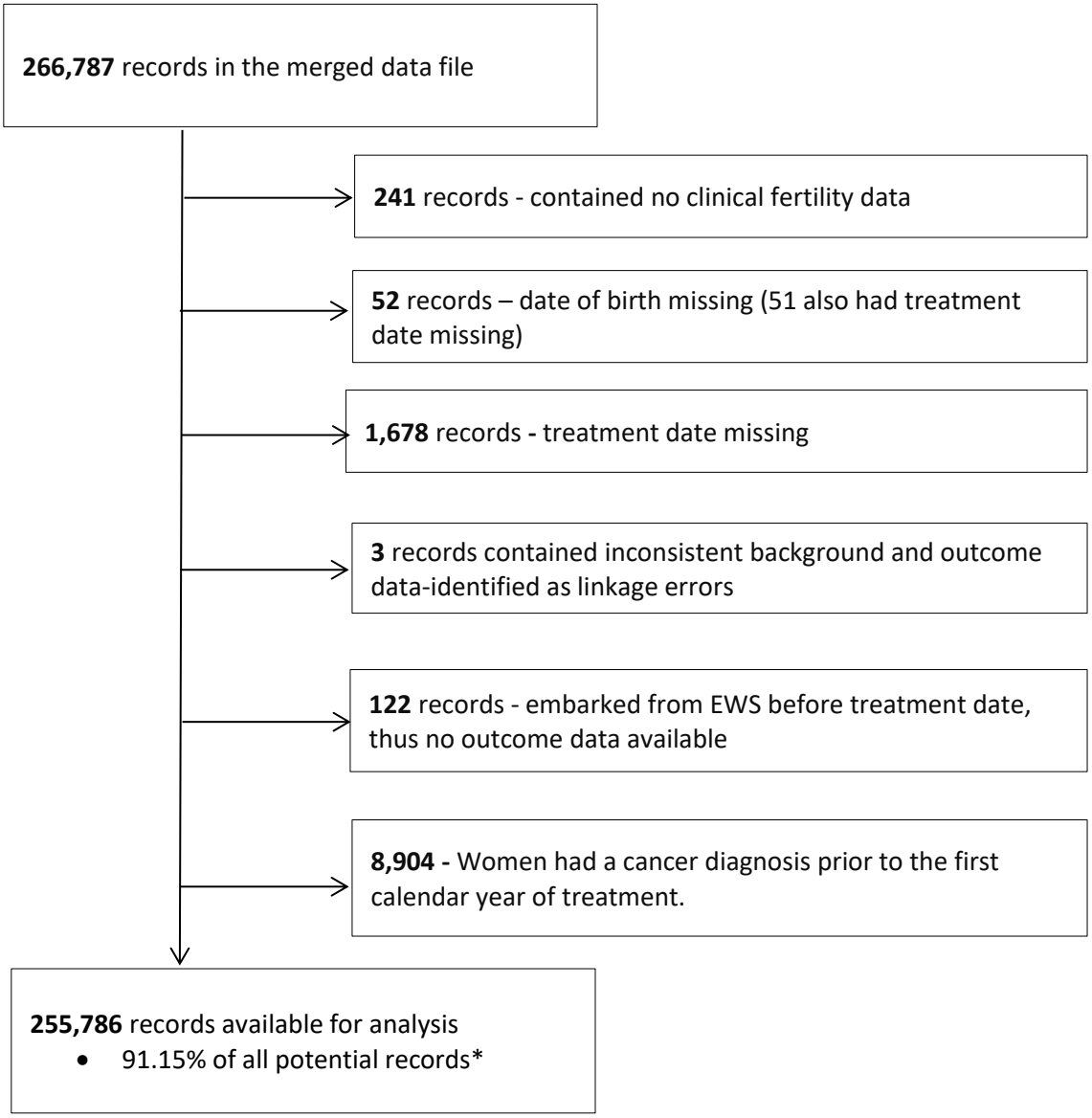


Figure 14*. Summary of Records excluded during analysis file construction and data cleaning (step 3). *255,786 records included from 280,616 records eligible for this study. This denominator excludes duplicate records and individuals recorded by the HFEA as women whose usual residence is outside of England, Wales and Scotland but who had ART in the UK 1991-2010 (described above).*

Defining specific cancers

Outcome	ICD9 codes	ICD10 codes
All breast cancer	1740-9, 2330 &2383	C500-9, D050-9 & D486
In-situ carcinoma of breast	2330	D050-9
Invasive breast cancer	1740-9	C500-9
All ovarian cancer	1830-9, 2362	C56, C570-4, C481, D391
Invasive ovarian cancer	1830-9 (excluding morphology codes 8442/8451/8462/8472/8473) 2362	C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473)
Borderline ovarian cancer	1830 (with morphology codes 8442/8451/8462/8472/8473).	D391, C56 (with morphology codes 8442/8451/8462/8472/8473).
Corpus uteri cancer	1820-8	C54

***Table 12**. Definition of cancer outcomes by ICD topography codes (some definitions also include morphology codes).*

The definitions in the above table were applied to the outcome data to identify cancers of the breast, ovary and corpus uteri in the merged, cleaned dataset. These definitions are based on SEER ICD-O-3 and O-2 site/ histology validation lists[225], with input from Dr Rupali Arora, Consultant Pathologist, University College London Hospitals.

Data Analysis (Step 4)

The total cohort experience was compared to an external standard. Observed cancer outcomes, as defined in *table 12*, were compared to expected values. The relative risk was measured by the ratio of observed/ expected, the Standardised incidence ratio (SIR).

Expected cancers were calculated multiplying person-years at risk by corresponding national incidence rates (by 5-year age band and individual calendar year) for the general female population of England & Wales. By using corresponding age and sex specific national rates, this study accounts for sex and indirectly standardizes for age.

Person-years at risk were calculated from the date an individual women was considered at risk, (the date of first treatment, estimated as mid-point of first treatment year), until the end of follow up. Follow-up terminates for each individual on the date of any cancer diagnosis, death, emigration or study end (28th March 2011), whichever came first.

Ideally, time dependent variables, which change values at the age at which new events occur (e.g. births, pregnancies, number of treatment cycles), would be analysed in a time dependent fashion. However, intermediate dates required for time dependent analysis were not available from the HFEA. Therefore, time at risk for time dependent variables were instead defined at the time which that variable became static. For this study, this was approximated as date of last treatment cycle. For example, number of treatment cycles is no longer a time-dependent variable after the last treatment date. For variables which could still potentially be time dependent after completion of last treatment cycle, the variable has been defined to express the fact that it cannot be considered as time dependent. For example, number of births could potentially change after completion of last treatment cycle. Therefore analyses were instead expressed in terms of number of live births at completion of last treatment cycle.

95% confidence intervals, 2-sided *P*-values and trends were calculated assuming a Poisson distribution[226]. Sensitivity analyses excluded the first 12 months of follow-up. Analyses were performed using STATA, version 12[224].

Example Power Calculations

At the start of this study, an example power calculation was undertaken. For the purposes of this example power calculation, expected numbers of cancers were calculated, based on English age-standardized rates per 100,000 women, assuming a cohort of 230,000 (estimated by the HFEA) and mean follow-up of 10.1 years, power calculations are based on the Poisson distribution[226].

Cancer site	α	1-β	Expected	Minimum detectable risk
Breast	0.01	90	3766	1.06
Ovary	0.01	90	375	1.21
Uterus	0.01	90	365	1.25

Table 13*. Example power calculation providing minimum detectable risk for cancer of the breast, ovary and Uterus. Although the cohort was ultimately larger than estimated here, the longer follow-up predicted accounts for the higher numbers of expected cancers in this power calculation compared to the main analysis*.

National Rates

As detailed above, expected cancers were calculated by multiplying person-years at risk by corresponding national incidence rates (by 5-year age band and individual calendar year) for the general female population of England & Wales. Annual national incidence rates 1991-1998 are for England and Wales, thereafter national rates refer to England only as rates were not published for England and Wales combined thereafter. For years 2009, 2010 & 2011, annual incidence rates were not available at the time of analysis, therefore rates from 2008 were used as the best available estimate of national rates for these years.

Similarly, national rates for borderline ovarian cancers were not available from 1991-2003. From available national incidence rates from 2004-2011, incidence rates are highly variable from year to year and a strong trend is not observable. Therefore, average incidence rate (2004-2011) were used to approximate annual age-specific incidence from 1991-2003. If annual incidence rates are in fact rising, using average rates from 2004-2011 to estimate rates from earlier years will result in over-estimates of expected values and thus bias towards the null hypothesis of no increased incidence in the study cohort.

Stratifying by potential confounding factors

Data relating to some potential confounding, moderating & mediating factors were obtained for each cohort member from the HFEA database, unfortunately data for all potentially important confounding factors were not available (*Table 14*).

As these potentially important confounding factors were not available on a population basis, where they were available for cohort members, analyses were stratified using these variables. Trend tests for SIRs across different levels of each variable were calculated, where appropriate using the Poisson distribution[226].

Factor	HFEA variable possible proxy	Variable used in analysis
Type of hormonal exposure	Nil – hormonal treatment relatively standard throughout study period.	Nil
Duration of hormonal exposure	Number of stimulated cycles	**1. Grouped number of stimulated cycles**
Age at hormonal exposure	Age at first treatment cycle	**2. Grouped age at first treatment**
Underlying subfertility	• Broad Cause Subfertility • Endometriosis • Tubal Factors • Ovulation problems (inc. PCOS - Unfortunately PCOS was not recorded separately in HFEA database)	**3. Broad Cause Infertility** **4. Endometriosis** **5. Tubal Disease** **6. Ovulatory Problems**
Gravida & Parity	• Gravida- Proxy= Grouped number of pregnancies at completion of last ART cycle. • Parity- Proxy=Grouped number of live births, at completion of last ART cycle • Multiple live birth indicator	**7.Grouped Number of Pregnancies** **8. Grouped number of live births** **9. Multiple birth**
Maternal age at first birth	Nil available	Nil
Breast feeding	Nil available	Nil
Oral contraceptives	Nil available	Nil
Body-mass index	Nil available; BMI in women having ART during the study period is likely to be ≤30 due to treatment entry regulations, even though high BMI is associated with sub-fertility.	Nil

Table 14. *Potentially important confounding, moderating and mediating factors and their availability or otherwise for analyses of this study.*

Within cohort analysis

Within cohort analyses were performed where specific groups required further investigation in comparison to other cohort sub-groups. Cox-proportional hazard regression analysis was used given varying rates with age, and constantly varying risk sets. Hazard ratios and 95% confidence intervals were calculated assuming proportional hazards [227], formally tested for each model. Analyses were performed using STATA, version 12[224].

Missing data

Given that most variables had complete data, complete case analysis was used. Where data are missing, 'unrecorded' categories have been generated.

Numerical data		
Variable	**No. with missing data (%)**	**Person-years missing data**
Age at first treatment	0	N/A
Number of stimulated cycles	8 (0.003)	57.9
Number of live births	85 (0.03)	414.3
Duration of infertility	49,482 (19.3%)	324,952.9
Categorical data		
Infertility cause	11,500 (4.5%)	64,638.0
History of Endometriosis, Tubal disease, Ovulatory problems	0	N/A
Multiple birth	0	N/A

Table 15. *Missing data for each confounding, moderating or mediating variable.*

Study approval

Ethical approval for this section of the study was obtained from the London Research Ethics Committee (*Appendix 3*). Waiver of the requirement for individual consent was obtained under section 251 of the NHS act 2006[215] from the UK Health Research Authority Confidentiality Advisory Group and the Privacy Advisory Committee of Scotland (*Appendix 3*).

Further individual approvals were additionally required and obtained from the Human Fertilisation & Embryology Authority, NHS- Digital & General Register Office for Scotland. (Appendix 3)

Chapter 3- Cancer risk in women after assisted reproduction; Results

Cohort demographics

255 786 women contributed 2 257 789 person years' follow-up to the analysis. The average follow-up was 8.8 years with a range from 1 to 19 years. 41% were followed up for at least 10 years (n= 105 436).

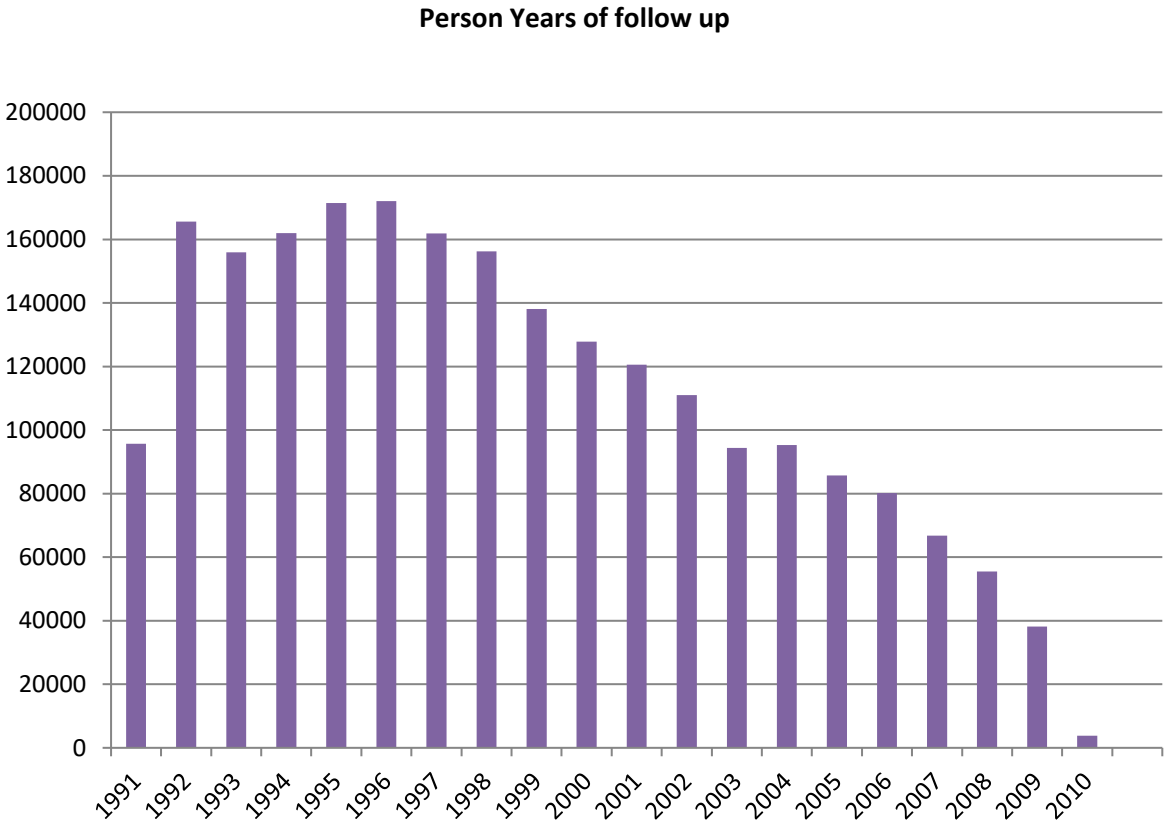


***Figure 15**. Person-years follow-up in women who had assisted conception, by year of first treatment[1].*

The average age at first treatment was 34.5 years old. 44% of women included in the cohort were diagnosed with at least one female factor (n=111 658; diagnoses included endometriosis, tubal disease and ovulatory disorders (presumed predominantly polycystic ovary disease, based on previously known national prevalence of various ovulatory disorders)). Infertility was unexplained in 19% of women (n= 47 757), and was due only to male factors in 33% (n= 84 871). Average duration of infertility was 4.9 years. On average, women had 1.8 stimulated cycles, with only 20% of the cohort (n=50 485) having more than two stimulated cycles. Almost half the study population had at least one live birth at treatment completion (*table 16)*.

Characteristic	Total N=255, 786	Women who developed a cancer of the breast, ovary or corpus uteri N=3,155	Women who did not develop a cancer of the breast, ovary or corpus uteri N= 252,631
Mean age at first treatment- years (+/- Standard Deviation (SD))	34.5 +/- 4.8	36.3 +/- 4.7	34.5 +/- 4.8
Age at first treatment (years), No. (%)			
< 25	5,671 (2)	20 (1)	5,651 (2)
25-29	39,932 (16)	259 (8)	39,673 (16)
30- 34	92,788 (36)	961 (31)	91,827 (36)
35- 39	85,868 (34)	1,244 (39)	84,624 (34)
40-44	28,174 (11)	563 (18)	27,611 (11)
45+	3,353 (1)	108 (3)	3,245 (1)
Cause of infertility, No. (%)			
Any female factor	111,658 (44)	1,626 (52)	110,032 (44)
Male factor only	84,871 (33)	915 (29)	83,956 (33)
Unexplained	47,757 (19)	474 (15)	47,283 (19)
Unrecorded	11,500 (5)	140 (4)	11,360 (5)
History of endometriosis, No. (%)	18,630 (7)	281 (9)	18,349 (7)
History of tubal disease, No. (%)	66,370 (26)	1045 (33)	65,325 (26)
History of ovulatory disorder, No. (%)	36,016 (14)	451 (14)	35,565 (14)
Mean duration of infertility reported at completion of last cycle, Years (+/- SD)	4.9 +/- 3.3	5.6 +/- 3.9	4.8 +/- 3.3
Average number of stimulated cycles (+/- SD)	1.8 +/-1.2	1.8 +/- 1.3	1.8 +/- 1.2
Average number of live births at completion of last cycle (+/- SD)	0.6 +/- 0.7	0.6 +/- 0.7	0.6 +/- 0.7
Number of live births at completion of last cycle, No. (%)			
0	129,217 (51)	1,775 (56)	127,442 (50)
1	96,839 (38)	1,011 (32)	95,828 (38)
2+	29,645 (12)	368 (12)	29,277 (11)
Unrecorded	85 (0)	1 (0)	84 (0)
Any multiple births recorded at completion of last cycle, No. (%)	29,366 (11)	304 (10)	29,062 (12)

***Table 16**; Characteristics of 255,786 women who underwent assisted reproduction in Great Britain, 1991-2010[1]*

Type of cancer	Person years follow-up	Observed cancers	Expected cancers	Standardized Incidence Ratio (95%CI)	Absolute Excess Risk† (95% CI)
Including the first year of follow-up					
Breast‡	2 257 789	2578	2641.2	0.98 (0.94 to 1.01)	-2.8 (-7.1 to 1.8)
Corpus uteri§	2 257 789	164	146.9	1.12 (0.95 to 1.30)	0.8 (-0.3 to 2.0)
Ovary	2 257 789	405	291.82	**1.39 (1.26 to 1.53)**	**5.0 (3.3 to 6.9)**
Excluding the first year of follow-up					
Breast‡	2 004 121	2384	2501.6	0.95 (0.92 to 0.99)	-5.9 (-10.6 to -1.0)
Corpus uteri§	2 004 121	157	141.79	1.11 (0.94 to 1.30)	0.8 (-0.4 to 2.1)
Ovary	2 004 121	356	271.9	**1.31 (1.18 to 1.45)**	**4.2 (2.44 to 6.10)**

Table 17. *Relative and absolute excess risks of cancers of breast, ovary, and corpus uteri among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, including and excluding the first year after the start of treatment. †Breast cancer=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486. ‡Corpus uteri cancer=ICD-9 codes 1820-1828 and ICD-10 code C54. §Ovarian cancer=ICD-9 codes 1830-1839 and 2362; ICD-10 codes C56, C570-C574, C481, C482, and D391.*[1]

Breast cancer

No increased risk of breast cancer was observed within the cohort. 2578 breast cancers were observed compared to 2641.2 expected (standardised incidence ratio (SIR) 0.98 (95% confidence interval (CI) 0.94 to 1.01); absolute excess risk −2.8 cases per 100 000 person years (95% CI −7.1 to 1.8); *Table 17*).

More than three quarters (76%) of breast tumours were ductal carcinomas (n=1963), 9% lobular (n=228), 12% other epithelial tumours (n=319), and 3% non-epithelial or unspecified (n=68).

There were no significantly raised risks or significant trends across categories by grouped age at first treatment (P=0.13), infertility duration (P=0.20) and number of live births (P=0.56); *Table 18*. There was a trend towards increasing risk with increasing number of cycles, though this did not reach statistical significance (P= 0.07; *Table 18*). Women who had at least one multiple birth appeared to have a slightly higher risk of breast cancer (SIR 1.10; 95% CI 0.97 to 1.24) but this risk was not statistically different from general population rates or from women who did not have a multiple birth as 95% confidence intervals overlapped significantly.

Significant risk reductions were observed with increasing duration since treatment completion (P=0.01), and in women with any female factor or only male factor infertility (*table 18*). Increased risks were detected in women who had unrecorded cause of infertility (*table 18*).

No difference was seen between risk of developing breast cancer at premenopausal and postmenopausal ages. Analysis of attained age at cancer diagnosis revealed 2055 breast cancers observed in women aged under 50 years, compared to 2101.1 expected (SIR 0.98; 95% CI 0.94 to 1.02) and 523 cancers observed in women over 50 years of age compared to 540.1 expected (SIR 0.97 (95% CI 0.89 to 1.06).

Factor	Person-years follow-up	All Breast Cancer†		
		Observed cancers	SIR	95%CI
Age at first treatment (years)				
<25	48,187	14	1.32	0.72 to 2.21
25-29	381,964	185	0.92	0.79 to 1.06
30-34	866,351	774	0.95	0.89 to 1.02
35-39	714,056	1033	0.97	0.91 to 1.03
40-44	218,767	479	1.02	0.93 to 1.12
45+	28,463	93	1.09	0.89 to 1.34
		Trend across categories P=0.13		
Infertility cause				
Any female factor	1,109,593	1279	0.95	0.90 to 1.00
Male factor only	757,063	774	0.92	0.86 to 0.99
Unexplained	326,495	416	1.10	1.00 to 1.21
Unrecorded	64,638	109	**1.49**	**1.24 to 1.80**
History of endometriosis				
Yes	181,279	214	0.98	0.86 to 1.12
No	2,076,509	2364	0.98	0.94 to 1.02
History of tubal disease				
Yes	710,522	826	0.96	0.90 to 1.03
No	1,547,266	1752	0.98	0.94 to 1.03
History ovulatory problems				
Yes	311,523	357	0.92	0.83 to 1.02
No	1,946,265	2221	0.99	0.95 to 1.03
Duration of infertility at last cycle (years)				
< 2	133,067	171	0.95	0.82 to 1.11
2-3	439,560	527	1.05	0.96 to 1.14
4-5	447,739	520	0.99	0.90 to 1.07
6-7	271,583	316	0.91	0.82 to 1.02
8-9	151,580	197	0.95	0.83 to 1.10
10+	209,751	322	0.95	0.85 to 1.05
Unrecorded	324,953	404	1.07	0.97 to 1.18
		Trend across categories P=0.20		
Total number of stimulated cycles				
0 – 'natural cycle' only	90,973	142	0.88	0.74 to 1.04
1	1,041,791	1203	0.98	0.92 to 1.03
2	473,125	585	1.01	0.93 to 1.09
3-4	306,137	420	1.03	0.93 to 1.13
5+	66,149	107	1.08	0.89 to 1.31
		Trend across categories P=0.07		
Total number of live births at last cycle completion				
0	1,009,134	1299	0.99	0.93 to 1.04
1	718,998	843	1.03	0.96 to 1.10
2+	249,685	314	0.92	0.82 to 1.03
		Trend across categories P=0.56		
Multiple birth as recorded at last cycle completion				
Yes	232,824	258	1.10	0.97 to 1.24
No	1,745,409	2199	0.98	0.94 to 1.02
Time since last treatment (years)				
0-3	687,180	525	1.04	0.95 to 1.13
3-6	486,191	529	1.04	0.95 to 1.13
6-10	444,324	657	1.00	0.93 to 1.08
10-15	296,445	590	0.93	0.86 to 1.01
15+	64,091	156	0.86	0.73 to 1.01
		Trend across categories P=0.01		

***Table 18**. Standardised incidence ratios (SIRs) for breast cancer among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors. †Breast cancer=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486. [1]*

Factor	Person-years follow-up	All Breast Cancer- excluding first 12 months of follow up		
		Observed cancers	SIR	95%CI
Overall	2,004,121	2384	0.95	0.92 to 0.99
Age at first treatment (years)				
<25	42,574	11	1.05	0.53 to 1.88
25-29	342,334	171	0.87	0.74 to 1.01
30-34	774,230	723	0.92	0.86 to 0.99
35-39	628,952	955	0.95	0.89 to 1.02
40-44	190,890	436	1.01	0.92 to 1.11
45+	25,142	88	1.13	0.91 to 1.39
		Trend across categories P=0.03		
Infertility cause				
Any female factor	998,634	1224	0.95	0.90 to 1.00
Male factor only	672,834	727	0.91	0.85 to 0.98
Unexplained	279,249	377	1.08	0.98 to 1.20
Unrecorded	53,406	56	0.87	0.66 to 1.13
History of endometriosis				
Yes	162,795	204	0.98	0.85 to 1.12
No	1,841,327	2180	0.95	0.91 to 0.99
History of tubal disease				
Yes	644,518	800	0.97	0.90 to 1.04
No	1,359,603	1584	0.95	0.90 to 0.99
History ovulatory problems				
Yes	275,753	333	0.91	0.82 to 1.02
No	1,728,369	2051	0.96	0.92 to 1.00
Duration of infertility at last cycle (years)				
< 2	116,371	142	0.84	0.71 to 1.00
2-3	373,788	481	1.04	0.95 to 1.14
4-5	392,584	498	1.00	0.92 to 1.10
6-7	242,061	298	0.91	0.81 to 1.02
8-9	136,379	185	0.94	0.81 to 1.08
10+	189,948	305	0.94	0.84 to 1.05
Unrecorded	275,893	360	1.06	0.95 to 1.17
		Trend across categories P=0.47		
Total number of stimulated cycles				
0 – 'natural cycle' only	81,304	136	0.90	0.76 to 1.07
1	912,394	1107	0.96	0.90 to 1.01
2	410,483	545	1.01	0.93 to 1.10
3-4	265,687	381	1.01	0.91 to 1.11
5+	57,107	100	1.10	0.90 to 1.34
		Trend across categories P=0.13		
Total number of live births at last cycle completion				
0	882,844	1166	0.95	0.89 to 1.00
1	623,485	801	1.04	0.97 to 1.12
2+	220,364	301	0.94	0.84 to 1.05
Unrecorded	332	1	2.13	0.05 to 11.86
		Trend across categories P=0.48		
Multiple birth as recorded at last cycle completion				
Yes	203,766	253	**1.15**	**1.01 to 1.30**
No	1,523,258	2016	0.96	0.92 to 1.00
Time since last treatment (years)				
0-3	435,973	337	0.99	0.88 to 1.10
3-6	486,191	529	1.04	0.95 to 1.13
6-10	444,324	657	1.00	0.93 to 1.08
10-15	296,445	590	0.93	0.86 to 1.01
15+	64,091	156	0.86	0.73 to 1.01
		Trend across categories P=0.06		

***Table 19**. Sensitivity analysis, excluding the first 12 months of follow up in women who underwent assisted reproduction in Great Britain, 1991-2010. Standardised incidence ratios (SIRs) for all breast cancer, stratified by various factors. †Breast cancer=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486.*[1]

After exclusion of the first 12 months of follow-up, breast cancer risk was significantly reduced compared with age standardised expectation (SIR 0.95 (95%CI 0.92 to 0.99), P=0.02; *table 18*).

Invasive and in-situ breast cancer

There was no increased risk of invasive breast cancer, in fact there was a non-significantly reduced risk of developing invasive breast cancer in this cohort compared to age standardised risks in the general female population (SIR 0.96 (95%CI 0.92 to 1.00) *table 20*; absolute risk reduction 4.4 cases per 100 000 person years (95% CI 8.5 to 0.2)).

There was no increased risk of invasive breast cancer by increasing grouped age at first treatment (P=0.30), duration of infertility (P=0.11), number of stimulated cycles (P=0.27) or number of live births (P=0.37; *table 20*). Risk was significantly decreased with increasing time elapsed since completion of last treatment cycle (P=0.005). The only sub-group with increased risk of invasive breast cancer was women for whom a cause of infertility was unrecorded (*table 20*). Exclusion of the first 12 months of follow-up reduced the risks of invasive breast cancer further, making this previously observed tendency to reduced risk, statistically significant (*table 21*).

A small increased risk of in situ breast cancer was detected compared with age standardised national rates (291 cancers observed *v* 253.5 cancers expected; SIR 1.15 (95% CI 1.02 to 1.29); absolute excess risk 1.7 cases per 100 000 person years (95% CI 0.2 to 3.2); *table 20*). This was associated with increasing number of treatment cycles (P=0.03).

Factor¶	Person-years follow-up	Invasive Breast Cancer††			In-situ Breast Cancer‡‡		
		Obs	SIR	95%CI	Obs	SIR	95%CI
Overall	2,257,789	2272	0.96	0.92 to 1.00	**291**	**1.15**	**1.02 to 1.29**
Age at first treatment (yrs)							
<25	48,187	14	1.43	0.78 to 2.39	0	0.00	0.00 to 4.34
25-29	381,964	168	0.91	0.78 to 1.06	16	1.10	0.63 to 1.78
30-34	866,351	685	0.92	0.86 to 1.00	**85**	**1.27**	**1.02 to 1.57**
35-39	714,056	925	0.97	0.91 to 1.04	100	0.94	0.77 to 1.15
40-44	218,767	411	1.00	0.90 to 1.10	66	1.23	0.95 to 1.56
45+	28,463	69	0.94	0.73 to 1.19	**24**	**2.12**	**1.36 to 3.15**
		Trend across categories P=0.30			Trend across categories P=0.47		
Infertility cause							
Any female factor	1,109,593	1118	0.92	0.87 to 0.98	151	1.14	0.97 to 1.34
Male factor only	757,063	676	0.89	0.83 to 0.96	93	1.18	0.95 to 1.44
Unexplained	326,495	374	1.10	0.99 to 1.22	42	1.18	0.85 to 1.59
Unrecorded	64,638	**104**	**1.58**	**1.30 to 1.92**	5	0.73	0.24 to 1.70
History of endometriosis							
Yes	181,279	186	0.95	0.82 to 1.10	26	1.25	0.81 to 1.83
No	2,076,509	2086	0.96	0.92 to 1.00	**265**	**1.14**	**1.01 to 1.28**
History of tubal disease							
Yes	710,522	725	0.94	0.87 to 1.01	92	1.11	0.89 to 1.36
No	1,547,266	1547	0.97	0.92 to 1.01	**199**	**1.17**	**1.01 to 1.34**
History of ovulatory problems							
Yes	311,523	315	0.91	0.81 to 1.02	41	1.05	0.75 to 1.42
No	1,946,265	1957	0.97	0.92 to 1.01	**250**	**1.17**	**1.03 to 1.32**
Duration of infertility at last cycle (yrs)							
< 2	133,067	156	0.97	0.83 to 1.14	15	0.82	0.46 to 1.35
2-3	439,560	464	1.03	0.94 to 1.13	61	1.26	0.97 to 1.62
4-5	447,739	461	0.97	0.89 to 1.07	52	1.03	0.77 to 1.35
6-7	271,583	278	0.90	0.79 to 1.01	35	1.03	0.72 to 1.44
8-9	151,580	169	0.92	0.78 to 1.06	27	1.31	0.86 to 1.91
10+	209,751	279	0.92	0.82 to 1.04	42	1.15	0.83 to 1.56
Unrecorded	324,953	355	1.05	0.94 to 1.16	**48**	**1.37**	**1.01 to 1.82**
		Trend across categories P=0.11			Trend across categories P=0.58		
Total no. of stimulated cycles							
0 – 'natural cycle' only	90,973	121	0.85	0.71 to 1.02	21	1.14	0.71 to 1.74
1	1,041,791	1073	0.97	0.91 to 1.03	121	1.02	0.85 to 1.22
2	473,125	512	0.98	0.90 to 1.07	70	1.25	0.97 to 1.58
3-4	306,137	371	1.01	0.92 to 1.12	47	1.18	0.87 to 1.57
5+	66,149	85	0.96	0.77 to 1.91	**21**	**2.11**	**1.31 to 3.23**
		Trend across categories P=0.27			Trend across categories **P=0.03**		
Total no. of live births after last treatment							
0	1,009,134	1154	0.98	0.92 to 1.04	135	1.04	0.87 to 1.23
1	718,998	732	0.99	0.92 to 1.07	**107**	**1.37**	**1.12 to 1.65**
2+	249,685	276	0.90	0.80 to 1.02	37	1.07	0.76 to 1.48
Unrecorded	414	<5	#	#	<5	#	#
		Trend across categories P=0.37			Trend across categories P=0.32		
Any multiple birth							
Yes	232,824	234	1.10	0.97 to 1.25	22	1.05	0.66 to 1.58
No	1,745,409	1928	0.96	0.92 to 1.00	**258**	**1.16**	**1.02 to 1.31**
Time since last treatment (yrs)							
0-3	687,180	488	1.05	0.96 to 1.15	37	1.06	0.71 to 1.39
3-6	486,191	476	1.03	0.94 to 1.12	51	1.24	0.93 to 1.63
6-10	444,324	556	0.94	0.87 to 1.02	**95**	**1.52**	**1.23 to 1.85**
10+	296,445	510	0.93	0.85 to 1.01	75	0.98	0.77 to 1.22
15+	64091	132	0.86	0.72 to 1.02	22	0.85	0.54 to 1.29
				Trend P=0.005			Trend across categories P=0.29

***Table 20**. Standardised incidence ratios (SIRs) for invasive and in-situ breast cancer among 225 786 women after ART, Great Britain, 1991-2010. †† 'Invasive Breast Cancer'= ICD-9: 1740-9: ICD-10:C500-9. ‡‡ 'In-situ Breast Cancer'= ICD-9: 2330: ICD-10: D050-9. # <5 observations, thus data redacted.*[1]

Factor	Person-years follow-up	Type of Breast Cancer- excluding first 12 months of follow up					
		Invasive Breast Cancer††			In-situ Breast Cancer‡‡		
		Obs	SIR	95%CI	Obs	SIR	95%CI
Overall	2,004,121	2089	0.93	0.89 to 0.97	**280**	**1.15**	**1.02 to 1.29**
Age at first treatment (yrs)							
<25	42,574	11	1.14	0.57 to 2.04	0	0.00	0.00 to 4.41
25-29	342,334	154	0.85	0.72 to 1.00	16	1.12	0.64 to 1.81
30-34	774,230	635	0.89	0.82 to 0.96	**84**	**1.29**	**1.03 to 1.59**
35-39	628,952	850	0.95	0.89 to 1.02	97	0.95	0.77 to 1.16
40-44	190,890	373	0.99	0.89 to 1.09	61	1.19	0.91 to 1.53
45+	25,142	66	0.99	0.76 to 1.26	**22**	**2.06**	**1.29 to 3.12**
			Trend P=0.07			Trend P=0.67	
Infertility cause							
Any female factor	998,634	1068	0.93	0.87 to 0.98	146	1.14	0.96 to 1.34
Male factor only	672834	632	0.88	0.81 to 0.95	90	1.18	0.95 to 1.45
Unexplained	279,249	337	1.08	0.97 to 1.20	<45	#	
Unrecorded	53,406	52	0.90	0.67 to 1.18	<5	#	
History of endometriosis							
Yes	162,795	176	0.94	0.81 to 1.09	26	1.28	0.84 to 1.88
No	1,841,327	1913	0.93	0.89 to 0.97	**254**	**1.13**	**1.00 to 1.28**
History of tubal disease							
Yes	644,518	701	0.95	0.88 to 1.02	90	1.11	0.89 to 1.36
No	1,359,603	1388	0.92	0.87 to 0.97	**190**	**1.17**	**1.01 to 1.34**
History of ovulatory problems							
Yes	275,753	294	0.90	0.80 to 1.01	38	1.01	0.72 to 1.39
No	1,728,369	1795	0.94	0.89 to 0.98	**242**	**1.17**	**1.03 to 1.33**
Duration of infertility at last cycle (yrs)							
< 2	116,371	128	0.85	0.71 to 1.02	14	0.80	0.44 to 1.34
2-3	373,788	422	1.02	0.92 to 1.12	57	1.25	0.95 to 1.63
4-5	392,584	439	0.99	0.90 to 1.08	52	1.08	0.80 to 1.41
6-7	242,061	260	0.88	0.78 to 1.00	35	1.07	0.75 to 1.49
8-9	136,379	159	0.90	0.77 to 1.06	25	1.25	0.81 to 1.85
10+	189,948	262	0.91	0.80 to 1.03	42	1.19	0.86 to 1.60
Unrecorded	275,893	311	1.02	0.91 to 1.14	**48**	**1.49**	**1.10 to 1.97**
			Trend P=0.30			Trend P=0.53	
Total no. stimulated cycles							
0 – 'natural cycle' only	81,304	115	0.87	0.72 to 1.04	21	1.20	0.74 to 1.83
1	912,394	981	0.95	0.89 to 1.01	117	1.03	0.85 to 1.23
2	410,483	472	0.97	0.89 to 1.07	70	1.32	1.03 to 1.66
3-4	265,687	334	0.99	0.88 to 1.10	45	1.19	0.87 to 1.60
5+	57,107	79	0.98	0.77 to 1.22	**20**	**2.14**	**1.31 to 3.31**
			Trend P=0.27			**Trend P=0. 03***	
Total no. live births after last treatment							
0	882,844	1027	0.94	0.88 to 0.99	129	1.04	0.87 to 1.23
1	623,485	691	1.00	0.93 to 1.08	**106**	**1.43**	**1.17 to 1.72**
2+	220,364	263	0.92	0.81 to 1.04	37	1.12	0.79 to 1.55
Unrecorded	332	<5	#	#	<5	#	#
			Trend P=0.71			Trend P=0.21	
Any multiple birth							
Yes	203,766	230	1.16	1.01 to 1.32	21	1.04	0.65 to 1.59
No	1,523,258	1751	0.93	0.89 to 0.98	**252**	**1.19**	**1.05 to 1.35**
Time since last treatment (yrs)							
0-3	435,973	307	0.98	0.87 to 1.09	30	1.18	0.80 to 1.69
3-6	486,191	476	1.03	0.94 to 1.12	51	1.24	0.93 to 1.63
6-10	444,324	556	0.94	0.87 to 1.02	**95**	**1.52**	**1.23 to 1.85**
10+	296,445	510	0.93	0.85 to 1.01	75	0.98	0.77 to 1.22
15+	64,091	132	0.86	0.72 to 1.02	22	0.85	0.54 to 1.29
			Trend P=0.07			Trend P=0.07	

Table 21. *Invasive and in-situ breast cancer, sensitivity analysis, excluding first 12 months follow up in women after ART in Great Britain, 1991-2010. †† 'Invasive Breast Cancer'= ICD-9:1740-9: ICD-10:C500-9. ‡‡ 'In-situ Breast Cancer'= ICD-9: 2330: ICD-10: D050-9. # <5 observations, thus data redacted.*[1]

Breast Cancer: Within-cohort analysis

Within-cohort proportional hazards regression analysis, considering women who have first ART treatment aged under 25 as the baseline group and any diagnosis of breast cancer as the outcome. No significant difference was seen in hazard ratio between baseline age group and other age groups at first treatment (*table 22*). Comparing women who have ART aged under 25 years to all other cohort members as a group, again considering the outcome of any type of breast cancer, does not reveal any significant differences in hazard (*table 23*).

Age at first treatment	Hazard Ratio	95% CI	
		Lower	Upper
<25 years	1.00	Baseline	
25-29	1.16	0.59	2.28
30-34	1.32	0.67	2.60
35-39	1.37	0.69	2.69
40-44	1.45	0.73	2.87
45-49	1.66	0.81	3.39
50+	0.80	0.24	2.70

***Table 22**. Cox regression analysis of diagnosis of breast cancer in a cohort of women who underwent assisted reproduction in Great Britain, 1991-2010, by age at first treatment. 'Breast cancer'=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486.*

Age at first treatment	Hazard Ratio	95% CI	
		Lower	Upper
>=25 years	1.00	Baseline	
<25 years	0.57	0.25	1.31

Table 23. *Cox regression analysis of diagnosis of breast cancer in a cohort of women who underwent assisted reproduction in Great Britain, 1991-2010, by age at first treatment. 'Breast cancer'=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486.*

Ovarian cancer

An overall increased risk of ovarian cancer was seen in the study cohort in comparison to general population rates (SIR 1.39 (95%CI 1.26 to 1.53); AER 5.0 cases per 100,000 person-years (95%CI 3.3 to 6.9); *table 17*).

Increased risks were observed in most age groups (by age at first treatment). However, a highly significant trend of increasing risk with decreasing age at first treatment was identified (*P*<0.001; *table 24*). Increased risks were seen in women who had any diagnosis of female factor infertility (SIR 1.66 (95%CI 1.46 to 1.88); *table 24)*. Risks were highest in women with a diagnosis of endometriosis (SIR 2.31 (95%CI 1.74 to 3.01); *table 24*) or tubal disease (SIR 1.68 (95%CI 1.43 to 1.97); *table 24*). No increased risk was seen where infertility was male factor only (SIR 1.05 (95%CI 0.85 to 1.27)) or unexplained (SIR 0.96 (95%CI 0.69 to 1.31); *table 24*). Risks decreased significantly with increasing number of live births (*P*=0.001; *table 24*): highest risks were seen in women remaining nulliparous after completion of treatment (SIR 1.57 (95%CI 1.37 to 1.79); *table 24*). No association between risk and increasing infertility duration (*P*=0.15), number of cycles (*P*=0.86) or duration since treatment completion (*P*=0.74) was observed.

Factor	Person-years follow-up	Ovarian Cancer‖		
		Observed	SIR	95% CI
Age at first treatment (years)				
<25	48,187	6	2.21	0.81 to 4.80
25-29	381,964	**64**	**2.16**	**1.67 to 2.76**
30-34	866,351	**142**	**1.52**	**1.28 to 1.80**
35-39	714,056	**134**	**1.23**	**1.03 to 1.45**
40-44	218,767	50	1.05	0.78 to 1.38
45+	28,463	9	0.97	0.45 to 1.85
		Trend across categories **P<0.001**		
Infertility cause				
Any female factor	1,109,593	**246**	**1.66**	**1.46 to 1.88**
Male factor only	757,063	98	1.05	0.85 to 1.27
Unexplained	326,495	40	0.96	0.69 to 1.31
Unrecorded	64,638	**21**	**2.59**	**1.60 to 3.95**
History of endometriosis				
Yes	181,279	**55**	**2.31**	**1.74 to 3.01**
No	2,076,509	**350**	**1.31**	**1.17 to 1.45**
History of tubal disease				
Yes	710,522	**158**	**1.68**	**1.43 to 1.97**
No	1,547,266	**247**	**1.25**	**1.10 to 1.41**
History ovulatory problems				
Yes	311,523	55	1.28	0.97 to 1.67
No	1,946,265	**350**	**1.41**	**1.26 to 1.56**
Duration of infertility at last cycle (years)				
< 2	133,067	28	1.44	0.96 to 2.09
2-3	439,560	**73**	**1.30**	**1.02 to 1.64**
4-5	447,739	**74**	**1.27**	**1.00 to 1.60**
6-7	271,583	**60**	**1.61**	**1.23 to 2.07**
8-9	151,580	**36**	**1.64**	**1.15 to 2.27**
10+	209,751	**57**	**1.60**	**1.21 to 2.08**
Unrecorded	324,953	42	1.02	0.74 to 1.38
		Trend across categories P=0.15		
Total number of stimulated cycles				
0 – 'natural cycle' only	90,973	17	0.99	0.58 to 1.59
1	1,041,791	**196**	**1.44**	**1.25 to 1.66**
2	473,125	**87**	**1.38**	**1.10 to 1.70**
3-4	306,137	53	1.23	0.92 to 1.60
5+	66,149	17	1.67	0.97 to 2.67
		Trend across categories P=0.86		
Total number of live births at last cycle completion				
0	1,009,134	**222**	**1.57**	**1.37 to 1.79**
1	718,998	**114**	**1.25**	**1.03 to 1.50**
2+	249,685	34	0.93	0.64 to 1.30
Unrecorded	414	0	0.00	0.00 to 49.93
		Trend across categories **P=0.001**		
Any multiple birth as recorded at last cycle completion				
Yes	232,824	33	1.23	0.85 to 1.73
No	1,745,409	**337**	**1.39**	**1.24 to 1.54**
Time since last treatment (years)				
0-3	687,180	**99**	**1.54**	**1.25 to 1.88**
3-6	486,191	**73**	**1.27**	**1.00 to 1.60**
6-10	444,324	84	1.24	0.99 to 1.53
10-15	296,445	**86**	**1.39**	**1.11 to 1.71**
15+	64,091	**28**	**1.57**	**1.05 to 2.27**
		Trend across categories P=0.74		

Table 24*. Standardised incidence ratios (SIRs) for ovarian cancer among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors*. ‖ *'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*[1]

Factor	Person-years follow-up	All Ovarian Cancer‖ - excl first 12m follow-up		
		Observed	SIR	95% CI
Age at first treatment (years)				
<25	42,574	<5	#	#
25-29	342,334	55	**1.99**	**1.50 to 2.59**
30-34	774,230	124	**1.42**	**1.18 to 1.69**
35-39	628,952	118	1.16	0.96 to 1.39
40-44	190,890	47	1.07	0.78 to 1.42
45+	25,142	9	1.06	0.49 to 2.02
		Trend across categories **P=0.001**		
Infertility cause				
Any female factor	998,634	**221**	**1.58**	**1.38 to 1.81**
Male factor only	672,834	88	1.01	0.81 to 1.24
Unexplained	279,249	33	0.88	0.60 to 1.23
Unrecorded	53,406	**14**	**1.98**	**1.08 to 3.33**
History of endometriosis				
Yes	162,795	**49**	**2.19**	**1.62 to 2.89**
No	1,841,327	**307**	**1.23**	**1.10 to 1.38**
History of tubal disease				
Yes	644,518	**151**	**1.69**	**1.44 to 1.69**
No	1,359,603	205	1.12	0.97 to 1.29
History ovulatory problems				
Yes	275,753	43	1.08	0.78 to 1.45
No	1,728,369	**313**	**1.35**	**1.20 to 1.51**
Duration of infertility at last cycle (years)				
< 2	116,371	23	1.26	0.82 to 1.93
2-3	373,788	62	1.23	0.94 to 1.57
4-5	392,584	66	1.23	0.95 to 1.57
6-7	242,061	**57**	**1.63**	**1.24 to 2.12**
8-9	136,379	**33**	**1.60**	**1.10 to 2.24**
10+	189,948	**50**	**1.49**	**1.10 to 1.96**
Unrecorded	275,893	36	0.99	0.69 to 1.37
		Trend across categories P=0.13		
Total no. of stimulated cycles				
0 – 'natural cycle' only	81,304	15	0.94	0.53 to 1.55
1	912,394	**174**	**1.39**	**1.19 to 1.61**
2	410,483	**77**	**1.33**	**1.05 to 1.67**
3-4	265,687	48	1.22	0.90 to 1.16
5+	57,106	13	1.41	0.75 to 2.41
		Trend across categories P=0.95		
Total no. of live births at last cycle completion				
0	882,844	**189**	**1.45**	**1.25 to 1.67**
1	623,485	**109**	**1.31**	**1.07 to 1.58**
2+	220,364	29	0.86	0.57 to 1.23
Unrecorded	332	<5	#	#
		Trend across categories **P=0.01**		
Any multiple birth				
Yes	203,766	31	1.26	0.86 to 1.79
No	1,523,258	**296**	**1.33**	**1.18 to 1.49**
Time since last treatment (years)				
0-3	435,973	**56**	**1.32**	**1.00 to 1.71**
3-6	486,191	**73**	**1.27**	**1.00 to 1.60**
6-10	444,324	84	1.24	0.99 to 1.53
10-15	296,445	**86**	**1.39**	**1.11 to 1.71**
15+	64,091	**28**	**1.57**	**1.04 to 2.27**
		Trend across categories P=0.46		

Table 25. *Sensitivity analysis, excluding the first 12 months of follow up in women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors*. ‖ *'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.* [1] *# <5 observations, thus data redacted.*

Invasive ovarian cancer

A significant excess in invasive ovarian tumours was observed when these were classified separately (264 observed vs. 188.12 expected; SIR 1.40; 95%CI 1.24 to 1.58; AER 3.4 cases per 100,000 person years (95%CI 2.0 to 4.9); *table 26*).

As noted with all ovarian cancer, a highly significant trend of increasing risk of invasive ovarian tumour was observed with decreasing age at first treatment (*P*=0.002; *table 26*). A diagnosis of any female factor infertility was associated with increased risk (SIR 1.66; 95%CI 1.41 to 1.94; *table 26*), predominantly endometriosis (SIR 2.47; 95%CI 1.75 to 3.39; *table 26*) or tubal disease (SIR 1.71; 95%CI 1.40 to 2.08; *table 26).* Importantly risk was not raised in women treated for either male factor infertility only or for unexplained infertility (SIR 1.09; 95%CI 0.84 to 1.39 and SIR 0.98; 95%CI 0.64 to 1.44 respectively; *table 26*). Increasing parity was associated with significantly decreased risks (*P*=0.0001), again women remaining nulliparous after treatment being at highest risk (SIR 1.67; 95%CI 1.42 to 1.95; *table 26*). No significant variation in risk was noted with number of treatment cycles (*P*=0.29), duration of infertility (*P*=0.25) or with duration since completion of treatment (*P*=0.44).

A third of invasive ovarian tumours were serous (n=87), a quarter were endometrioid (n=66), and 8% were mucinous (n=22). The remaining tumours were either unspecified epithelial tumours (18%; n=45) or non-epithelial or unspecified invasive tumours (17%; n=44).

Sensitivity analysis, excluding the first 12 months of follow-up, did not substantially change results (*table 27*).

Factor	Person-years follow-up	Invasive Ovarian Tumours§§			Borderline Ovarian Tumours‖‖		
		Obs	SIR	95% CI	Obs	SIR	95% CI
Overall	2,257,789	**264**	**1.40**	**1.24 to 1.58**	**141**	**1.36**	**1.15 to 1.60**
Age at first treatment (years)							
<25	48,187	<5	#		<5	#	
25-29	381,964	**35**	**2.33**	**1.63 to 3.25**	**29**	**1.98**	**1.33 to 2.85**
30-34	866,351	**81**	**1.46**	**1.16 to 1.82**	**61**	**1.61**	**1.23 to 2.07**
35-39	714,056	**97**	**1.32**	**1.07 to 1.61**	37	1.04	0.73 to 1.43
40-44	218,767	40	1.13	0.80 to 1.53	10	0.82	0.39 to 1.50
45+	28,463	<10	#		<5	#	
		Trend **P=0.002**			Trend **P<0.001**		
Infertility cause							
Any female factor	1,109,593	**161**	**1.66**	**1.41 to 1.94**	**85**	**1.66**	**1.33 to 2.05**
Male factor only	757,063	65	1.09	0.84 to 1.39	33	0.96	0.66 to 1.35
Unexplained	326,495	26	0.98	0.64 to 1.44	14	0.92	0.50 to 1.55
Unrecorded	64,638	**12**	**2.35**	**1.21 to 4.10**	**9**	**3.00**	**1.37 to 5.70**
History of endometriosis							
Yes	181,279	**38**	**2.47**	**1.75 to 3.39**	**17**	**2.03**	**1.18 to 3.25**
No	2,076,509	**226**	**1.31**	**1.14 to 1.49**	**124**	**1.30**	**1.08 to 1.55**
History of tubal disease							
Yes	710,522	**105**	**1.71**	**1.40 to 2.08**	**53**	**1.62**	**1.21 to 2.12**
No	1,547,266	**159**	**1.25**	**1.07 to 1.46**	88	1.24	0.99 to 1.53
History of ovulatory problems							
Yes	311,523	33	1.16	0.80 to 1.63	22	1.52	0.96 to 2.31
No	1,946,265	**231**	**1.45**	**1.27 to 1.65**	**119**	**1.33**	**1.11 to 1.60**
Duration of infertility at last cycle (years)							
< 2	133,067	16	1.23	0.70 to 1.99	12	1.89	0.98 to 3.30
2-3	439,560	**53**	**1.48**	**1.11 to 1.93**	20	0.99	0.61 to 1.53
4-5	447,739	**53**	**1.42**	**1.06 to 1.85**	21	1.02	0.63 to 1.55
6-7	271,583	**40**	**1.63**	**1.16 to 2.21**	20	1.57	0.96 to 2.42
8-9	151,580	**27**	**1.84**	**1.21 to 2.67**	9	1.24	0.57 to 2.36
10+	209,751	**40**	**1.60**	**1.14 to 2.18**	17	1.61	0.94 to 2.58
Unrecorded	324,953	25	0.97	0.63 to 1.43	17	1.12	0.65 to 1.79
		Trend P=0.25			Trend P=0.42		
Total no. of stimulated cycles							
0 – 'natural cycle' only	90,973	13	1.04	0.55 to 1.78	<5	#	
1	1,041,791	**129**	**1.47**	**1.23 to 1.75**	**67**	**1.39**	**1.08 to 1.77**
2	473,125	**56**	**1.37**	**1.03 to 1.78**	31	1.40	0.95 to 1.98
3-4	306,137	**42**	**1.48**	**1.06 to 1.99**	11	0.75	0.37 to 1.33
5+	66,149	**14**	**2.04**	**1.11 to 3.42**	<5	#	
		Trend P=0.29			Trend P=0.18		
Total no. of live births after last treatment							
0	1,009,134	**156**	**1.67**	**1.42 to 1.95**	**66**	**1.38**	**1.07 to 1.75**
1	718,998	**78**	**1.34**	**1.06 to 1.67**	36	1.09	0.76 to 1.51
2+	249,685	20	0.81	0.50 to 1.26	14	1.16	0.63 to 1.95
Unrecorded	414	0	0.00	0 to 74.89	0	0.0	0 to 149.79
		Trend **P=0.001**			Trend P=0.34		
Any multiple birth							
Yes	232,824	22	1.34	0.84 to 2.03	11	1.06	0.53 to 1.90
No	1,745,409	**232**	**1.45**	**1.27 to 1.65**	**105**	**1.27**	**1.04 to 1.54**
Time since last treatment (years)							
0-3	687,180	**62**	**1.73**	**1.33 to 2.22**	37	1.30	0.92 to 1.79
3-6	486,191	45	1.27	0.93 to 1.71	28	1.27	0.85 to 1.84
6-10	444,324	**63**	**1.37**	**1.05 to 1.75**	21	0.96	0.59 to 1.46
10+	296,445	**63**	**1.38**	**1.06 to 1.77**	23	1.39	0.88 to 2.08
15+	64091	21	1.52	0.94 to 2.32	7	1.75	0.70 to 3.60
		Trend P=0.44			Trend P=0.84		

Table 26. *Standardised incidence ratios (SIRs) for invasive and borderline ovarian cancer among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors. See overleaf for key.*[1]

Table 26. Key *§§ 'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).* ‖‖ *'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473). # <5 observations, thus data redacted.*

Borderline ovarian cancer

There were significantly more borderline ovarian tumours than expected (141 observed vs. 103.7 expected; SIR 1.36 (95%CI 1.15 to 1.60 respectively); AER 1.7 cases per 100,000 person years (95%CI 0.7 to 2.8); *table 26*).

As with invasive ovarian tumours, significant increased risks of borderline ovarian tumours were associated with age at first treatment (*P*<0.001; *table 26*) and any diagnosis of female factor infertility (SIR 1.66; 95%CI 1.33 to 2.05; *table 26*), particularly endometriosis (SIR 2.03; 95%CI 1.18 to 3.25; *table 26*), or tubal disease (SIR 1.62; 95%CI 1.21 to 2.12; *table 26*). Women treated because of male factor only infertility or unexplained infertility were not at increased risk (SIR 0.96; 95%CI 0.66 to 1.35 and SIR 0.92; 95%CI 0.50 to 1.55 respectively).

Risks did not significantly vary with: number of cycles (*P*=0.18), parity (*P*=0.34), infertility duration (*P*=0.42), or duration since treatment completion (*P*=0.84). 45% of borderline tumours were serous (n=64), 34% mucinous (n=48), <2% endometrioid (n<5), <2% other or unspecified epithelial tumours (n<5), and 18% non-epithelial or unspecified (n=25).

Sensitivity analysis, excluding the first 12 months follow-up, reduced the risk of borderline ovarian tumour (SIR 1.19; 95%CI 0.98 to 1.43; *Table 27*) and risk in relation to endometriosis (SIR 1.57; 95%CI 0.81 to 2.73; *table 27*).

Factor	Person-years follow-up	Excluding first 12 months of follow up					
		Invasive ovarian cancer §§			Borderline ovarian cancer///		
		Obs	SIR	95% CI	Obs	SIR	95% CI
Overall	2,004,121	**244**	**1.37**	**1.21 to 1.56**	112	1.19	0.98 to 1.43
Age at first treatment (years)							
<25	42,574	<5	#	#	<5	#	#
25 to 29	342,334	**32**	**2.24**	**1.53 to 3.16**	**23**	**1.72**	**1.09 to 2.58**
30-34	774,230	**76**	**1.44**	**1.13 to 1.80**	**48**	**1.39**	**1.02 to 1.84**
35-39	628,952	**87**	**1.25**	**1.01 to 1.55**	31	0.96	0.65 to 1.37
40-44	190,890	39	1.17	0.83 to 1.60	8	0.74	0.32 to 1.46
45+	25,142	<10	#	#	<5	#	#
			Trend **P=0.01**			Trend **P=0.01**	
Infertility cause							
Any female factor	998,634	**155**	**1.67**	**1.42 to 1.96**	**66**	**1.40**	**1.09 to 1.79**
Male factor only	672,834	60	1.06	0.81 to 1.37	28	0.90	0.60 to 1.30
Unexplained	279,249	20	0.82	0.50 to 1.27	13	0.98	0.52 to 1.67
Unrecorded	53,406	9	1.99	0.91 to 3.78	5	1.98	0.64 to 4.61
History of endometriosis							
Yes	162,795	**37**	**2.51**	**1.77 to 3.47**	12	1.57	0.81 to 2.73
No	1,841,327	**207**	**1.27**	**1.10 to 1.45**	100	1.16	0.94 to 1.41
History of tubal disease							
Yes	644,518	**101**	**1.72**	**1.40 to 2.09**	**50**	**1.65**	**1.23 to 2.18**
No	1,359,603	**143**	**1.20**	**1.01 to 1.42**	62	0.97	0.75 to 1.25
History of ovulatory problems							
Yes	275,753	32	1.19	0.82 to 1.61	11	0.84	0.42 to 1.51
No	1,728,369	**212**	**1.40**	**1.22 to 1.61**	**101**	**1.25**	**1.02 to 1.52**
Duration of infertility at last cycle (years)							
< 2	116,371	15	1.23	0.69 to 2.02	8	1.41	0.61 to 2.79
2-3	373,788	**47**	**1.43**	**1.05 to 1.90**	15	0.85	0.48 to 1.41
4-5	392,584	**49**	**1.40**	**1.03 to 1.85**	17	0.92	0.54 to 1.47
6-7	242,061	**39**	**1.67**	**1.19 to 2.29**	18	1.55	0.92 to 2.45
8-9	136,379	**25**	**1.78**	**1.15 to 2.63**	8	1.21	0.52 to 2.37
10+	189,948	**35**	**1.46**	**1.02 to 2.03**	15	1.55	0.87 to 2.55
Unrecorded	275,893	21	0.90	0.56 to 1.38	15	1.13	0.63 to 1.87
			Trend P=0.39			Trend P=0.17	
Total no. of stimulated cycles							
0 – 'natural cycle' only	81,304	13	1.11	0.59 to 1.90	<5	#	#
1	912,394	**118**	**1.43**	**1.19 to 1.72**	56	1.30	0.98 to 1.69
2	410,483	50	1.32	0.98 to 1.73	27	1.37	0.90 to 1.99
3-4	265,687	**39**	**1.48**	**1.05 to 2.02**	9	0.69	0.32 to 1.31
5+	57,107	11	1.74	0.87 to 3.11	<5	#	#
			Trend P=0.48			Trend P=0.30	
Total no. of live births at last cycle							
0	882,844	**136**	**1.55**	**1.30 to 1.84**	53	1.24	0.93 to 1.62
1	623,485	**77**	**1.42**	**1.12 to 1.78**	32	1.09	0.75 to 1.54
2+	220,364	18	0.78	0.46 to 1.23	11	1.01	0.51 to 1.81
Unrecorded	332	0	0.00	0.0 to 99.86	0	0.00	0.0 to 149.8
			Trend **P=0.01**			Trend P=0.46	
Multiple birth							
Yes	203,766	21	1.37	0.85 to 2.09	10	1.08	0.52 to 1.99
No	1,523,258	**210**	**1.41**	**1.22 to 1.61**	86	1.17	0.93 to 1.44
Time since last treatment (years)							
0-3	435,973	**39**	**1.62**	**1.15 to 2.21**	17	0.93	0.54 to 1.48
3-6	486,191	45	1.27	0.93 to 1.71	28	1.27	0.85 to 1.84
6-10	444,324	**63**	**1.37**	**1.05 to 1.75**	21	0.96	0.59 to 1.46
10-15	296,445	**63**	**1.38**	**1.06 to 1.77**	23	1.39	0.88 to 2.08
15+	64,091	21	1.52	0.94 to 2.32	7	1.75	0.70 to 3.60
			Trend P=0.85			Trend P=0.21	

Table 27*. Sensitivity analysis, excluding the first 12 months of follow up in women who underwent assisted reproduction in Great Britain, 1991-2010. See overleaf for full Key.*

Table 27. *Sensitivity analysis, excluding the first 12 months of follow up in women who underwent assisted reproduction in Great Britain, 1991-2010. Standardised incidence ratios (SIRs) for all, invasive and borderline ovarian cancer, stratified by various factors.* [§§] *'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).* [‖‖] *'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473).*[1]*# <5 observations, thus data redacted.*

Ovarian cancer and association with risk factors

Women who were recorded as having had at least one birth by the end of treatment and who *did not* have a diagnosis of endometriosis, **did not** have an increased risk of ovarian cancer overall (SIR 1.03; 95%CI 0.86 to 1.22; *table 28*), invasive (SIR 1.03; 95%CI 0.82 to 1.27; *table 2*8, or borderline tumours (SIR 1.02; 95%CI 0.75 to 1.35; *table 28*).

Nulliparous women (who did not have any birth recorded at completion of treatment), who did not have a diagnosis of endometriosis were at higher risks of all types of ovarian cancer compared to age standardised population based rates (*table 28*). Risks were higher in parous women diagnosed with endometriosis (*table 28*). Women who were nulliparous with a diagnosis of endometriosis had greater risk of invasive ovarian tumour (SIR 2.64; 95%CI 1.69 to 3.93; *table 28*) than women with just one of these risk factors. However, in contrast, nulliparous women with endometriosis did not have significantly raised risks of being diagnosed with a borderline tumour (SIR 1.47; 95%CI 0.59 to 3.04; *table 28*), though nulliparity and endometriosis were each separately associated with increased risk (*table 28*).

Factor	Person-years follow-up	Type of ovarian cancer					
		All ovarian cancer‖		Invasive cancer§§		Borderline tumours‖‖	
		Obs	SIR (95%CI)	Obs	SIR (95%CI)	Obs	SIR (95%CI)
No diagnosis of endometriosis and at least one birth recorded by treatment completion	1,036,996	133	1.03 (0.86 to 1.22)	85	1.03 (0.82 to 1.27)	48	1.02 (0.75 to 1.35)
No diagnosis of endometriosis and no births recorded by treatment completion	1,039,514	**217**	**1.57 (1.37 to 1.79)**	**141**	**1.56 (1.32 to 1.84)**	**76**	**1.57 (1.24 to 1.97)**
Diagnosis of endometriosis and at least one birth recorded by treatment completion	79,870	24	**2.41 (1.55 to 3.59)**	**14**	**2.22 (1.21 to 3.72)**	**10**	**2.76 (1.33 to 5.08)**
Diagnosis of endometriosis and no birth recorded by treatment completion	101,368	**31**	**2.24 (1.52 to 3.18)**	**24**	**2.64 (1.69 to 3.93)**	7	1.47 (0.59 to 3.04)

Table 28*. Standardized incidence ratios for all ovarian cancers, invasive and borderline ovarian tumours among 225,786 women who underwent assisted reproduction in Great Britain, 1991–2010, by presence or absence of known risk factors endometriosis and nulliparity.* ‖*'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.* §§ *'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).* ‖‖ *'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473).*[1]

The significant association noted between decreasing age at first treatment and increasing risk of invasive ovarian tumour was observed in women with at least one of endometriosis or nulliparity (*P*<0.001), but not in those who had neither risk factor (*P*=0.62;*table 29*).

Factor	Person-years follow-up	Type of ovarian tumour					
		All ovarian tumours‖		Invasive ovarian tumour§§		Borderline ovarian tumour‖‖	
		Obs	SIR (95%CI)	Obs	SIR (95%CI)	Obs	SIR (95%CI)
Age at first treatment if at least one risk factor (endometriosis, nulliparity) recorded							
<25 years	25,787	<5	#	<5	#	<5	#
25-29 years	197,309	**44**	**2.84 (2.06 to 3.81)**	**26**	**3.28 (2.14 to 4.80)**	**18**	**2.37 (1.40 to 3.74)**
30-34 years	448,040	**97**	**1.97 (1.60 to 2.40)**	**55**	**1.86 (1.40 to 2.43)**	**42**	**2.13 (1.54 to 2.88)**
35-39 years	399,110	**93**	**1.50 (1.21 to 1.84)**	**70**	**1.67 (1.30 to 2.11)**	23	1.15 (0.73 to 1.72)
40-44 years	137,314	33	1.11 (0.76 to 1.56)	24	1.09 (0.70 to 1.61)	9	1.17 (0.54 to 2.23)
45+ years	13,233	<5	#	<5	#	<5	#
		Trend **P<0.001**		Trend **P<0.001**		Trend **P=0.01**	
Age at first treatment if no risk factors recorded							
<25 years	22,400	<5	#	<5	#	<5	#
25-29 years	184,655	20	1.42 (0.87 to 2.19)	<10	#	11	1.57 (0.78 to 2.80)
30-34 years	418,312	45	1.02 (0.75 to 1.37)	26	1.01 (0.66 to 1.48)	19	1.05 (0.63 to 1.63)
35-39 years	314,946	41	0.87 (0.62 to 1.18)	27	0.86 (0.57 to 1.25)	14	0.89 (0.49 to 1.50)
40-44 years	81,453	17	0.94 (0.55 to 1.51)	16	1.19 (0.68 to 1.93)	<5	#
45+ years	15,231	<10	#	5	1.21 (0.39 to 2.82)	<5	#
		Trend P=0.07		Trend P=0.62		Trend **P=0.02**	

Table 29. *Risk of any ovarian cancer, invasive and borderline ovarian tumours in women with and without endometriosis and or nulliparity, stratified by age at first treatment.* ‖*'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.* §§ *'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).* ‖‖ *'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473).*[1]

Ovarian Cancer: within- cohort analysis

Association with endometriosis

In a univariate analysis, considering time to diagnosis of any type of ovarian cancer as the outcome variable and history of endometriosis as the covariate, women with a diagnosis of endometriosis have a significantly higher hazard ratio compared to the baseline group of women without endometriosis (Hazard ratio (HR) 1.86; 95%CI 1.40 to 2.48; *table 30)*. This significant risk remains after controlling for parity (HR 1.76; 95%CI 1.30 to 2.39; *table 29*), history of cervical problems (HR 1.86; 95%CI 1.40 to 2.48; *table 30*), history of tubal problems (HR 1.91; 95%CI 1.43 to 2.55; *table 30*), history of ovulatory problems (predominantly polycystic ovary syndrome; HR 1.86; 95% CI 1.39 to 2.48; *table 30*) and controlling for all of these co-variates simultaneously (HR 1.82; 95% CI 1.34 to 2.46; *table 30*).

Covariates included	No. cohort members	Hazard Ratio	95% Confidence Interval	
			Lower	Upper
History of Endometriosis	255,786	**1.86**	**1.40**	**2.48**
History of Endometriosis; Parity	254,756	**1.76**	**1.30**	**2.39**
History of Endometriosis; History of Cervical problems	255,786	**1.86**	**1.40**	**2.48**
History of Endometriosis; History of tubal problems	255,786	**1.91**	**1.43**	**2.55**
History of Endometriosis; History of ovulatory problems	255,786	**1.86**	**1.39**	**2.48**
History of Endometriosis; Parity; History of Cervical problems; History of tubal problems; History of ovulatory problems	254, 756	**1.82**	**1.34**	**2.46**

Table 30. *Uni and multi variate Cox Proportional Hazard Regression models investigating the association between time to ovarian cancer diagnosis and endometriosis in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Association with Parity (Number of live births recorded at end of treatment)

In a univariate analysis, considering time to diagnosis of any type of ovarian cancer as the outcome variable and number of live birth as the predictor variable, women with one and two to three and live births had significantly lower hazard ratios than women who did not have a live birth recorded at end of treatment (*table 31*). Women with four or more birth had a lower hazard ratio, however this group contained fewer women and 95% confidence interval was not significant (HR 0.43; 95%CI 0.11 to 1.73; *table 31*). Test for trend across groups, after controlling for endometriosis indicated reduced hazard ratio with increasing parity (n= 254,671; HR 0.80; 95%CI 0.68 to 0.93). These findings remained essentially unchanged after controlling for history of endometriosis, history of cervical problems, history of tubal problems and history of ovulatory problems (*table 31*).

Covariates included	No. live births at treatment end	No. cohort members	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Parity only	0	254,756	1.00	Baseline	
	1		**0.76**	**0.60**	**0.96**
	2-3		**0.66**	**0.46**	**0.96**
	4+		0.43	0.11	1.73
Parity; History of Endometriosis;	0	254,756	1.00	Baseline	
	1		**0.76**	**0.60**	**0.97**
	2-3		**0.68**	**0.47**	**0.99**
	4+		0.46	0.11	1.84
Parity; History of Cervical problems	0	254,756	1.00	Baseline	
	1		**0.76**	**0.60**	**0.96**
	2-3		**0.66**	**0.45**	**0.96**
	4+		0.43	0.11	1.73
Parity; History of tubal problems	0	254,756	1.00	Baseline	
	1		**0.76**	**0.60**	**0.96**
	2-3		**0.63**	**0.43**	**0.92**
	4+		0.38	0.10	1.55
Parity; History of ovulatory problems	0	254,756	1.00	Baseline	
	1		**0.76**	**0.60**	**0.96**
	2-3		**0.66**	**0.45**	**0.96**
	4+		0.43	0.11	1.73
Parity; History of Endometriosis; History of Cervical problems; History of tubal problems; History of ovulatory problems	0	254,756	1.00	Baseline	
	1		**0.77**	**0.61**	**0.97**
	2-3		**0.65**	**0.45**	**0.94**
	4+		0.41	0.10	1.64

Table 31. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and parity in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Association with broad cause of infertility

Women within the study cohort with unexplained infertility did not have significantly different risk of ovarian cancer compared to women with male factor only infertility (HR 0.94; 95%CI 0.64 to 1.37; *table 32*). Women with unrecorded cause of infertility had a significantly higher hazard ratio (HR 2.61; 95%CI 1.62 to 4.18). These findings remained essentially unchanged after controlling for parity, history of endometriosis, history of cervical problems, history of tubal problems and history of ovulatory problems (*table 32*).

Covariates included	Infertility Cause	No. cohort members	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Infertility cause (broad) only	Any female factor	255,786	**1.59**	**1.25**	**2.02**
	Male factor Only		1.00	Baseline	
	Unexplained		0.94	0.64	1.37
	Unrecorded		**2.61**	**1.62**	**4.18**
Infertility cause; History of Endometriosis	Any female factor	255,786	**1.45**	**1.13**	**1.87**
	Male factor Only		1.00	Baseline	
	Unexplained		0.94	0.64	1.37
	Unrecorded		**2.61**	**1.62**	**4.18**
Infertility cause; Parity	Any female factor	254,756	**1.60**	**1.25**	**2.05**
	Male factor Only		1.00	Baseline	
	Unexplained		0.90	0.61	1.35
	Unrecorded		**2.49**	**1.48**	**4.19**
Infertility cause; Parity; History of Endometriosis	Any female factor	254,756	**1.48**	**1.14**	**1.92**
	Male factor Only		1.00	Baseline	
	Unexplained		0.90	0.61	1.35
	Unrecorded		**2.48**	**1.47**	**4.18**
Infertility cause; Parity; History of Endometriosis; History of Cervical problems; History of tubal problems; History of ovulatory problems	Any female factor	254,756	1.66	0.95	2.89
	Male factor Only		1.00	Baseline	
	Unexplained		0.90	0.61	1.35
	Unrecorded		**2.48**	**1.47**	**4.18**

Table 32. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and broad cause of infertility in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Women with female factor cause of infertility, other than endometriosis, had a significantly lower hazard ratio compared to women with a diagnosis of endometriosis and no other female factor of infertility (HR 0.62; 95%CI 0.43 to 0.89; *table 32*). Women with a diagnosis of endometriosis plus another cause of female factor infertility had a similar hazard ratio to women with endometriosis only (HR 0.86; 95%CI 0.46 to 1.60; *table 33*).

Infertility Cause: Female factors only	**Hazard Ratio**	**95% CI**	
		Lower	**Upper**
Endometriosis only	1.00	Baseline	
Endometriosis plus another female factor	0.86	0.46	1.60
Other female factor without endometriosis	**0.62**	**0.43**	**0.89**

Table 33. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and causes of female factor infertility in women who had ART in Great Britain 1991-2010, n=111,199. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Association with age at first treatment

No significant difference in hazard ratio was seen between women by age group at first treatment (*table 34*). Controlling for history of endometriosis, parity, history of cervical problems, history of tubal problems, and history of ovulatory problems did not materially affect results (*table 34*). Test for trend across groups was also non-significant (HR 0.89; 95% CI 0.77 to 1.03; n=254,756).

Covariates included	Age group at first treatment	No. cohort members	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Age at first treatment only	<25 years	255,786	0.44	0.13	1.45
	25-29 years		1.07	0.76	1.52
	30-34 years		1.00	Baseline	
	35-39 years		0.85	0.65	1.11
	40-44 years		0.74	0.50	1.08
	45+ years		0.65	0.29	1.46
Age at first treatment; History of Endometriosis	<25 years	255,786	0.45	0.13	1.49
	25-29 years		1.08	0.76	1.53
	30-34 years		1.00	Baseline	
	35-39 years		0.86	0.66	1.12
	40-44 years		0.76	0.53	1.11
	45+ years		0.70	0.31	1.58
Age at first treatment; History of Endometriosis; Parity	<25 years	254,756	0.55	0.16	1.96
	25-29 years		1.15	0.80	1.64
	30-34 years		1.00	Baseline	
	35-39 years		0.81	0.62	1.07
	40-44 years		0.78	0.53	1.14
	45+ years		0.77	0.34	1.74
Age at first treatment; History of Endometriosis; Parity; History of Cervical problems; History of tubal problems; History of ovulatory problems	<25 years	254,756	0.53	0.15	1.88
	25-29 years		1.11	0.78	1.60
	30-34 years		1.00	Baseline	
	35-39 years		0.83	0.63	1.09
	40-44 years		0.82	0.56	1.21
	45+ years		0.88	0.38	2.03

Table 34. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and grouped age at first treatment in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Association with number of stimulated cycles

No significant difference in hazard ratio was observed between cohort members who had no stimulated cycles (natural cycle ART only) and women who had one, two, three to four, five to six or seven or more stimulated cycles (*table 35*). Controlling for parity, history of endometriosis, history of cervical problems, history of tubal problems and history of ovulatory problems did not materially affect these results (*table 35*). Test for trend across groups showed no overall trend (HR 1.02; 95%CI 0.91 to 1.13; n=254,663). Excluding women who had natural cycle ART only did not change this result (HR 1.01; 95%CI 0.90 to 1.14; n=244,914). Comparing women who only had natural cycle ART to those who received any stimulated cycles also showed no significant difference in hazard ratio, both using univariate analysis (HR 1.23; 95%CI 0.75 to 2.04; *table 36*) and when controlling for endometriosis and parity (HR 1.18; 95%CI 0.72 to 1.95; *table 36*).

Covariates included	No. of stimulated cycles	No. cohort members	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
No. of stimulated cycles only	0	254,756	1.00	Baseline	
	1		1.25	0.75	2.08
	2		1.20	0.70	2.05
	3-4		1.14	0.65	1.99
	5-6		1.76	0.86	3.59
	7+		1.33	0.39	4.56
No. of stimulated cycles; History of Endometriosis	0	254,748	1.00	Baseline	
	1		1.22	0.73	2.03
	2		1.18	0.69	2.01
	3-4		1.11	0.63	1.94
	5-6		1.72	0.84	3.53
	7+		1.31	0.38	4.50
No. of stimulated cycles; Parity	0	254,663	1.00	Baseline	
	1		1.23	0.74	2.04
	2		1.17	0.68	2.00
	3-4		1.09	0.62	1.92
	5-6		1.70	0.83	3.47
	7+		1.31	0.38	4.49
No. of stimulated cycles; History of Endometriosis; Parity;	0	254,663	1.00	Baseline	
	1		1.20	0.72	2.00
	2		1.15	0.67	1.96
	3-4		1.07	0.61	1.88
	5-6		1.67	0.82	3.42
	7+		1.29	0.38	4.44
No. of stimulated cycles; History of Endometriosis; Parity; ; History of Cervical problems; History of tubal problems; History of ovulatory problems	0	254,663	1.00	Baseline	
	1		1.12	0.66	1.88
	2		1.07	0.62	1.84
	3-4		0.99	0.56	1.75
	5-6		1.53	0.74	3.16
	7+		1.18	0.34	4.06

Table 35. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and number of stimulated cycles in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Covariates included	Natural cycle only vs. Stimulated cycles	No. cohort members	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Natural cycle vs. Stimulated cycles only	Natural cycle only	254, 663	1.00	Baseline	
	Any no. of stimulated cycles		1.23	0.75	2.04
Natural cycle vs. Stimulated cycles; History of Endometriosis; Parity	Natural cycle only	254,663	1.00	Baseline	
	Any no. of stimulated cycles		1.18	0.72	1.95

Table 36. *Uni and multi variate Cox Proportional Hazard regression models investigating the association between time to ovarian cancer diagnosis and natural vs. stimulated cycles in women who had ART in Great Britain 1991-2010. Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, and D391.*

Corpus uteri cancer

The overall risk of corpus uteri cancer was not significantly raised in the cohort in comparison to age standardised general population rates (SIR 1.12; 95%CI 0.95 to 1.30; AER 0.8 cases per 100,000 (95%CI -0.3 to 2.0); *table 17*). Over 92% (n=152) of corpus uteri tumours were epithelial, 70% (n=107) of which were endometrioid. 8% were non-epithelial or unspecified (n=12). Women diagnosed with an ovulatory disorder were observed to have significantly increased risk (SIR 1.59; 95%CI 1.13 to 2.17; *table 36*). A highly significant trend of increasing risk with decreased parity (P<0.001) was also found. Having a multiple birth significantly decreased risk (SIR 0.42; 95%CI 0.14 to 0.99; *table 37*). There was no significant variation in risk with number of cycles (P=0.19), age at first treatment (P=0.28) or duration since treatment completion (P=0.12). Sensitivity analysis, excluding the first 12 months follow-up did not substantially change results (*table 38*).

Factor	Person-years follow-up	Corpus Uteri Cancer §		
		Obs	SIR	95% CI
Age at first treatment (years)				
<25	48,187	0	0.00	0.00 to 6.97
25-29	381,964	10	1.24	0.60 to 2.29
30-34	866,351	43	1.19	0.86 to 1.60
35-39	714,056	72	1.22	0.96 to 1.54
40-44	218,767	33	0.96	0.66 to 1.35
45+	28,463	6	0.68	0.25 to 1.48
		Trend across categories P=0.28		
Infertility cause				
Any female factor	1,109,593	**97**	**1.25**	**1.02 to 1.53**
Male factor only	757,063	41	0.91	0.65 to 1.24
Unexplained	326,495	16	0.78	0.45 to 1.27
Unrecorded	64,638	**10**	**2.53**	**1.21 to 4.66**
History of endometriosis				
Yes	181,279	9	0.75	0.35 to 1.43
No	2,076,509	155	1.15	0.98 to 1.34
History of tubal disease				
Yes	710,522	59	1.23	0.93 to 1.58
No	1,547,266	105	1.06	0.87 to 1.29
History ovulatory problems				
Yes	311,523	**39**	**1.59**	**1.13 to 2.17**
No	1,946,265	125	1.02	0.85 to 1.21
Duration of infertility at last cycle (years)				
< 2	133,067	6	0.55	0.20 to 1.20
2-3	439,560	23	0.82	0.52 to 1.23
4-5	447,739	30	1.03	0.70 to 1.47
6-7	271,583	27	1.38	0.91 to 2.01
8-9	151,580	16	1.34	0.77 to 2.18
10+	209,751	**37**	**1.68**	**1.18 to 2.31**
Unrecorded	324,953	18	0.92	0.54 to 1.45
		Trend across categories **P<0.001**		
Total number of stimulated cycles				
0 – 'natural cycle' only	90,973	8	0.66	0.28 to 1.29
1	1,041,791	**89**	**1.29**	**1.04 to 1.59**
2	473,125	29	0.91	0.61 to 1.30
3-4	306,137	24	1.06	0.68 to 1.58
5+	66,149	7	1.24	0.50 to 2.55
		Trend across categories P=0.19		
Total number of live births at last cycle completion				
0	1,009,134	**122**	**1.61**	**1.34 to 1.92**
1	718,998	24	0.53	0.34 to 0.79
2+	249,685	11	0.54	0.27 to 0.96
Unrecorded	414	0	0.00	0.00 to 99.86
		Trend across categories **P<0.001**		
Any multiple birth as recorded at last cycle completion				
Yes	232,824	5	0.42	0.14 to 0.99
No	1,745,409	152	1.17	1.00 to 1.38
Time since last treatment (years)				
0-3	687,180	28	1.39	0.92 to 2.00
3-6	486,191	29	1.28	0.85 to 1.83
6-10	444,324	38	1.07	0.76 to 1.47
10-15	296,445	45	0.99	0.72 to 1.33
15+	64,091	17	0.98	0.57 to 1.57
		Trend across categories P=0.12		

Table 37. *Standardised incidence ratios (SIRs) for corpus uteri cancer among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors.§ 'Corpus Uteri Cancer'= ICD-9: 1820-8; ICD-10: C54.*[1]

Factor	Person-years follow-up	Corpus Uteri Cancer- excluding first 12 months follow- up		
		Observed cancers	SIR	95%CI
Overall	2,004,121	157	1.12	0.94 to 1.30
Age at first treatment (years)				
<25	42,574	0	0.00	0.00 to 7.13
25-29	342,334	8	1.01	0.44 to 2.00
30-34	774,230	41	1.16	0.83 to 1.58
35-39	628,952	70	1.23	0.96 to 1.55
40-44	190,890	32	0.97	0.67 to 1.37
45+	25,142	6	0.71	0.26 to 1.56
		Trend across categories P=0.54		
Infertility cause				
Any female factor	998,634	**95**	**1.26**	**1.02 to 1.54**
Male factor only	672,834	40	0.92	0.66 to 1.25
Unexplained	279,249	16	0.83	0.47 to 1.35
Unrecorded	53,406	6	1.67	0.61 to 3.64
History of endometriosis				
Yes	162,795	9	0.78	0.35 to 1.47
No	1,841,327	148	1.14	0.96 to 1.34
History of tubal disease				
Yes	644,518	57	1.21	0.92 to 1.57
No	1,359,603	100	1.06	0.86 to 1.28
History ovulatory problems				
Yes	275,753	**38**	**1.65**	**1.17 to 2.27**
No	1,728,369	119	1.00	0.83 to 1.20
Duration of infertility at last cycle (years)				
< 2	116,371	<5	## *	## *
2-3	373,788	22	0.83	0.52 to 1.26
4-5	392,584	30	1.07	0.73 to 1.54
6-7	242,061	27	1.43	0.94 to 2.07
8-9	136,379	16	1.38	0.79 to 2.24
10+	189,948	**37**	**1.72**	**1.21 to 2.38**
Unrecorded	275,893	<20	#	#
		Trend across categories **P<0.001**		
Total number of stimulated cycles				
0 – 'natural cycle' only	81,304	8	0.68	0.30 to 1.35
1	912,394	**85**	**1.29**	**1.03 to 1.59**
2	410,483	29	0.95	0.64 to 1.37
3-4	265,687	24	1.12	0.72 to 1.66
5+	57,107	5	0.94	0.31 to 2.19
		Trend across categories P=0.81		
Total number of live births at last cycle completion				
0	882,844	**116**	**1.60**	**1.32 to 1.92**
1	623,485	24	0.56	0.36 to 0.83
2+	220,364	11	0.56	0.28 to 1.00
Unrecorded	332	0	0.00	0.0 to 99.86
		Trend across categories **P<0.001**		
Multiple birth as recorded at last cycle completion				
Yes	203,766	5	0.44	0.14 to 1.03
No	1,523,258	146	1.18	1.00 to 1.39
Time since last treatment (years)				
0-3	435,973	22	1.58	0.99 to 2.39
3-6	486,191	29	1.28	0.85 to 1.83
6-10	444,324	38	1.07	0.76 to 1.47
10-15	296,445	45	0.99	0.72 to 1.33
15+	64,091	17	0.98	0.57 to 1.57
		Trend across categories P=0.06		

***Table 38**. Sensitivity analysis, excluding the first 12 months of follow up in women who underwent assisted reproduction in Great Britain, 1991-2010. Standardised incidence ratios (SIRs) for corpus uteri cancer, stratified by various factors. § 'Corpus Uteri Cancer'= ICD-9: 1820-8; ICD-10: C54*[1]

Further investigation of & relationships between covariates

Age distribution

Age distribution is skewed within age bands (for almost every age band); for younger age bands, there is skewing towards the top of each age band; for older age bands, there is skewing towards the bottom of each age band. Whilst this bias is present, it is minimised by the fact that many study participants have a duration of follow-up of 10 years (n=105 436; 41%) and the average duration of follow up was close to 10 years, (8.8 years).

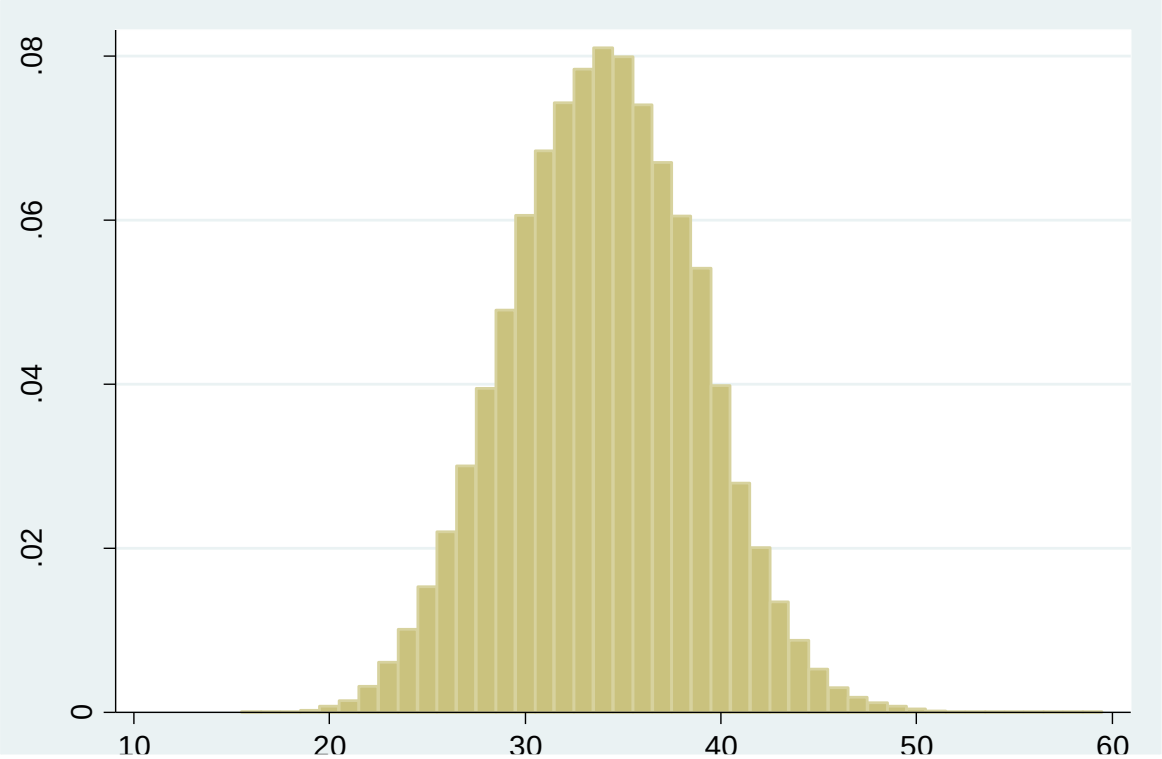


Figure 16. *Age distribution at first treatment in whole years in 255,786 women who had ART in Great Britain between 1991 and 2010.*

The mean time from first to last treatment was 1.1 years (SD 1.8, range-0-19).

Characteristics by grouped age at first treatment

A greater proportion of women who are younger at first treatment are treated because of male factor only infertility compared to women who were older at first treatment and to the cohort as a whole (*table 39*). A smaller proportion of women who were younger at first treatment had unexplained infertility, compared to the cohort as a whole (*table 39*).

Grouped age at first treatment	Broad infertility cause (%)				
	Any female factor	Male only	Unexplained	Unrecorded	Total
<25	2637 (46.5)	2290 (40.4)	497 (8.8)	247 (4.4)	5671 (2.2)
25-29	19228 (48.2)	14808 (37.1)	4717 (11.8)	1182 (3.0)	39932 (15.4)
30-34	41402 (44.6)	32751 (35.3)	15590 (16.8)	3045 (3.3)	92788 (36.3)
35-39	34789 (40.5)	27390 (31.9)	19659 (22.9)	4030 (4.7)	85868 (33.6)
40-44	11568 (41.1)	7198 (25.5)	6858 (24.3)	2550 (9.1)	28174 (11.1)
45-49	1852 (59.7)	418 (13.5)	424 (13.7)	410 (13.2)	3104 (1.2)
50+	182 (73.1)	16 (6.4)	15 (6.0)	36 (14.5)	249 (0.1)
Total	111658 (43.7)	84871i(33.2)	47757 (18.7)	11500 (4.5)	255786

Table 39*. Grouped age at first treatment by broad cause of infertility in women treated with ART in Great Britain 1991-2010.*

A smaller proportion of women who are younger at first treatment have endometriosis compared to the whole cohort (3.9% vs. 7.3%; *table 40*).

Grouped age at first treatment	History of endometriosis (%)		
	No	Yes	Total
<25	5452 (96.1)	219 (3.9)	5671 (2.2)
25-29	37273 (93.3)	2659 (6.7)	39932 (15.4)
30-34	85099 (91.7)	7689 (8.3)	92788 (36.3)
35-39	79258 (92.3)	6610 (7.7)	85868 (33.6)
40-44	26784 (95.1)	1390 (4.9)	28174 (11.1)
45-49	3043 (98.0)	61 (2.0)	3104 (1.2)
50+	247 (99.2)	<5	249 (0.1)
Total	237156 (92.7)	18630 (7.3)	255786

Table 40*. Grouped age at first treatment by history of endometriosis in women treated with ART in Great Britain 1991-2010.*

A slightly greater proportion of women who had treatment at a younger age had a diagnosis of tubal disease compared to the group as a whole (28.7% vs. 25.9%; *table 41*)

Grouped age at first treatment	Tubal Disease (%)		
	No	Yes	Total
<25	4043 (71.3)	1628 (28.7)	5671 (2.2)
25-29	28065 (70.3)	11867 (29.7)	39932 (15.4)
30-34	67553 (72.8)	25235 (27.2)	92788 (36.3)
35-39	64383 (75.0)	21485 (25.0)	85868 (33.6)
40-44	22431 (79.6)	5743 (20.4)	28174 (11.1)
45-49	2710 (87.3)	394 (12.7)	3104 (1.2)
50+	231 (92.8)	18 (7.2)	249 (0.1)
Total	189416 (74.1)	66370 (25.9)	255786

***Table 41**. Grouped age at first treatment by history of tubal disease in women treated with ART in Great Britain 1991-2010.*

A slightly greater proportion of women who had treatment at a younger age had a diagnosis of ovulatory problems compared to the group as a whole (18% vs. 14.1%; *table 42*). A much larger proportion of women who are older at first treatment had ovulatory disorders (*table 42*).

Grouped age at first treatment	Ovulatory Problems (%)		
	No	Yes	Total
<25	4649 (82.0)	1022 (18.0)	5671 (2.2)
25-29	33572 (84.1)	6360 (15.9)	39932 (15.4)
30-34	80729 (87.0)	12059 (13.0)	92788 (36.3)
35-39	76431 (89.0)	9437 (11.0)	85868 (33.6)
40-44	22744 (80.7)	5430 (19.3)	28174 (11.1)
45-49	1568 (50.5)	1536 (49.5)	3104 (1.2)
50+	77 (30.9)	172 (69.1)	249 (0.1)
Total	219770 (85.9)	36016 (14.1)	255786

***Table 42**. Grouped age at first treatment by history of ovulatory problems in women treated with ART in Great Britain 1991-2010.*

Women with ovulatory disorders

Women with an ovulatory disorder had a similar duration of infertility to the cohort as a whole.

Duration of Infertility	Ovulatory disorders (%)	No recorded ovulatory disorders (%)	Total (%)
<2 years	1947 (5.4)	15247 (6.9)	17194 (6.7)
2-3yrs	8893 (24.7)	58636 (26.7)	67529 (26.4)
4-5yrs	7881 (21.9)	48322 (22.0)	56203 (22.0)
6-7yrs	4377 (12.2)	25569 (11.6)	29946 (11.7)
8-9yrs	2228 (6.2)	13166 (6.0)	15394 (6.0)
>=10yrs	3084 (8.6)	16954 (7.7)	20038 (7.8)
Unrecorded	7606 (21.1)	41876 (19.1)	49482 (19.4)
Total	36016	219770	255786

***Table 43**. Duration of infertility at last treatment by history of ovulatory problems in women treated with ART in Great Britain 1991-2010.*

Women who had an ovulatory disorder tended to have fewer cycles than the cohort as a whole and a higher proportion had unstimulated cycles compared to the cohort in general (*Tables 44 & 45*).

Number of stimulated treatment cycles	Ovulatory disorders (%)	No recorded ovulatory disorders (%)	Total (%)
0	4414 (12.3)	5367 (2.4)	9781 (3.8)
1	17398 (48.3)	114272 (52.0)	131670 (51.5)
2	8014 (22.3)	55828 (25.4)	63842 (25.0)
3-4	4995 (13.9)	36229 (16.5)	41224 (16.1)
5-6	911 (2.5)	6379 (2.9)	7290 (2.9)
7+	282 (0.8)	1689 (0.8)	1971 (0.8)
Unrecorded	2 (0.01)	6 (0)	8 (0)
Total	36016	219770	255786

***Table 44**. Number of stimulated cycles at end of last treatment by history of ovulatory problems in women treated with ART in Great Britain 1991-2010.*

Women who had ovulatory disorders had a similar number of live births compared to the cohort as a whole (*table 45*).

No of live births recorded by the end of treatment	Ovulatory disorders (%)	No recorded ovulatory disorders (%)	Total (%)
0	18312 (50.84)	110905 (50.46)	129217 (50.52)
1	13782 (38.27)	83057 (37.79)	96839 (37.86)
2-3	3697 (10.26)	23896 (10.87)	27593 (10.79)
4+	213 (0.59)	1839 (0.84)	2052 (0.80)
Unrecorded	12 (0.03)	73 (0.03)	85 (0.03)
total	36016	219770	255786

Table 45*. Number of live births at end of last treatment by history of ovulatory problems in women treated with ART in Great Britain 1991-2010.*

Women who remained nulliparous at completion of last treatment cycle

Just over half of the cohort remained nulliparous at the completion of their last treatment cycle (n=129,217; 50.5%). The age at which this sub-group had their first treatment was similar to the cohort as a whole (*table 46*).

Grouped age at first treatment	Nulliparous women (%)	Parous women (%)	Total (%)
<25	2899 (2.24)	2772 (2.19)	5671 (2.22)
25-29	18828 (14.57)	21104 (16.67)	39932 (15.61)
30-34	42454 (32.85)	50334 (39.77)	92788 (36.28)
35-39	45253 (35.02)	40615 (32.09)	85868 (33.57)
40-44	18092 (14.00)	10082 (7.97)	28174 (11.01)
45-49	1605 (1.24)	1499 (1.18)	3104 (1.21)
50+	86 (0.07)	163 (0.13)	249 (0.1)
total	129217	126569	255786

Table 46*. Grouped age at first treatment by parity at completion of last treatment in women treated with ART in Great Britain 1991-2010.*

Women who remained nulliparous at the end of last treatment had similar broad cause of infertility compared to the cohort as a whole *(table 47*) although a slightly higher proportion of this cohort had a history of endometriosis (*table 48*). They also had a slightly longer duration of infertility than the rest of the cohort (as recorded at last treatment; *table 49*).

Infertility Cause	Nulliparous women (%)	Parous women (%)	Total (%)
Any Female factor	56086 (43.40)	55572 (43.91)	11658 (43.65)
Male only Factor	42847 (33.16)	42024 (33.20)	84871 (33.18)
Unexplained	23975 (18.55)	23782 (18.79)	47757 (18.67)
Unrecorded	6309 (4.88)	5191 (4.1)	11500 (4.50)
Total	129217	126569	255786

Table 47*. Broad cause of infertility by parity at completion of last treatment in women treated with ART in Great Britain 1991-2010.*

History of Endometriosis	Nulliparous women (%)	Parous women (%)	Total (%)
No	118978 (92.08)	118178 (93.37)	237156 (92.72)
Yes	10239 (7.92)	8391 (6.63)	18630(7.28)
Total	129217	126569	255786

Table 48*. History of Endometriosis by parity at completion of last treatment in women treated with ART in Great Britain 1991-2010.*

Duration of Infertility	Nulliparous women (%)	Parous women (%)	Total (%)
<2 years	8175 (6.33)	9019 (7.13)	17194 (6.72)
2-3yrs	33570 (25.98)	33959 (26.83)	67529 (26.40)
4-5yrs	30564 (23.65)	25639 (20.26)	56203 (21.97)
6-7yrs	17180 (13.30)	12766 (10.09)	29946 (11.71)
8-9yrs	9117 (7.06)	6277 (4.96)	15394 (6.02)
>=10yrs	12782 (9.89)	7256 (5.73)	20038 (7.83)
Unrecorded	17829 (13.80)	31653 (25.01)	49482 (19.35)
Total	129217	126569	255786

Table 49*. Duration of infertility by parity at completion of last treatment in women treated with ART in Great Britain 1991-2010.*

Women who remained nulliparous at completion of last treatment had slightly more treatment cycles than the rest of the cohort (*table 50*).

Number of stimulated treatment cycles	Nulliparous women (%)	Parous women (%)	Total (%)
0	4790 (3.71)	4991(3.94)	9781 (3.82)
1	63165 (48.88)	68505(54.12)	131670 (51.48)
2	33518 (25.94)	30324(23.96)	63842(24.96)
3-4	22748 (17.60)	18476(14.60)	41224(16.12)
5-6	3960 (3.06)	3330(2.63)	7290 (2.85)
7+	1033 (0.80)	938(0.74)	1971(0.77)
Unrecorded	3 (0)	5(0)	8(0)
total	129217	126569	255786

Table 50*. Number of stimulated treatment cycles by parity at completion of last treatment in women treated with ART in Great Britain 1991-2010.*

Unrecorded Cause of Infertility

Women with unrecorded cause of infertility, (n=11,500) had significantly increased rates of breast, ovarian and corpus uteri cancer. Those with unrecorded cause of infertility had treatment more recently, at older ages, with fewer cycles, shorter duration of infertility, more 'freeze-all' cycles (data for 'freeze-all' cycles are available for only a sub-set of our cohort; women who had children after assisted conception between 1992 and 2008; *table 51*). Women with unrecorded cause of infertility had a higher cancer incidence within the first 12 months.

Variable	Whole cohort average (95%CI)	Unrecorded cause of infertility cohort average (95%CI)	Test statistic
First treatment year	2002.0 (2002.0 to 2002.1)	2005.5 (2005.4 to 2005.5)	**P<0.001**
Age at first treatment (years)	34.4 (34.4 to 34.4)	36.3 (36.2 to 36.4)	**P<0.001**
Number of treatment cycles	1.77 (1.76 to 1.77)	1.51 (1.49 to 1.53)	**P<0.001**
Duration of infertility at last treatment cycle	4.90 (4.89 to 4.92)	3.69 (3.62 to 3.77)	**P<0.001**
'Freeze -all' cycle	11.9% (11.7 to 12.1)	13.2% (12.1 to 14.8)	-
Proportion of cancers diagnosed within 12months of first treatment.	6.2% (5.3 to 7.0)	45.7% (37.5 to 54.0)	**P<0.001**

***Table 51**. Selected demographics by recorded vs unrecorded cause of infertility in women treated with ART in Great Britain 1991-2010.[1]*

Chapter 4- Cancer risk in children born after assisted reproduction; data sources & study methods

National registry of childhood tumours (NRCT)

The NRCT is one of the largest national population-based childhood cancer registry in the world, collecting reliable information on all children under 15 years diagnosed with cancer in the UK. It ascertains & amalgamates cases of childhood cancer from: -

- UK regional and national cancer registries
    - At the time of the study, there were 10 regional cancer registries in England, Wales & Scotland (plus one in Northern Ireland- outside this study region), each regularly & routinely providing data to the NRCT.
- The Children's Cancer and Leukaemia Group (CCLG)
    - This is the organization that co-ordinates paediatric oncology in the UK and Ireland. Amongst its many roles, it collects information about all patients seen by any Paediatric oncologists in the UK and Ireland. The CCLG database also regularly and routinely provides data to the NRCT.
- Clinical trials
    - All MRC funded leukemia trials share their data with the NRCT at trial completion.
- Death certificates
    - NRCT routinely receives copies of death certificates from ONS relating to individuals under the age of 20 years where a neoplasm is recorded as the underlying cause of death.
    - Death certificates for all individuals recorded on the NRCT are also routinely received, through NHS-Digital systems, and are used to supplement and validate existing case data.
- ONS/ HES detailed clinical information relating to cancer diagnoses & co-morbidity information.
- ONS birth records for over 90% of children recorded on the NRCT
    - Details include parental details and birth event details.

- The majority of children for whom the NRCT does not hold ONS birth registrations are either born outside of the UK, or have been legally adopted, both factors making them unlikely to be part of the study cohort. [228]

Data Completeness & Quality

The NRCT is a highly reliable validated database, consistently collecting data for over 99% of eligible cases, as appraised in a capture-recapture estimate published immediately prior to the start of this study[228]. Ascertainment was slightly lower in one region (Thames 98-99%) and for two diagnostic subgroups (Germ-cell and Gonadal cancer 98-99%; Melanoma 97-98%)[228].

Case information is verified and updated through a series of follow-up enquires through the CCLG network. Diagnostic codes received are verified against written descriptions by medically qualified personnel and coding systems are standardised and periodically updated. International Classification of Diseases for Oncology 3rd edition was used during this study period[228,229].

HFEA data base

The HFEA purpose, access to the HFEA database, HFEA data collection and data entry are discussed in *Chapter 2*. The HFEA dataset recorded 110, 886 births after assisted conception during the study period, 1992-2008. However 290 records were not available for use due to retrospectively removed consent and were not included in this study.

Linkage methods: Data linkage pathway:

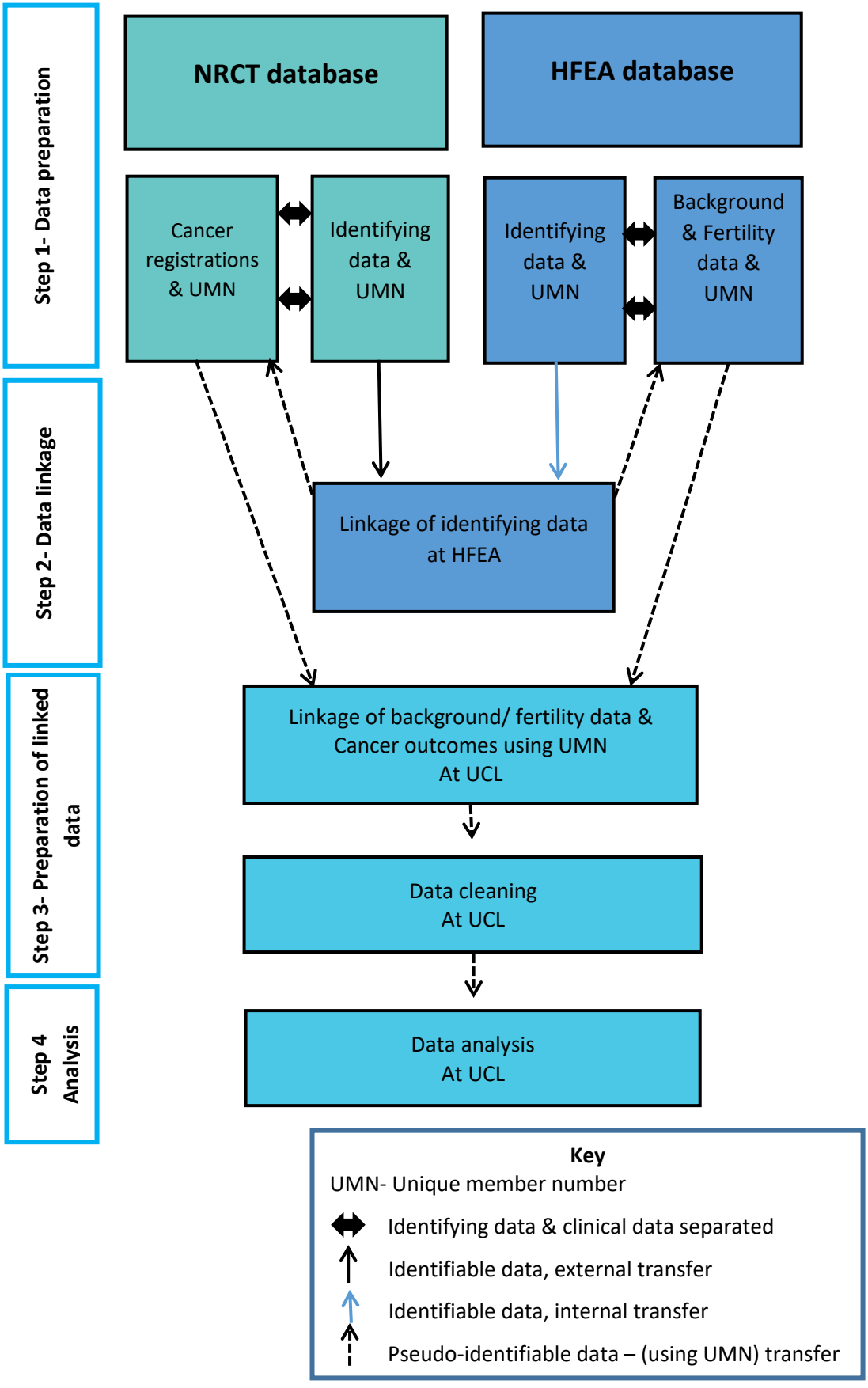


***Figure 17**; Overview of data linkage pathway for investigation of cancer risk in children born after ART*

Feasibility/ Pilot study

Given that the study aimed to investigate cancer in children born after ART using a novel dataset (HFEA database) which has not previously been used in such linkage studies, a feasibility pilot study was initially undertaken and evaluated. Births in the year from 1st January to 31st December 1998 formed the basis of this pilot.

Pilot Data preparation (Step 1)

NRCT data: 1042 records of UK children born in 1998, who developed cancer under 15 years of age and had a birth certificate available, were identified on the NRCT database. 169 further 1998 births were registered on NRCT but without birth registration details. Most of these 169 individuals were either born outside of the UK or have been legally adopted. Of the 1042 NRCT records available for the pilot study*:

- 84 had no birth weight (as Scottish birth certificates did not record birth weight)
- 10 had two separate cancer diagnoses
- 870 had no recorded co-morbidities
- 125 had a single recorded co-morbidity
- 31 had 2 recorded co-morbidities
- 10 had 3 recorded co-morbidities
- 5 had 4 recorded co-morbidities
- 1 had 6 recorded co-morbidities (max. of 10 co-morbidities recordable in the NRCT database)

All 1042 records were assigned NRCT unique member numbers (UMNs). Cancer registration details and all other clinical data were separated from identifiable data, ensuring that both clinical and identifiable parts of each record were attached to the same UMN. This was manually

* By the time of the main linkage project, birth registrations were available for 1087 children in this year. These additional 45 birth certificates were acquired during the data preparation phase of this study; the study team worked with the ONS to ensure all birth certificates were available when a child had been born within England, Scotland & Wales and had not been legally adopted.

validated on a random sample of 20 cases prior to separation. Identifiable details for these 1042 records of children born in the year 1998, recorded as having subsequently developed cancer (by the NRCT), were then securely exported to the HFEA using 'data depot' transfer.

HFEA data: 5,564 individuals were identified by the HFEA as having been born after ART in 1998 and being available for linkage[*]. However, as this HFEA identifiable data had never been used for research previously, there were concerns about the validity of the data fields. In order to ensure that this pilot did not miss a genuine match because of an error in the HFEA recorded date of birth, the whole of the HFEA database of children born after assisted conception between 1992 and 2008, those with recorded dates of birth in the future (e.g. >2011, when the pilot was undertaken), and those with Null dates of birth were all included in the pilot matching process. All records were assigned an HFEA unique member number (UMN) and clinical/ background details were separated from identifiable data, ensuring that both clinical and identifiable parts of each record were attached to the same UMN. A random sample of these were manually validated from correct UMN's prior to identifiable and clinical data being separated.

[*] This number is again smaller than the eventual total available for the main project. The larger numbers eventually available were the result of extensive HFEA data preparation, ensuring all eligible records were identified and ready for the main linkage project.

HFEA Data Validation:

In order to develop the linkage protocol, all variables available for matching and validating were assessed for their completeness across all years to be included in the main linkage (1992-2008, see *table 51: HFEA meta-data*). Variables were also assessed for their validity. Each field was assessed as either containing: i) Valid data ii) the word "NULL" or equivalent iii) being completely blank or iv) "Effectively Null", that is data which is so far from the norm that we can consider it highly likely to be the result of a data collection or more likely data input error. For example, 534 the HFEA records had no recorded birth weight (recorded as "NULL"). However, 905 records had a birth weight recorded as under 600g. Examples of these include many birth weights recorded as being 1g and the majority of others recorded as ending in a zero (250g, 300g, etc.). By chance one would expect approximately 90% of birth weights not to end in a zero. Few appeared to be a genuine extremely low birth weight. Therefore, given concerns that most birth weights recorded as being <600g were the result of input errors, a decision was made to treat all birth weights under 600g as being null values for the purposes of deterministic matching, (but not for analysis; see below). Thus 1439 records, (534 "Null" records, plus 905 records <600g), were treated as being null for birth weight.

Pilot Data linkage strategy (Step 2)

Matching was done with SQL®, using exact matching (designed to be inclusive of all potential matches), followed by probabilistic matching using Jaro Winkler® software.

Initial broad deterministic match criteria:

i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g

AND

ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null

This very broad criteria produced 222, 539 potential matches. Jaro Winkler software was then applied to these potential matches using:

i) Father's Surname

ii) Father's Forename

iii) Mother's Forename

For each of these variables, a probability of match between HFEA details and NRCT details was produced (max = 1, min=0) for each of the 222,539 potential matches.

For each potential match, these three scores were added together, producing a potential maximum score of 3. All potential matches with a score greater than 2, 989 potential matches, were viewed independently by the author of this study and by Mrs Kathryn Bunch. These 989 potential matches were manually validated using:

i) Child forename

ii) Child Surname

iii) Twin Status

iv) Mothers Surname

v) Mothers Forename at birth

vi) Mothers Surname at birth

vii) Mothers place of birth

viii) Fathers place of birth

In addition, the following variables used in the deterministic linkage stage were viewed:

ix) Date of birth

x) Birth weight

xi) Mothers Forename

xii) Fathers Forename

xiii) Fathers Surname

A clash was defined as a complete incompatibility of information between the HFEA and NRCT data for a particular variable. For example:

Mothers Forename: Helen compared with Beverly[*]

Date of Birth: 03/04/1998 compared with 03/04/2007

Both of which are unlikely to have occurred by input error.

- If no clashes occurred, the case was deemed to be a match
- If more than one clash occurred, the cases were not deemed to be a match
- If exactly one clash occurred, the HFEA were asked for further variables on this record

The study team were not allowed to view further HFEA variables, (UK ethical approvals process dictated that only pre-specified variables were permitted for use in the pilot; for the main linkage, permission for use of these additional variables had been granted). Thus, HFEA staff reviewed these additional variables and considered if these cases were potential matches. This was then discussed with the study team, using pseudo anonymization; For

[*] Names and dates have been altered for patient confidentiality.

example, the HFEA staff would say sex does/ does not match, day/ month/ year of birth does/ doesn't match, year of birth is out by 1 digit, digit reversal likely etc.

Results of pilot linkage: 4 matches were confirmed as no clashes of data occurred. 6 other potential matches were explored further using additional HFEA identifiable variables not used in matching. The further variables used to confirm/ deny these 6 potential matches included:

a) Sex of Child
b) Mothers Date of Birth
c) Fathers Date of Birth
d) Treatment Cycle Date
e) Treatment Centre

One of these 6 other potential matches was considered a match. Therefore, these variables were included in the main linkage protocol after further approvals were granted.

Variable	No. records where field is valid	No. records "NULL"	No. records blank	No. records 'effectively NULL' *	% Apparently Valid data
Date of birth	110,204	374	0	18	99.6%
Sex of Child	Male- 56,265 Female-54,219	112	0	0	99.9%
Birth weight	109, 157	534	0	Total of 905 records with BW <600g	98.7%
Child's Surname	12,332	97,671	0	593	11.2%
Child's Forename	11,402	97,670	0	1524	10.3%
Child's Town of Birth	70,738	39,689	61	108	64.0%
Child's District of Birth	18,833	91,452	298	13	17.0%
Child's Town ***or*** District of Birth	71,650	38,787	51	108	64.8%
Country of Birth	'England'- 20,520 'Scotland'- 2,100 'Wales'- 1,048 'UK'- 43,886	38,861	0	4181 cases born outside of Great Britain	61.1%
Mother's Surname	110,596	0	0	0	100%
Mother's Forename	110,588	0	8	0	100.0%
Mother's Surname at Birth	51,237	58,714	209	436	46.3%
Mother's Forename at Birth	3,323	106,895	377	1	3.0%
Mother's Date of Birth	110,569	1	0	26	100.0%
Father's Surname	110,450	138	8	0	99.9%
Father's Forename	110,384	202	8	2	99.8%
Father's Date of Birth	110,282	257	0	57	99.7%

* See above for details

Variable	No. records where field is valid	No. records "NULL"	No. records blank	No. records 'effectively NULL' *	% Apparently Valid data
Mother's Town or District of Birth	62,505	47,045	0	1046	56.5%
Mother's Country of Birth	64,396	46,190	0	10	58.2%
Father's Town or District of Birth	61,143	48,354	0	1099	55.3%
Father's Country of Birth	63,100	47,485	0	11	57.1%
Treatment Cycle Start Date	110,596	0	0	0	100%
Treatment Centre No/ Name	110,594	0	0	2	100.0%

***Table 52**: HFEA meta-data for all identifiable variables in all 110,596 HFEA records included in the **main linkage**[3]*

Main linkage: Data preparation (step 1)

HFEA: 110,596 HFEA records detailing individuals born 1992-2008 or with a null date of birth were available for linkage in the main project. This included 4,181 recorded as being born outside of England, Wales or Scotland by the HFEA. It also included 34 records where the date of birth was actually recorded as being outside of the study period, but the HFEA provided their records for linkage in error. These records 4,215 records, whilst not included in the analysis stage, were included in the linkage stage in order that potential matches not be excluded where HFEA had recorded place or date of birth incorrectly*. Given the HFEA's statutory role in collecting this data, it is considered almost complete population data[214].

All 110,596 records were assigned HFEA unique member numbers (UMNs). Clinical/ background details were separated from identifiable data, ensuring that both clinical and identifiable parts of each record were attached to the same UMN. A random sample of these were manually validated prior to data separation to ensure UMN were assigned correctly.

Further HFEA Identifiable data validation prior to linkage:

In addition to the validation of variables completed as part of the pilot study (*see above*), further validation of identifiable variables was undertaken prior to main linkage.

1. **Time-lapse between HFEA Treatment Cycle Date and HFEA Date of Birth**

Of the 110,204 records with valid date of birth ≥ 1992 & ≤2008 (excluding those with NULL or effectively NULL date of birth):

- 262 records had a delivery date on or before cycle date (15 were on treatment cycle date)
    - All were considered as having a missing date of birth for linkage purposes.

* No such potential matches were found for those records; *Table 52*.

- 1306 records had a delivery date < 5.5 months after cycle date (equating to 22 weeks gestational age at birth, and thus not compatible with life).
    - All were considered as having a missing date of birth for linkage purposes.
- 108,636 records had a delivery date ≥ 5.5 months after cycle date
    - 563 of which had a delivery date ≥10 months after treatment cycle date, one being 5 years and 7 months after treatment cycle date. All of these were considered valid and are likely to represent cryopreserved treatment cycles*.

2. Recorded multiple births compared to number of individuals at each birth event

- There were 23 cases where a birth had been recorded as a multiple birth, but with only one individual recorded as being born at that birth event.
    - All of these records were included in the linkage using the values for these variables as originally recorded by the HFEA because they could represent multiple birth events where a still born infant has not been recorded by the HFEA in error (still birth events should be included by the HFEA but are not validated using birth records).

NRCT: 14,896 records of UK children born, 1992-2008, who developed cancer under 15 years of age were identified on the NRCT database. All 14,896 records were assigned NRCT unique member numbers (UMNs). Cancer registration details and all other clinical data were separated from identifiable data, manually validating a random sample to ensure that both clinical and identifiable parts of each record were attached to the same UMN. Identifiable details for these 14,896 records were securely exported to the HFEA using 'data depot' transfer.

* Unfortunately, this could not be verified given separation of identifiable and clinical data had occurred by the time these variables were validated.

Main linkage: Linkage specification (step 2)

Multiple linkages were undertaken in order to make sure that linkage results included all potential matches. Each linkage consisted of three steps:

1. Broad, deterministic matching performed using SQL®. Deterministic matching was designed to be inclusive of all potential matches.
2. Probabilistic matching using Jaro Winkler® software. The aim of this step was to sort results of deterministic matching in order of most to least likely to be a true match.
3. Manual validation of each likely match. Potential matches were then manually reviewed by two researchers individually (the study author and Mrs Kathryn Bunch). The following variables were manually viewed to decide the validity of each potential match:
    - Child Date of Birth
    - Birth Weight
    - Sex
    - Multiple Birth Status
    - Child Forename
    - Child Surname
    - Child Place of Birth
    - Treatment centre (compared to mother address at time of birth from NRCT- using very broad limits as we are aware some people travel to other regions for ART treatment).
    - Mothers Surname
    - Mothers Forename
    - Mothers Surname at birth
    - Mothers Date of Birth
    - Mothers Place of Birth
    - Fathers Surname

- Fathers Forename
- Fathers Date of Birth
- Fathers Place of Birth

If a potential match contained two or more variables where the information from the HFEA and NRCT clashed, the potential match was discounted. A clash was defined as 'actual conflicting data'.

Examples of clashes[*]*:*

Mothers Forename:	*HFEA: Louise*	*NRCT: Tracey Jane*
Place of Birth:	*HFEA: Southampton*	*NRCT: London*
Fathers Surname:	*HFEA: Ward*	*NRCT: Walker*

Examples of differing information not considered as a 'clash':*

Mothers Forenames:	*HFEA: Lynda*	*NRCT: Lynda Margaret*
Place of Birth:	*HFEA: London*	*NRCT: UCLH*
Fathers Surname:	*HFEA: Williams*	*NRCT: Williams- Jones*

If the two researchers, did not agree on the status of a potential match or both researchers felt there was insufficient data to confirm or refute a potential match, a third researcher (thesis

[*] Names and dates have been altered for patient confidentiality.

secondary supervisor, Dr Beverley Botting), acted as final adjudicator. There were a total of 9 cases referred to Dr Botting. Three of these 9 cases were accepted as a match, 6 were not and were thus included in the analyses as non-cases.

Details of each linkage, and the different criteria used in each are included in *table 52*. All matches were applied to:

- The 110, 596 HFEA records of children, born after ART, with year of birth between 1992 and 2008 (as reported by the HFEA), or Null year of birth or 'effectively' null year of birth AND
- The 14,896 records of children documented by the NRCT as having being born between 1992 and 2008 and having developed cancer in England, Wales or Scotland, before their 15th birthday, before 01.01.2009 AND who have birth record details available.

Match No.	SQL Broad Linkage Criteria	Jaro Winkler Probabilistic matching	Details of Matches
M1	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null	Probabilistic matching then applied to all 4,674,445 potential matches: for i) Father's Surname ii) Father's Forename iii) Mother's Forename For each of variable, a probability (max = 1, min=0) was generated for each potential matches. Scores combined (JW score) - Max total of 3, min total of 0.	*Number of matches-* 4,674,445 *Number viewed manually-* 507 (JW score≥ 2.35) *Numbers of new matches found-* 102
M2	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Mothers date of birth exact match	As M1, but only those not previously viewed were considered (i.e. JW score ≤ 2.35).	*Number of matches-* 244 *Number viewed manually-* 244 *Numbers of New matches found-* 1
M3	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Fathers date of birth exact match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 212 *Number viewed manually-* 212 *Numbers of New matches found-* 0
M4	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Mothers forename perfect or partial match **AND** iv) Mothers surname (any) perfect match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 27 *Number viewed manually-* 27 *Numbers of New matches found-* 1
M5	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Fathers forename perfect or partial match **AND** iv) Fathers surname (any) or mothers surname at birth perfect match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 20 *Number viewed manually-* 20 *Numbers of New matches found-* 2

Match No.	SQL Broad Linkage Criteria	Jaro Winkler Probabilistic matching	Details of Matches
M6	**Abandoned Search**		
M7	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Mothers forename 'reverse' partial match (i.e. HFEA: Louisa matches NRCT: Claire Louisa)	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 15 *Number viewed manually-* 15 *Numbers of New matches found*-0
M8	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Fathers forename 'reverse' partial match (i.e. HFEA: James matches to NRCT: Peter James)	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 10 *Number viewed manually-* 10 *Numbers of New matches found-* 0
M9	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Mothers HFEA forename perfect or partial match **AND** iv) Mothers surname (any) perfect match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 0 *Number viewed manually-* *N/A* *Numbers of new matches found-* N/A
M10	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) HFEA mothers forename at birth perfect or partial match NRCT mothers forename **AND** iv) Mothers surname (any) perfect match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 378- but all based on blank HFEA forename at birth (all effectively NULL). *Number viewed manually-* *N/A* *Numbers of new matches found-* N/A
M11	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) HFEA mothers forename at birth perfect or partial match to NRCT mothers alternative forename	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 0 *Number viewed manually-* *N/A* *Numbers of new matches found-*

Match No.	SQL Broad Linkage Criteria	Jaro Winkler Probabilistic matching	Details of Matches
	AND iv) Mothers surname (any) perfect match		N/A
M12	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) HFEA Fathers forename perfect or partial match to NRCT Fathers alternative forename **AND** iv) Fathers surname or mothers surname at birth as recorded by the HFEA, perfect match to of NRCT father's surname	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 0 *Number viewed manually-* *N/A* *Numbers of new matches found-* N/A
M13	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Mothers forename perfect or partial match (using NRCT 'Mothers Forename' recorded at diagnosis not on Birth record) **AND** iv) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 10 *Number viewed manually-* 10 *Numbers of new matches found-* 0
M14	i) Birth weights matching within 100g (OR null or effective null) **AND** ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** iii) Fathers forename perfect or partial match (using NRCT 'Fathers Forename' recorded at diagnosis not as appears on birth record) **AND** iv) Fathers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT Fathers surname	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Number of matches-* 6 *Number viewed manually-* 6 *Numbers of new matches found-* 0
M15	i) Mothers forename full or partial match **AND** ii) Mothers surname (HFEA) full match to any NRCT mother surname **AND** iii) Birth-weight NOT NULL or 'effectively' NULL	No JW criteria applied to this match	*Number of matches-* 147 *Number viewed manually-* 147 *Numbers of new matches found-* 11

Match No.	SQL Broad Linkage Criteria	Jaro Winkler Probabilistic matching	Details of Matches
M16	i) Mothers forename full or partial match **AND** ii) Mothers surname (HFEA) full match to any NRCT mother surname **AND** iii) Birth-weight NOT NULL or 'effectively' NULL **AND** iv) Date of Birth exact match		*Number of matches-* 4 *Number viewed manually-* 4 *Numbers of new matches found-* 0
M17	i) Birth weights matching within 100g **AND** ii) Mothers forename perfect or partial match (using any recorded NRCT 'Mothers Forename') recorded on birth record) **AND** iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname **AND** iv) Date of birth is NOT NULL	JW Total score (for mothers forename, fathers forename, fathers surname scores combined as in M1) less than 2.35	*Number of matches-* 2384 *Number viewed manually-* 2384 *Numbers of new matches found-* 0
M18	i) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts OR Date of Birth Null **AND** ii) Mother forename partial reverse match (e.g. 'Sarah Jane' on the NRCT birth record matches to 'Jane' on the HFEA record) **AND** iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname		*Number of matches-* 69 *Number viewed manually-* 69 *Numbers of new matches found-* 0
M19	i) Birth weights matching within 100g **AND** ii) Mothers forename perfect or partial match (using any recorded NRCT 'Mothers Forename') recorded on birth record) **AND** iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname **AND** iv) Date of birth is NOT NULL	JW Total score (for mothers forename, fathers forename, fathers surname scores combined as in M1) less than 2.35	*Number of matches-* 294 *Number viewed manually-* 294 *Numbers of new matches found-* 0

Table 53*: Linkage protocol to identify numbers of children born in England, Wales or Scotland after ART, 1992-2008, as recorded by the HFEA, who subsequently develop childhood cancer, as recorded by the NRCT before their 15th birthday and before 01.01.2009[3].*

Data cleaning (step 3)

Merging HFEA/ NRCT data

HFEA background and parental fertility data and HFEA assigned UMN for all cohort members was securely transferred to the University of Oxford (without identifiable data). Oxford University holds the NRCT. The thesis author carried out data cleaning and data analysis for this section of the study at Oxford University.

Using the NRCT assigned UMN's, clinical data relating to cancer diagnoses (as recorded by the NRCT) were merged with HFEA background data, such that individuals who were born after ART and developed cancer had both HFEA background data and NRCT clinical data available for analysis.

All children identified as having been born outside of England, Wales or Scotland using HFEA recorded 'Place of birth' were removed manually (n=4,181). A further 34 cases recorded by the HFEA as born in 2009 and included by the HFEA in the cohort in error were also removed manually. These processes were validated by manual review of 30 records, selected at random, comparing the main file, (including cases marked for removal), to a list of HFEA UMN's that required removal.

Cleaning of HFEA variables

Data cleaning was undertaken using STATA, version 11[230]. Initially, all 'NULL' entries were removed and thus converted into missing data. Variables were renamed appropriately.

Date of birth of child: All dates were converted into STATA[230] format. For 8 records, the date of birth was recorded as 01.01.1900. Date of birth for these records was marked as missing data. In one case a twin birth was recorded as being in April 1966. From the embryo transfer date, it

was deduced that this should be 1996, and a transposition of parental/ child date of birth was ruled out. Therefore this record was corrected and considered a keystroke error in the HFEA database. A singleton, recorded as born in 1963, was investigated and most probably a transposition of maternal and child date of birth. This value was marked as missing and was regarded as a data error rather than a simple keystroke error. Investigation of a singleton born 2060 revealed a simple keystroke error when the expected date of delivery was calculated using embryo transfer date, (should have been 2006 and did not resemble either parental date of birth). This was corrected to 2006. Investigation of a singleton born 2077 revealed a simple keystroke error, the expected date of delivery was in 2007 when calculated using embryo transfer date, (2077 did not resemble either parental date of birth). This was corrected to 2007.

Birth weight: Birth weight was treated as 'effectively null' for the matching stage when a birth weight was recorded as being under 600g. This was done, despite birth weights between 300g and 600g being compatible with life, because the data for birthweights under 600g were, most frequently 'round numbers' that were considered by the research team as being potential keystroke errors. Had this not been done, and if some of these birthweights between 300g and 600g were in fact keystroke errors, potential matches may not have been identified as birth weight was used as in the deterministic linkage stage (though not in all linkages; *See table 52*). For the analysis stage, though the research team were still suspicious that many of the birth weights between 300g to 600g could have been keystroke errors, it is still possible that they did actually represent real birthweights. Therefore, birthweights less than 300g and greater than 6000g were treated as being effectively null as these were considered generally incompatible with life or extremely unlikely to be genuine birthweights (n=378). The relationship between birthweight and gestation is considered in *figure 22*.

Gestation: Weeks between embryo transfer and birth dates were used as a proxy for gestation. It was decided that 19 weeks would be the minimum acceptable time between embryo transfer and birth.

This equates to a gestation (defined as weeks between last menstrual period and birth) of 22 weeks; 2 weeks between last menstrual period and egg collection/ embryo formation, 1 week (at the very maximum) of in-vitro embryo development (usually no more than 5-6 days), and 19 weeks between embryo transfer and birth. Gestations of less than 22 weeks at birth are not compatible with life. 373 records with gestations below 22 weeks were considered to have missing data for this variable.

The maximum possible time between embryo transfer and birth is 41 weeks. This equates to a gestation (defined as weeks between last menstrual period and birth) of 43 weeks; 2 weeks between last menstrual period and egg collection/ embryo formation, minimum of 1-2 days of in-vitro embryo development, and 41 weeks between embryo transfer and birth. Gestations of more than 43 weeks at birth are not compatible with life. 693 records with gestations above 43 weeks were considered to have missing data for this variable.

Type of assisted conception: This variable originally included 18 different responses. This was mainly because identical treatments were recorded in different ways, (such as ICSI being referred to as IVF plus ICSI), but also included specific details of practices used alongside ART (such as blastocyst transfer or assisted hatching). Type of ART was re-classified as being either:

- IVF
- ICSI (also including rarer types of micromanipulation)
- Unrecorded.

Stage at embryo transfer: This variable was derived using number of days between gamete mixing and embryo transfer. Records stating 1,2 or 3 days between embryo mixing and gamete transfer were classed as cleavage embryo transfers , those with 4,5 or 6 days were considered as blastocyst transfers. 43,190 records either had a value for this variable of more than 6 days (considered to be a missing value), or had missing data originally.

Days at embryo transfer	Cleavage vs Blastocyst transfer	Number of cases
1	Cleavage	312
2	Cleavage	37401
3	Cleavage	15635
4	Blastocyst	404
5	Blastocyst	4289
6	Blastocyst	237

Table 54: *Calculation of cleavage/ blastocyst transfer from days at embryo transfer.*

Maternal year of birth: All mothers recorded as being born after 1988 (n= 26) had children recorded as being born less than 2 years after maternal year of birth. Therefore all maternal dates of birth after 1988 were considered missing. There are no mothers recorded as being born earlier than 1946.

Paternal year of birth: 47 fathers were recorded as being born after 1988. Of these 47, 3 were over 16 at the time of their child's birth; all others were under the age of 16 and therefore were considered missing. Father's date of birth recorded as 1900 were also considered missing.

Maternal/ parental age at birth of child: These were calculated by subtracting child year of birth from parental year of birth. Thus value maybe +/- one year from the true value as only year of birth of parents were available. Minimum and maximum values were plausible and means were consistent with expected values.

Infertility duration: 178 records had minus values for years of infertility duration. Values for all of these records were considered missing. 3 records had values of infertility duration greater than the woman's age at childbirth, again, values for these records were considered as missing data.

Years since last pregnancy: 359 records had minus values for years since last pregnancy. These were considered to be missing. 44 records had values of years since last pregnancy equating to the women being less than 13 years of age at last pregnancy, therefore these values were considered as missing.

Previous maternal live births: 857 records had invalid values and were considered to have missing data.

Study entry & exit: Study entry date or start of time at risk was considered to be date of birth. Study exit date was considered to be the earlier of: -

- Date at cancer diagnosis
- Study end (31.12.2008)
- Child's 15th birthday
- 368 records were excluded as date of birth was missing and therefore it was not possible to calculate person-years at risk.

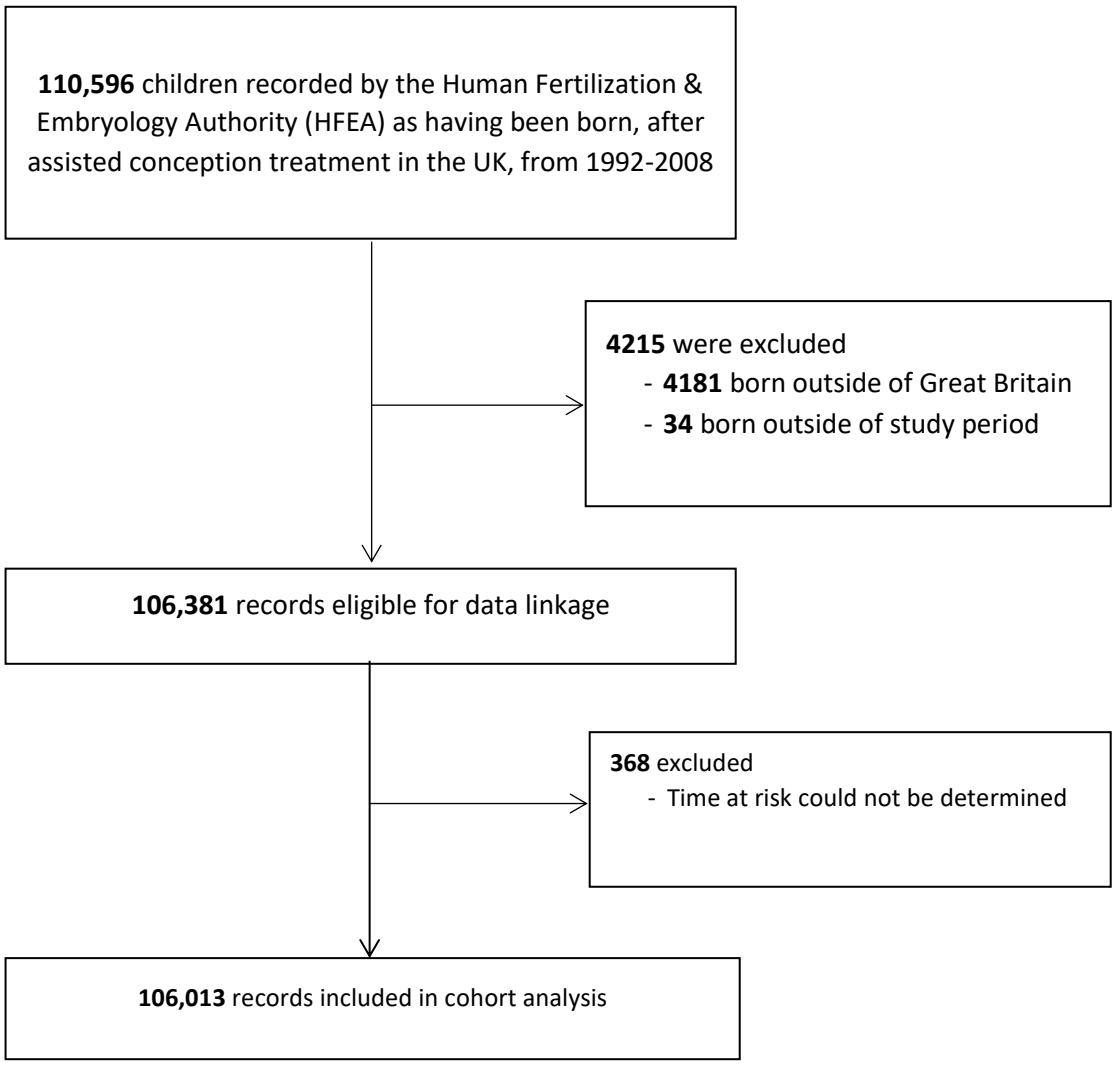


***Figure 18**: Overview of included/ excluded records*[3]

Data Analysis: (Step 4)

The numbers of cases in the cohort were compared with the number expected, based on annual age-specific incidence rates in Britain for childhood cancer 1992-2008, as recorded by the NRCT. Analyses were in terms of the Standardised Incidence Ratio (SIR), measured by the ratio of observed/expected.

Person-years at risk were calculated from date of birth until the earliest of cancer diagnosis date, child's 15th birthday or December 31, 2008. Person-years at risk were stratified by age at diagnosis (0, 1-4, 5-9 and 10-14 years), gestation, birth weight, sex, multiple births, maternal and paternal age, assisted conception type, fresh or cryopreserved embryos, maternal parity, and parental infertility cause.

Calculated Person-years at risk were used in conjunction with NRCT cancer incidence rates for the general population of Britain of the same age and time period, to determine the expected numbers of cases in the cohort, if their risk was the same as that in the general population[226]. Frequency of observed cancers was assumed to follow a Poisson distribution. For each SIR, 95% confidence intervals (CI) based on the Poisson distribution were calculated. Tests of the hypothesis that an SIR is equal to one are based on 2-sided p-values and calculated based on χ^2 test[226]. The Absolute Excess Risk (AER) corresponding to each SIR was also calculated. The units per million person-years are used as these are the units usually used in childhood cancer registration data. Analyses were performed using STATA, Version 11 software[230].

Analyses:	ICCC3 Groups	ICCC3 codes[229]
All cancers (as a group)	I-X	11-122
A prior selected cancers		
a. Leukaemia	I	11-15
b. Neuroblastoma	IV	41
c. Retinoblastoma	V	51
All cancers as diagnostic subgroups		
d. Leukaemia	I	11-15
e. Central Nervous System tumours	III	31-36
f. Neuroblastoma and peripheral nerve tumours	IV	41-42
g. Retinoblastoma	V	51
h. Renal tumours	VI	61-63
i. Hepatic tumours	VII	71
j. Bone Tumours and extra osseous sarcomas	VIIII & IX	81-95
i. Osteosarcomas	VIIIIa	
ii. Ewing's sarcoma	VIIIc & IXd (divisions 1,2)	
iii. Rhabdomyosarcoma	IXa	
iv. Other sarcomas	VIIIb; VIIId; VIIIe; IXb; IXc; IXd (divisions 3-11); IXe	
k. Germ Cell Tumours	X	101-105

***Table 55**; Summary of analyses for childhood cancer study.*

As potential mediating/ moderating factors cannot be controlled for with conventional analyses (due to lack of a suitable comparator group), analyses were stratified for the following potential mediating factors:

- Sex
- Age
- Birthweight
- Gestation
- Multiple births

And the following potential moderating factors: -

- Maternal parity
- Type of assisted reproduction
- Fresh vs. cryopreserved cycles

And by: -

- Cause of parental infertility

It was not possible to take into account death and emigration in the cohort of children born after assisted conception. However, such events are rare and not likely to differ substantially between the ART cohort and the national birth cohort.

Cancer in children born after donor assisted reproduction

Once the investigation into cancer risk in children born after non-donor ART was complete, a very similar process was undertaken investigating cancer risk in children born after donor assisted conception. The main difference being that HFEA regulations stipulate those persons not employed by the HFEA are not permitted to view donor assisted conception identifying data. Therefore data linkage was undertaken by HFEA staff, under direct supervisions of the study author; communication about linkage details being pseudo-anonymised.

Donor linkage: Data preparation (step 1)

HFEA data: 12,223 records were identified by the HFEA as being born 1992-2008 inclusive in England, Scotland or Wales, after donor assisted conception. This was defined as 'all treatments or procedures, including in-vitro handling of both human oocytes and sperm or embryos, for the purpose of establishing a pregnancy' using donor oocytes, sperm or embryos[4]. Records where the birth was recorded as being outside of England, Scotland or Wales were excluded[*]. As with the main data linkage, given the HFEA's statutory role in collecting this data for regulatory purposes, this data is considered almost complete population data. 37 records, (0.3% of total cohort), were excluded as the families had removed their consent to use these records retrospectively. Therefore 12,186 records were available for linkage.

[*] As this linkage occurred after the main childhood linkage, the HFEA team were aware that records, where a birth had occurred outside of England, Scotland and Wales, had been included in the linkage file previously, and ensured such cases were not included in the donor linkage dataset.

HFEA staff undertook pre-linkage data validation processes identical to those completed prior to the main linkage project. This included ensuring delivery dates which were not compatible with cycle treatment dates were treated as effectively null; for the purposes of linkage.

NRCT data: The exact NRCT dataset as used in the main childhood linkage was also used in this linkage; *see above*.

Donor linkage: Linkage specification (step 2)

As above, HFEA regulations stipulate that persons not employed by the HFEA are not permitted to view identifiable data pertaining to donor assisted conception treatment cycles, including that related to children born as a result. Therefore data linkage was undertaken by two different members of HFEA staff, independently from each other. The linkage protocol was identical to that used in the main linkage and described in detail in *table 53.* All potential matches were reviewed pseudo-anonymously by the study author and by Mrs K Bunch. HFEA staff recorded the degree to which the data on HFEA and NRCT records matched; For example birthweight matched within 10g or 100g etc., Maternal forename full match, maternal second name matched but double barrelled when recorded on NRCT etc. In two cases, though it was felt that a match was very unlikely by both the study author and Mrs Bunch, very minor doubts remained. Thus these two cases were additionally reviewed by the thesis second supervisor, Dr Botting. Both cases were unanimously rejected as being matches.

Data cleaning (step 3)

Merging donor HFEA/ NRCT data

HFEA background and parental fertility data and HFEA assigned UMN for all donor cohort members were securely transferred to the University of Oxford (who hold the NRCT data), without identifiable data. The author carried out data cleaning and analysis for this section of the study at Oxford University.

Using the NRCT assigned UMN's, clinical data relating to cancer diagnoses were merged with HFEA background data. Therefore, as with the main study, individuals who were born after donor ART and developed cancer had both HFEA background data and NRCT clinical data available for analysis.

Cleaning of HFEA variables

Data cleaning was undertaken using STATA, version 11[230]. Variables were renamed appropriately and 'NULL' entries were removed and thus converted into missing data.

Date of birth of child/ Study Entry/ Study Exit dates: All dates were converted into STATA[230] format. Study entry date/ start of time at risk was considered to be date of birth. Study exit date was considered to be the earlier of: -

- Date at cancer diagnosis
- Study end (31.12.2008).
- Child's 15th birthday
- 49 records were excluded as it was not possible to calculate person-years at risk, because of missing/ invalid date of birth.

HFEA variables were cleaned and validated using the same data cleaning protocols as for the main childhood linkage process. These are described above.

Data Analysis: (Step 4)

Person-years at risk were stratified by sex, age at diagnosis (0, 1-4, 5-9 and 10-14 years), birth weight, gestation, multiple birth, maternal parity, maternal and paternal age, assisted conception type, fresh or cryopreserved embryos, and parental infertility cause.

Calculated Person-years at risk were used in conjunction with NRCT cancer incidence rates for the general population of Britain of the same age and time period, to determine the expected numbers of cases in the cohort, if their risk was the same as that in the general population[226].

The numbers of cases were then compared with expected numbers. Analyses were in terms of the Standardised Incidence Ratio (SIR), measured by the ratio of observed/expected.

The number of observed cancers was assumed to follow a Poisson distribution. For each SIR, 95% confidence intervals (CI) based on the Poisson distribution were calculated. Tests of the hypothesis that an SIR is equal to one are based on 2-sided p-values and calculated based on χ^2 test[226]. The Absolute Excess Risk (AER) corresponding to each SIR were also calculated.

Study approval

Ethical approval for this section of the study was obtained from the London Research Ethics Committee (*appendix 3*). Waiver of the requirement for individual consent was obtained under section 251 of the NHS act 2006[215] from the UK Health Research Authority Confidentiality Advisory Group (*appendix 3*).

Further individual approvals were additionally required and obtained from the Human Fertilisation & Embryology Authority, and NRCT Caldecott guardian.

Chapter 5- Cancer risk in children born after assisted reproduction; Results

Children born after non-donor assisted conception

Characteristics of the study population

The final cohort included 106,013 children born in Britain between 1992 and 2008, from 83,697 non-donor assisted conception pregnancies. These 106,013 children contributed a total of 700,705 person-years at risk to the analysis. Children born towards the end of the study period contributed relatively fewer person-years of follow-up than children born in earlier years despite the larger numbers of children born in later years. This is due to the relatively short period of follow-up for later birth year cohorts. The average duration of follow-up was 6.6 years.

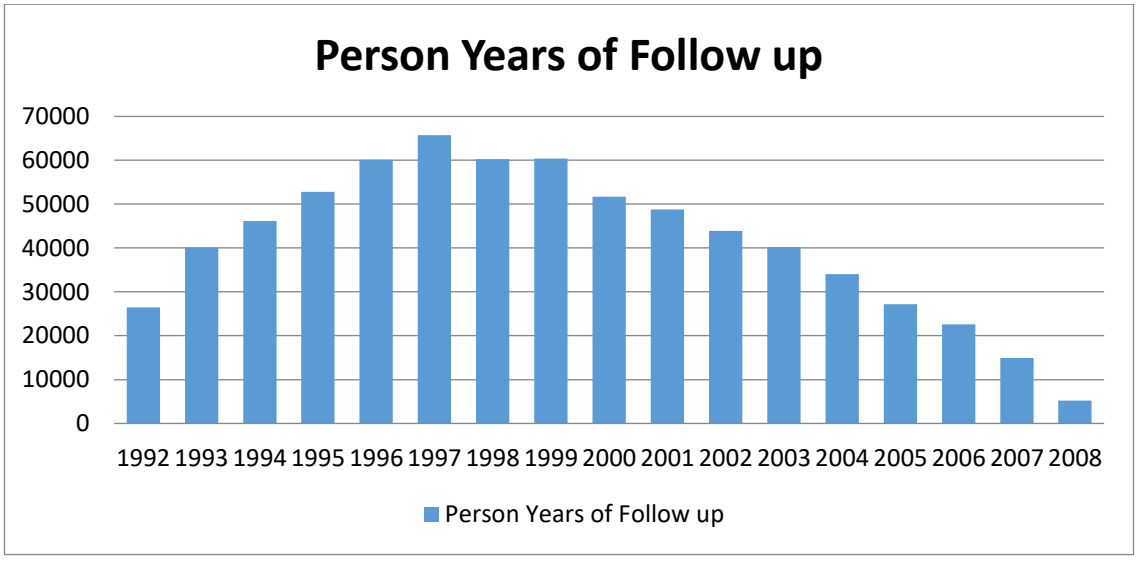


Figure 19; *Cohort of children born after non-donor assisted reproduction; contribution of each birth year cohort to total person years of follow up.*[3]

Year of Birth	No of Children born after assisted conception	% of cohort	Cumulative % of Cohort	Person Years of follow up	Person Years as % of total
1992	1768	1.7	1.7	26491	3.7
1993	2676	2.5	4.2	40108	5.7
1994	3185	3.0	7.2	46154	6.6
1995	3925	3.7	10.9	52830	7.5
1996	4818	4.5	15.4	60124	8.6
1997	5723	5.4	20.8	65733	9.4
1998	5756	5.4	26.2	60275	8.6
1999	6371	6.0	32.2	60414	8.6
2000	6108	5.7	37.9	51747	7.4
2001	6538	6.2	44.1	48780	7.0
2002	6792	6.4	50.4	43915	6.3
2003	7332	6.9	57.3	40171	5.7
2004	7563	7.1	64.4	34020	4.9
2005	7789	7.3	71.8	27164	3.9
2006	9061	8.5	80.3	22592	3.2
2007	10005	9.4	89.7	14958	2.1
2008	10603	10.0	99.7	5228	0.7
Missing Values *(Excluded*)	368	0.3	100.0	N/A	N/A
Totals	106,381	100	100	700,704	100

Table 56; *Cohort of Children born after non-donor assisted reproduction by year of birth, including person years contributed to analysis by each birth year cohort*.[3]

Baseline demographics were similar for all cohort members, regardless of their outcome status (***t****able 57*). The mean age at diagnosis was 4.2 years old (±3.3, SD).

Variable		Total cohort of children born after assisted conception	Cohort members who have not developed cancer	Cohort members who have developed cancer
No. of cases		106,381	106,273	108
Sex (%)	Male	54,143 (51)	54,079 (51)	60 (56)
	Female	52,134 (49)	52,082 (49)	48 (44)
Multiple births (%)	Singletons	62,195 (58)	62,127 (59)	65(60)
	Any Multiple Births	44,154 (42)	62,127 (41)	43 (40)
Mean birth weight g	(SD g, Range g)	2863 (792, 300- >6000)	2854 (791, 301- >5900)	2919 (782, 680- >4300)
Birth weight group (%)	<2500g	31,294 (30)	31,263 (30)	31 (29)
	2500g- 3999g	68,189 (65)	68,121 (65)	68 (63)
	≥4000g	5,986 (6)	5,977 (6)	9 (8)
Gestational age at birth	Weeks (SD)	37.4 (3.2)	37.5 (3.2)	37.5 (3.2)
Type of ART (%)	IVF	61,521 (58)	61,455 (58)	63 (58)
	ICSI*	42,719 (40)	42,679 (40)	40 (37)
	Not recorded	2,141 (2)	2,136 (2)	5 (5)
Fresh/ frozen cycles (%)	Fresh Cycle	93,689 (88)	93,588 (88)	93 (86)
	Cryopreserved Cycle	12,554 (12)	12,539 (12)	15 (14)
Stage at embryo transfer (%)	Blastocyst	5,773 (5)	5,769-5,773 (5)	5 (0-4)
	Cleavage	57,418 (54)	57,372 (54)	41 (38)
	Not recorded	43,190 (41)	43,191 (41)	65 (60)
Maternal age at birth of child	Years (SD)	34.3 (4.0)	34.3 (4.0)	33.9 (4.0)
Paternal age at birth of child	Years (SD)	37.2 (5.8)	37.2 (5.8)	37.6 years (6.6)
Infertility cause (%)	Both Male & Female	18,063 (17)	18,034 (17)	28 (26)
	Female Factor only	27,681 (26)	27,650 (26)	29 (27)
	Male Factor only	24,427 (23)	24,407 (23)	16 (15)
	Unexplained	33,840 (32)	33,807 (32)	32 (30)
	Not recorded	2,370 (2)	2,366-2,370 (2)	<5 (0-4)
Duration of infertility	Years (SD, Range)	4.9 (2.9, 0- >30)	4.9 (2.9, 0- >30)	5.3 (3.2, 0- >15)
Previous ART cycles	Mode (Range)	0; 51% (0->20)	0; 51% (0->20)	0; 49% (0- >5)
Previous live births (%)	0	94,696 (90)	94,589 (90)	100 (94)
	1	9,923 (9.5)	9,915 (9.5)	7 (6)
	>1	421 (0.5)	421 (0.5)	0

***Table 57**; Demographics comparing all children born after non-donor ART to children born after non-donor ART who did and did not develop cancer. *ICSI (intracytoplasmic sperm injection) plus other micromanipulation. [3]*

Birthweight

Birthweight distribution is skewed slightly. Birthweight usually follows a *normal* distribution. This skewed distribution is likely to represent more babies born at lower birthweights and born prematurely in this cohort in comparison to the general population.

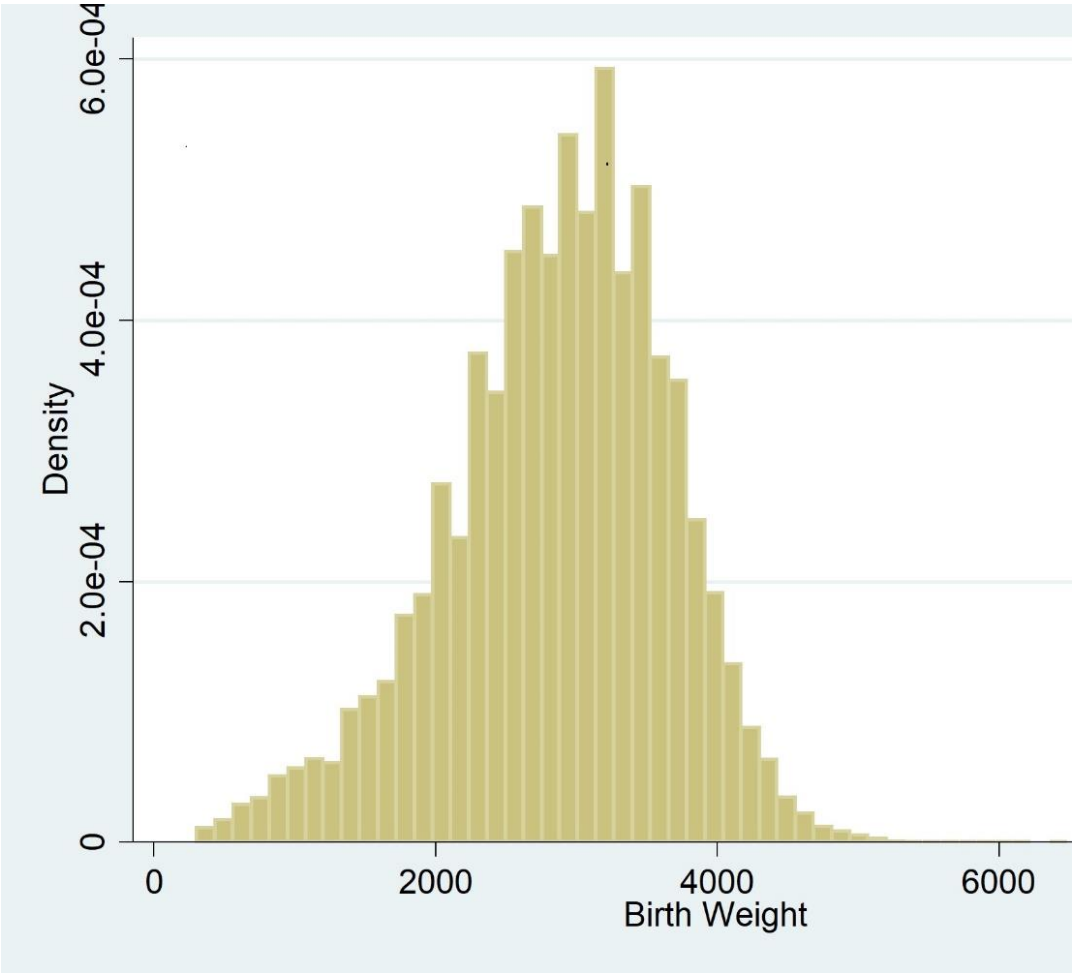


***Figure 20**; Distribution of birthweight (g), within the cohort of children born after assisted conception in Great Britain, 1992-2008*

No difference was observed in birthweight between children born after different types of assisted conception.

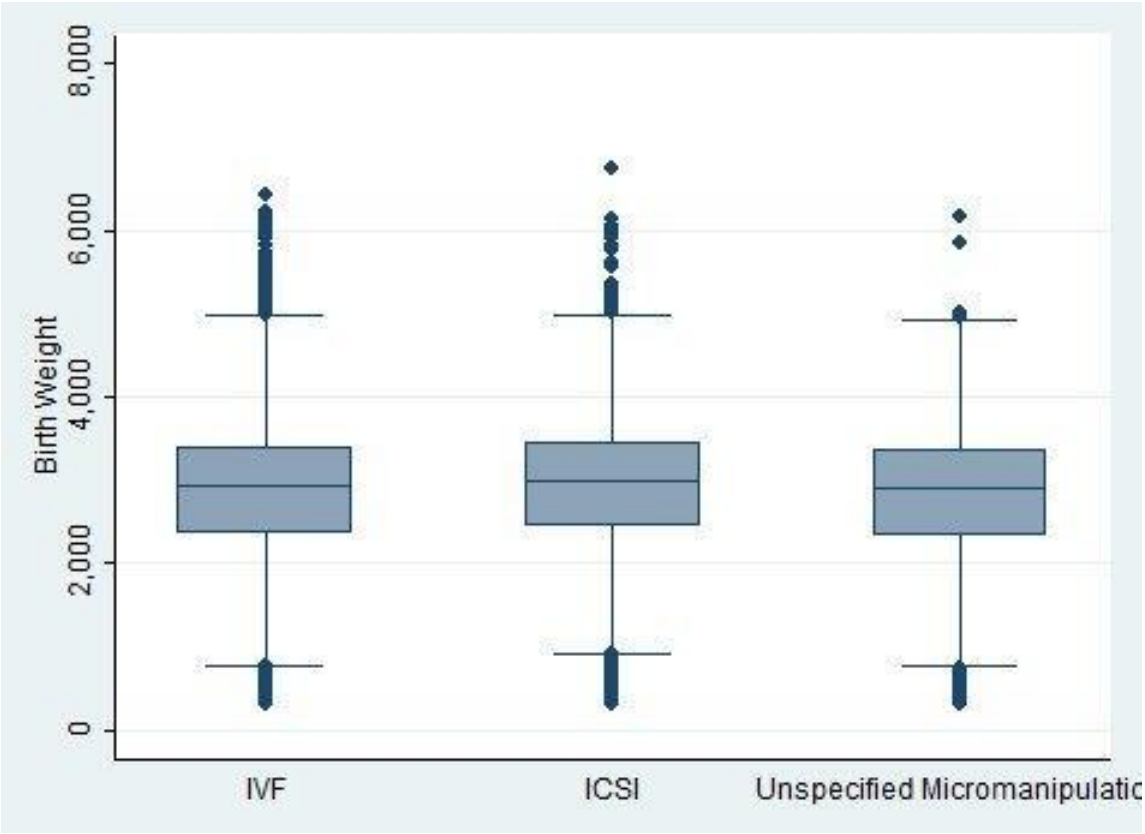


Figure 21; *Birthweights by different types of assisted conception within the cohort of children born after assisted conception in Great Britain, 1992-2008*

As expected, birthweight has a generally linear association with gestation. There were a number of children with gestations above 35 weeks who had recorded birthweights between 300g and 600g, suggesting treating these as effectively null for the linkage process was appropriate.

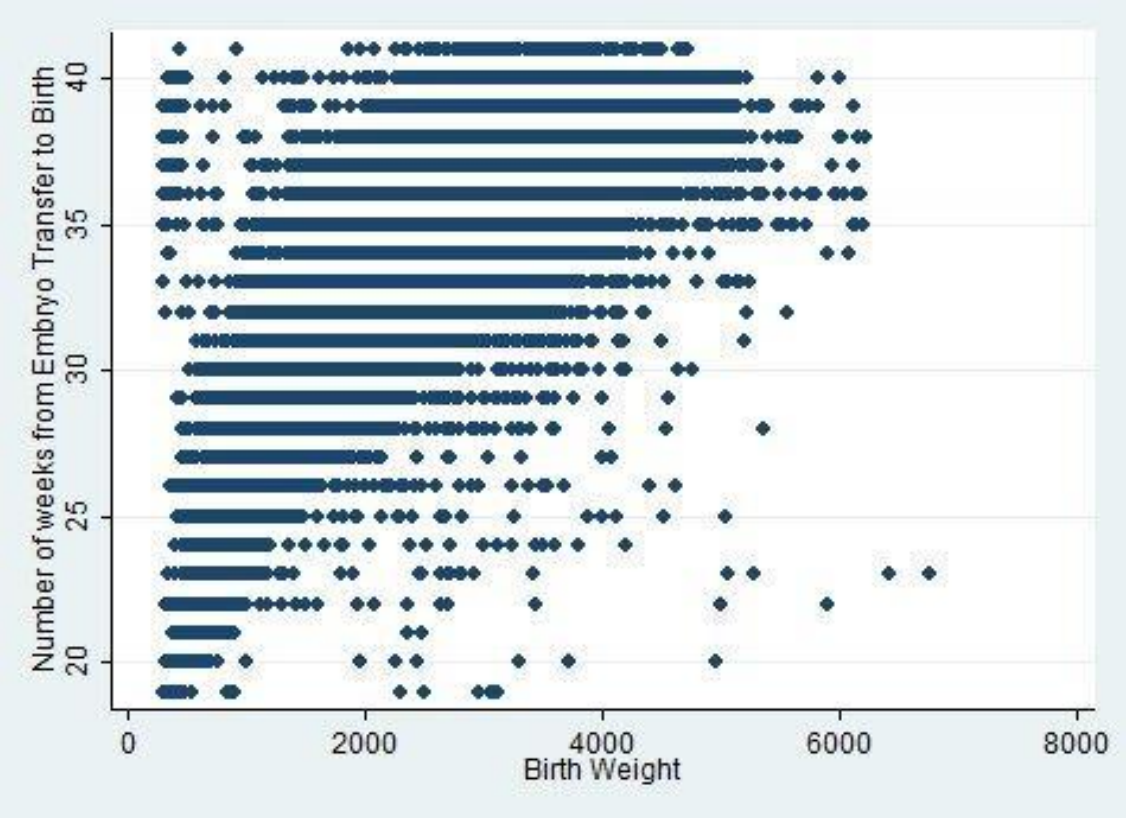


***Figure 22**; Birthweight by recorded gestation within the cohort of children born after assisted conception in Great Britain, 1992-2008*

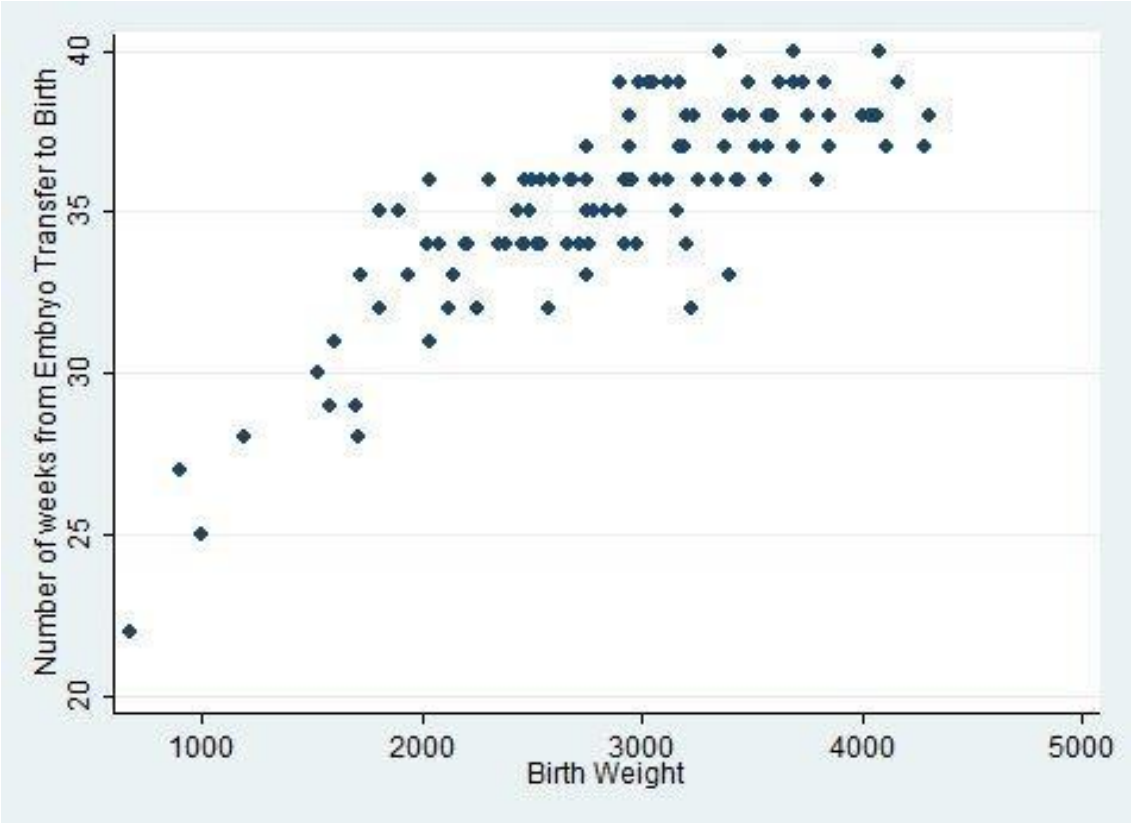


Figure 23; *Birthweight by recorded gestation in children born after assisted conception and diagnosed with cancer under the age of 15 years in Great Britain, 1992-2008*

Overall cancer risk

The records of 108 children were successfully linked to NRCT records and therefore these individuals were identified as having been diagnosed with cancer between birth and the sooner of age fifteen years or 1/1/2009. 109.7 cancers were expected, based on age and sex specific national cancer incidence rates. Therefore the standardised incidence ratio was 0.98 (95% CI 0.81 to 1.19; *P*=0.871; *table 58*).

There was no material difference in results when stratified by sex, age, birth weight, gestational age at birth, singleton vs multiple birth, maternal parity, maternal and paternal age, type of assisted conception, fresh versus cryopreserved embryos and cause of parental infertility (*table 59*).

Co-morbidities were identified in 21 children born after non-donor assisted conception and subsequently diagnosed with cancer. Three children were known to have a coexisting respiratory conditions. Three children, all of whom developed a hepatoblastoma, had co-morbidities relating to premature birth. Three cases of leukaemia were diagnosed in children with trisomy 21 (Downs syndrome; compared to 1.5 expected based on NRCT data; post hoc analysis). Other co-morbidities included developmental disorders, eczema and a number of minor or unspecified congenital anomalies. No child, other than those with trisomy 21, had a diagnosis known to be associated with the development of cancer, including no children recorded as having an imprinting disorder. All retinoblastomas were unilateral.

Cancer Type *	Person years of follow up**	Observed	Expected	Standardized Incidence Ratio	95% Confidence Interval
All cancers	700, 705	108	109.7	0.98	0.81 to 1.19
Leukaemia	701,047	34	37.53	0.91	0.63 to 1.27
CNS tumors	701,138	22	25.78	0.85	0.54 to 1.29
Neuroblastoma	701,165	9	10.20	0.88	0.40 to 1.68
Retinoblastoma	701,193	#	#	0.59	0.12 to 1.73
Renal tumors	701,162	8	8.5	0.94	0.41 to 1.86
Hepatic tumors	701,165	6	1.83	**3.27**	**1.20 to 7.12†**
Bone tumors and extra osseous sarcomas	701,134	20	8.56	**2.34**	**1.34 to 3.61‡**
Osteosarcoma	701,206	#	#	2.95	0.61 to 8.62
Ewing's Sarcoma	701,202	#	#	2.47	0.67 to 6.32
Rhabdomyosarcoma	701,162	#	#	**2.62**	**1.26 to 4.82†**
Other Sarcomas	701,205	#	#	1.42	0.29 to 4.15
Germ cell tumors	701,203	#	#	0.56	0.07 to 2.03

Table 58; *Observed vs. expected numbers for all cancers and site specific cancer groups. *Cancer type classified according to ICCC3 coding[27], see Table 54 for further details of cancer classification. **Slightly more total person years at risk are included in analyses considering rarer cancers than when considering all cancers as a whole or more common cancers. This is because, in order to maximize the number of person-years available for analysis, individuals were censored from further analysis once they developed the specific cancer being considered and were not censored when they developed any other cancer type. Therefore, by definition, more individuals develop more common cancers and thus contribute fewer person years at risk as they are censored from analyses at the date of diagnosis. # Cells containing <5 observations censored as per ethics regulations.[3]* † P<0.05, ‡ P<0.01

Factor		All cancers				
		Person years follow up	Obs**	Exp	SIR	95% CI
Overall		700,705	108	109.70	0.98	0.81 to 1.19
Sex	Male	358,853	60	59.73	1.00	0.77 to 1.29
	Female	341,852	48	49.97	0.96	0.71 to 1.27
Age at Diagnosis (years)	0	100,532	17	19.93	0.85	0.50 to 1.37
	1-4	307,932	54	58.22	0.93	0.70 to 1.21
	5-9	218,839	29	23.74	1.22	0.82 to 1.75
	10-14	73,401	8	7.80	1.03	0.44 to 2.02
Birth Weight	<2500g	218,117	31	34.49	0.90	0.61 to 1.28
	2500-3999g	440,171	68	69.27	0.98	0.76 to 1.24
	≥4000g	36,617	9	5.94	1.52	0.69 to 2.88
Gestation	≤ 31 weeks	43,418	7	6.67	1.05	0.42 to 2.16
	32-36 weeks	161,139	27	24.94	1.08	0.71 to 1.58
	≥ 37 weeks	487,974	73	76.83	0.95	0.75 to 1.20
Singleton/ multiple birth	Singleton	396,569	65	62.54	1.04	0.80 to 1.33
	Multiple	304,136	43	45.46	0.95	0.69 to 1.27
Maternal previous live births	0	644,270	100	100.20	1.00	0.81 to 1.21
	1 or more	52,457	7	8.77	0.80	0.32 to 1.65
Maternal age at birth of child	<30 years	92,325	14	14.22	0.98	0.54 to 1.65
	30-39 years	553,694	87	86.71	1.00	0.80 to 1.24
	40+ years	54,423	7	8.74	0.80	0.32 to 1.65
Paternal age at birth of child	<30 years	49,606	6	7.56	0.79	0.29 to 1.73
	30-39 years	466,258	66	72.65	0.91	0.70 to 1.16
	40+ years	183,571	35	29.27	1.20	0.83 to 1.66
Parental infertility cause	Both Male & Female	166,862	28	24.39	1.15	0.76 to 1.66
	Female factor only	176,555	29	27.85	1.04	0.70 to 1.50
	Male factor only	96,536	16	17.43	0.92	0.53 to 1.49
	Unexplained	250,328	32	38.18	0.84	0.57 to 1.18
	Not recorded	10,423	#	#	1.62	0.34 to 4.75
Type of Assisted conception	IVF	469,686	63	70.92	0.89	0.68 to 1.14
	ICSI*	220,540	40	36.93	1.08	0.77 to 1.48
	Not recorded	10,478	5	1.85	2.70	0.88 to 6.31
Fresh/ Cryopreserved cycle	Fresh	623,485	93	97.42	0.95	0.77 to 1.17
	Cryopreserved	76,149	15	12.11	1.24	0.69 to 2.04
	Not recorded	1,071	#	#	0.00	0.00 to 18.34

Table 59; *Observed vs. expected for 'all cancers', stratified by potential mediating and moderating factors. *ICSI (intracytoplasmic sperm injection) plus other micromanipulation. ** Observed cases presented by specific variable do not always add up to the total number of cases as the outcome 'not recorded' is only presented where there were 1,000 or more person years at risk available. # Cells containing <5 observations censored as per ethics regulations.*[3]

Risk according to cancer type

No excess risk of most cancer types was observed in children born after non-donor assisted conception during this study. This includes leukaemia, neuroblastoma, retinoblastoma, central nervous system tumours, renal and germ-cell tumours (*table 58*).

Hepatoblastoma

6 cases of hepatic tumours were noted compared to 1.8 cases expected, (SIR 3.27; 95%CI 1.20 to 7.12; P=0.03; *table 58*). All of these were hepatoblastomas and for this subgroup the SIR was 3.64, (95%CI 1.34 to 7.93; P=0.02; absolute excess risk 6.21 cases per million person-years; 95%CI 0.79 to 16.27). When stratified by various mediating and modifying factors, this increased risk of hepatoblastoma was associated with low birth weight, (SIR in children with birth weight <2500g is 10.29; 95%CI 3.34- 24.02; *P*= 0.003; *table 60*). Infants who had a birth weight of less than 1000g were at greatest risk, (SIR 51.31; 95%CI 6.2-185.3; P=0.015). There also appeared to be an association between development of hepatoblastoma in this cohort and higher order births, (SIR 5.80; 95%CI 1.58 to 14.84), gestation ≤31 weeks, (SIR 30.00; 95%CI 6.19 to 87.67). Hepatoblastomas were almost all diagnosed in children aged 1-4 years old, (5 cases; SIR 6.21 95%CI 2.02 to 14.49; *table 60*). An excess of hepatoblastomas were also observed in those who had fresh embryo transfer, (SIR 3.44; 95%CI 1.12 to 8.02), IVF, (SIR 5.18; 95%CI 1.68 to 12.1), maternal age 30-39 years at time of birth, (SIR 3.85; 95%CI 1.25 to 8.98), zero previous maternal live births, (SIR 4.06; 95%CI 1.49 to 8.83) and unexplained cause of parental infertility, (SIR 5.56; 95%CI 1.16 to 16.5).

3 of the 6 cohort members who subsequently developed hepatoblastoma had co-morbidities recorded by the NRCT. All three were related to prematurity and none to conditions known to be related to cancer development, including imprinting disorders.

Factor		Hepatoblastoma		
		Person years follow up	SIR	95% CI
Overall		701,165	**3.64**	**1.34 to 7.93†**
Sex	Male	359,108	3.19	0.66 to 9.32
	Female	342,058	4.24	0.88 to 12.4
Age at Diagnosis (years)	0	100,541	1.28	0.03 to 7.16
	1-4	308,062	**6.21**	**2.02 to 14.49‡**
	5-9	219,070	0.00	0 to 54.22
	10-14	73,491	0.00	0 to 354.53
Birth Weight	<2500g	218,240	**10.20**	**3.31 to 23.81‡**
	2500-3999g	440,482	0.95	0.02 to 5.28
	≥4000g	36,645	0.00	0.00 to 32.0
Gestation	≤31 weeks	43,442	**30.00**	**6.19 to 87.67‡**
	32-36 weeks	161,264	5.51	0.67 to 19.92
	≥37 weeks	488,281	0.86	0.02 to 4.76
Singleton/ multiple birth	Singleton	396,834	2.09	0.25 to 7.55
	Multiple	304,332	**5.80**	**1.58 to 14.84†**
Maternal previous live births	0	644,688	**4.06**	**1.49 to 8.83†**
	1 or more	52,495	0.00	0.00 to 19.97
Maternal age at birth of child	<30 years	92,374	4.90	0.12 to 27.3
	30-39 years	554,074	**3.85**	**1.25 to 8.98†**
	40+ years	54,454	0.00	0.00 to 20.84
Paternal age at birth of child	<30 years	49,629	0.00	0.00 to 28.61
	30-39 years	466,577	**3.70**	**1.01 to 9.48**
	40+ years	183,689	4.31	0.52 to 15.58
Parental infertility cause	Both Male & Female	167,006	3.39	0.09 to 18.9
	Female factor only	176,683	4.66	0.57 to 16.85
	Male factor only	96,578	0.00	0.00 to 8.39
	Unexplained	250,456	**5.65**	**1.16 to 16.5†**
	Not recorded	10,443	0.00	0.00 to 84.58
Type of Assisted conception	IVF	469,995	**5.18**	**1.68 to 12.1†**
	ICSI*	220,674	1.56	0.04 to 8.71
	Not recorded	10,496	0.00	0 to 85.57
Fresh/ Cryopreserved cycle	Fresh	623,876	**3.44**	**1.12 to 8.02†**
	Cryopreserved	76,218	5.24	0.13 to 29.21
	Not recorded	1,071	0.00	0.00 to 1381

Table 60; *Observed vs. expected cases of Hepatoblastoma stratified by potential mediating factors*. **ICSI (intracytoplasmic sperm injection) plus other micromanipulation. # Cells containing <5 observations censored as per ethics regulations.* † P<0.05, ‡ P<0.01 [3]

Sarcomas including Rhabdomyosarcoma

Cohort members developed bone and extra-osseous sarcomas in significantly greater numbers than expected, (20 observed vs 8.6 expected cases; SIR 2.34; 95%CI 1.43 to 3.61; P=0.002; *table 58*). This was predominantly, but not exclusively due to an excess of rhabdomyosarcomas, 10 cases were observed in the cohort compared to an expected 3.8 cases, (SIR 2.62; 95% CI 1.26 to 4.82; P=0.02; *table 58*). There were also non-significant excess observed cases of osteosarcoma, (SIR 2.95; 95% CI 0.61 to 8.62; *table 58*), Ewing's sarcoma, (SIR 2.47; 95%CI 0.67 to 6.32; *table 58*), and to a lesser extent other sarcoma's, (SIR 1.42; 95%CI 0.29 to 4.15; *table 58*).

The absolute excess risk of rhabdomyosarcoma was small, 8.82 cases per million person-years at risk. Risks did not differ significantly according to birthweight, gestation or age at diagnosis. Excess risks were seen higher order births (SIR 3.66; 95%CI 1.34 to 7.96; *table 61*), in girls, (SIR 3.82; 95%CI 1.40 to 8.31; *table 61*), and in children born to older fathers, (SIR 5.93; 95% CI 2.18 to 12.90; *table 61*). Other subgroups with apparent excess risks included those born to mothers who had no previous live births, (SIR 2.87; 95%CI 1.38 to 5.27; *table 61*), born to mothers aged 30-39 years old at the time of birth, (SIR 2.98; 1.36 to 5.66; *table 61*), those born after ICSI, (SIR 3.97; 1.29 to 9.26; *table 61*), and those whose parental cause of infertility was not recorded, (SIR 31.78; 95%CI 3.85 to 114.8; *table 61*).

There were 5 cases of embryonal rhabdomyosarcoma compared to 2.16 cases expected (SIR 2.16; 95%CI 0.75 to 5.41). There were also 5 cases of non-embryonal rhabdomyosarcoma compared to 1.66 expected cases (SIR 3.02; 95%CI 0.98 to 7.04).

Factor		Rhabdomyosarcoma		
		Person years follow up	SIR	95% CI
Overall		701,162	**2.26**	**1.26 to 4.82**
Sex	Male	359,107	1.78	0.49 to 4.57
	Female	342,055	**3.82**	**1.40 to 8.31**
Age at Diagnosis (years)	0	100,541	0.00	0 to 6.55
	1-4	308,068	2.68	0.98 to 5.83
	5-9	219,062	3.21	0.66 to 9.38
	10-14	73,491	5.54	0.03 to 5.96
Birth Weight	<2500g	218,257	2.59	0.53 to 7.56
	2500-3999g	440,462	2.49	0.91 to 5.42
	≥4000g	36,644	4.75	0.12 to 26.49
Gestation	≤31 weeks	43,462	4.38	0.11 to 24.23
	32-36 weeks	161,260	3.46	0.71 to 10.11
	≥37 weeks	488266.96	1.87	0.61 to 4.37
Singleton/ multiple birth	Singleton	396,840	1.83	0.50 to 4.72
	Multiple	304322.57	**3.66**	**1.34 to 7.96**
Maternal previous live births	0	644,685	**2.87**	**1.38 to 5.27**
	1 or more	52,495	0.00	0.00 to 9.99
Maternal age at birth of child	<30 years	92,382	2.02	0.05 to 11.25
	30-39 years	554,063	**2.98**	**1.36 to 5.66**
	40+ years	54,454	0.00	0.00 to 9.97
Paternal age at birth of child	<30 years	49,621	7.57	0.92 to 27.36
	30-39 years	466,585	0.79	0.10 to 2.84
	40+ years	183,685	**5.93**	**2.18 to 12.90**
Parental infertility cause	Both Male & Female	167,008	2.34	0.28 to 8.45
	Female factor only	176,678	2.06	0.25 to 7.43
	Male factor only	96,578	0.00	0 to 5.05
	Unexplained	250,466	3.01	0.82 to 7.70
	Not recorded	10,431	**31.78**	**3.85 to 114.8**
Type of Assisted conception	IVF	470,000	2.01	0.65 to 4.70
	ICSI*	220,665	**3.97**	**1.29 to 9.26**
	Not recorded	10,496	3.65	0.75 to 10.67
Fresh/ Cryopreserved cycle	Fresh	623,865	2.95	0.28 to 8.45
	Cryopreserved	76,227	0.00	0 to 7.11
	Not recorded	1,071	0.00	0 to 545

Table 61; *Observed vs. expected cases of rhabdomyosarcoma stratified by potential mediating factors.* * ICSI plus other micromanipulation. **Observed cases presented by outcome of specific variable do not always add up to the total number of cases as the variable outcome 'not recorded' is only presented where 1,000 or more person years at risk are available. *# Cells containing <5 observations censored as per ethics regulations.* † P<0.05, ‡ P<0.01 [3]

Donor results

12,137 children contributed 95,389 person years follow-up to the analysis of cancer risk in children born after assisted conception involving donor gametes or donor embryos[2]. The average duration of follow-up was 7.86 years. Records of 12 children were successfully linked to NRCT records and thus identified as having developed cancer before the earliest of either their 15 birthday or study endpoint (01/01/2009). This was slightly, but not significantly less than expected (12 cases observed compared to 14.4 cases expected; SIR 0.83; 95% CI 0.43-1.45; *P*=0.502). The median age at diagnosis was 2.6 years (inter quartile range 1.2-5.2 years).

During linkage, two other cases were considered as potential matches, but discounted as being successful matches by all three members of the linkage team independently (Dr C Williams, Mrs K Bunch & Dr B Botting). Including these two discounted 'cases' in a sensitivity analysis did not substantially alter results (SIR 0.97; 95% CI 0.53-1.63; *P*=0.915). Cohort members who developed cancer had broadly similar demographics to those who did not develop cancer (*table 62*).

Results were also broadly unchanged when stratified by potential modifying & mediating factors such as sex, age at diagnosis, birthweight, multiple births, maternal parity, type of ART and fresh vs. frozen cycle (*table 63*). However, the small number of events in some strata have resulted in widened confidence intervals and thus provide less precise risk estimates.

Variable		Whole cohort	Children who have not developed Cancer	Children who have developed Cancer
No. of cases		12,186	12,174	12
Sex (%)	Male	6,326 (52)	6,317 (52)	3 (25)
	Female	5,851 (48)	5,848 (48)	9 (75)
Multiple births (%)	Singletons	6,697 (55)	6,690 (55)	7 (58)
	Multiple Births	5,489 (45)	5,484 (45)	5 (42)
Birth weight	Mean (SD) g	2,790 (842)	2790 (842)	2719 (703)
Birth weight group (%)	<2499g	3,980 (33)	3,976 (33)	4 (33)
	2500g-3999g	7,379 (61)	7,371 (61)	8 (67)
	≥4000g	679 (6)	679 (6)	0 (0)
Gestation at birth	Mean (SD)	37.1 (3.3)	37.1 (3.3)	37.1 (3.4)
Type of Assisted conception (%)	IVF	9,764 (80)	9,753 (80)	11 (92)
	ICSI*	2,110 (17)	2,110 (17)	0
	Not recorded	310 (3)	309 (3)	1 (8)
Fresh/ frozen cycles (%)	Fresh Cycle	10,207 (84)	10,197 (84)	10 (83)
	Cryopreserved Cycle	1,949 (16)	1,947 (16)	2 (17)
Stage at embryo transfer (%)	Blastocyst	5,402 (44)	5,398 (44)	4 (33)
	Cleavage	370 (3)	370 (3)	0
	Not recorded	6,414 (53)	6,406 (53)	8 (67)
Maternal age at birth of child	Mean (SD) years	37.8 (6.2)	37.8 (6.2)	38.5 (7.0)
Paternal age at birth of child	Mean (SD) Years	40.3 (7.4)	40.3 (7.4)	41.8 (11.7)
Infertility cause (%)	Both Male & Female	2,734 (22)	2,729 (22)	5 (42)
	Female Factor only	2,847 (23)	2,844 (23)	3 (25)
	Male Factor only	4,706 (39)	4,703 (39)	3 (25)
	Unexplained	740 (6)	740 (6)	0 (0)
	Not recorded	1,159 (10)	1,158 (10)	1 (8)
Duration of infertility	Mean (SD) years	6.1 (4.1)	6.1 (4.1)	8.6 (6.1)
Previous Maternal assisted conception Cycles (%)	0	4,799 (39)	4,793 (39)	6 (50)
	1 or more	7,385 (61)	7,379 (61)	6 (50)
Previous Maternal Live Births (%)	0	2,546 (21)	2,543 (21)	3 (25)
	1 or more	2,535 (21)	2,533 (21)	2 (17)
	Unknown	7,105 (58)	7,098 (58)	7 (58)

Table 62; *Demographics comparing all children born after non-donor ART to children born after non-donor ART who did and did not develop cancer* *ICSI (Intracytoplasmic sperm injection) plus other micromanipulation.[2]

Mediating/ Moderating Factor	All Cancer		
	Person years follow-up	SIR	95% CI
Overall	95,389	0.83	0.43-1.45
Sex			
Male	49,418	1.13	0.52-2.14
Female	45,970	0.47	0.10-1.36
Age group at diagnosis (years)			
0	11,734	1.29	0.27-3.78
1-4	38,917	0.82	0.30-1.79
5-9	31,688	0.82	0.18-2.57
10-14	13,051	0.00	0.00-2.14
Birth weight (g)			
<2500	33,048	0.80	0.22-2.05
2500g-3999	56,398	0.93	0.40-1.84
≥4000	4,776	0.00	0.00-4.00
Multiple Births			
Singletons	50,331	0.91	0.37-1.87
Multiple Births	45,058	0.74	0.24-1.73
Previous maternal live births			
0	18,940	1.04	0.21-3.03
1 or more	21,165	0.62	0.08-2.25
Type of ART			
IVF	83,548	0.89	0.44-1.58
ICSI*	10,083	0.00	0.00-1.76
Not recorded	1,734	3.26	0.08-18.2
Fresh/ Cryopreserved cycle			
Fresh	80,153	0.83	0.40-1.52
Cryopreserved	14,830	0.88	0.11-3.18
Not recorded	406	0.00	0.00-55.7

***Table 63*;** *Risk of any childhood cancer in children born after donor assisted conception, stratified by potential mediating/ moderating factors.* *ICSI (Intracytoplasmic sperm injection) plus other micromanipulation.[2]

Cancer Type* and ICCC3 categories	Person years of follow up	Standardized Incidence Ratio	95% Confidence Interval
All cancers *ICCC-3 groups I to X11*	95,389	0.83	0.43-1.45
Leukemia *ICCC-3 group I*	95,445	0.61	0.13-1.78
CNS tumors *ICCC-3 group III*	95,435	1.17	0.32-2.99
Neuroblastoma *ICCC-3 group IV*	95,464	0	0.00-2.30
Retinoblastoma *ICCC-3 group V*	95,452	3.29	0.40-11.87
Renal tumors *ICCC-3 group VI*	95,460	0.94	0.02-5.25
Hepatic tumors *ICCC-3 group VII*	95,454	**9.12**	**1.11-32.95**
Bone tumors and extra osseous sarcomas *ICCC-3 groups VIII and IX*	95,464	0	0.00-2.50
Osteosarcoma *ICCC-3 group VIIIa*	95,464	0	0.00-18.38
Ewing's Sarcoma *ICCC-3 group VIIIc,* *IXd division 1& 2*	95,464	0	0.00-12.41
Rhabdomyosarcoma *ICCC-3 group IXa*	95,464	0	0.00-5.91
Other Sarcomas *ICCC-3 groups VIIIb, VIIId, VIIIe IXb, IXc, IXd divisions 3 to 11, IXe*	95,464	0	0.00-10.45
Germ cell tumors *ICCC-3 group X*	95,464	0.00	0.00-6.59

Table 64; *Observed vs. expected numbers for all cancers and site specific cancer groups.*[2] *Cancer type classified according to ICCC3 coding[27]

Significantly more hepatic tumours were identified compared to expected numbers (2 observed vs 0.22 expected; SIR 9.12; 95%CI 1.11-32.95; *P*=0.058). Both of these tumours were hepatoblastomas (2 vs. 0.19; SIR 10.28; 95%CI 1.25-37.14; *P*=0.052; Absolute excess risk 18.66 cases per million person-years at risk). Excess risk was only observed in babies with a birth weight under 2500g (2 observed vs. 0.06 expected; SIR 31.64; 95%CI 3.83-114.30; *P*=0.02).

		Hepatoblastoma		
Mediating/ Moderating Factor		**Person years of follow up**	**SIR**	**95% CI**
Overall		95,454	10.28	1.25-37.14
Sex	Male	49,471	8.76	0.22-48.83
	Female	45,983	12.43	0.32-69.27
Age Group at Diagnosis (years)	0	11,735	11.49	0.29-64.04
	1-4	38,934	10.10	0.25-56.26
	5-9	31,719	0	0-410.37
	10-14	13,066	0	0-2475.81
Birth Weight	<2500g	33,060	31.64	3.83-114.30
	2500g-3999g	56,450	0	0-262.55
	≥4000g	4,776	0	0-182.22
Multiple Births	Singletons	50,369	9.37	0.24-25.18
	Multiple Births	45,085	11.40	0.29-63.49
Maternal Previous Live Births	0	18,963	0	0-74.95
	1 or more	21,172	0	0-70.27
Type of assisted conception	IVF	83,609	12.71	1.54-45.93
	ICSI *	10,083	0	0-95.01
	Not recorded	1,739	0	0-530.22
Fresh/ Cryopreserved cycle	Fresh	80,210	12.27	1.49-44.33
	Cryopreserved	14,838	0	0-95.38
	Not recorded	406	0	0-6966.82

Table 65; *Risk of Hepatoblastoma in children born after donor assisted conception, stratified by potential mediating/ moderating factors. *ICSI (Intracytoplasmic sperm injection) plus other micromanipulation.* [2]

Chapter 6-

Discussion and Conclusions

Long-term safety of assisted reproductive therapy is increasingly important in the context of the growing use of such techniques worldwide, with more than 8 million children born as a result to date[7]. Follow-up studies have been difficult in the past due to a variety of factors. Clinicians who undertake ART are rarely involved in longer term care of women, nor are they often involved in resulting births or paediatric care. Due to this, early long-term outcome studies tended to be small, based on few exposed cases, and often case series or case-control studies. Long-term cancer risk has been even more challenging to investigate systematically, as the outcome of interest is often relatively rare, particularly for childhood cancers and some cancers in women. Therefore studies investigating cancer after assisted conception need to be large, preferably using datasets covering whole populations, with robust means of identifying outcomes of interest and including consideration of various moderating, mediating and confounding factors.

In the UK, access to such a population based ART registry, the Human Fertility & Embryology Authority dataset, was made possible in 2009/2010. It is in this context, this thesis was planned; incorporating analysis of both cancer in women after assisted conception and their ART conceived children. The aim of undertaking both studies in parallel was to provide families and clinicians with full information surrounding cancer risks related to assisted conception.

Over the last 10 years, other research groups around the globe have attempted to undertake relatively similar studies. Results from this thesis are considered alongside those more recent studies, as well as those published previously, scrutinising consistency, or lack thereof, between them.

Cancer in women after assisted reproductive therapy

Breast cancer

There was no overall increased risk of breast cancer in this cohort of over a quarter of a million women who has assisted reproduction in the UK between 1991 and 2010, when followed-up for an average of 8.8 years (range 1 year to 19 years). This is consistent with the findings of most published studies[68-74,76]. One of the few previously published studies to have suggested an increased risk of breast cancer found only a marginal increases in risk, just reaching statistical significance[75].

A number of studies have suggested an association between age at first treatment and risk of breast cancer[69,70,78]. Pappo et al found age over 40 years at first treatment was associated with a borderline significant increased risk of breast cancer[70]. A borderline increased risk of breast cancer was also found by Sergentanis et al in a large systematic review of eight cohort studies in women over 30 years at first treatment[69]. In contrast, Stewart et al found an increased risk of breast cancer in women who were aged under 24 years[78]. This thesis found no association between age at first treatment and risk (***P***=0.13) and no significant increased risk in any age group.

Significant reductions in risk of breast cancer was found in some sub-group analyses. For example, women who had assisted reproduction because of male factor only were found to have significantly reduced risks of developing breast cancer than the age-standardised population in general (SIR 0.92; 95% CI 0.86 to 0.99). The reasons behind such risk reductions are not clear. This may possibly be because of beneficial lifestyle changes most women make before going through assisted reproduction, for example, most do not smoke[51] and exercise regularly[51]. During the study period, women had a BMI of more than 30 did not qualify for NHS

funding of their treatment in the UK. Thus cohort members may have been less likely to be obese than the age-standardised general population, though data on BMI were not available to this study. These factors are known to be protective in the development of breast cancer[231]. It is possible that such beneficial lifestyles may counteract other possible confounders such as older age at first birth. Unfortunately data on these possible confounders were not available for further analysis of this.

A significant trend towards decreasing risk with increasing time since last treatment was also found. Reasons behind this finding are unclear. Analyses of attained age at cancer diagnosis found no significant difference in risks, compared to the general age standardised population, in either women over 50 years of age, most of whom will be postmenopausal, nor in women aged under 50 years at diagnosis, most of whom will be pre or peri-menopausal. Therefore menopausal status is unlikely to be influencing this observed trend.

It is postulated that having ART, may mean that cancers might be detected at an earlier stage than they might otherwise have been in individuals having this treatment. This is not only because of the multiple medical examinations and investigations that would not have otherwise happened in apparently healthy young women, but also because the women going through this treatment themselves may be more health conscious during a period of treatment. They may pick up on more subtle cancer signs/ symptoms earlier than they might have done otherwise. If this was true, a peak in cancer diagnoses should be observed within the first 12 months of follow-up. In order to mitigate this potential source of bias, sensitivity analyses, (excluding the first 12 months of treatment) were also undertaken for most of the analyses in the woman's cancer section of this thesis. This type of sensitivity analysis would also reduce the possibility of increased risks due to reverse causation; women who have assisted reproduction due to a very recently diagnosed cancer, rather than developing a cancer as a result of assisted conception.

A significant reduction in the risk of developing any type of breast cancer was observed when the first 12 months of follow-up were excluded. This risk reduction was seen predominately in invasive breast cancers, and not in in-situ breast cancers.

Invasive breast cancer

Fortunately, no increased risk of invasive breast cancer was found in this cohort of 255, 786 women who has assisted reproduction in the UK between 1991 and 2010, when followed-up for an average of 8.8 years (range 1 year to 19 years). In fact, a slight reduction in risk, compared to age standardised population rates, which was not quite significant, was observed. The most likely explanation for this is the beneficial lifestyles of many women in this cohort in terms of risk factors for developing invasive breast cancer, such as reduced levels of smoking and possibly obesity, when compared to the general age standardised female population[51,231]. As above, excluding the first 12 months of follow-up meant that this trend towards a reduction in risk of invasive breast cancer in this population became significant. Given how long an invasive breast cancer usually takes to develop, this observation is mostly likely to represent lead time bias; invasive breast cancers which would have occurred anyway, being detected at a slightly earlier time due to the medical contacts and improved health-conscious attitudes which occur because of assisted reproductive treatments. It is also possible that this significant reduction may represent exclusion of breast cancer cases which were diagnosed immediately before ART and therefore reduction in bias due to reverse causation.

Excluding the first 12 months of follow-up is unlikely to exclude cancers caused by assisted reproduction. Breast cancer doubling time does vary with cancer sub-type, however, a recent prospective study showed a fastest doubling time of 77 days and an average doubling time of 174 days[232], meaning cancers caused or induced by assisted reproduction itself are unlikely to present in the first 12 months after treatment.

The only sub-group in this cohort who had increased risks of invasive breast cancer were those who had unrecorded cause of infertility. As this sub-group were observed to have increased risks of many types of cancer, this is discussed separately below.

In-Situ Breast Cancer

A small but significantly increased risk of in-situ breast cancer was observed in this cohort, compared to age-standardised population rates. The absolute excess risk was small (1.7 cases per 100,000 person years at risk (95% CI 0.2 to 3.2). A causal association, between risk of in-situ breast cancer and assisted reproduction is suggested by the 'does-response' type of association observed (increasing risk associated with increasing number of treatment cycles). However, if this relationship was truly causal, one would expect the overall risk of breast cancer to be increased in this cohort.

Other potential explanations for this increased risk of developing in-situ breast cancer include '*over diagnosis'* (a form of surveillance bias); cancers that may never have become symptomatic during a woman's lifetime, being detected because of increased medical contact due to assisted reproduction. This may also potentially explain the apparent dose response relationship. It is possible that a woman's own perception, and indeed their clinicians' perception, of the health risks associated with assisted reproduction may increase with the number of treatment cycles. Therefore, women who have had more treatment cycles may be more likely to undergo surveillance for breast cancer, (both through formal screening programs and informally).

The observed increased risk of in-situ breast cancer and its association with increasing number of treatment cycles may also potentially be as a result of confounding by socio-economic status. As most of the cycles included in our dataset were privately funded, those who had more cycles

might be of higher socio-economic status. Taylor and Cheng's relatively small cohort study of women with a breast cancer diagnosis found women of lower socio-economic status were more likely to have invasive disease, and women of higher socio-economic status more likely to have in-situ disease [233]. Whilst this type of confounding *could* conceivably be playing a role in this observed association, it seems relatively unlikely and this observed association remains largely unexplained.

No other studies in women after assisted conception examining invasive and in-situ breast cancers *separately* were identified. Therefore there are no other data with which to compare this finding.

A within cohort analysis looking at the risk of developing any breast cancer was undertaken to examine how age at first treatment affected the within cohort experience. No differences between women who had first treatment aged under 25 years and any other age group, nor with all other cohort members as a whole were observed.

Ovarian Cancer

More ovarian cancers were observed in this cohort of over a quarter of a million women who has assisted reproduction in the UK between 1991 and 2010, compared to age-standardised expectations, when followed-up for an average of 8.8 years (range 1 year to 19 years). This was both for invasive and for borderline ovarian tumours. Excess risks remained after sensitivity analysis, excluding the first 12 months of follow-up, though the increased risk of borderline ovarian tumours became non-significant.

The absence of an association between increasing number of cycles, time since last treatment and increasing risks is evidence against a causal relationship between ovarian cancer and assisted conception. The lack of increased risks in women who had assisted conception because of male factors only and those who had unexplained infertility is also evidence to dispute causation. In contrast, the highly significant trend towards increasing risk of ovarian cancer in individuals who were younger at first treatment does support a causal association.

As is the case with most of the other studied site-specific cancers, women with unrecorded cause of infertility have a significant excess of ovarian cancer. This is discussed below.

Invasive Ovarian Cancer and associations with known risk factors

The observed associations between female causes of infertility, particularly endometriosis and tubal disease, and all ovarian cancer risks were more pronounced when considering invasive ovarian cancer. Those who had assisted conception only due to male factor infertility, had no increased risk of invasive ovarian cancer. There was also a significant trend towards decreasing

risks of invasive ovarian cancer and increasing parity, those who remained nulliparous after completion of the last treatment cycle having the highest risk.

Endometriosis is a known risk factor for invasive ovarian cancer, particularly endometrioid and clear cell tumours[43,44]. Nulliparity is also a known risk factor for ovarian cancer, a significant inverse association existing between parity and risk[43,44].

As this study was not able to control for these known risk factors, and because initial results suggested that they were influencing multiple different analyses, results were stratified specifically for endometriosis, for the presence/ absence of at least one recorded birth and both of these factors combined.

Women who had no recorded birth at the end of treatment but did not have a diagnosis of endometriosis, had significant risk of invasive ovarian cancer. Women who had a diagnosis of endometriosis but had at least one birth recorded by the end of treatment had an even higher risk of ovarian cancer. The effect of these two risk factors combined appeared to be additive as the group of women who had both endometriosis and no recorded birth by the end of treatment had even higher risks of developing invasive ovarian cancer.

Importantly, women who had at least one recorded birth by the end of treatment and who *did not* have a diagnosis of endometriosis, did not have an increased risk of invasive ovarian cancer. Nor did they have an increased risk of *any* ovarian tumour.

Within cohort analysis further supports the association between ovarian cancer and endometriosis, more so as this increased risk was essentially unchanged when other causes of female factor infertility and parity are controlled for.

Within cohort analysis, investigating parity also supports a reduction in risk with an increase in parity, again this relationship remained when endometriosis, and other causes of female factor infertility were controlled for.

Within cohort analysis showed no association between risk of ovarian cancer and number of stimulated cycles. Again this is essentially unchanged when endometriosis, other causes of female factor infertility and parity are controlled for.

This combined evidence supports the theory that the main factor involved in the association between assisted reproduction and invasive ovarian cancer development is related to the existing characteristics of service users, and not the assisted reproductive treatments themselves.

Indeed, studies that were able to control for known confounders have tended to not observe increase risks of ovarian cancer[42,71,72,84], but when theses known confounders were not accounted for, significant associations have been observed[84]. A large, more recently published study investigating cancer outcomes in a cohort of 30,625 women who have had assisted reproductive treatments, in comparison to both the general population and to a cohort of sub-fertile women who were not treated, found an increased risk of invasive ovarian cancer (SIR - 1.43; 95% CI 1.18 to 1.71). However, once results were adjusted for the effect of parity, no increased risks were observed (aHR- 1.02; 95% CI 0.70 to 1.50)[234].

Unfortunately, this thesis did not have access to a sufficiently large comparable cohort of women, who did not have assisted reproduction in whom confounding variables were available, (*with or without subfertility*). Thus it was not possible to control for known risk factors. However, the considerable size of our cohort and the data available meant that it was possible to investigate confounding factors by stratification.

The significant association between decreasing age at first treatment and increasing risk was only seen in invasive ovarian cancer in women who had either or both known risk factors of endometriosis and nulliparity. This potentially represents a previously found association between development of endometriosis at an early age with increased risks of ovarian cancer [235].

Borderline Ovarian Tumours and associations with known risk factors

An excess of borderline ovarian tumours was observed compared to age-standardised expectation. This is in keeping with results from three other cohort studies from the Netherlands[83,234] and Australia[85]. Van Leeuwen et al. found the risk of borderline ovarian tumours significantly increased in a cohort of 19,146 women who received assisted reproductive treatments compared to 6,006 sub-fertile women who did not have such treatment (SIR 1.76; 95%CI 1.16 to 2.56)[83]. This increased risk remained when age, parity and subfertility cause were adjusted for[83]. The same group have recently published a larger study[234], and have observed a larger increased risk in borderline ovarian tumours when compared with both the general population (SIR 2.20; 95%CI 1.66 to 2.86) and to a cohort of sub-fertile women who were not treated (HR 1.84; 95% CI 1.08 to 3.14)[234].

Stewart et al.'s population cohort study in the state of Western Australia found an increased rate of borderline ovarian tumours (HR 2.46; 95%CI 1.20 to 4.37). However this study did not

find that the rate was increased in women with endometriosis and they did not observe the protective effect of birth[85]. These results are in slight contrast to some of results observed in this current cohort.

This thesis founds increased risks of borderline ovarian tumours associated with a diagnosis of endometriosis (in parous women) and to a lesser, but still significant extent, with nulliparity (in women without endometriosis). The effects of these potential risk factors were not additive; the risk of borderline ovarian cancer in women with both nulliparity and endometriosis was not raised in comparison to age-standardised expectation. Additionally, the association between development of borderline ovarian cancer and decreasing age at first treatment was present in both women who had endometriosis and/or nulliparity and in women with neither of these factors. These results suggest that whilst endometriosis and nulliparity might be influencing the development of borderline ovarian cancers to some degree, there are also other factors influencing this association.

The increased risks of borderline ovarian cancer may be the result of a causative association with ART. However the lack of dose response provides evidence against this. The lack of a dose response relationship was also a feature of the increased risks of borderline ovarian tumours found by the recently published cohort from the Netherlands[234].

Other explanations for this observed excess risk may be related to surveillance bias. Ultrasound screening has been shown to increase the frequency of borderline ovarian tumour diagnosis[236]. Women who have undergone assisted reproduction are likely to have pelvic ultrasounds more frequently than the age-standardised general female population. Such surveillance bias causing excess borderline ovarian tumours is suggested, to some degree, by a reduction in risk, such that

risk became non-significant after the first 12 months of follow-up were excluded. However, sensitivity analyses in other studies suggest surveillance bias as an unlikely explanation for observed increased risks[83,85]. It was not possible to further differentiate a genuine increase from surveillance bias as a cause for the increased risk of borderline ovarian tumours in this cohort.

Corpus Uteri Cancer

The overall risk of corpus uteri cancer was not increased in this cohort of over a quarter of a million women who has assisted reproduction in the UK between 1991 and 2010, when followed-up for an average of 8.8 years (range 1 year to 19 years). There have been a few previous studies specifically investigating the association between assisted reproduction and uterine cancers. Most of these studies recorded only a handful of cancer events[71,73,74]. Two of the largest studies published have recorded 49[76] and 15[72] endometrial cancers occurring in women who have had assisted conception. Both of these studies suggested no increase in overall risk of endometrial cancer in this cohort. This thesis included 164 cases of uterine cancer in exposed women.

Women who had any female factor cause of infertility had an increased risk of uterine cancer. This appears to be largely driven by an increased risk in women who were diagnosed with an ovulatory disorder. This is likely due to the fact that the majority of women who have assisted reproduction and have a diagnosis of an ovulatory disorder are likely to have polycystic ovary disease (PCOD). PCOD is a known risk factor for corpus uterine cancer, specifically endometrial cancer[63] (65% of all corpus uteri cancers in the cohort were endometrioid).

A significant excess of uterine cancer cases were found in women who did not have a live birth recorded by the end of the last treatment cycle, compared to age-standardised expectation.

Women who had one or more live births recorded by the end of the last treatment cycle had a significant reduction in the risk of corpus uteri cancer. These findings are in line with previous research; nulliparity is a known risk factor for corpus uteri cancer and conversely, parity is a known protective factor[62,237].

A highly significant trend was observed between increasing duration of infertility and increasing risk of corpus uteri cancer. Interpreting this result is challenging. Duration of infertility does not appear to be acting as a proxy for increasing age (a known risk factor[67]); there is no observed association between age at first treatment and risk, nor between time since last treatment and risk.

Obesity is also a known risk factor for endometrial cancer[237]. Unfortunately we were not able to control for this. As mentioned above, although obesity is associated with infertility and indeed can often be associated with PCOS, most women who undergo assisted reproduction exercise regularly[51] and in the UK at the time of this study, women had to have a BMI of less than 30 to qualify for NHS funding of their treatment. Therefore it is likely, but not certain, that not controlling for body mass index may have caused an underestimation of results, (however if this cohort has a higher average BMI than the UK age-standardised female population, not controlling for BMI would cause an overestimation of results).

Other known risk factors for corpus uteri cancer, and particularly for endometrial cancer include age at menopause and age at last birth[67]. As women in our cohort are likely to be both younger at age of menopause and older at age of first birth, not controlling for these factors is likely to mean our results may be an underestimation of the true risks.

As is the case with most of the other cancers investigated, women with unrecorded cause of infertility have a significant excess of corpus uteri cancer.

Unrecorded cause of Infertility

Women who had an unrecorded cause of infertility in this cohort, were found to have increased risk of breast, ovarian and uterine cancers. As this appeared unusual, further analysis of this group was undertaken. Compared with the average experience of the study cohort as a whole, these women had assisted reproduction more recently, were older at first treatment, had a shorter duration of infertility, fewer treatment cycles and had more 'freeze all' cycles (though data on 'freeze-all' cycles was limited).

This sub-group also had vastly increased risks of having a cancer diagnosed within the first 12 months of treatment; the proportion of women with a cancer diagnosed in the first 12 months of follow-up in this sub-group was 45.7%, compared to 6.7% in the total cohort). Thus excess cancer risks observed in this sub-group may in fact represent bias due to reverse causation; that is women in whom cancer or its treatment results in the need for assisted reproduction, rather than cancer arising as a result of assisted reproductive treatment. The fact that significantly increased risks of breast cancer, specifically invasive cancer, were not observed after exclusion of the first 12 months of follow-up suggests a significant degree of reverse causation in this sub-group. HFEA data collection forms during the study period did not include cancer or cancer treatment as a recordable cause of infertility. Thus, it is likely that most women who had ART due to cancer treatment did not have a cause of infertility recorded.

This study aimed to reduce possible bias due to reverse causation by excluding women in who a cancer diagnosis was recorded in years prior to the year of first treatment. However, the lack of precise treatment dates meant that it was not possible to exclude women who had cancer in the same calendar year as, but in the months before, their first assisted reproductive treatment. The fact that some results, such as the risk of developing any type of ovarian cancer, remained

significant even after excluding the first 12 months of follow-up, means that there may also be further unknown causes for observed increased risks in this small subgroup.

Strengths of this study

Most previously published studies investigating risks of breast, ovarian and corpus uteri cancer in women who have had assisted reproduction are relatively small[70,73] and/or have short duration of follow-up[76], with relatively few cancer events[72,74]. Two of the largest previously published studies were undertaken by Luke et al[76] and Brinton et al[72]. Luke et al investigated cancer outcomes in 113,226 women after assisted reproduction treatments across three US states. However results were concentrated on a sub-population of 53,859 in whom data relating to their first assisted conception status was recorded[76]. Follow up in this study was for an average of 4.87 years[76]. Brinton et al investigated cancer outcomes in a cohort of 87,403 women, 67,608 of whom had had some kind of fertility treatment[72]. Whilst the follow up for this study was longer (8.1 years on average), the study included 41, 45 and 522 cases of ovarian, endometrial and breast cancers respectively. This compares to 405*, 164 and 2,578 cases respectively in this thesis.

The large size of the current study, including 255,786 women who have had assisted conception, not only means that risk estimates can be given more precisely but also that the risk of type 2 errors is minimised. This is particularly important as some of the outcomes being investigated are relatively rare. Therefore relatively large cohorts are needed to ensure that the number of events are large enough to produce robust risk estimates.

* This includes 264 cases of invasive ovarian cancer and 141 borderline ovarian tumours.

The large sample size also means that this study is able to investigate results in some subgroups; for example risk of ovarian cancer in sub-cohorts of women with and without endometriosis, nulliparity and both.

Whilst the average follow-up in this cohort was 8.8 years, 105,436 women were followed up for at least 10 years and 65,000 person-years of follow-up was at least 15 years beyond the date of last treatment.

This study also had a very high % of successfully linked records, over 95% of all eligible records. Linkage validation exercises estimated linkage error in this study to be low (<0.02%). Extensive data validation processes in the final linked cohort additionally identified 3 linkage errors and these records were excluded. Thus whilst potential linkage errors may have occurred, this study can confidently report the rate of such potential errors is likely to be very low.

Limitations and potential sources of bias

Whilst the follow-up period was reasonable compared to many other published studies, the average age at the end of follow-up was 43.3 years old. This means that most of the cohort have not yet reached the age when most reproductive cancers usually occur[57,67,238]. Therefore the possibility of different risk profiles for any of the cancers studied cannot be excluded. This is a significant limitation as the peak incidence of all cancer studies occur beyond the age of 43 years. Therefore it is important that further studies investigate the risk profile of similarly exposed women through and beyond the ages where the peak incidence of these cancers occur.

Whilst there is a lot of information about the reproductive demographics of this cohort, not all relevant information is available. For example, this study was not able to investigate or separate some known risk factors for ovarian cancer from other potential effects. These known risk factors include age at menarche, age at menopause and use of oral contraception. Increasing age at menopause increases invasive ovarian cancer risk[44]. This cohort is likely to have, on

average, a lower age of menopause than the general female population. Therefore not controlling for this confounder is likely to underestimate results. It is slightly harder to speculate what the effect oral contraceptive use might have on ovarian cancer risk in this cohort. Oral contraceptive use decreases the risk of developing invasive ovarian cancer[44]. Women who intentionally delay conception, many of whom do so using oral contraception, may make up a substantial proportion of this cohort. However, infertility by its very definition means that these women are not currently using contraception and are not likely to have used this for some time. If the first situation is predominant within the cohort, not controlling for oral contraceptive use would produce an underestimation of true risk. If the second situation is predominant, not controlling for oral contraceptive use would result in an overestimation of true risk. Unfortunately it is not possible to disentangle the effects of such potential confounding factors further.

Other potentially important demographics such as smoking status, body mass Index and socio-economic status are also not available. Therefore it is not possible to investigate the potential effect of these factors.

Some cohort studies have been able to compare the cohort experience to that of an external cohort of women who have a degree of sub-fertility, but who have not been treated with assisted reproductive therapies [72,83,234]. These comparisons have the advantage of controlling for some known and potentially unknown confounding factors, as the populations being compared are more likely to have similar demographics and background characteristics than exposed women with the general age-standardised female population. This kind of comparison has advantages, however, it is not without its own inherent selection bias, particularly related to the factors which influence which women with subfertility go on to have assisted conception and which women do not.

The large sample size of this study enabled stratification by certain confounders. In this way, it was possible to further investigate observed associations and draw some conclusions from this. Indeed, the conclusions reached about the cause of increased risks of invasive ovarian cancer were very similar to those reached by a subsequently published study which did include a cohort of untreated infertile women[234].

Another potential limitation related to the use of the general population as a comparator, is that comparison rates also include the exposed cohort, in this case, women who have had assisted reproduction within the study timeframe in the UK. Jones and Swerdlow have previously modelled this effect to estimate the degree of bias in different circumstances[239]. They estimate that this type of bias only results in substantial underestimation of risk when the prevalence of exposure in the population as a whole is large, or the incidence ratios are large, or both[239]. As ratios tended to be less than 2.0 in this study, and less than 5% of the general female population had assisted reproductive treatment during the study period, this type of bias is likely to have been minimal[239].

Overall, the available HFEA database population for the entire study period represents approximately 93.7% of the at-risk source population. The vast majority of the 'missing' population had ART in 2010, immediately after prospective consent was brought in (It is estimated that at few as 22.5% of treated women during this year are included in this study. As this cohort accounts for less than 1% of person-years of follow up, this is not considered a large source of bias. However, in retrospect it might have been better to exclude this year completely from this study.

The lack of intermediate dates to allow time dependent analysis of certain factors is a limitation of this study. Therefore we are not able to properly identify any non-linear time dependent associations in our data. In order to continue to use variables that would ideally be analysed as

time-dependent, this study uses such variables at the point at which they cease to change. For example, number of live births becomes a static variable when number of pregnancies at date of last treatment is used; Number of stimulated cycles becomes static when total number of stimulated cycles are used. Expressing these variables in a such a static manner means that for analyses to be correct, time at risk for each cohort member has be started from the date when the variable became static (in this case, end of last recorded cycle).

Additionally, some of these time dependent variables, for example number of live births also have the potential to change post-treatment. Therefore this study is limited by the fact that it was not possible to account for this. Future studies, for example linking to all birth records, should consider if it is feasible to try to take this into account.

Women who had a diagnosis of cancer in years prior to the year of first treatment were excluded. However, the lack of precise treatment dates meant that dates of treatment are considered to be the midpoint of first treatment year. This mainly caused problems relating to the cohort of women who had a cancer diagnosis prior to, but in the same year as their first assisted conception cycle. Whilst it was not possible to exclude this cohort, undertaking a sensitivity analysis, excluding the first 12 months of follow-up showed that this generally was not a big issue, except within the cohort of women with an unrecorded cause of infertility.

Further information about infertility diagnoses may have been beneficial in this study. For example, in order to interpret risks relating to uterine cancer in women with ovulatory disorders, it has been assumed that most women in this sub-cohort had a diagnosis of PCOS (suggested by Dr Melanie Davis (study collaborator, HFEA advisory board member and assisted conception specialist)). However, it would have been useful to have reliable data about this. Additionally, data relating to types of ovarian stimulation used would have been valuable. However ovarian stimulation regimens used in assisted reproduction did not change substantially over the study 19 year study period. Gonadotrophins and human chorionic gonadotropins were generally used

for ovarian stimulation and to trigger ovulation respectively throughout the study period. New, recombinant and highly purified versions were used in the latter years of the study period, but these are essentially equivalent. Other treatments have been used in the years before and the years after the study period; Clomiphene citrate was no longer routinely used for ovarian stimulation in assisted conception by 1991 and gonadotrophin releasing hormone agonists, used in down-regulation cycles were not generally replaced by antagonists until after the end of the study period. Progesterone support has been used throughout the study period.

Information about the number of eggs collected per cycle, and thus by proxy the number of ovarian punctures per cycle may also have been very useful to further investigate mechanisms that may, or may not, lead to the development of ovarian tumours. Unfortunately this data was not available.

Limited data relating to pre-implantation genetic diagnosis (PGD) was available. However the indication for this procedure was not. Therefore it was not possible to exclude women who had PGD because of genetic pre-disposition to reproductive cancers (for example due to the BRCA gene). Whilst there may have been a few cases in this cohort, this is unlikely to have been a significant cause of bias.

The Human Fertility & Embryology Authority started collecting data about assisted conception cycles in 1991 for regulatory purposes. The initial intention was not to use this data for research. Therefore data was not always collected and aggregated in ways that benefit research. For example, no information was collected about how infertility diagnoses were made. In some instances data collection sheets were quite misleading. This was definitely the case relating to data about pregnancies and births for certain years. Extensive data cleaning of all study variables identified this problem and data which appeared inconsistent were treated as missing (see

chapter 2). Errors like these were hopefully all identified during the data cleaning process, however we cannot be certain that this is the case for all such data collection errors.

Finally, missing data was a limitation in this study. Missing data relating to participant or treatment characterises were deal with by creating 'unrecorded' categories which were also analysed. Duration of infertility and infertility cause are the only main variables with a significant proportion of missing data (*see table 15*). Missing or incomplete outcome data was relatively rare in this cohort and was dealt with on a case by case basis (*see Chapter* 2). There were also problems relating to missing comparator rates. For example at the time of analysis, national rates for breast, uterine and ovarian cancers were not available for 2009, 2010 and 2011. Therefore trends for surrounding years were considered and, in the example given above, rates for 2008 were used as a proxy. Now that these rates have been published, it can be seen that rates did not change substantially for any analysed cancer from 2008 to 2011 [57,67,238].

Cancer in children born after non-donor assisted conception

This study, the largest of its kind at the time of publication[3], showed no overall increased risk of cancer in 106,013 children born after assisted conception in Great Britain (1991-2010), when followed up for an average of 6.6 years, (SIR 0.98; 95%CI 0.81 to 1.19). No significant excess or reduced risks were observed when results were stratified by available mediating and moderating factors such as birth weight, gestation, multiple birth, fresh vs cryopreserved embryo transfer, maternal parity, parental age at birth and cause of parental infertility.

These results contrast, to some degree, with previous studies. For example, a previous systematic review and meta-analysis showed a small significant increased risk in the overall risk of cancer in children born after assisted conception (RR 1.33; 95%CI 1.02 to 1.98) particularly leukaemia and neuroblastoma[240]. This is very similar to the meta-analysis in *chapter 1*, (SIR 1.32; 95%CI 1.09 to 1.55). The difference in results between these meta-analyses and this study may be because a number of smaller studies, (and even some case-control studies), are included in the meta-analyses and thus they could include systematic bias. Even a relatively large single study, published before these results, which also showed a small significant increased risk of cancer, (OR 1.34; 95%CI 1.02 to 1.76), still included few exposed cases[201]. However, despite not showing an increase in overall cancer risk, the results of this current study may not be in complete contrast to previous studies as the confidence intervals all overlap.

Two large population based studies, with somewhat similar methodology and published shortly after this study, have similar results[241,242]. The committee of Nordic ART and safety (CoNARTaS; a collaboration of Nordic researchers, studying long-term safety outcomes of assisted reproduction in Denmark, Sweden, Norway and Finland), included 91,796 children born after assisted conception in a record linkage study comparing rates of childhood cancer to that observed in a matched control group, (4:1, controls to exposed cohort members)[241]. They found no significant difference in cancer risk between the two cohorts (aHR 1.08; 95%CI 0.91 to 1.27;

adjusted for country, maternal age, parity, sex, gestational age and birth defects)[241]. Whilst our study includes more children born after assisted conception, the CoNARTaS study had an average follow-up of 9.5 years and was conducted over a 25 year period, compared to 6.6 years average follow-up, with a maximum of 15 years follow-up, over a 17 year time period in this current study[3,241].

Spector et al published another similar population based cohort study of 275,686 children born after IVF in 5 US states, comparing observed rates of cancer to that seen in a control group (10:1 controls to each child born after IVF)[242]. They too found no significant difference in overall cancer rates between exposed and control groups (aHR 1.17; 95%CI 1.00 to 1.36), though their results were closer to an overall significantly increased risk than either our study or the CoNARTaS study[3,241,242]. This borderline overall increase was largely driven by an increase in hepatic cancer, (HR 2.46; 95%CI 1.29 to 4.70; mainly hepatoblastoma)[242]. They included a larger cohort of children born after assisted conception than this thesis, but had a shorter duration of follow-up (between 4.5 and 4.7 years on average)[242].

In addition to these two large population-based studies, a number of smaller studies have also been subsequently published[243,244]. Hargreave et al. undertook a retrospective cohort study investigating cancer in children born after maternal fertility treatment, including 37,156 children born after assisted conception, comparing cancer incidence to that occurring in a cohort of children whose mothers did not have fertility treatment, adjusting for year of birth. The study concluded an increased risk of cancer overall in children born after frozen embryo transfer, (n=14 cases in a cohort of 3,356 children; HR 2.43; 95%CI 1.44 to 4.11)[243]. This compares to no increased risk of cancer seen in our cohort of 12,554 children born after frozen embryo transfer (15 cancers observed, vs 12.22 expected; SIR 1.24; 95% CI 0.69-2.04). Spector et al considered cancer rates in children born after frozen embryo transfer and did not find any excess of cancer overall in this group (HR 1.06; 95%CI 0.79 to 1.42)[242]. Sundh et al also included a larger cohort of

children born after frozen embryo transfer than Hargreave et al, (n=8,042)[241]. Though they did not compare rates of cancer in children born after frozen embryo transfer to those born after spontaneous conception, specifically they found no significant association between the mode of conception (fresh IVF, fresh ICSI or frozen embryo transfer) and cancer (*P*=0.62)[241].

Spaan et al compared cancer risk in 24,269 children born after assisted conception to that observed in 13,761 children born after spontaneous conception, 4,181 children born after non-ART fertility treatment and another cohort of 5,479 (non-ART conceived, but unclear if born after spontaneous conception or other fertility treatments)[244]. No increase in overall cancer rates were found in children born after assisted conception compared with either children born to after spontaneous conception to infertile parents, (HR 1.00; 95% CI 0.72 to 1.38) and with the general population, (SIR 1.11; 95%CI 0.90 to 1.36) after a median follow-up period of 21 years. They found a non-significantly increased risk of cancer in cryopreserved embryos, (aHR 1.08; 95%CI 0.65 to 4.95), but this was based on four events[244].

There are a number of possible causes for the differences in findings between these five studies. Firstly, the larger three studies[241,242], (including those from this thesis[3]), have results based on higher numbers of cases in much larger cohorts than the studies by Hargreave[243] and Spaan[244]. This suggests the possibility that findings of increased cancer risk in children born after frozen embryo transfer may be chance findings, particularly as results from Spaan[244] are non-significantly raised. However, the studies by Hargreave and Spaan have longer duration of follow-up than those of Sundh, Spector and this current study, (21years[243] & 11.3years[244] vs. 9.5years[241], 4.5 years[242] and 6.6 years[3] respectively). It is at least possible that increased risks, including those relating to frozen embryo transfer, may only become evident into adolescence and young adulthood.

Hepatoblastoma

Spector et al.'s observation of a significant excess of hepatoblastoma cases[242] mirrors results from this thesis, (SIR- 3.64; 95%CI 1.34 to 7.93)[3]. A previous, case-control study, including 58 affected children, suggested an association between parental infertility and the development of hepatoblastoma (relative risk (RR) 9.2; 95%CI 2.1 to 31.5)[245]. However, only one of the 58 children were confirmed, and 5 more suspected, to have been born after assisted conception[245]. Data from this case-control study was subsequently re-examined, using further telephone interviews[246], and by combining this data with that from similar US case-control studies[247]. Both re-evaluations provided evidence that this apparent association may be mediated by the known risk factor of low birth weight[246-249].

Spector et al did not adjust their results for low birthweight as they argue that birthweight and gestational age could be on the causal pathway between assisted conception and increased cancer risk[242]. Indeed, in our current study, low-birth weight appeared to be a strong mediating factor between assisted conception and the development of hepatoblastoma. An excess of hepatoblastoma was observed in children with a birthweight <2500g, (SIR 10.20; 95% 3.31 to 23.81), but not in children with birthweights ≥2500g, (SIR 0.95; 95%CI 0.02 to 5.28 for children with birthweights ≥2500g to <4000g and SIR 0.00; 95%CI 0.00 to 32.00 in children with birthweights ≥4000g). Infants with extremely low birth weight had the greatest risk of developing hepatoblastoma (SIR 51.31; 95%CI 6.2 to 185.3). Children born after assisted conception have consistently been shown to be at higher risk of having both low birthweight and lower gestational age at birth compared to children born after spontaneous conception[33,103].

The CoNARTaS study did not observe a significant increased risk in hepatic cancer, though they found a non-significant increased risk (HR 2.16; 95% CI 0.74 to 9.26). They did not adjust for birthweight, but did adjust for gestation, (largely collinear variables). However adjustment for

gestation (as well as maternal age & parity, country of birth, birth & chromosomal defects), made no material difference to this result[241].

The apparent increased hepatoblastoma risk associated with high order births and low gestational age in this thesis are likely to represent collinearity with low birthweight. Association between hepatoblastoma and fresh embryo transfer, maternal age 30-39 years and no previous live births are also not particularly surprising; they are likely to represent the overall increased risk, as these categories contribute a greater percentage of person-years at risk than other sub-categories. The age at diagnosis seen in this thesis was perhaps slightly higher than expected as most cases of hepatoblastoma present within the first year of life[250]. It is hard to explain why children whose parents had unexplained fertility should have an increased risk of hepatoblastoma. This may be a chance finding.

Importantly for families, the absolute excess risk of hepatoblastoma detected by this thesis was very small (AER 6.21 cases per million person-years at risk).

Sarcoma's including Rhabdomyosarcoma

Cohort members developed bone and extra-osseous sarcomas in significantly greater numbers than expected. This was predominantly, but not exclusively, due to an excess of rhabdomyosarcoma; non-significant excess risks of osteosarcoma, Ewing's sarcoma, and other sarcoma's, were observed.

The absolute excess risk of Rhabdomyosarcoma was small, 8.82 cases per million person-years at risk. Risks did not differ significantly according to birthweight, gestation or age at diagnosis. Excess risks in children whose mothers had no previous live births and those whose mothers were aged 30-39 years at the time of birth are likely to represent the overall increased risk as these sub-categories contributed the largest proportion of person-years at risk compared to other sub-categories.

Increased risks of rhabdomyosarcoma in higher order births are difficult to explain as twins have been shown to be less likely to develop cancer overall than singletons and other factors associated with high order births such as low birthweight are not known to be risk factors for the development of rhabdomyosarcoma[247,251].

An excess of rhabdomyosarcoma was observed in children born to older fathers. Increased morbidity and mortality has been associated with advanced paternal age by previous studies[252]. This includes a number of studies suggesting an increased risk of leukaemia in children born to older fathers, and a potential increase in retinoblastoma risk[252,253]. There is no previous evidence linking rhabdomyosarcoma to older paternal age at birth to the knowledge of this author.

It is also difficult the provide explanation for those whose parental cause of infertility was not recorded. This may be a chance finding.

A non-significant excess of soft tissue sarcoma's (mainly rhabdomyosarcomas) was also detected by Spector et al (HR 1.50; 95%CI 0.81 to 2.84)[242].

Previous studies have reported an excess of imprinting disorders in children born after assisted conception, caused by epigenetic anomalies, (most commonly loss of methylation at the KvDMR1 locus within the region KCNQ1)[110,131,254-257]. Imprinting disorders in general are known to be associated with the development of specific types of cancer, including Wilms' tumour, hepatoblastoma and rhabdomyosarcoma[258]. Aberrations of KCNQ1 causing Beckwith-Wiedemann syndrome, has specifically been linked to increased risks of developing both hepatoblastoma and rhabdomyosarcoma, but not to developing Wilms' tumour (often more commonly associated with Beckwith-Wiedemann's syndrome caused by either uniparental disomy or hyper-methylation of a different region of the same gene)[142].

None of the 16 children who developed a rhabdomyosarcoma or a hepatoblastoma in this current study had a diagnosis of an imprinting disorder, or even of a co-morbidity which might be consistent with a diagnosis of an imprinting disorder. Therefore, if the association between rhabdomyosarcoma and/ or hepatoblastoma and being born after assisted conception noted in this thesis is being mediated by imprinting disorders, then either these imprinting disorders are undiagnosed subclinical presentations, or they were not reported by their treating physicians, which seems unlikely given the known high quality of the NRCT data[228] .

Other types of childhood cancer

This thesis found no significant excess risk of all other types of childhood cancer, including leukaemia, CNS tumours and retinoblastoma in 106,013 children born after assisted conception in Great Britain (1991-2010), when followed up for an average of 6.6 years.

A number of studies have reported an increased risk of Leukaemia[201,240,243,259,260]. A systematic review of 25 cohort and case-control studies published before September 2012 found a significant raised risk of any haematological cancer in children born after medically assisted reproduction, (RR 1.59; 95%CI 1.32-1.91; medically assisted reproduction also includes children born after non- ART fertility treatment such as ovulation induction; results remained significant when restricted to children born after assisted reproduction only) [240]. The largest cohort study to be included in this review found 18 cases, compared to 12.3 expected in a cohort of 26,692 exposed children (RR 1.46; 95%CI 0.87 to 2.13)[201]. Whilst this study was population-based and used reliable registry data, other cohort studies included in the systematic review used hypothetical cohorts and were not strictly population based[240]. The largest case control study to be included in this review to consider leukaemia as an outcome included 24 exposed cases[259]. Their results included some overlapping data with the above study; excluding overlapping data they found non-significantly raised risks (RR 1.66; 95%CI 0.82 to 3.37)[259]. The controls for this study were hospitalised children with non-cancer diagnoses. This control group may not be representative of the general population. The bias this may cause, in addition to the effect of consent bias, may lead to less reliable results.

A number of recent moderate sized cohort studies, have also found increases in leukaemia in children born after assisted conception. Reigstad et al, found an increased risk of Leukaemia in a registry based population cohort study, including 25,782 children born after assisted

conception in Norway (HR 1.67; 95%CI 1.02 to 2.73)[261]. Spaan et al found a non-significantly raised risk of acute lymphoblastic leukaemia in their long-term cohort of children born after assisted conception (HR 2.44; 95%CI 0.81 to 7.37; based on 17 exposed cases; see above for full study description)[244]. Hargreave et al found a significantly increased risk of leukaemia in children born after frozen embryo transfer, based on 5 cases in a cohort of 3,356 exposed children (HR 2.87; 95%CI 1.19 to 6.93)[243]. This thesis did not find an increased risk in this group (SIR 0.48; 95%CI 0.06 to 1.74). However this is based on only two exposed cases compared to 4.14 expected.

Conversely, this thesis found no excess of leukaemia (SIR 0.91; 95%CI 0.63 to 1.27; based on 34 exposed cases, vs. 37.5 expected)[3]. Similarly, other very large population based cohort studies also found no increased risk (Spector et al., HR 0.93; 95%CI 0.70 to 1.22; based on 93 cases[242]; Sundh et al., HR 1.06; 95% CI 0.80 to 1.41; based on 61 cases[241]).

The studies which suggested an increased risk of leukaemia were either relatively smaller good quality population based cohort studies[201,243,244,261], or included potentially biased data from case-control studies or hypothetical cohorts[243,259]. Studies which did not find increased risks, including this thesis, tended to be based on more exposed cases from much larger population based cohorts[3,241,242], theoretically resulting in more robust risk estimates. As discussed above, these larger population based cohorts tended to have a slightly shorter duration of follow-up than the slightly smaller cohort studies. However, it would be difficult to imagine that duration of follow-up would have a significant effect on leukaemia risk as the peak incidence for leukaemia is 0-4 years of age, and all studies had a longer average duration of follow-up than 4 years[262].

The CoNARTaS collaboration found a significantly increased risk of cancer of the central nervous system (aHR 1.44; 95%CI 1.01 to 2.05; based on 42 exposed cases)[241] . This excess was also seen in an earlier cohort study in Sweden (15 CNS tumours compared to 8 expected; RR 1.85; 95%CI 1.04 to 3.05)[201]. Most, if not all, cases reported by the earlier study are likely to be included in the latter study. A systematic review also reported an excess of CNS tumours that just reached significance, (RR 1.88; 95% CI 1.02 to 3.46), but again this conclusion is largely based on the same data[240].

This thesis did not observe increased risks of central nervous system tumours (SIR 0.85; 95% CI 0.54 to 1.29; based on 22 exposed cases). No significant excess was seen in the largest similar study to date (HR 1.26; 95%CI 0.89 to 1.79; based on 59 exposed cases[242]). Other slightly smaller cohort studies similarly did not find an excess of this type of tumour (aHR 0.29; 95%CI 0.47 to 1.79[261]; SIR 0.97; 95% CI 0.57 to 1.53[244]; HR 1.22; 95%CI 0.79 to 1.89[243]).

Strengths of study

The main strength of this study are similar to the strengths of the women's section of this thesis, namely is its large sample size and its use of high quality data from two population based databases. The HFEA have a legal duty to collect data relating to assisted conception cycles, including relating to offspring born as a result. Thus population coverage throughout the study population was assumed to be almost complete, though the amount of missing data did significant increase from 2010 onwards when patients were asked prospectively for consent to use their data for research, (both identifying data and anonymous data). The NRCT is also a high quality database and is considered virtually complete[228].

Whilst there were difficulties posed linking these two datasets, (namely the lack of a unique identifier common to both datasets), the linkage protocol used was robust and exhaustive, designed to be inclusive, particularly where data was missing or there was any suspicious of data errors.

Therefore, the author is confident that any child born after assisted conception in England, Scotland or Wales between 1992 and 2008, and whom developed cancer before the sooner of their 15th birthday or 31st December 2008, is extremely likely to have been identified by this study.

Robust risk estimates with high levels of precision were possible given the large sample size of this study. Risk estimates were also broadly similar to those published by two equally large population based studies, which is reassuring[241,242].

Limitations and potential sources of bias

The lack of a suitable control group with data on mediating, moderating and confounding factors was a significant limitation to this study, as was the case with the woman's cancer section of this thesis. This meant that it was not possible to adjust analyses for these variables. In some cases this may be a significant limitation. However some previous studies, investigating cancer in children after assisted reproduction, have shown that adjusting analyses for a number of potential confounding factors did not significantly affect results; these include maternal age[201,243], paternal age[243], maternal smoking[201,243], maternal body mass index[201], maternal educational level[243] and previous maternal cancer[243] . Whilst is was not possible to adjust analyses, it was possible to investigate a variety of moderating and mediating factors by stratification, given the large cohort size. For example this study was able to investigate the effect of singleton verses multiple births, birth weight and premature delivery, all of which are known or suspected to affect cancer risk in this population [245,248,251].

This study did not have data about other potential confounding factors such as respiratory diagnoses, previously shown to have a possible effect on cancer development among a previous cohort[201]. However, only three of the 108 children who developed cancer in this cohort had a respiratory diagnosis, and thus it is unlikely adjusting for this factor will have had any material effect on results.

This study also did not include a cohort of children born to parents with similar characteristics but who were spontaneously conceived; for example born to parents with infertility/ subfertility diagnoses but whose children were born after assisted conception. The benefit of this type of comparison cohort would be to control for unknown, subtle or complex confounding factors, particularly relating to parental characteristics.

This study was not able to censor for the competing risks of death and emigration in this cohort, which are likely to be small. An estimated 600 members of the cohort, (0.6%), would have died during the study period, under normal circumstances, (extrapolating from national data for survival to 15 years of age)[263]. Estimating of the numbers lost to follow-up due to emigration is slightly more difficult. It would be reasonable to assume that not more than 2% of this cohort emigrated during the study period. There is no specific reason, nor any evidence, to suggest that these competing risks occur at a greater frequency in children born after assisted conception than in spontaneously conceived children.

This study used NRCT cancer registrations to calculate expected incidence of cancer in the cohort. Therefore, comparison rates also include children in the exposed cohort. It was not possible to calculate comparator rates for spontaneously conceived children alone, as there were no information about emigration and deaths. As this cohort represents less than 5% of the general population over the study time period, (children born after assisted conception accounted for approximately 0.5% of births in 1992 and 1.8% in 2008), and incidence ratios tended relatively low, in most, but not all comparisons, bias resulting from this is likely to be minimal[239].

This study had a follow-up of only 6.6 years on average, shorter than the CoNARTaS study[241]. As the peak age at diagnosis for multiple types of childhood cancer occur before 6.6 years of age, this study is able to provide good evidence that risks of these types of childhood tumour are not increased in children born after assisted conception compared to the general population of Britain. This includes leukaemia and several types of embryonal tumours. However, for tumours which have a peak incidence beyond 6.6 years of age, (including Hodgkin's lymphoma and bone tumours), this study provides less certain risk estimates.

In addition, the shorter duration of follow-up for children born towards the end of the study period means that if there were to be a trend related to later study years, this might have been overlooked or misinterpreted.

Cancer in children born after donor assisted conception

No increase in overall cancer risk was found in this, the largest study, to the best of the author's knowledge, investigating cancer risk in children born after assisted conception involving donor gametes or donor embryos. Children born after donor assisted conception who subsequently developed cancer had broadly similar demographics to those who did not develop cancer. Stratifying for potential modifying and mediating factors such as sex, age at diagnosis, birthweight, multiple births, maternal parity, type of ART and fresh vs. frozen cycle, did not significantly alter results.

More hepatoblastomas were observed than expected, (SIR 10.28; 95%CI 1.25 to 37.14), and as with the cohort of children born after non-donor assisted conception, there is evidence to suggest that this increased risk is mediated by low birth weight. Low birth weight is a known risk factor in the development of hepatoblastoma[247,248] and has been a consistent finding in children born after assisted conception[33,103].

Strengths, limitations and potential sources of bias

This, novel study, is relatively large, given the fact that donor assisted conception is less common than non-donor assisted conception. It utilises the same virtually complete and high quality databases as the study investigating cancer risk in children born after non-donor assisted conception. Whilst the study author was not able to undertake the linkage directly, it was possible to oversee the process anonymously (study author was present throughout the linkage phase). As with the main childhood cancer linkage, the author is confident that the

completeness of the databases and the robust and exhaustive linkage protocol has resulted in the vast majority, if not all, potential cases being identified. A sensitivity analysis, including two records which were unanimously rejected as being exposed cases by the study authors, showed no difference in results and is an additional strength of this study.

Results for this study reflected those observed in the main study, however, the smaller numbers of events resulted in wider confidence intervals and a lesser degree of precision and certainty surrounding risk estimates. Smaller numbers also meant that stratification by potential mediating and moderating factors was significantly less robust and resulted in very wide confidence intervals in some sub-analyses.

What I have learnt from this thesis

Undertaking these studies has been a very big challenge for the author and for the wider team. I have obviously furthered my knowledge substantially about assisted reproduction techniques, and about the specific cancers studied, including aetiology & disease courses, risk factors, and disease classification.

I have also learnt a great deal about linkage methods, including that very high and reliable match rates can be achieved when several different linkage methods are combined, even when identifiable variables available are not always ideal. Additionally I have also learnt also about the HFEA dataset, and that identifiable variables are largely missing for children.

I also learnt a lot about the other datasets I used. During my many visits to NHS-Digital's linkage office I was able to identify other potential linkages routes/ methods that could but were not being used by NHS-Digital. For example I was able to identify how, using maternal records combined with birth records, it is possible to identify all children born to women who have had ART in the UK. Not only would this be incredibly useful for studying cancer and indeed other

outcomes in children born after ART, this method could also be used to better estimate parity in women who have had ART. Indeed NHS-Digital could, and I believe now are using this method for multiple other studies where a mother- child link could be useful. I only able to identify this method because I undertake both projects included in this thesis side by side.

Potential for Further Studies

Follow-up studies, looking at all considered types of cancer in women after assisted conception are necessary. These studies should include follow-up to, and past, average ages when cancers of interest most commonly occur.

The observed association between in-situ breast cancer and assisted conception has not been reported previously, to our knowledge. It is particularly important to investigate this further as some observations are slightly conflicting; there appears to be a dose response relationship, however the overall risk of breast cancer is not increased. It would be important to design further studies to allow differentiation between a causal relationship and surveillance/ over diagnosis bias.

Further studies investigating the potential association between ovarian cancer and assisted reproduction are indicated. Whilst this study provided quite strong evidence that the increased risks of ovarian cancer in this cohort were mediated by nulliparity, endometriosis or both of these factors, studies which are able to control for these factors could further clarify this finding.

Studies investigating the association between borderline ovarian cancer and assisted conception are undoubtedly warranted. Evidence from this thesis could not differentiate between a

causative association and potential surveillance bias. Future studies should be designed to mitigate, or identify, the effect of surveillance bias where possible.

Studies investigating uterine cancer risk are also needed. Those that are able to control for or investigate factors such BMI, age at menopause and age at last birth would be particularly useful as this thesis was not able to do this. Diagnosis of polycystic ovary disease was suspected, but not confirmed, to be the cause of an increased risk of uterine cancer in women with ovulatory disorder in this thesis. Studies confirming this and excluding any other cause for this might also be helpful.

Whilst results from this thesis are generally reassuring, and concur with other large population based studies, further studies investigating childhood cancer risk after ART are warranted. Specific types of cancer which should be investigated, include hepatoblastoma, rhabdomyosarcoma and other types of sarcoma, (as indicated by the findings of this thesis). Further studies considering leukaemia and CNS tumours are also indicated. Children born after frozen embryo transfer should also be analysed separately if possible, as was the case in this thesis.

Further studies investigating cancer in children born after assisted conception should be large and population based. Where possible, including a cohort of children not born after assisted conception would be helpful, particularly cohorts born to sub-fertile mothers after spontaneous conception. As childhood cancer is thankfully rare, only in large population based studies, such as included in this thesis, is it possible to include enough exposed cases to ensure risk estimates are robust and chance findings are minimised. Longer follow-up studies, including of this study

cohort, are indicated. This is to ensure that risk estimates for cancers with a peak incidence beyond 6.6 years of age are robust.

Whilst results related to cancer outcomes in children born after *donor* assisted conception from this thesis are generally reassuring, small numbers of exposed cases and corresponding wide confidence intervals mean that further, larger population based studies are necessary.

It is also important that future studies, including in the UK, build upon linkage methods to investigate other health outcomes in children born after assisted conception. Examples of such outcomes include epilepsy and other neurological as well as neurodevelopmental conditions and hypertension and cardiovascular outcomes. Many of these outcomes are, like childhood cancer, relatively rare and thus lessons learnt from this thesis and similar studies about follow-up may be pertinent for such studies. In the UK, these studies could and indeed in some cases are being carried out using this linkage method outlined above.

Conclusions

This thesis represents three very large population-based linkage cohort studies, investigating various aspects of cancer occurring after assisted conception. Cancer outcomes in women who have had assisted conception in Britain between 1991 and 2010 and cancer outcomes in children born after assisted conception, both donor and non-donor, in Britain between 1992 and 2008 were investigated.

No overall increased risk of invasive breast cancer was observed in women after assisted conception, which is reassuring. Some significant decreases in risks were found in a variety of sub-analyses. It is likely, but not certain, that this represents the beneficial effect of a predominance of healthy lifestyles in this cohort. Conversely, an increase risk of in-situ breast cancer was found. This result was slightly perplexing as there was some evidence to suggest a causative relationship, including a dose-response relationship, but also some evidence against this, including no overall increased risk of breast cancer.

An overall increased risk of ovarian cancer was observed in women who had assisted conception. This was seen for both invasive and borderline ovarian tumours. This excess of ovarian tumours was, reassuringly, not observed in women who had assisted conception for male factor only infertility, nor in those with unexplained infertility and no association with number of cycles was seen. This provides evidence against a causal relationship. Additionally, this thesis was able to show that women who did not have the known risk factors of endometriosis and/ or nulliparity ***did not*** have an increased risk of developing an invasive ovarian tumour. This includes women who contributed just under half of all person-years at risk. These two known risk factors were shown have an approximately additive effect on the risk of developing an invasive ovarian tumour.

An excess of borderline ovarian tumours was also observed. As with invasive ovarian tumours, there was an observed association between nulliparity and endometriosis, but this relationship was less clear; women with both endometriosis and nulliparity did not have a significant increased risk. The nature of the observed association between assisted conception and borderline ovarian cancer is not clear and may be causative or may be due to various forms of bias, including surveillance bias.

There was no significant overall increased risk of corpus uteri cancer observed. Women with ovulatory disorders were observed to have a significantly increased risk. This is likely to represent the known association between poly-cystic ovary disease and endometrial cancer.

Children born after assisted conception were not shown to have an increased risk of cancer overall, up to an average follow-up age of 6.6 years. An increased risk of hepatoblastoma was observed, and was highly associated with low birthweight, a known risk factor likely to be mediating this association. Importantly, absolute excess risk, of developing a hepatoblastoma was very low in this cohort. An excess of sarcoma, particularly Rhabdomyosarcoma was observed in this cohort. The cause of this is unclear. Again, importantly, absolute excess risk, was very low.

The results of this study were largely in accordance with results of two other similar, large studies, investigating childhood cancer, published shortly afterwards. In combination, this work is able to provide some evidence that the risks of childhood cancer does not appear to be raised in individuals born after assisted reproduction.

Overall cancer risk in children born after donor assisted conception were also not significantly raised. Again an increased risk of hepatoblastoma, related to low birth weight, was observed. Absolute risks were thankfully very low.

At the time of publication, all three studies produced by this thesis represented the largest such study in their specific areas. All have been published in high impact journals, two in very high impact journals.

This thesis can, and hopefully has already had a direct impact on assisted conception service users. This thesis could provide reliable information for treating clinicians, both reproductive specialists and oncology specialists, who may be asked about potential associations by patients and their families. Results from this thesis may also possibly be used by public health specialists, particularly when planning future oncology services.

Results can be used to provide reliable information with which to council couples who are thinking of undergoing assisted reproductive treatment. These results may also be useful to women who have already had assisted conception, both those who have and have not developed cancer. For women with background characteristics known to be associated with cancer, such as those who do not have children, this study may provide further awareness of those cancer risks. To women without such factors, this study will hopefully provide at least some reassurance.

Families who already have children born after assisted conception will also hopefully find the results from this thesis useful. Whilst it should be stressed that additional research is warranted to further quantify and explore various risks, results from this thesis are generally reassuring.

References

1. Williams CL, Jones ME, Swerdlow AJ, et al. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation. *Bmj* 2018; **362**: k2644.
2. Williams CL, Bunch KJ, Murphy MFG, et al. Cancer risk in children born after donor ART. *Human reproduction* 2018; **33**(1): 140-6.
3. Williams CL, Bunch KJ, Stiller CA, et al. Cancer risk among children born after assisted conception. *The New England journal of medicine* 2013; **369**(19): 1819-27.
4. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Human reproduction* 2009; **24**(11): 2683-7.
5. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human reproduction* 2007; **22**(6): 1506-12.
6. Watts G. IVF pioneer Robert Edwards wins Nobel prize. *Bmj* 2010; **341**: c5533.
7. Adamson GD, Zegers-Hochschild F, Dyer S, et al. ICMART world report 2014. *Human reproduction* 2018; **33**: i65.
8. HFEA. Fertility Treatment in 2010. *Trends and figures*, 16/11/2011, 2011. http://www.hfea.gov.uk/docs/2011-11-16_-_Annual_Register_Figures_Report_final.pdf (accessed.
9. HFEA. Long-term trends data. 2008. http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/2588.html.
10. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet* 1978; **2**(8085): 366.
11. Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. *Nature* 1983; **305**(5936): 707-9.
12. Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 1990; **344**(6268): 768-70.
13. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992; **340**(8810): 17-8.
14. Trounson A, Wood C, Kausche A. In vitro maturation and the fertilization and developmental competence of oocytes recovered from untreated polycystic ovarian patients. *Fertility and sterility* 1994; **62**(2): 353-62.
15. Beesley R, Robinson R, Propst A, Arthur N, Retzloff M. Impact of day 3 or day 5 embryo transfer on pregnancy rates and multiple gestations. *Fertility and sterility* 2009; **91**(5): 1717-20.
16. Martins WP, Nastri CO, Rienzi L, van der Poel SZ, Gracia CR, Racowsky C. Obstetrical and perinatal outcomes following blastocyst transfer compared to cleavage transfer: a systematic review and meta-analysis. *Human reproduction* 2016; **31**(11): 2561-9.
17. HFEA. Fertility Treatment in 2010; Facts and Figures. *Human Fertilisation & Embryology Authority*, 2010. http://www.hfea.gov.uk/docs/2011-11-16_-_Annual_Register_Figures_Report_final.pdf (accessed.
18. Casper RF. Clinical uses of gonadotropin-releasing hormone analogues. *CMAJ* 1991; **144**(2): 153-8.
19. Joint-Formulary-Committee. British National Formulary. 73rd ed. London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society; 2017.
20. HFEA. Commonly used fertility drugs2015. http://www.hfea.gov.uk/common-fertility-drugs.html (accessed 05/07/2017).
21. Calhaz-Jorge C, de Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. *Human reproduction* 2016; **31**(8): 1638-52.

22. Heino A, Gissler M, Hindori-Mohangoo AD, et al. Variations in Multiple Birth Rates and Impact on Perinatal Outcomes in Europe. *PloS one* 2016; **11**(3): e0149252.
23. Medicine. PCoASfR. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. *Fertility and sterility* 2012; **97**(4): 825-34.
24. HFEA. State of the fertility sector: 2016–17. In: Authority HFE, editor. London: Human Fertilisation & Enbryology Authority; 2017.
25. Vlahos NF, Gregoriou O. Prevention and management of ovarian hyperstimulation syndrome. *Annals of the New York Academy of Sciences* 2006; **1092**: 247-64.
26. Nelson SM. Prevention and management of ovarian hyperstimulation syndrome. *Thrombosis research* 2017; **151 Suppl 1**: S61-S4.
27. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Human reproduction update* 2002; **8**(6): 559-77.
28. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. *Journal of assisted reproduction and genetics* 2010; **27**(2-3): 121-8.
29. Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC, 3rd, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology (ART) treatment and outcome. *Fertility and sterility* 2010; **94**(4): 1399-404.
30. Henriksson P, Westerlund E, Wallen H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. *Bmj* 2013; **346**: e8632.
31. Kallen B, Finnstrom O, Nygren KG, Otterblad Olausson P, Wennerholm UB. In vitro fertilisation in Sweden: obstetric characteristics, maternal morbidity and mortality. *BJOG : an international journal of obstetrics and gynaecology* 2005; **112**(11): 1529-35.
32. Ginstrom Ernstad E, Wennerholm UB, Khatibi A, Petzold M, Bergh C. Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. *American journal of obstetrics and gynecology* 2019; **221**(2): 126 e1- e18.
33. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *Bmj* 2004; **328**(7434): 261.
34. Siddhartha N, Reddy NS, Pandurangi M, Tamizharasi M, Radha V, Kanimozhi K. Correlation of serum estradiol level on the day of ovulation trigger with the reproductive outcome of intracytoplasmic sperm injection. *Journal of human reproductive sciences* 2016; **9**(1): 23-7.
35. Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture. *Cancer research* 1988; **48**(2): 246-53.
36. Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2005; **14**(1): 98-107.
37. Feng D, Zhao T, Yan K, et al. Gonadotropins promote human ovarian cancer cell migration and invasion via a cyclooxygenase 2-dependent pathway. *Oncology reports* 2017.
38. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer biology & medicine* 2017; **14**(1): 9-32.
39. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *Journal of the National Cancer Institute* 1983; **71**(4): 717-21.
40. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* 1971; **2**(7716): 163.
41. Casagrande JT, Louie EW, Pike MC, Roy S, Ross RK, Henderson BE. "Incessant ovulation" and ovarian cancer. *Lancet* 1979; **2**(8135): 170-3.

42. Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. *The Cochrane database of systematic reviews* 2013; **8**: CD008215.
43. Ovarian Cancer Research Fund Alliance (OCRFA). Ovarian Cancer Statistics. 2016. http://www.ovariancancer.org/about/statistics/ (accessed 11th April 2016).
44. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016; **34**(24): 2888-98.
45. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *American journal of epidemiology* 1992; **136**(10): 1184-203.
46. Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008; **371**(9609): 303-14.
47. Schouten LJ, Rivera C, Hunter DJ, et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2008; **17**(4): 902-12.
48. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *The New England journal of medicine* 2016; **375**(8): 794-8.
49. Pandey S, Maheshwari A, Bhattacharya S. The impact of female obesity on the outcome of fertility treatment. *Journal of human reproductive sciences* 2010; **3**(2): 62-7.
50. Choices NHS. Can I get IVF treatment on the National Health Service? 23/7/2015 2015. http://www.nhs.uk/chq/Pages/889.aspx?CategoryID=54.
51. Domar AD, Conboy L, Denardo-Roney J, Rooney KL. Lifestyle behaviors in women undergoing in vitro fertilization: a prospective study. *Fertility and sterility* 2012; **97**(3): 697-701 e1.
52. Lambertini M, Santoro L, Del Mastro L, et al. Reproductive behaviors and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis of epidemiological studies. *Cancer treatment reviews* 2016; **49**: 65-76.
53. Collaborative-Group-on-Hormonal-Factors-in-Breast-Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *The Lancet Oncology* 2012; **13**(11): 1141-51.
54. Wohlfahrt J, Andersen PK, Mouridsen HT, Melbye M. Risk of late-stage breast cancer after a childbirth. *American journal of epidemiology* 2001; **153**(11): 1079-84.
55. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. *The New England journal of medicine* 1994; **331**(1): 5-9.
56. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *Journal of the National Cancer Institute* 2011; **103**(3): 250-63.
57. Cancer-research-UK. Breast Cancer Risk Factors. 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/risk-factors#heading-Eleven (accessed 13/07/2017.
58. Collaborative-Group-on-Hormonal-Factors-in-Breast-Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347**(9017): 1713-27.
59. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362**(9382): 419-27.
60. Collaborative-Group-on-Hormonal-Factors-in-Breast-Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30

countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; **360**(9328): 187-95.
61. Sjogren LL, Morch LS, Lokkegaard E. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. *Maturitas* 2016; **91**: 25-35.
62. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. *Placenta* 2008; **29 Suppl B**: 169-77.
63. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Human reproduction update* 2014; **20**(5): 748-58.
64. Schonfeld SJ, Hartge P, Pfeiffer RM, et al. An aggregated analysis of hormonal factors and endometrial cancer risk by parity. *Cancer* 2013; **119**(7): 1393-401.
65. Mueck AO, Seeger H, Rabe T. Hormonal contraception and risk of endometrial cancer: a systematic review. *Endocrine-related cancer* 2010; **17**(4): R263-71.
66. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. *Obstetrics and gynecology* 2010; **116**(5): 1197-205.
67. Cancer-Reserach-UK. Uterine Cancer Risk Factors. 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/risk-factors#heading-Twelve (accessed 13/07/2017.
68. Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast cancer research and treatment* 2015; **150**(2): 405-13.
69. Sergentanis TN, Diamantaras AA, Perlepe C, Kanavidis P, Skalkidou A, Petridou ET. IVF and breast cancer: a systematic review and meta-analysis. *Human reproduction update* 2014; **20**(1): 106-23.
70. Pappo I, Lerner-Geva L, Halevy A, et al. The possible association between IVF and breast cancer incidence. *Annals of surgical oncology* 2008; **15**(4): 1048-55.
71. Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999; **354**(9190): 1586-90.
72. Brinton LA, Trabert B, Shalev V, Lunenfeld E, Sella T, Chodick G. In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services. *Fertility and sterility* 2013; **99**(5): 1189-96.
73. Yli-Kuha AN, Gissler M, Klemetti R, Luoto R, Hemminki E. Cancer morbidity in a cohort of 9175 Finnish women treated for infertility. *Human reproduction* 2012; **27**(4): 1149-55.
74. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after in vitro fertilization. *Human reproduction* 2011; **26**(1): 253-8.
75. Reigstad MM, Larsen IK, Myklebust TA, et al. Risk of breast cancer following fertility treatment--a registry based cohort study of parous women in Norway. *International journal of cancer* 2015; **136**(5): 1140-8.
76. Luke B, Brown MB, Spector LG, et al. Cancer in women after assisted reproductive technology. *Fertility and sterility* 2015; **104**(5): 1218-26.
77. Dor J, Lerner-Geva L, Rabinovici J, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. *Fertility and sterility* 2002; **77**(2): 324-7.
78. Stewart LM, Holman CD, Hart R, Bulsara MK, Preen DB, Finn JC. In vitro fertilization and breast cancer: is there cause for concern? *Fertility and sterility* 2012; **98**(2): 334-40.
79. Jensen A, Sharif H, Svare EI, Frederiksen K, Kjaer SK. Risk of breast cancer after exposure to fertility drugs: results from a large Danish cohort study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2007; **16**(7): 1400-7.
80. Jensen A, Sharif H, Kjaer SK. Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study. *American journal of epidemiology* 2009; **170**(11): 1408-14.

81. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *The New England journal of medicine* 1994; **331**(12): 771-6.
82. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecologic oncology* 2013; **128**(2): 260-4.
83. van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Human reproduction* 2011; **26**(12): 3456-65.
84. Siristatidis C, Sergentanis TN, Kanavidis P, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis. *Human reproduction update* 2013; **19**(2): 105-23.
85. Stewart LM, Holman CD, Finn JC, Preen DB, Hart R. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. *Gynecologic oncology* 2013; **129**(2): 372-6.
86. Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet* 1995; **346**(8981): 995-1000.
87. Lerner-Geva L, Geva E, Lessing JB, Chetrit A, Modan B, Amit A. The possible association between in vitro fertilization treatments and cancer development. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2003; **13**(1): 23-7.
88. Kristiansson P, Bjor O, Wramsby H. Tumour incidence in Swedish women who gave birth following IVF treatment. *Human reproduction* 2007; **22**(2): 421-6.
89. Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study. *Bmj* 2009; **338**: b249.
90. Saso S, Louis LS, Doctor F, et al. Does fertility treatment increase the risk of uterine cancer? A meta-analysis. *European journal of obstetrics, gynecology, and reproductive biology* 2015; **195**: 52-60.
91. Skalkidou A, Sergentanis TN, Gialamas SP, et al. Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility. *The Cochrane database of systematic reviews* 2017; **3**: CD010931.
92. HFEA. Fertility Treatment 2019, trends and figures. May 2021 2021. https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/ (accessed 4th August 2021 2021).
93. Roberts WE, Morrison JC, Hamer C, Wiser WL. The incidence of preterm labor and specific risk factors. *Obstetrics and gynecology* 1990; **76**(1 Suppl): 85S-9S.
94. Bodeau-Livinec F, Zeitlin J, Blondel B, et al. Do very preterm twins and singletons differ in their neurodevelopment at 5 years of age? *Archives of disease in childhood Fetal and neonatal edition* 2013; **98**(6): F480-7.
95. Blondel B, Kogan MD, Alexander GR, et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. *American journal of public health* 2002; **92**(8): 1323-30.
96. Rydhstroem H, Heraib F. Gestational duration, and fetal and infant mortality for twins vs singletons. *Twin research : the official journal of the International Society for Twin Studies* 2001; **4**(4): 227-31.
97. Fox NS, Rebarber A, Klauser CK, Roman AS, Saltzman DH. Intrauterine growth restriction in twin pregnancies: incidence and associated risk factors. *American journal of perinatology* 2011; **28**(4): 267-72.
98. Schinzel AA, Smith DW, Miller JR. Monozygotic twinning and structural defects. *The Journal of pediatrics* 1979; **95**(6): 921-30.
99. Rossi AC, D'Addario V. Neonatal outcomes of assisted and naturally conceived twins: systematic review and meta-analysis. *Journal of perinatal medicine* 2011; **39**(5): 489-93.
100. Hansen M, Colvin L, Petterson B, Kurinczuk JJ, de Klerk N, Bower C. Twins born following assisted reproductive technology: perinatal outcome and admission to hospital. *Human reproduction* 2009; **24**(9): 2321-31.

101. Henningsen AA, Gissler M, Skjaerven R, et al. Trends in perinatal health after assisted reproduction: a Nordic study from the CoNARTaS group. *Human reproduction* 2015; **30**(3): 710-6.
102. Pinborg A, Wennerholm UB, Romundstad LB, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Human reproduction update* 2013; **19**(2): 87-104.
103. McDonald SD, Han Z, Mulla S, et al. Preterm birth and low birth weight among in vitro fertilization twins: a systematic review and meta-analyses. *European journal of obstetrics, gynecology, and reproductive biology* 2010; **148**(2): 105-13.
104. Storgaard M, Loft A, Bergh C, et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. *BJOG : an international journal of obstetrics and gynaecology* 2017; **124**(4): 561-72.
105. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Human reproduction update* 2012; **18**(5): 485-503.
106. Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies and the risk of birth defects. *The New England journal of medicine* 2012; **366**(19): 1803-13.
107. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. *Birth defects research Part A, Clinical and molecular teratology* 2010; **88**(3): 137-43.
108. Lazaraviciute G, Kauser M, Bhattacharya S, Haggarty P. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. *Human reproduction update* 2014; **20**(6): 840-52.
109. Sutcliffe AG, Peters CJ, Bowdin S, et al. Assisted reproductive therapies and imprinting disorders--a preliminary British survey. *Human reproduction* 2006; **21**(4): 1009-11.
110. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. *American journal of human genetics* 2003; **72**(1): 156-60.
111. Guo XY, Liu XM, Jin L, et al. Cardiovascular and metabolic profiles of offspring conceived by assisted reproductive technologies: a systematic review and meta-analysis. *Fertility and sterility* 2017; **107**(3): 622-31 e5.
112. Belva F, Painter R, Bonduelle M, Roelants M, Devroey P, De Schepper J. Are ICSI adolescents at risk for increased adiposity? *Human reproduction* 2012; **27**(1): 257-64.
113. Belva F, Henriet S, Liebaers I, Van Steirteghem A, Celestin-Westreich S, Bonduelle M. Medical outcome of 8-year-old singleton ICSI children (born >or=32 weeks' gestation) and a spontaneously conceived comparison group. *Human reproduction* 2007; **22**(2): 506-15.
114. Rumbold AR, Moore VM, Whitrow MJ, et al. The impact of specific fertility treatments on cognitive development in childhood and adolescence: a systematic review. *Human reproduction* 2017: 1-19.
115. Spangmose AL, Malchau SS, Schmidt L, et al. Academic performance in adolescents born after ART-a nationwide registry-based cohort study. *Human reproduction* 2017; **32**(2): 447-56.
116. Ponjaert-Kristoffersen I, Bonduelle M, Barnes J, et al. International collaborative study of intracytoplasmic sperm injection-conceived, in vitro fertilization-conceived, and naturally conceived 5-year-old child outcomes: cognitive and motor assessments. *Pediatrics* 2005; **115**(3): e283-9.
117. Goldbeck L, Gagsteiger F, Mindermann I, Strobele S, Izat Y. Cognitive development of singletons conceived by intracytoplasmic sperm injection or in vitro fertilization at age 5 and 10 years. *Journal of pediatric psychology* 2009; **34**(7): 774-81.
118. Lidegaard O, Pinborg A, Andersen AN. Imprinting diseases and IVF: Danish National IVF cohort study. *Human reproduction* 2005; **20**(4): 950-4.

119. Hvidtjorn D, Grove J, Schendel DE, et al. Cerebral palsy among children born after in vitro fertilization: the role of preterm delivery--a population-based, cohort study. *Pediatrics* 2006; **118**(2): 475-82.
120. Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. *Lancet* 2002; **359**(9305): 461-5.
121. Wang FF, Yu T, Chen XL, Luo R, Mu DZ. Cerebral palsy in children born after assisted reproductive technology: a meta-analysis. *World J Pediatr* 2021; **17**(4): 364-74.
122. Kallen B. The risk of neurodisability and other long-term outcomes for infants born following ART. *Seminars in fetal & neonatal medicine* 2014; **19**(4): 239-44.
123. Sun Y, Vestergaard M, Christensen J, Zhu JL, Bech BH, Olsen J. Epilepsy and febrile seizures in children of treated and untreated subfertile couples. *Human reproduction* 2007; **22**(1): 215-20.
124. Kettner LO, Kesmodel US, Ramlau-Hansen CH, et al. Fertility Treatment and Childhood Epilepsy: A Nationwide Cohort Study. *Epidemiology* 2017; **28**(3): 412-8.
125. Romundstad LB, Romundstad PR, Sunde A, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* 2008; **372**(9640): 737-43.
126. Andersen AN, Pinborg A, Loft A. Neonatal outcome in singletons conceived after ART. *Lancet* 2008; **372**(9640): 694-5.
127. Santos F, Hyslop L, Stojkovic P, et al. Evaluation of epigenetic marks in human embryos derived from IVF and ICSI. *Human reproduction* 2010; **25**(9): 2387-95.
128. Chen SL, Shi XY, Zheng HY, Wu FR, Luo C. Aberrant DNA methylation of imprinted H19 gene in human preimplantation embryos. *Fertility and sterility* 2010; **94**(6): 2356-8, 8 e1.
129. Katari S, Turan N, Bibikova M, et al. DNA methylation and gene expression differences in children conceived in vitro or in vivo. *Human molecular genetics* 2009; **18**(20): 3769-78.
130. Katagiri Y, Aoki C, Tamaki-Ishihara Y, et al. Effects of assisted reproduction technology on placental imprinted gene expression. *Obstetrics and gynecology international* 2010; **2010**.
131. Gicquel C, Gaston V, Mandelbaum J, Siffroi JP, Flahault A, Le Bouc Y. In vitro fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCN1OT gene. *American journal of human genetics* 2003; **72**(5): 1338-41.
132. Sanchez-Delgado M, Riccio A, Eggermann T, et al. Causes and Consequences of Multi-Locus Imprinting Disturbances in Humans. *Trends in genetics : TIG* 2016; **32**(7): 444-55.
133. Stouder C, Deutsch S, Paoloni-Giacobino A. Superovulation in mice alters the methylation pattern of imprinted genes in the sperm of the offspring. *Reprod Toxicol* 2009; **28**(4): 536-41.
134. Suzuki J, Jr., Therrien J, Filion F, Lefebvre R, Goff AK, Smith LC. In vitro culture and somatic cell nuclear transfer affect imprinting of SNRPN gene in pre- and post-implantation stages of development in cattle. *BMC developmental biology* 2009; **9**: 9.
135. Cheng Y, Wang K, Kellam LD, et al. Effects of ooplasm manipulation on DNA methylation and growth of progeny in mice. *Biology of reproduction* 2009; **80**(3): 464-72.
136. Rivera RM, Stein P, Weaver JR, Mager J, Schultz RM, Bartolomei MS. Manipulations of mouse embryos prior to implantation result in aberrant expression of imprinted genes on day 9.5 of development. *Human molecular genetics* 2008; **17**(1): 1-14.
137. Shi W, Haaf T. Aberrant methylation patterns at the two-cell stage as an indicator of early developmental failure. *Molecular reproduction and development* 2002; **63**(3): 329-34.
138. Higashimoto K, Soejima H, Saito T, Okumura K, Mukai T. Imprinting disruption of the CDKN1C/KCNQ1OT1 domain: the molecular mechanisms causing Beckwith-Wiedemann syndrome and cancer. *Cytogenetic and genome research* 2006; **113**(1-4): 306-12.
139. Ehrlich M. DNA hypomethylation in cancer cells. *Epigenomics* 2009; **1**(2): 239-59.
140. Romanelli V, Nakabayashi K, Vizoso M, et al. Variable maternal methylation overlapping the nc886/vtRNA2-1 locus is locked between hypermethylated repeats and is frequently altered in cancer. *Epigenetics* 2014; **9**(5): 783-90.

141. Chang AS, Moley KH, Wangler M, Feinberg AP, Debaun MR. Association between Beckwith-Wiedemann syndrome and assisted reproductive technology: a case series of 19 patients. *Fertility and sterility* 2005; **83**(2): 349-54.
142. Weksberg R, Nishikawa J, Caluseriu O, et al. Tumor development in the Beckwith-Wiedemann syndrome is associated with a variety of constitutional molecular 11p15 alterations including imprinting defects of KCNQ1OT1. *Human molecular genetics* 2001; **10**(26): 2989-3000.
143. DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP. Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. *American journal of human genetics* 2002; **70**(3): 604-11.
144. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. *European journal of human genetics : EJHG* 2010; **18**(1): 8-14.
145. Liang G, Weisenberger DJ. DNA methylation aberrancies as a guide for surveillance and treatment of human cancers. *Epigenetics* 2017; **12**(6): 416-32.
146. Beta M, Chitipothu S, Khetan V, Biswas J, Krishnakumar S. Hypermethylation of adenomatosis polyposis coli-2 and its tumor suppressor role in retinoblastoma. *Current eye research* 2015; **40**(7): 719-28.
147. Tao YF, Xu LX, Lu J, et al. Early B-cell factor 3 (EBF3) is a novel tumor suppressor gene with promoter hypermethylation in pediatric acute myeloid leukemia. *Journal of experimental & clinical cancer research : CR* 2015; **34**: 4.
148. Davidsson J, Lilljebjorn H, Andersson A, et al. The DNA methylome of pediatric acute lymphoblastic leukemia. *Human molecular genetics* 2009; **18**(21): 4054-65.
149. Parodi F, Carosio R, Ragusa M, et al. Epigenetic dysregulation in neuroblastoma: A tale of miRNAs and DNA methylation. *Biochimica et biophysica acta* 2016; **1859**(12): 1502-14.
150. Halcrow PW, Dancer M, Panteah M, Walden C, Ohm JE. Molecular Changes Associated With Tumor Initiation and Progression of Soft Tissue Sarcomas: Targeting the Genome and Epigenome. *Progress in molecular biology and translational science* 2016; **144**: 323-80.
151. Costa AL, Lobo J, Jeronimo C, Henrique R. The epigenetics of testicular germ cell tumors: looking for novel disease biomarkers. *Epigenomics* 2017; **9**(2): 155-69.
152. Li W, Liu J, Galvin JA. Epigenetics and Common Ophthalmic Diseases. *The Yale journal of biology and medicine* 2016; **89**(4): 597-600.
153. Feinberg AP, Tycko B. The history of cancer epigenetics. *Nature reviews Cancer* 2004; **4**(2): 143-53.
154. Williams C, Constantine A, Sutcliffe A. Systematic review and meta-analysis of cancer risk in children born after assisted reproduction. *Archives of disease in childhood* 2011; **96**(Suppl 1): A6-A.
155. Moore SW, Sasco AJ, Dechelotte P, Satge D. In vitro fertilization and brain tumors. *Journal of Neurosurgery* 2007; **106**(5): 418-.
156. Sasco AJ, Lutz P, Pinget M, Becmeur F, Satge D, Born A. Paternal Treatment for Sterility and Neonatal Neuroblastoma. *British Medical Journal* 1994; **309**(6951): 410-.
157. Melamed I, Bujanover Y, Hammer J, Spirer Z. Hepatoblastoma in an infant born to a mother after hormonal treatment for sterility. *N Engl J Med* 1982; **307**(13): 820.
158. Khashu M, Osiovich H, Sargent MA. Congenital mesoblastic nephroma presenting with neonatal hypertension. *J Perinatol* 2005; **25**(6): 433-5.
159. Shibahara H, Mitsuo M, Fujimoto K, et al. Prenatal sonographic diagnosis of a fetal renal mesoblastic nephroma occurring after transfer of a cryopresesved embryo. *Human reproduction* 1999; **14**(5): 1324-7.
160. Shuman C, Smith AC, Steele L, et al. Constitutional UPD for chromosome 11p15 in individuals with isolated hemihyperplasia is associated with high tumor risk and occurs following assisted reproductive technologies. *American Journal of Medical Genetics Part A* 2006; **140A**(14): 1497-503.
161. Toren A, Sharon N, Mandel M, et al. 2 Embryonal Cancers After In-Vitro Fertilization. *Cancer* 1995; **76**(11): 2372-4.

162. Valera ET, Brassesco MS, De Sa ACJ, Silva R, Scrideli CA, Tone LG. Two Additional Cases of Childhood Embryonal Tumors in Brazilian Children Born From Assisted Reproductive Technologies. *Journal of Pediatric Hematology Oncology* 2009; **31**(10): 801-2.
163. Yigiter M, Arda IS, Kiyici H, Hicsomez A. Congenital mesoblastic nephroma rich from mitosis after in vitro fertilization: a case report. *Journal of Pediatric Surgery* 2008; **43**(5).
164. Anteby I, Cohen E, Anteby E, BenEzra D. Ocular manifestations in children born after in vitro fertilization. *Archives of Ophthalmology* 2001; **119**(10): 1525-9.
165. Barbosa RH, Vargas FR, Lucena E, Bonvicino CR, Seuanez HN. Constitutive RBI mutation in a child conceived by in vitro fertilization: implications for genetic counseling. *Bmc Medical Genetics* 2009; **10**.
166. Cruysberg JRM, Moll AC, Imhof SM. Bilateral sporadic retinoblastoma in a child born after in vitro fertilization. *Archives of Ophthalmology* 2002; **120**(12): 1773-.
167. Lee I, Finger PT, Grifo JA, Rausen AR, Rebarber A, Barad DH. Retinoblastoma in a child conceived by in vitro fertilisation. *British Journal of Ophthalmology* 2004; **88**(8): 1098-9.
168. Self J, Bush K, Baral VR, Puvanachandra N, Puddy VF, Hodgkins P. Bilateral retinoblastoma presenting at retinopathy of prematurity screening. *Archives of Disease in Childhood-Fetal and Neonatal Edition* 2010; **95**(4): F292-F.
169. Abu-Arja R, El Sheikh A, Sato Y, Shimada H, Radhi M. Synchronous Primary Neuroblastoma in Monozygotic Twins with Distinct Presentation, Pathology, and Outcome. *Pediatric blood & cancer* 2010; **54**(6): 856-.
170. Brassesco MS, Valera ET, de Oliveira FM, et al. 8q Deletion in MYCN-amplified Neuroblastoma of a Child Born From Assisted Reproductive Technology. *Journal of Pediatric Hematology Oncology* 2009; **31**(3): 215-9.
171. Langer T, Deeg KH, Hummer P, Paulides M, Beck JD, Klinge J. Postnatal respiratory distress in a dichorial twin with congenital thoracic neuroblastoma after assisted reproduction by intracytoplasmatic sperm injection. *Pediatric blood & cancer* 2007; **48**(3): 358-60.
172. Merks JH, Ceelie N, Caron HN, Hennekam RC. Neuroblastoma, maternal valproic acid use, in-vitro fertilization and family history of mosaic chromosome 22: coincidence or causal relationship? *Clinical Dysmorphology* 2004; **13**(3): 197-8.
173. Cohen ZR, Achiron R, Feldman Z. Prenatal sonographic diagnosis of lateral ventricle choroid plexus papilloma in an in vitro fertilization-induced pregnancy. *Pediatric Neurosurgery* 2002; **37**(5): 267-70.
174. Das A, Simmons C, Danielpour M. A congenital brain tumor associated with assisted in vitro fertilization - Case report. *Journal of Neurosurgery* 2005; **103**(5): 451-3.
175. Kim YD, Kim KJ, Lee YH. Secondary leukemia in a child conceived using in vitro fertilization. *Pediatrics International* 2008; **50**(6): 831-2.
176. Morof DF, Levine D, Stringer KF, Grable I, Folkerth R. Congenital glioblastoma multiforme - Prenatal diagnosis on the basis of sonography and magnetic resonance imaging. *Journal of Ultrasound in Medicine* 2001; **20**(12): 1369-75.
177. Rizk T, Nabbout R, Koussa S, Akatcherian C. Congenital brain tumor in a neonate conceived by in vitro fertilization. *Childs Nervous System* 2000; **16**(8): 501-2.
178. Maruyama K, Ikeda H, Koizumi T, Tsuchida Y. Prenatal and postnatal histories of very low birthweight infants who developed hepatoblastoma. *Pediatrics International* 1999; **41**(1): 82-9.
179. Al-Hindi. S, Al-Khuzaie. J, Al-Awadhi. M, Malik. A. Malignant testicular tumour in an infant. *Bahrain Medical Bulletin* 2001; **23**(4): 185-6.
180. Cabay RJ, Setty S, Schwartz JL, Yao M, Schmidt ML, Gordon SC. Pediatric Squamous Cell Carcinoma Arising in an Alpha-Fetoprotein-Producing Mature Cystic Teratoma of the Mandible. *Pediatric blood & cancer* 2009; **52**(1): 130-2.
181. Cecen E, Gunes D, Uysal KM, Yuceer N, Ozer E. Atypical teratoid/rhabdoid tumor in an infant conceived by in vitro fertilization. *Childs Nervous System* 2010; **26**(2): 263-6.
182. Kramer S, Ward E, Meadows AT, Malone KE. Medical and drug risk factors associated with neuroblastoma: a case-control study. *J Natl Cancer Inst* 1987; **78**(5): 797-804.

183. Michalek AM, Buck GM, Nasca PC, Freedman AN, Baptiste MS, Mahoney MC. Gravid health status, medication use, and risk of neuroblastoma. *American journal of epidemiology* 1996; **143**(10): 996-1001.
184. Olshan AF, Smith J, Cook MN, et al. Hormone and fertility drug use and the risk of neuroblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *American journal of epidemiology* 1999; **150**(9): 930-8.
185. Puumala SE, Ross JA, Olshan AF, Robison LL, Smith FO, Spector LG. Reproductive history, infertility treatment, and the risk of acute leukemia in children with down syndrome: a report from the Children's Oncology Group. *Cancer* 2007; **110**(9): 2067-74.
186. Puumala SE, Spector LG, Wall MM, et al. Infant leukemia and parental infertility or its treatment: a Children's Oncology Group report. *Human reproduction* 2010; **25**(6): 1561-8.
187. Roman E, Ansell P, Bull D. Leukaemia and non-Hodgkin's lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? *British journal of cancer* 1997; **76**(3): 406-15.
188. Schuz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *International journal of epidemiology* 1999; **28**(4): 631-9.
189. Schwartzbaum JA. Influence of the Mothers Prenatal Drug Consumption on Risk of Neuroblastoma in the Child. *American journal of epidemiology* 1992; **135**(12): 1358-67.
190. Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, van Zanen GE. Are maternal fertility problems related to childhood leukaemia? *Int J Epidemiol* 1985; **14**(4): 555-9.
191. Kobayashi N, Matsui I, Tanimura M, et al. Childhood Neuroectodermal Tumors and Malignant-Lymphoma After Maternal Ovulation Induction. *Lancet* 1991; **338**(8772): 955-.
192. Mallol-Mesnard N, Menegaux F, Lacour B, et al. Birth characteristics and childhood malignant central nervous sytem tumors: the ESCALE study (French Society for Childhood Cancer). *Cancer detection and prevention* 2008; **32**(1): 79-86.
193. Bergh T, Ericson A, Hillensjo T, Nygren KG, Wennerholm UB. Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. *Lancet* 1999; **354**(9190): 1579-85.
194. Ericson A, Nygren KG, Olausson PO, Kallen B. Hospital care utilization of infants born after IVF. *Human reproduction* 2002; **17**(4): 929-32.
195. Kallen B, Finnstrom O, Nygren KG, Olausson PO. In vitro fertilization in Sweden: child morbidity including cancer risk. *Fertility and sterility* 2005; **84**(3): 605-10.
196. Pinborg A, Loft A, Rasmussen S, et al. Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. *Human reproduction* 2004; **19**(2): 435-41.
197. Moll AC, Imhof SM, Cruysberg JR, Schouten-van Meeteren AY, Boers M, van Leeuwen FE. Incidence of retinoblastoma in children born after in-vitro fertilisation. *Lancet* 2003; **361**(9354): 309-10.
198. Pinborg A, Loft A, Aaris Henningsen AK, Rasmussen S, Andersen AN. Infant outcome of 957 singletons born after frozen embryo replacement: the Danish National Cohort Study 1995-2006. *Fertility and sterility* 2010; **94**(4): 1320-7.
199. Brinton LA, Kjaer SK, Thomsen BL, et al. Childhood tumor risk after treatment with ovulation-stimulating drugs. *Fertil Steril* 2004; **81**(4): 1083-91.
200. M. Hargreave AJ, S. Kjaer. Infertility and the risk of cancer in children. World Congress of Gynecology and Obstetrics: International Journal of Obstetrics & Gynaecology 2009. p. S639.
201. Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Cancer risk in children and young adults conceived by in vitro fertilization. *Pediatrics* 2010; **126**(2): 270-6.
202. Pinborg A, Loft A, Nyboe Andersen A. Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy. *Acta obstetricia et gynecologica Scandinavica* 2004; **83**(11): 1071-8.
203. Marees T, Dommering CJ, Imhof SM, et al. Incidence of retinoblastoma in Dutch children conceived by IVF: an expanded study. *Human reproduction* 2009; **24**(12): 3220-4.

204. Rufat P, Olivennes F, de Mouzon J, Dehan M, Frydman R. Task force report on the outcome of pregnancies and children conceived by in vitro fertilization (France: 1987 to 1989). *Fertility and sterility* 1994; **61**(2): 324-30.
205. Klip H, Burger CW, de Kraker J, van Leeuwen FE. Risk of cancer in the offspring of women who underwent ovarian stimulation for IVF. *Human reproduction* 2001; **16**(11): 2451-8.
206. Bruinsma F, Venn A, Lancaster P, Speirs A, Healy D. Incidence of cancer in children born after in-vitro fertilization. *Human reproduction* 2000; **15**(3): 604-7.
207. Doyle P, Bunch KJ, Beral V, Draper GJ. Cancer incidence in children conceived with assisted reproduction technology. *Lancet* 1998; **352**(9126): 452-3.
208. Bradbury BD, Jick H. In vitro fertilization and childhood retinoblastoma. *British journal of clinical pharmacology* 2004; **58**(2): 209-11.
209. White L, Giri N, Vowels MR, Lancaster PA. Neuroectodermal tumours in children born after assisted conception. *Lancet* 1990; **336**(8730): 1577.
210. Odone-Filho V, Cristofani LM, Bonassa EA, Braga PE, Eluf-Neto J. In vitro fertilization and childhood cancer. *Journal of pediatric hematology/oncology* 2002; **24**(5): 421-2.
211. Lerner-Geva L, Toren A, Chetrit A, et al. The risk for cancer among children of women who underwent in vitro fertilization. *Cancer* 2000; **88**(12): 2845-7.
212. Raimondi S, Pedotti P, Taioli E. Meta-analysis of cancer incidence in children born after assisted reproductive technologies. *British journal of cancer* 2005; **93**(9): 1053-6.
213. UK Human Fertilisation and Embryology Act. c37. United Kingdom; 1990.
214. UK Human Fertilisation and Embryology Act. United Kingdom; 2008.
215. National Health Service Act. c41; 2006.
216. Parkin DM CV, Ferlay J, Galceran J, Storm HH, Whelan SL. Comparability and Quality Control in Cancer Registration. Lyon: International Agency for Research on Cancer, 1994.
217. Office-for-National-Statistics. Cancer Registrations, 1971 to 2011. 19th June 2014 2014. http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--43--2012/stb-cancer-registrations-2012.html#tab-Cancer-registrations--1971-to-2011 (accessed 15th June 2015).
218. Information-Services-Division-Scotland. Scottish Cancer Registry. 2010. http://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry.asp (accessed 15th June 2015).
219. Brewster DH, Stockton DL. Ascertainment of breast cancer by the Scottish Cancer Registry: an assessment based on comparison with five independent breast cancer trials databases. *Breast* 2008; **17**(1): 104-6.
220. Bohensky MA, Jolley D, Sundararajan V, et al. Data linkage: a powerful research tool with potential problems. *BMC health services research* 2010; **10**: 346.
221. Hagger-Johnson G, Harron K, Goldstein H, Aldridge R, Gilbert R. Probabilistic linkage to enhance deterministic algorithms and reduce data linkage errors in hospital administrative data. *Journal of innovation in health informatics* 2017; **24**(2): 891.
222. Gilbert R, Lafferty R, Hagger-Johnson G, et al. GUILD: GUidance for Information about Linking Data setsdagger. *J Public Health (Oxf)* 2017: 1-8.
223. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS medicine* 2015; **12**(10): e1001885.
224. Stata-Corp. Stata Statistical Software: Release 12. College Station Tx: Stata Corp LP; 2013.
225. National-Cancer-Institute. ICD-O-3 SEER Site/Histology Validation List. In: Surveillance-Epidemiology-and-End-Results-Program, editor.; 2015.
226. Breslow NE, Day NE. Statistical Methods in Cancer Research. Lyon, France: International Agency for Research on Cancer.; 1987.
227. Cox D. Regression Models and life tables. *Journal of the Royal Statistical Society* 1972; **34**(2): 187-202.

228. Kroll ME, Murphy MF, Carpenter LM, Stiller CA. Childhood cancer registration in Britain: capture-recapture estimates of completeness of ascertainment. *British journal of cancer* 2011; **104**(7): 1227-33.
229. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer* 2005; **103**(7): 1457-67.
230. Stata-Corp. Stata Statistical Software: Release 11. College Station Tx, USA: Stata Corp LP; 2009.
231. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *The Lancet Oncology* 2001; **2**(3): 133-40.
232. Nakashima K, Uematsu T, Takahashi K, et al. Does breast cancer growth rate really depend on tumor subtype? Measurement of tumor doubling time using serial ultrasonography between diagnosis and surgery. *Breast Cancer* 2019; **26**(2): 206-14.
233. Taylor A, Cheng KK. Social deprivation and breast cancer. *J Public Health Med* 2003; **25**(3): 228-33.
234. Spaan M, van den Belt-Dusebout AW, Lambalk CB, et al. Long-Term Risk of Ovarian Cancer and Borderline Tumors After Assisted Reproductive Technology. *Journal of the National Cancer Institute* 2021; **113**(6): 699-709.
235. Melin A, Sparen P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Human reproduction* 2006; **21**(5): 1237-42.
236. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *The Lancet Oncology* 2009; **10**(4): 327-40.
237. Raglan O, Kalliala I, Markozannes G, et al. Risk factors for endometrial cancer: An umbrella review of the literature. *International journal of cancer* 2019; **145**(7): 1719-30.
238. Cancer-Research-UK. Ovarian Cancer Risk Factors. 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/risk-factors (accessed 13/07/2017.
239. Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *American journal of epidemiology* 1998; **148**(10): 1012-7.
240. Hargreave M, Jensen A, Toender A, Andersen KK, Kjaer SK. Fertility treatment and childhood cancer risk: a systematic meta-analysis. *Fertility and sterility* 2013; **100**(1): 150-61.
241. Sundh KJ, Henningsen AK, Kallen K, et al. Cancer in children and young adults born after assisted reproductive technology: a Nordic cohort study from the Committee of Nordic ART and Safety (CoNARTaS). *Human reproduction* 2014; **29**(9): 2050-7.
242. Spector LG, Brown MB, Wantman E, et al. Association of In Vitro Fertilization With Childhood Cancer in the United States. *JAMA Pediatr* 2019; **173**(6): e190392.
243. Hargreave M, Jensen A, Hansen MK, et al. Association Between Fertility Treatment and Cancer Risk in Children. *Jama* 2019; **322**(22): 2203-10.
244. Spaan M, van den Belt-Dusebout AW, van den Heuvel-Eibrink MM, et al. Risk of cancer in children and young adults conceived by assisted reproductive technology. *Human reproduction* 2019; **34**(4): 740-50.
245. McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. *American journal of epidemiology* 2006; **163**(9): 818-28.
246. Puumala SE, Ross JA, Feusner JH, et al. Parental infertility, infertility treatment and hepatoblastoma: a report from the Children's Oncology Group. *Human reproduction* 2012; **27**(6): 1649-56.
247. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weights. *Pediatrics* 2009; **124**(1): 96-104.
248. Spector LG, Johnson KJ, Soler JT, Puumala SE. Perinatal risk factors for hepatoblastoma. *British journal of cancer* 2008; **98**(9): 1570-3.

249. Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, Eden TO. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. *European journal of cancer* 2005; **41**(5): 741-8.
250. de Fine Licht S, Schmidt LS, Rod NH, et al. Hepatoblastoma in the Nordic countries. *International journal of cancer* 2012; **131**(4): E555-61.
251. Murphy MF, Bunch KJ, Chen B, Hemminki K. Reduced occurrence of childhood cancer in twins compared to singletons: protection but by what mechanism? *Pediatric blood & cancer* 2008; **51**(1): 62-5.
252. Nybo Andersen AM, Urhoj SK. Is advanced paternal age a health risk for the offspring? *Fertility and sterility* 2017; **107**(2): 312-8.
253. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *International journal of epidemiology* 2001; **30**(6): 1428-37.
254. Sutcliffe AG, D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B. Minor congenital anomalies, major congenital malformations and development in children conceived from cryopreserved embryos. *Human reproduction* 1995; **10**(12): 3332-7.
255. Maher ER, Brueton LA, Bowdin SC, et al. Beckwith-Wiedemann syndrome and assisted reproduction technology (ART). *Journal of medical genetics* 2003; **40**(1): 62-4.
256. Hiura H, Okae H, Miyauchi N, et al. Characterization of DNA methylation errors in patients with imprinting disorders conceived by assisted reproduction technologies. *Human reproduction* 2012; **27**(8): 2541-8.
257. Halliday J, Oke K, Breheny S, Algar E, D JA. Beckwith-Wiedemann syndrome and IVF: a case-control study. *American journal of human genetics* 2004; **75**(3): 526-8.
258. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol* 2018; **14**(4): 229-49.
259. Petridou ET, Sergentanis TN, Panagopoulou P, et al. In vitro fertilization and risk of childhood leukemia in Greece and Sweden. *Pediatric blood & cancer* 2012; **58**(6): 930-6.
260. Reigstad MM, Oldereid NB, Omland AK, Storeng R. Literature review on cancer risk in children born after fertility treatment suggests increased risk of haematological cancers. *Acta paediatrica* 2017; **106**(5): 698-709.
261. Reigstad MM, Larsen IK, Myklebust TA, et al. Risk of Cancer in Children Conceived by Assisted Reproductive Technology. *Pediatrics* 2016; **137**(3): e20152061.
262. Cancer-Reserach-UK. Leukaemia incidence by age. 04/10/2021 2021. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia/incidence#heading-One (accessed 12/10/2021 2021).
263. Office for National Statistics. Interim Life Tables United Kingdom 1980-80 to 2008-2010. 2010.

Appendix 1; Search terms for systematic reviews

Women:

MEDLINE & EMBASE were searched on 20.11.2014 & repeated 13.02.2017

MEDLINE

'Cancer' OR 'Carcinoma' OR 'Tumour' OR ' Tumor' OR 'Neoplasm' (MeSH term)

AND

'ART' OR 'Assisted Reproductive Technique*' OR 'Assisted Reproductive Technolog*' OR 'IVF' OR 'Reproductive Techniques, Assisted' (MeSH term) OR 'Reproduction techniques' (Previous MeSH term) OR 'Fertilization in Vitro' (previous MeSH term)

Restricted to under 18 year olds. No other restrictions used.

EMBASE

'Cancer' OR 'Carcinoma' OR 'Tumour' OR 'Tumor' OR 'Neoplasm' (Subject heading)

AND

'ART' OR 'Assisted Reproductive Technique*' OR 'Assisted Reproductive Technolog*' OR 'IVF' OR 'infertility therapy' (subject heading) OR 'fertilization in vitro' (subject heading) OR 'intracytoplasmic sperm injection' (subject heading).

Children:

MEDLINE & EMBASE were searched on 21.10.2010 & repeated on 03.11.2011

MEDLINE

'Cancer' OR 'Carcinoma' OR 'Tumour' OR 'Tumor' OR 'Neoplasm' (MeSH term)

AND

'ART' OR 'Assisted Reproductive Technique*' OR 'Assisted Reproductive Technolog*' OR 'IVF' OR 'Reproductive Techniques, Assisted' (MeSH term) OR 'Reproduction techniques' (Previous MeSH term) OR 'Fertilization in Vitro' (previous MeSH term)

Restricted to under 18 year olds. No other restrictions used.

EMBASE

'Cancer' OR 'Carcinoma' OR 'Tumour' OR 'Tumor' OR 'Neoplasm' (Subject heading)

AND

'ART' OR 'Assisted Reproductive Technique*' OR 'Assisted Reproductive Technolog*' OR 'IVF' OR 'infertility therapy' (subject heading) OR 'fertilization in vitro' (subject heading) OR 'intracytoplasmic sperm injection' (subject heading).

Appendix 2; HFEA data capture sheet, provided by HFEA 2009

PATIENT-FEMALE

DEMO
Patient name
Patient Surname
Patient Surname at birth if different
DOB
Town/District of Birth
Country of Birth
NHS No.
Passport No.
Country of Issue
Disability?
Ethnic group
travelled from abroad?
partner?

GYN/OBS
Previous natural pregnancies
previous ivf pregnancies
previous di pregnancies
natural births
IVF births
DI births
infertility duration (years)
tubal
endometriosis
uterine
menopausal
ovulatory (PCO)
ovarian failure
genetic disorder
no male partner
male factor
unexplained
other

INTENTION TO TREAT
Patient no.
Current Surname
Stimulation Date or LMP

DI
Patient no.
Current Surname
Sperm Donor
Imported Donor
NHS Funded?
Stimulated
Natural
LMP or Stimulation date
Previous DI cycles?

IVF/ICSI
Patient no.
Current Surname
Surrogacy?
Donor Sperm?
donor eggs?
NHS Funded?
Natural/Stimulated?
Drug type?
Eggs
Inseminated
assisted hatching
no. transferred
embryo stage
discarded no.
frozen no.
donated no.

PARTNER

Patient name
Patient Surname
Patient Surname at birth if different
DOB
Town/District of Birth
Country of Birth
NHS No.
Passport No.
Country of Issue
Disability?
Ethnic group
travelled from abroad?
SEX

ANDRO
Female infertility
azoospermia
oligozoospermia
genetic disorder avoidance

he is the partner of...
please use current surname

NO ET
failed thaw
OHSS
abnormal fert
ftf
pos genetic test

EARLY OUTCOME
Negative
Biochemical
Miscarriage
Ectopic
Heterotopic
Molar
IUFP
gestational sacs no.

OUTCOME
Termination? Why?
Fetal reduction?
Sac no.
Misc
Ectopic
Heterotopic
Neonatal death
still birth

Live birth
weight
sex
del date
NHS no.
forename and surname
Birth town/Country

Congenital anomalies
None
Uncertain
Yes

Appendix 3; Study Approvals

a) Women's study research ethics committee approval

NHS

National Research Ethics Service

Royal Free Hospital & Medical School Research Ethics Committee
Royal Free Hospital NHS Trust
Royal Free Hospital
South House, Block A
Pond Street
London
NW3 2QG

Telephone: 0207 794 0581
Facsimile: 0207 794 0714

23 March 2010

Dr Alastair Sutcliffe
Senior Lecturer and Consultant in Paediatrics
UCL, Institute of Child Health
Institute of Child Health
30 Guilford Street
London
WC1N 1CH

Dear Dr Sutcliffe

Study Title: **Do hormonal treatments for assisted reproduction increase risks of cancer or mortality in women? A national cohort study**
REC reference number: **10/H0720/18**
Protocol number: **1**

The Research Ethics Committee reviewed the above application at the meeting held on 17 March 2010. Thank you for attending to discuss the study.

Ethical opinion

The researcher explained that the principal research objective is to assess and evaluate the potential risk of cancer, especially reproductive related cancers (ovarian, breast and endometrial), in relation to the type of treatment and length of hormonal medicines treatments in women undergoing fertility treatment.

The Chairman has found a document on the web that enables the Secretary of State to make provisions, in regulations requiring or regulating the disclosure of information falling within section 31(2) for research purposes it states that
"Information can be disclosed for the purposes of medical research where the Secretary of State considers it necessary or expedient in the public interest or in the interest of improving patient care....." A copy of the documents is with the application

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to

management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		02 February 2010
REC application		
Protocol	1	25 November 2009
Investigator CV		
Evidence of insurance or indemnity	1	02 February 2010
Letter from Funder	1	14 December 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

b) Women's study, section 251 approval

NIGB

Ethics and Confidentiality Committee

Dr Alastair Sutcliffe
General and Adolescent Paediatric Unit
Institute of Child Health
30 Guilford Street
WC1N 1EH

NIGB Office,
Floor 7,
New Kings Beam House,
22 Upper Ground,
London,
SE1 9BW.

Tel: (020) 7633 7052
Email: eccapplications@nhs.net

03 February 2011

Dear Dr Sutcliffe

ECC 5-04 (b)/2010 - Do hormonal treatments for assisted reproduction increase risks of cancer or mortality in women? A national cohort study

Thank you for applying for support under section 251 of the NHS Act 2006 to process patient identifiable information without consent.

Background

It has been agreed that the HFEA will delegate the handling and assessment of all applications, with a medical purpose, under the Human Fertilisation and Embryology (HFE) Act 1990 to the National Information Governance Board Ethics and Confidentiality Committee (ECC). Under this delegated authority, the ECC considers and recommends to the HFEA whether to grant or refuse permission to use identifiable register information, or to impose conditions upon its use. As data controller of the Register, the HFEA will take a final decision based upon this recommendation, and then if disclosure is permitted will work with the applicant to enable use of the dataset. In terms of disclosure of patient information not contained in the HFEA register, the ECC will take the final decision under section 251 of the NHS Act 2006.

Context

This application from University College London aimed to link data from the Human Fertilisation and Embryology Authority to the National Health Service Central Register in order to assess the risk of cancer and death in women who have undergone hormonal therapy as part of assisted reproduction therapy. In particular, flagging would be applied to the cohort and the team would request to be notified of future cancers and deaths. The exposed cohort would consist of all women aged 18-55 who had fertility treatment between the period of 1991 – 2007, and the non-exposed cohort would be all other women in the UK over the same time period. The following identifiers were requested to permit the linkage activity: place of birth, name and surname, date of birth and town/district of birth.

Outcome

Members agreed this to be a clear application and that the large numbers involved in the cohort rendered consent impracticable. It was understood that the linkage activity would be carried out by

the NHS Information Centre, and therefore the researcher would not be in receipt of any identifiable data, therefore minimising any potential breaches of confidentiality. Members also commended the extent of user involvement and welcomed the efforts that had been made in this aspect.

As a whole, Members considered this to be a clearly articulated application with a high public interest in the outcomes, and therefore recommended support under section 251, subject to the following specific and standard conditions of approval.

Conditions of approval

This provisional approval was subject to the following conditions:

1. A favourable opinion to be received from a REC. (This has been received)
2. A data sharing agreement to be in place between all parties (This has been received)
3. Formal confirmation from the HFEA that they approve access to the HFEA Register dataset (This confirmation has been received)
4. Confirmation of satisfactory security arrangements (the arrangements have been confirmed as satisfactory)

Following satisfactory resolution of the conditions of approval, I am pleased to confirm that this study has received final approval under section 251. Our Register of approved applications will shortly be updated to include this approval.

Annual Review

Please note that your approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report on the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements. You will need to supply an annual review by 03 February 2012. Please ensure that this is received approximately 8 weeks prior to this submission deadline so as to ensure that any potential queries can be resolved so as to ensure seamless approval coverage.

[redacted]

I would also like to take this opportunity to wish you every success in this study.

Yours sincerely

Natasha Dunkley
NIGB Approvals Manager

Ethics and Confidentiality Committee
Standard Conditions of Approval

The support provided under section 251 is subject to the following standard conditions.

The applicant will ensure that:

1. The requested patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and that there is no disclosure of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent of the Secretary of State is facilitated and supported.
8. The wishes of people who have withheld or withdrawn their consent are respected.
9. The NIGB Office is notified of any significant changes which impact on the approval of the application.

c) Women's study, Human Fertilisation & Embryology Authority Approval

Dr Alastair Sutcliffe
Senior Lecturer and Consultant in Paediatrics
UCL, Institute of Child Health
30 Guildford Street
London
WC1N 1EH

15 October 2010

Dear Dr Sutcliffe,

Study title: Do hormonal treatments for assisted reproduction increase risks of cancer or mortality in women? A national cohort study.
Your ref: 09GP13 **NIGB ref:** ECC (HFEA) 5-04 (b) 2010

and

Study title: Are children born after assisted reproduction at increased risk of cancer? A population based linkage study.
Your ref: 09GP17 **NIGB ref:** ECC (HFEA) 5-04 (a) /2010

You have previously been informed by the NIGB ECC that both your planned studies have been approved in principle after consideration by both the ECC and the HFEA Register Research Panel. However, there were remaining issues to do with data linkage that still needed to be resolved for the 'cancer in women' study. We are now in the position to confirm that, based on the documentation you provided and after further consideration by the HFEA Register Research Panel we can grant final approval for both studies.

The decision to grant access is based on the documents submitted as follows:

Cancer in women after ART
Protocol
NIGB Application Form
HFEA Data Capture Sheet
UCL Systems Level Security Policy
Updated NHS IC document explaining why linkage cannot be performed at the HFEA, received 7th October 2010

Childhood cancer after ART
Details of Research Project
NIGB Application Form
HFEA Data Capture Sheet
Proposed data flow

Human Fertilisation and Embryology Authority
21 Bloomsbury Street London WC1B 3HF
Telephone: 020 7291 8200
Fax: 020 7291 8201
Website: www.hfea.gov.uk

Chair: Professor Lisa Jardine CBE
Chief Executive: Alan Doran CB

Initial request email from Carrie Williams, dated 21/04/2010
Minutes of meeting 01/12/2009 HFEA

Both
Caldicott Guardian's Letter, dated 21/04/2010

Conditions
The agreement to grant access to the identifying information from the HFEA Register is based on the following conditions:

- The NHS IC SLSP should be supplied as soon as possible.
- No prospective linkage (flagging) can be done, i.e. fertility treatment status must not be flagged on the NHS IC dataset. The linkage must be performed once and then results kept separately. Further approval should be sought to update the linkage again in the future.
- The Panel was happy for the research team to keep the results of the linkage itself (encrypted unique study number, patient ID), but in this case the HFEA will keep the encryption key.

Fees
Fees for the identification, extraction and preparation of data will be levied at a rate of £250 per half day, up to a maximum of £5000. An estimate of the cost can be provided once your requirements are confirmed. The invoice for the full amount will be issued at the time the data is provided.

[redacted]

We look forward to working with you and your team on these interesting and important projects.

Yours sincerely,

[redacted]

Peter Thompson
Director of Strategy and Information

[redacted]

cc: Natasha Dunkley, Approvals Manager, National Information Governance Board

Human Fertilisation and Embryology Authority
21 Bloomsbury Street London WC1B 3HF
Telephone: 020 7291 8200
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Website: www.hfea.gov.uk

Chair: Professor Lisa Jardine CBE
Chief Executive: Alan Doran CB

d) NHS-Digital Data Sharing Agreement

Data Sharing Agreement final with customer approval

DARS-NIC-29554-L0P4F-v1.5

NHS Digital

Data Sharing Agreement

1.Parties

This Data Sharing Agreement is made between:

1.1 **The Health & Social Care Information Centre** (the **HSCIC**), a body corporate established pursuant to section 252 of the Health and Social Care Act 2012 whose address is 1 Trevelyan Square, Boar Lane, Leeds LS1 6AE; and

1.2 The party whose details are set out in **Annex A: section 1b** of this document (the **Data Recipient**):

2.Status of this Agreement

2.1 This Data Sharing Agreement (**DSA**) comprises the details set out in this document, the Data Sharing Framework Contract made between HSCIC and the Data Recipient and referred to in **Annex A: section 1b** of this document, the terms and conditions of which are expressly incorporated into this DSA.

2.2 In the event of any conflict between the elements of this DSA, the Special Conditions in **Annex A: section 6** of this document shall prevail, followed by the Data Sharing Framework Contract (including its Schedules), followed by the remainder of this document.

2.3 Capitalised terms used in this DSA shall bear the meanings given to them in the Data Sharing Framework Contract, unless defined elsewhere in this DSA.

3.Term of this DSA

3.1 This DSA shall commence on the Start Date specified in **Annex A: section 1a** of this document and shall continue, unless terminated earlier in accordance with the terms of this DSA or the Data Sharing Framework Contract, until the End Date specified in **Annex A: section 1a** of this document

4.Data Details

4.1 The detailed specification shown below, sets out details of the data that will be provided by the HSCIC to the Data Recipient under this DSA (the **Data**).

4.2 The HSCIC shall supply the Data to the Data Recipient or its nominated Data Processor in accordance with the method set out in **Annex B** of this document .

4.3 Where the information below states that the Data Recipient is entitled to sub-licence the Data, the Data Recipient shall comply with the sub-licensing conditions set out in **Annex A: section 10**

5.Data Processor

5.1 The Data Recipient wishes to engage the party whose details are set out in **Annex A: section 1c** (the **Data Processor**) to act as its data processor to carry out the processing activities set out in the same section in respect of the Data.

5.2 The HSCIC consents to the appointment by the Data Recipient of the Data Processor for the processing activities set out in **Annex A: section 5**. The Data Recipient shall be responsible for all acts and omissions of the Data Processor as if they were acts and omissions of the Data Recipient under this DSA.

6.Charges

6.1 The Data Recipient shall pay the charges set out in **Annex A: section 11** (where applicable), in accordance with the payment terms contained in the Data Sharing Framework Contract.

7.Terms and Conditions

7.1 The Data Sharing Framework Contract sets out the legal terms and conditions which apply to the transfer and use of Data supplied to the Data Recipient under this DSA. Some of the key terms are reproduced below for the Data Recipient's information purposes

7.1.1 Where Non-Identifiable Data has been supplied by the HSCIC and then it becomes Personal Data in the hands of the Data Recipient, the Data Recipient shall become a Data Controller and shall be responsible for ensuring that the Data is processed in accordance with the DPA.

7.1.2 Use of the Data is for the sole purpose set out in **Annex A: section 5** (the **Purpose**).

7.1.3 Personnel processing the Data must be suitably trained and made aware of their responsibilities in handling the Data.

7.1.4 The Data must not be shared with any other organisation or named individual not explicitly referred to within this DSA.

7.1.5 If the Data is subject to a request under the Freedom of Information Act, then the HSCIC must be consulted before a response is provided.

7.1.6 Use of the Data must comply with all applicable legislation in relation to the Data (such as the Statistics and Registration Services Act 2007).

7.1.7 The Data must be accessed, processed and used within the European Economic Area only, unless permission has been granted by the HSCIC.

7.1.8 Information tools derived from this Data must not be provided to other organisations without the specific consent of the HSCIC.

7.1.9 The HSCIC retains copyright of the Data, unless otherwise instructed and this must be cited correctly as follows:

> Copyright © 2017, re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

7.1.10 The Data Recipient shall ensure that any publication derived from the Data by any party complies with the following guidance:

(a) Anonymisation Standard for Publishing Health and Social Care Data: http://www.isb.nhs.uk/library/standard/128; and

(b) Anonymisation: managing data protection risk code of practice: http://ico.org.uk/for_organisations/data_protection/topic_guides/anonymisation.

7.1.11 Where the Data derives from the Office for National Statistics, the Data Recipient must also comply with the following guidance:

(a) ONS Guidance for Health Statistics: http://www.ons.gov.uk/ons/guide-method/best-practice/disclosure-control-of-health-statistics/index.html; and

(b) ONS policy on protecting confidentiality within birth and death statistics and the Code of Practice for Official Statistics: http://www.ons.gov.uk/ons/guide-method/best-practice/disclosure-control-policy-for-birth-and-death-statistics/index.html.

7.1.12 Before undertaking any Publishing activity using the Data or any derived information, the Data Recipient must undertake an organisational risk assessment exercise to ensure compliance with the above guidelines.

7.1.13 The HSCIC reserves the right to undertake an audit with respect to the use and storage of the Data to ensure that the terms of this DSA are being abided by.

7.1.14 If the Data Recipient wishes to retain the Data beyond the expiration date of this DSA, it must contact the HSCIC not less than one month prior to the expiration date to request an extension to this DSA. Under no circumstances shall the Data Recipient retain the Data without an extant DSA in place.

8.Data Access

8.1 Under the terms of this DSA, the Data Recipient must ensure that access to the Data is managed, auditable and restricted to those individuals who need to process the Data for the specific purpose/s outlined in this DSA.

9.Data Security Requirements

9.1 The Data Recipient undertakes to comply with all of the information security provisions set out in the Data Sharing Framework Contract. Some of the key terms are reproduced at paragraph 9.2 below for the Data Recipient's information purposes only.

9.2 The Data Recipient must:

9.2.1 implement and maintain security standards, processes, procedures, practice and controls appropriate to the nature of the Data received and the harm that would be caused by its loss or disclosure;

9.2.2 process Personal Data and/or sensitive data only for health and social care purposes, and only for purposes described in this DSA which are consistent with the purposes recorded in the Data Recipient's data protection registration with the Information Commissioner's Office;

9.2.3 process the minimum data necessary (e.g. using age range rather than age if sufficient);

9.2.4 ensure that access to the Data is limited to those employees who need access to the Data for the purpose stated in this DSA;

9.2.5 ensure that the Data supplied is stored on a secure system password protected and that all computer terminals and other means of access are maintained securely in secure premises;

9.2.6 ensure the rights of individuals are met, such as satisfying subject access requests received, ensuring data accuracy and correcting errors, and handling objections and complaints;

9.2.7 permanently destroy/delete or erase the Data once it is no longer required for the purpose for which it was collected and confirming destruction to the HSCIC in accordance with this DSA;

9.2.8 ensure that all employees with access to the Data understand the confidential nature of the Data and their responsibilities;

9.2.9 report immediately to the HSCIC any security incidents relating to use of the Data, and any breaches of the terms of this DSA.

9.3 The named person must not share their password with any other person at any time. Once the Data has been transmitted by the HSCIC, the Data Recipient shall be responsible for the security of the Data.

Charges

10.Principles of charging

10.1 The HSCIC operates on a cost recovery basis, where the costs of data provision under this DSA are not fully covered by those statutory duties which are covered by its central organisational funding. The HSCIC does not seek to make an operating profit from providing services under this DSA.

10.2 The following charges shall be recouped via the Service Production Fee specified in **Annex A: section 11**

10.2.1 all design or implementation specific services required to generate bespoke datasets or extracts; and

10.2.2 all administration services associated with providing access to the same.

10.3 The following charges shall be recouped via the Licence Fee specified in **Annex A: section 11**

10.3.1 delivery and maintenance services to support the ongoing provision of bespoke datasets or extracts;

10.3.2 security and audit services in support of HSCIC stewardship of sensitive data.

10.4 The audit fees in **Annex A: section 11** represent the approximate expected cost to the Data Recipient where the HSCIC undertakes an audit which reveals that the Data Recipient either has not complied, or is not complying, with any of its obligations under the Data Sharing Framework Contract and/or this DSA

11.Sub-licensing conditions

11.1 The Data Recipient may only sub-licence the Data in accordance with the conditions set out in **Annex A: section 10**

11.2 Any breach of these sub-licensing conditions by the Data Recipient or the sub-licensee shall entitle the HSCIC to terminate this DSA.

Annex A: Application Summary

1a: General

Request Number	DARS-NIC-29554-L0P4F-v1.5
Request Title:	MR1208 - Do hormonal treatments for assisted reproduction increase risk of cancer or mortality?
DSA Start Date	12/11/2016
DSA End Date	29/12/2017

1b: Data Controller(s)

- University College London (UCL)

Data Controller University College London (UCL)

Gower Street
London
WC1E 6BT
England

Organisation Type: Academic

Data Controller Type: Sole Data Controller

HSCIC Framework Contract Reference: CON-321538-B5D8B

Contract Expiry Date:

Security Assurances for Data Controller

Type: IG Toolkit

Version: Version 13 (2015-16)

Date Completed: 18/04/2016

Comments:

Org Code: EE133902-SLMS-DSH

IGT Score: 71% Reviewed, Satisfactory

IGT Reviewed Date: 18/04/2016

Date Checked by HSCIC: 27/10/2016

DPA Registration

DPA Registration Number: Z6364106

DPA Organisation Name: University College London

Expiry Date: 28/01/2017

DPA Checked On : 27/10/2016

Activity Recorded:

Description of processing

The following is a broad description of the way this organisation/data controller processes personal information. To understand how your own personal information is processed you may need to refer to any personal communications you have received, check any privacy notices the organisation has provided or contact the organisation to ask about your personal circumstances.

Reasons/purposes for processing information

We process personal information to enable us to provide education and support services to our students and staff; advertising and promoting the university and the services we offer; publication of the university magazine and alumni relations, undertaking research and fundraising; managing our accounts and records and providing commercial activities to our clients. We also process personal information for the use of CCTV systems to monitor and collect visual images for the purposes of security and the prevention and detection of crime. To provide healthcare services for patients of NHS partner hospitals

Type/classes of information processed

We process information relevant to the above reasons/purposes. This may include:
•personal details
•family details
•lifestyle and social circumstances
•education details and student records
•education and employment details
•financial details
•disciplinary and attendance records
•vetting checks;
•goods or services provided
•visual images, personal appearance and behaviour
•information held in order to publish university publications

We also process sensitive classes of information that may include:
•racial or ethnic origin
•trade union membership
•religious or other similar beliefs
•physical or mental health details
•sexual life
•offences and alleged offences
•criminal proceedings, outcomes and sentences

Who the information is processed about

We process personal information about:
•students
•employees, contracted personnel
•suppliers, professional advisers and consultants
•business contacts
•landlords, tenants
•complainants, enquirers
•donors and friends of the University
•authors, publishers and other creators
•persons who may be the subject of enquiry
•third parties participating in course work
•health, welfare and social organisations
•friends of the University
•individuals captured by CCTV images
•patients of NHS partner hospitals

Who the information may be shared with

We sometimes need to share the personal information we process with the individual themself and also with other organisations. Where this is necessary we are required to comply with all aspects of the Data Protection Act (DPA). What follows is a description of the types of organisations we may need to share some of the personal information we process with for one or more reasons.

Where necessary or required we share information with:
•family, associates and representatives of the person whose personal data we are processing
•current, past or prospective employers
•healthcare, social and welfare organisations
•educators and examining bodies
•suppliers and service providers
•student union
•financial organisations
•debt collection and tracing agencies
•auditors
•police forces, security organisations
•courts and tribunals
•prison and probation services
•legal representatives
•local and central government
•consultants and professional advisers
•trade union and staff associations
•survey and research organisations
•press and the media
•voluntary and charitable organisations
•landlords

Undertaking Research

Personal information is also processed in order to undertake research, including research relating to health and for the diagnosis of patients. For this reason the information processed may include name, contact details, family details, lifestyle and social circumstances, financial details, good and services. The sensitive types of information may include physical or mental health details, racial or ethnic origin and religious or other beliefs and offences and alleged offences criminal proceedings, outcomes and sentences. This information may be about survey respondents. Where necessary or required this information may be shared with customers and clients, agents, service providers, survey and research organisations.

Transfers

It may sometimes be necessary to transfer personal information overseas. When this is needed information may be transferred to countries or territories around the world. Any transfers made will be in full compliance with all aspects of the data protection act.

1c: Data Processor(s)

- University College London (UCL)

Data Processor Area:	England/Wales
Organisation Address:	Gower Street London WC1E 6BT England

Security Assurances for Data Processor

Type:	IG Toolkit
Version:	Version 13 (2015-16)
Date Completed:	18/04/2016
Comments:	

Org Code: EE133902-SLMS-DSH

IGT Score:	71% Reviewed, Satisfactory
IGT Reviewed Date:	18/04/2016
Date Checked by HSCIC:	27/10/2016

DPA Registration

DPA Registration Number:	Z6364106
DPA Organisation Name:	University College London
Expiry Date:	28/01/2017
DPA Checked On:	27/10/2016

Activity Recorded:

As per data controller details

2. Locations

2a. Processing Location(s)

UCL- GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Location Area:	England & Wales
Organisation Address:	General and Adolescent Paediatric Unit 30 Guildford Street London WC1N 1EH

2b. Storage Location(s)

UCL- GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Location Area:	England & Wales
Organisation Address:	General and Adolescent Paediatric Unit 30 Guildford Street London WC1N 1EH

2c. Territory of use

England/Wales

3. Datasets Held/Requested

3a. Data Access Already Given

Dataset	Extract Type	Identifiability	Sensitivity	Periods	Legal Basis for Dissemination	Data Minimisation

MRIS - Flagging Current Status Report	Extract	Identifiable [Death] Entry Number OR Cancer Type [Death] Register Number OR Cancer Site [Death] Registration District OR Cancer Registration Number Supplied Member Number [Death] Registration Sub District OR Cancer Anniversary Year	Sensitive Event Date	N/A	National Health Service Act 2006 - s251 - 'Control of patient information'.	Cohort
MRIS - Cause of Death Report	Extract	Identifiable Cause of Death text C Cause of Death text A Third Forename of Deceased Other Forename of Deceased Also known as Surname of Deceased Date of Birth Second Forename of Deceased Cause of Death text E Cause of Death text B Maiden Name Cause of Death text D Supplied Member Number Address of Deceased Surname of deceased Event Details Date of Death First Forename of Deceased	Sensitive ICD9 Multiple Cause Code 5, ICD9 Multiple Cause Code 3, ICD10 Multiple Cause Code 14, ICD9 Multiple Cause Code 11, ICD10 Multiple Cause Code 13, ICD10 Multiple Cause Code 1, ICD9 multiple cause code 14, ICD9 Multiple Cause Code 15, ICD9 Multiple Cause Code 13, ICD9 Multiple Cause Code 7, ICD9 Multiple Cause Code 8, Event Date, ICD9 Underlying Cause, ICD9 Multiple Cause Code 1, ICD10 Multiple Cause Code 5, ICD9 Multiple Cause Code	N/A	National Health Service Act 2006 - s251 - 'Control of patient information'.	Cohort

			9, ICD9 Multiple Cause Code 6, ICD9 Multiple Cause Code 4, ICD10 Multiple Cause Code 3, ICD10 Multiple Cause Code 8, ICD10 Multiple Cause Code 4, ICD10 Multiple Cause Code 6, ICD10 Multiple Cause Code 12, ICD10 Underlying Cause, ICD10 Multiple Cause Code 9, ICD9 Multiple Cause Code 12, ICD10 Multiple Cause Code 11, ICD9 Multiple Cause Code 2, ICD10 Multiple Cause Code 2, ICD10 Multiple Cause Code 15, ICD10 Multiple Cause Code 7, ICD10 Multiple Cause Code 10, ICD9 Multiple Cause Code 10, Place of Death			

3b. Additional Data Access Requested

Dataset	Extract Type	Identifiability	Sensitivity	Periods	Legal Basis for Dissemination	Data Minimisation

3c. Patient objections

Patient Objections applied? Yes

4. Fair processing

1. Transparency- This project is open and transparent. This project has section 251 support. It also has Human Fertilization & Embryology Authority (HFEA) approval. It is published on the HFEA website and through HFEA networks. (http://www.hfea.gov.uk/docs/2010-09-14_Lay_Summary_of_Cancer_in_Women_after_ART_Study_Sutcliffe_Register_Research_Panel_Final.PDF)

2. Not detrimental to data subjects- No study subjects have or are expected to come to harm through this project. Subjects are not contacted directly and UCL only hold anonymous data.

3. Data handled reasonably- As above UCL only hold anonymous data for this project. Without receiving the list of UMN and identifiable data held at NHS digital (which will not be allowed to happen), UCL will never be able to identify any data subject from information held. Never the less the data is held securely, encrypted and password protected. In October 2016, UCL is moving this anonymous data to their Data Safe Haven (as part of a general move towards improving information governance within the organization).

5. Purpose/Methods/Outputs

5a. Objective for processing:

The objectives of this research project are: -

1. To investigate the relationship between hormonal treatment and site specific risks of cancer incidence, especially reproductive related cancers, in relation to type of treatment, especially type, duration and age of exogenous hormone exposure.

2. To establish if there is any link between cause-specific mortality and Assisted Reproductive Technology (ART) exposure.

Both of these objectives relate to long standing clinical questions to which answers are unclear (there is genuine clinical equipoise in this case). Data received from NHS digital are being analyzed to directly answer these research questions.

The assisted reproduction authority (HFEA) has approved and supports this research. The research is being undertaken by University College London. Outputs will relate to a similar but unrelated project (MR1318).

5b. Processing activities:

No further data dissemination is being requested. This request is for an extension to the data sharing agreement for the data already held.

Data processing for this project has been designed to ensure that identifiable data are seen by the fewest number of people at secure locations in secure methods as possible.

Identifiable data held by the Human Fertilisation and Embryology Authority (HFEA) has been encrypted and securely sent to NHS Digital (file 1 on attached data flow) who linked this data to MRIS. File 3 in the data flow was no required and thus was not sent. Cancer and Death outcomes were then securely transported to UCL along with unique member number (file 5 in data flow). This was then linked to HFEA clinical data (minus identified data) and resulted in file 8 which is still securely held at UCL and currently in the final stages of analysis. File 8 is largely anonymous as UCL staff members have never had (and will never have) the key file 9 which details unique member against corresponding identifiable data. The only identifiable data held by UCL is date of death.

Thus file 8 is held encrypted and securely at UCL. As mentioned further on in this application, this data is currently being transferred (within unit) to UCL's data safe haven in October 2016 as part of UCL's move to improved data security. Copies used for transfer will be securely deleted.

As mentioned further on, this data is currently being used to produce the first scientific paper which will be submitted to a broad medical journal (New England Journal of Medicine) to help inform IVF practitioners about cancer risks after assisted conception. A further paper regarding mortality risk in this cohort is at an earlier stage of analysis.

5c. Specific Outputs Expected, Including Target Date:

The main paper 'Risk of Ovarian, Breast and Endometrial Carcinoma in Women after assisted conception; 2.2 million person years of observation in Great Britain' is currently being drafted (along side final analysis). UCL expect this to submitted to a peer-reviewed journal (the New England Journal of Medicine) by the end of 2016. The main paper investigating mortality in this cohort is expected to be submitted to a peer-reviewed journal by mid 2017.

These journals are likely to be subscription only, however abstracts of this work will be open access. The main audience for these papers will be a broad scientific/ clinical audience, in order that clinicians disseminate results to their service users.

Additionally UCL will produce a report for the HFEA to publish open access on their website and disseminate via their networks (by end of 2017).

Outputs will contain only aggregate level data with small numbers suppressed in line with analysis guidance. This has been the case in published related work http://www.nejm.org/doi/full/10.1056/NEJMoa1301675#t=article

5d. Expected Measurable Benefits to Health and/or Social Care Including Target Date:

The benefits of this data sharing are not specifically measurable but are very important to assisted conception service users. The main benefit of this project is that it will provide assisted conception clinicians and service users with safety data regarding carcinoma risk. These risk estimates be the most robust ever produced, given the cohort size and strength. This is important given the high degree of uncertainty which surrounds cancer after assisted conception.

Most of these risk estimates are currently being finalized and therefore the main benefits of this study will be realized within the next 6-12 months, once scientific papers are published (2017) and the HFEA report is disseminated (before the end of 2017).

However preliminary cancer risks (breast, ovarian and endometrial) after assisted conception have already been presented at an international conference for assisted conception clinicians and were given widespread coverage (https://www.asrm.org/For_Women_Having_IVF_Infertility_Status_and_Diagnosis_Determine_Ovarian_Cancer_Risk/).

Related work on this cohort has provided reassurance that children born after assisted conception are not at overall greater risk of cancer than the general population. (http://www.nejm.org/doi/full/10.1056/NEJMoa1301675) (http://www.hfea.gov.uk/7913.html).

5e. Is the Purpose of this Application in Anyway Commercial?

No

6. Special Conditions

7. Approval Considerations

Materials Reviewed	Version	Date of Document	Date of Approval	Expiry / Review Date	Comments
Protocol	1	04/05/2010	04/05/2010	03/02/2017	SD1
Section 251 Support	1	03/02/2011	03/02/2011	03/02/2017	Original section 251 approval
Section 251 Support	1	17/04/2012	03/02/2011	03/02/2017	First annual review
Section 251 Support	1	18/06/2013	18/06/2013	03/02/2017	Second annual review

8. Period and Funding

8a. Data Retention

Indicative Data Retention Period: 29/12/2017

Reason for this Period:	UCL expect to complete analysis involving date of death by the end of 2017. Therefore this data will be deleted by 29/12/2017.

8b. Funding Sources

Type of Funding Source:	Public
Awarding Institution:	National Institute for Health Reserach
EU/International programme:	
Reference and title of project/activity:	DRF-405526
Year of submission/award:	
Applicant or Partner:	Applicant
Funding evidence URL:	

Type of Funding Source:	Public
Awarding Institution:	Cancer Research UK
EU/International programme:	
Reference and title of project/activity:	C36038/A11704.
Year of submission/award:	13/04/2011
Applicant or Partner:	Applicant
Funding evidence URL:	

9. ONS Users

10. Sub-licencing

Does sub-licensing apply?	No

11. Charges

Set up and first year service charge	£800.00
Annual Service Charge	£0.00

In the event that an audit by NHS Digital reveals that the data recipient either hasn't complied with, or is not complying with, any of its obligations under the Data Sharing Framework Contract or Data Sharing Agreement, the audit fees of £15,000.00 will be chargeable to the data controller named in this agreement.

Annex B: Additional technical information

1. Data to be received by HSCIC under this agreement

Linkage already carried out to NHS central register through MRIS system.

2. HSCIC data covered by this agreement

A summary of the datasets covered by this agreement are shown in section 3 above.

2a. Data already held

- **MRIS - Flagging Current Status Report**

Periods

N/A

Sensitive fields

[Event Date] Event Date

Identifiable fields

[[Death] Entry Number OR Cancer Type] [Death] Entry Number OR Cancer Type,
[[Death] Register Number OR Cancer Site] [Death] Register Number OR Cancer Site,
[[Death] Registration District OR Cancer Registration Number] [Death] Registration District OR Cancer Registration Number,
[Supplied Member Number] Supplied Member Number,
[[Death] Registration Sub District OR Cancer Anniversary Year] [Death] Registration Sub District OR Cancer Anniversary Year

Other fields

[Cancelled Event / Amended Event / Duplicated Patient Notification] Cancelled Event / Amended Event / Duplicated Patient Notification,
[Event Type] Event Type,
[Latest Posting] Latest Posting,
[Date of Latest Posting] Date of Latest Posting,
[[Blank] OR Cancer Behaviour] [Blank] OR Cancer Behaviour

Filters/minimisation efforts

Cohort

Data Transfer Method

MR products

MR reference number	MR1208
Bespoke/other	
Recommended method	Automated

Output

Output File description	csv
De-identified details	No
Data delivery	

- **MRIS - Cause of Death Report**

Periods

N/A

Sensitive fields

[ICD9 Multiple Cause Code 5] ICD9 Multiple Cause Code 5,
[ICD9 Multiple Cause Code 3] ICD9 Multiple Cause Code 3,
[ICD10 Multiple Cause Code 14] ICD10 Multiple Cause Code 14,
[ICD9 Multiple Cause Code 11] ICD9 Multiple Cause Code 11,
[ICD10 Multiple Cause Code 13] ICD10 Multiple Cause Code 13,
[ICD10 Multiple Cause Code 1] ICD10 Multiple Cause Code 1,
[ICD9 multiple cause code 14] ICD9 multiple cause code 14,
[ICD9 Multiple Cause Code 15] ICD9 Multiple Cause Code 15,
[ICD9 Multiple Cause Code 13] ICD9 Multiple Cause Code 13,
[ICD9 Multiple Cause Code 7] ICD9 Multiple Cause Code 7,
[ICD9 Multiple Cause Code 8] ICD9 Multiple Cause Code 8,
[Event Date] Event Date,
[ICD9 Underlying Cause] ICD9 Underlying Cause,
[ICD9 Multiple Cause Code 1] ICD9 Multiple Cause Code 1,
[ICD10 Multiple Cause Code 5] ICD10 Multiple Cause Code 5,
[ICD9 Multiple Cause Code 9] ICD9 Multiple Cause Code 9,
[ICD9 Multiple Cause Code 6] ICD9 Multiple Cause Code 6,
[ICD9 Multiple Cause Code 4] ICD9 Multiple Cause Code 4,
[ICD10 Multiple Cause Code 3] ICD10 Multiple Cause Code 3,
[ICD10 Multiple Cause Code 8] ICD10 Multiple Cause Code 8,
[ICD10 Multiple Cause Code 4] ICD10 Multiple Cause Code 4,
[ICD10 Multiple Cause Code 6] ICD10 Multiple Cause Code 6,
[ICD10 Multiple Cause Code 12] ICD10 Multiple Cause Code 12,
[ICD10 Underlying Cause] ICD10 Underlying Cause,
[ICD10 Multiple Cause Code 9] ICD10 Multiple Cause Code 9,
[ICD9 Multiple Cause Code 12] ICD9 Multiple Cause Code 12,
[ICD10 Multiple Cause Code 11] ICD10 Multiple Cause Code 11,
[ICD9 Multiple Cause Code 2] ICD9 Multiple Cause Code 2,
[ICD10 Multiple Cause Code 2] ICD10 Multiple Cause Code 2,
[ICD10 Multiple Cause Code 15] ICD10 Multiple Cause Code 15,
[ICD10 Multiple Cause Code 7] ICD10 Multiple Cause Code 7,
[ICD10 Multiple Cause Code 10] ICD10 Multiple Cause Code 10,
[ICD9 Multiple Cause Code 10] ICD9 Multiple Cause Code 10,
[Place of Death] Place of Death

Identifiable fields

[Cause of Death text C] Cause of Death text C,
[Cause of Death text A] Cause of Death text A,
[Third Forename of Deceased] Third Forename of Deceased,
[Other Forename of Deceased] Other Forename of Deceased,
[Also known as Surname of Deceased] Also known as Surname of Deceased,
[Date of Birth] Date of Birth,
[Second Forename of Deceased] Second Forename of Deceased,
[Cause of Death text E] Cause of Death text E,
[Cause of Death text B] Cause of Death text B,
[Maiden Name] Maiden Name,
[Cause of Death text D] Cause of Death text D,
[Supplied Member Number] Supplied Member Number,
[Address of Deceased] Address of Deceased,
[Surname of deceased] Surname of deceased,
[Event Details] Event Details,
[Date of Death] Date of Death,
[First Forename of Deceased] First Forename of Deceased

Other fields

[Cancelled Event / Amended Event / Duplicated Patient Notification] Cancelled Event / Amended Event / Duplicated Patient Notification,
[Date of Inquest] Date of Inquest,
[Place of Birth text] Place of Birth text,
[Event Type] Event Type,
[Gender of Deceased] Gender of Deceased,
[Latest Posting] Latest Posting,
[Date of Latest Posting] Date of Latest Posting,
[Date of Registration] Date of Registration,
[Occupation] Occupation

Filters/minimisation efforts

Cohort

Data Transfer Method

2b. Additional data provided under this agreement

3. Additional Information

Recommended product(s)

List Clean	No
Patient Status	Yes
Patient Tracking	No

Additional Technical Detail

Extension Only to HOLD data already received - no future dissemination of data

Annex C: Approval Information

Signed for and on behalf of the Information Asset Owner:	
Name:	Garry Coleman
Electronic approval reference:	51150DCE-4B03-CC4A-3944-8DF6B5FF76AB
Organisation Name:	The Health and Social Care Information Centre
Role:	Head of Business and Operational Delivery
Date/time:	27/01/2017

Signed for and on behalf of the Health and Social Care Information Centre:	
Name:	Terry Hill
Electronic approval reference:	5A637674-5C1F-587D-DAE2-6711229D42E8
Role:	Business and Operational Delivery Director
Date/time:	30/01/2017

Signed for and on behalf of the Data Recipient:	
Organisation Name:	University College London (UCL)
Electronic approval reference:	293f4d87-3f08-4c76-94f1-c0acfa000eed03/02/2017 13:22:18
Name:	Alastair Sutcliffe
Position in organisation:	
Date:	03/02/2017

e) Scottish Approval- women's study

General Register Office for Scotland
Cairnsmore House, Crichton Business Park, Dumfries,
DG1 4GW

Direct line 01387 259823 International +44 1387 259823
Facsimile 01387 247958
Email dumf-ubb.NHSCR-Scotland-Medical-Research@nhs.net

Any reply should be addressed to NHSCR

Dr A D Sutcliffe
Senior Lecturer in Child Health/Consultant Paediatrician.
General Adolescent Paediatric Unit
Institute of Child Health
30 Guildford Street
London
WC1N 1EH

Your reference

Our reference MR 1208

Date 13 January 2011

Dear Dr Sutcliffe

Do Hormonal Treatments for Assisted Reproduction Increase Risk of Cancer or Mortality? A National Cohort

The Privacy Advisory Committee has considered and approved your request to flag records in NHSCR to be informed of deaths, cancers, exits and postings in support of the above study. Information will be sent to you attached to study number only.

Conditions applied: None

Time period: As specified

Points highlighted: None

The approval of the Committee is for a period of 5 years from the date of this letter. Any change to the terms of your application, including changes in data user(s), additional data fields or extension of the time period approved must be requested through Susan Kerr, PAC Administrator on 0131 275 6455 or susan.kerr2@nhs.net

Please note that the following details about your application will be published under the following headings on the PAC website at http://www.isdscotland.org/isd/3048.html later this year:

Application Number	Date Received	Title	Summary	PAC Recommendation	NSS Decision	Date Completed

If you have any questions on how to progress your study in Scotland, please contact Isobel Wilson on 01387 259824 for advice.

Yours sincerely,

Dr Janet Murray
Consultant in Public Health Medicine

f) Children's study research ethics committee approval

NHS
National Research Ethics Service
North West London REC 2
Royal Free Hospital NHS Trust
Royal Free Hospital
South House, Block A
Pond Street
London
NW3 2QG

Telephone: 0207 794 0581
Facsimile: 0207 794 0714

23 June 2010

Dr Alastair Sutcliffe
Senior Lecturer in Child Health
Institute of Child Health
30 Guilford Street
London
30 Guilford Street, London
WC1N 1EH

Dear Dr Sutcliffe

Study Title: **Are children born after assisted reproduction at increased risk of cancer? A population based linkage study.**

REC reference number: **10/H0720/45**

The Research Ethics Committee reviewed the above application at the meeting held on 16 June 2010. Thank you for attending to discuss the study.

Ethical opinion

The background to this study is to establish if children born after assisted reproductive therapies ((ART) such as IVF), are at increased risk of developing childhood cancer compared to spontaneously conceived children. The committee recently approved a study similar to this one. This group of researcher have got permission from the Assisted Reproduction Database and the Childhood Cancer database to look at in formation on their database for researcher purposes.
The researcher gave copies of approval from these Groups to the committee
The study was approved

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Investigator CV		26 April 2010
Protocol	2.6	22 December 2009
REC application		
Summary/Synopsis		20 April 2010
Dr Carrie Williams CV		26 April 2010
Picture by ART Conceived Cancer Sufferer		
Evidence of insurance or indemnity		01 August 2009
Letter of Support - Infertility UK		18 December 2009
Letter of Support - ACEBABES		22 December 2009
Letter of Support - CCLG Mr Mark Gaze		
Written Questions from ART Parents		
Letter from Parentof ART Child who died of Cancer		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0720/45 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

Dr Michael Pegg
Chair

[redacted]

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" [SL-AR1 for CTIMPs, SL-AR2 for other studies]

Copy to: *Ms Sabine Klager*
[R&D office for NHS care organisation at lead site]

g) Children's study, section 251 approval

NIGB

Ethics and Confidentiality Committee

Dr Alastair Sutcliffe
General and Adolescent Paediatric Unit
Institute of Child Health
30 Guilford Street
London
WC1N 1EH

NIGB Office,
Floor 7,
New Kings Beam House,
22 Upper Ground,
London,
SE1 9BW.

Tel: (020) 7633 7052

Email: eccapplications@nhs.net

[redacted]

03 May 2011

Dear Dr Sutcliffe

ECC (HFEA) 5-04 (a) /2010 - Are children born after assisted reproduction at increased risk of cancer? A population based linkage study.

Thank you for applying for support under section 251 of the NHS Act 2006 and Health service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent.

This application has been processed in line with a memorandum of understanding developed between the Human Fertilisation and Embryology Authority (HFEA) and the NIGB Ethics and Confidentiality Committee (ECC). This application was originally considered by the Committee at its meeting on 02 June 2010.

Background

It has been agreed that the HFEA will delegate the handling and assessment of all applications with a medical purpose under the Human Fertilisation and Embryology (HFE) Act 1990 to the NIGB Ethics and Confidentiality Committee (ECC). Under this delegated authority, the ECC will consider and recommend to the HFEA whether to grant or refuse permission to use identifiable register information (or to impose conditions upon its use). As data controller of the Register, the HFEA will take a final decision based upon this recommendation, and then if disclosure is permitted will work with the applicant to enable use of the dataset. In terms of disclosure of patient information not contained in the HFEA register, the ECC will take the final decision under section 251 of the NHS Act 2006.

Outcome

Further to the update letter dated 28 June 2010, this confirmed that the Committee provided provisional approval under section 251 to access patient identifiable information from the UK Registry of Childhood Tumours (NRCT), and provided a recommendation of support to the HFEA to permit this linkage of data from the UK Registry of Childhood Tumours (NRCT) and the Human Fertilisation and Embryology Authority Register in order to assess the risk of cancer in children born after assisted reproduction. It is also understand that the HFEA accepted this

h) Caldicott Guardian Approval NRCT

DEPARTMENT OF PAEDIATRICS
CHILDHOOD CANCER RESEARCH GROUP

Richards Building, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LG
Tel: +44(0)1865 617800 Fax: +44(0)1865 617801
www.ccrg.ox.ac.uk

[redacted]

UNIVERSITY OF OXFORD

26 October 2021

National Information Governance Board Office
Floor 7
New Kings Beam House
22 Upper Ground
London
SE1 9BW

Dear Sir,

Are children born after assisted reproduction at increased risk of cancer? A population based linkage study.

The above study has been designed by Dr Alastair Sutcliffe and colleagues and will involve data extracted from the National Registry of Childhood Tumours (NRCT) maintained by the Childhood Cancer Research Group (CCRG) in Oxford.

The NRCT is affiliated to the National Association of Cancer Registries and has section 251 support under the NRS Act 2006 for its routine registry functions. The CCRG has adequate facilities and security procedures in place to ensure the safe handling of the patient identifiable information required by the study. Further details can be found in the relevant parts of the NIGB application form.

Yours faithfully,

[redacted]

Kathryn Bunch

Caldicott Guardian
Childhood Cancer Research Group

i) Caldicott Guardian Approval Great Ormond Street Institute of Child Health

Great Ormond Street Hospital for Children NHS Trust

Great Ormond Street
London WC1N 3JH

Tel: 020 7405 9200

Date 21/4/10

Dear representatives of the Ethics and Confidentiality Committee,

1. 'Are children born after assisted reproduction at increased risk of cancer? A population based linkage study.' A. Sutcliffe et al. Intitute of Child Health R&D Ref. 09GP17, UCL Data protection registration number Z6364106/2010/04/54.

2. 'Do hormonal treatments for assisted reproduction increase risks of cancer or mortality in women? A national cohort study'. A. Sutcliffe et al. Institute of Child Health R&D ref. 09GP13, UCL Data protection registration number Z6364106/2010/03/21.

I have been asked to review these studies in my capacity as Caldicott Guardian for Great Ormond Street Hospital NHS Trust. I am happy with the proposals from a "Caldicott" perspective.

Yours sincerely,

[redacted]

Mr Robert D Evans [MScD FDSRCS (Eng) FDSRCS (Ed) M.Orth RCS (Ed)]
Co-Medical Director/Caldicott Guardian

[redacted]

Appendix 4; Women's cancer selected Stata logs

a) Breast Cancer

All Breast Cancer.pdf

b) Ovarian Cancer

All ovarian cancer.pdf

c) Corpus Uteri Cancer

All Corpus Uteri cancer.pdf

Appendix 5; Children's cancer selected Stata logs

a) Childhood cancer, data cleaning logs

Childhood cancer data cleaning.pdf

b) Childhood cancer analysis

Childhood cancer Analysis part 1.pdf

Childhood cancer analysis part 2.pdf

Childhood cancer analysis part 3.pdf

c) Childhood cancer, donor data

Childhood cancer, donor.pdf

Appendix 6; Study Publications; a) Women's Study

Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation

Carrie L Williams,[1] Michael E Jones,[2] Anthony J Swerdlow,[2] Beverley J Botting,[1] Melanie C Davies,[3] Ian Jacobs,[3,4] Kathryn J Bunch,[5] Michael F G Murphy,[6] Alastair G Sutcliffe[1]

[1]UCL Great Ormond Street Institute of Child Health, London, UK
[2]Institute of Cancer Research, London, UK
[3]Institute for Women's Health, University College London Hospitals, London, UK
[4]University of New South Wales, Sydney, NSW, Australia
[5]National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK
[6]Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

Correspondence to:
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Cite this as: *BMJ* 2018;362:k2644
http://dx.doi.org/10.1136/bmj.k2644

Accepted: 4 June 2018

ABSTRACT

OBJECTIVE
To investigate the risks of ovarian, breast, and corpus uteri cancer in women who have had assisted reproduction.

DESIGN
Large, population based, data linkage cohort study.

SETTING AND PARTICIPANTS
All women who had assisted reproduction in Great Britain, 1991-2010, as recorded by the Human Fertilisation and Embryology Authority (HFEA).

INTERVENTIONS
HFEA fertility records for cohort members were linked to national cancer registrations.

MAIN OUTCOME MEASURES
Observed first diagnosis of ovarian, breast, and corpus uteri cancer in cohort members were compared with age, sex, and period specific expectation. Standardised incidence ratios (SIRs) were calculated by use of age, sex, and period specific national incidence rates.

RESULTS
255 786 women contributed 2 257 789 person years' follow-up. No significant increased risk of corpus uteri cancer (164 cancers observed *v* 146.9 cancers expected; SIR 1.12, 95% confidence interval 0.95 to 1.30) was found during an average of 8.8 years' follow-up. This study found no significantly increased risks of breast cancer overall (2578 *v* 2641.2; SIR 0.98, 0.94 to 1.01) or invasive breast cancer (2272 *v* 2371.4; SIR 0.96, 0.92 to 1.00). An increased risk of in situ breast cancer (291 *v* 253.5; SIR 1.15, 1.02 to 1.29; absolute excess risk (AER) 1.7 cases per 100 000 person years, 95% confidence interval 0.2 to 3.2) was detected, associated with an increasing number of treatment cycles (P=0.03). There was an increased risk of ovarian cancer (405 *v* 291.82; SIR 1.39, 1.26 to 1.53; AER 5.0 cases per 100 000 person years, 3.3 to 6.9), both invasive (264 *v* 188.1; SIR 1.40, 1.24 to 1.58; AER 3.4 cases per 100 000 person years, 2.0 to 4.9) and borderline (141 *v* 103.7; SIR 1.36, 1.15 to 1.60; AER 1.7 cases per 100 000 person years, 0.7 to 2.8). Increased risks of ovarian tumours were limited to women with endometriosis, low parity, or both. This study found no increased risk of any ovarian tumour in women treated because of only male factor or unexplained infertility.

CONCLUSIONS
No increased risk of corpus uteri or invasive breast cancer was detected in women who had had assisted reproduction, but increased risks of in situ breast cancer and invasive and borderline ovarian tumours were found in this study. Our results suggest that ovarian tumour risks could be due to patient characteristics, rather than assisted reproduction itself, although both surveillance bias and the effect of treatment are also possibilities. Ongoing monitoring of this population is essential.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Risks of reproductive cancers in women who have undergone assisted reproduction procedures are uncertain

Some previous studies have suggested a possible increased risk of breast cancer in women treated at younger ages and with multiple cycles; previous studies investigating endometrial cancer risk are underpowered

Early studies suggested increased risks of ovarian cancer in these women, while more recent studies are more reassuring, although inconsistent, regarding any increase in borderline ovarian tumours

WHAT THIS STUDY ADDS

In this large population based study, endometrial cancer was not increased in women who had assisted reproduction in Great Britain in 1991-2010 when compared with the general population

The risk of breast cancer overall and of invasive breast cancer was not increased, but there was a small increased risk of in situ breast cancer

Increased risks of ovarian cancer, both invasive and borderline, were observed but limited to women with other known risk factors; these findings require further investigation

Introduction

Assisted reproduction cycles usually involve exposure to supraphysiological levels of oestradiol, exogenous gonadotropins, and multiple ovarian punctures, all potentially carcinogenic.[1 2] Most concern surrounds the risks of breast, endometrial, and ovarian cancers after such exposures.[3-16]

Studies investigating breast cancer risks in women who underwent assisted reproduction are inconsistent.[3-12] Although some studies have shown an increased risk,[17] most studies do not show an overall increase of breast cancer in exposed women.[3-8 10] However, some suggest a possible increased risk within subgroups,[8 9] including women treated at younger ages[9] and with multiple cycles.[8] Most studies investigating endometrial cancer risk in exposed populations have not found a significant increased risk.[3 4 6 7 18] However, most studies have provided very imprecise estimates

due to small sample size and few events.[3 4 6 18] One study suggested an increased risk of endometrial cancer associated with exposure to gonadotrophins, commonly used as part of assisted reproductive technology.[19] Some early studies investigating fertility drugs used alone, such as single agent oral clomifene, suggested increased risks of ovarian cancer.[20] Others found no association between fertility drugs and ovarian cancer risk.[21] Recent investigations into their use as part of assisted reproduction have generally been more reassuring, but remain inconsistent and at risk of bias.[4 5 11] Some[13 14] but not all studies[6] have found an increase in borderline tumours.

Given previous inconsistent results, small study size, and lack of information on potential confounders, we undertook a population based linkage study in Britain to provide risk estimates for ovarian, breast, and corpus uteri cancer, in a cohort of over 266 000 women undergoing assisted reproduction, with information on potential confounders such as parity and infertility diagnosis.

Methods

Study population

We defined assisted reproduction as "treatments or procedures that include in vitro handling of both human oocytes and sperm or embryos, for the purpose of reproduction."[22] Records for all women undergoing assisted reproduction from January 1991 to September 2009, and those undergoing the same from October 2009 to December 2010 who gave their prospective consent, in England, Wales, and Scotland were obtained from the Human Fertilisation and Embryology Authority (HFEA).

UK law mandates reporting of all assisted reproduction cycles to the HFEA. For cycles performed before October 2009, research use of these data was permitted, but consent could be withdrawn retrospectively. Fewer than 300 women had done so before this study began (based on the level of reporting detail provided by the HFEA). The study cohort, January 1991 to September 2009, therefore represents about 99.7% of the at-risk population. For cycles performed October 2009 onwards, prospective consent was required. Overall consent was not provided for an estimated 7% of women undergoing assisted reproduction in 1991-2010 (about 20 000 women, based on reports from the HFEA), who were therefore not included in this study, representing a loss of less than 1% of person years' follow-up (figure S1, supplementary appendix).

Outcome data

HFEA records were linked to the National Health Service Central Registers of England, Wales, and Scotland (from which emigrations, deaths, and cancer registrations are reported to authorised medical researchers) in a one-off linkage. Completeness and accuracy of these registers have been described.[23-25] Overall, records of 266 787 (95.1%) eligible women were linked (box S1 and figure S1, supplementary appendix). Cancer diagnosis date, topography code (ICD-9/ICD-10 (international classification of diseases, 9th and 10th revisions)), morphology (ICD-O-2/ICD-O-3 (international classification of diseases for oncology, second and third revisions)), and behaviour (ICD-O-2/ICD-O-3) were available where an incident cancer was diagnosed. Women with cancer diagnoses (including non-melanoma skin cancer) recorded before the first treatment year were excluded from analyses. We obtained data relating to potential confounding factors such as infertility diagnosis, parity (as recorded at last treatment cycle completion), and treatment details (including number of stimulated cycles and age at first treatment) for each cohort member from the HFEA database. These data are a combination of patient reported and clinic reported information (table S1). Information regarding infertility diagnoses are reported to the HFEA by assisted reproduction clinics, based on investigations undertaken by that clinic; by the referring clinician; or occasionally by patient self report.

Statistical analyses

Follow-up was calculated from date of first treatment (estimated as the mid-point of the first treatment year) until the date of any cancer diagnosis, death, emigration, or study end (March 2011), whichever came first. For analyses involving number of cycles, infertility duration, and live and multiple births, person years at risk were calculated from date of last treatment (estimated as mid-point of the last treatment year), because the HFEA did not record intermediate dates required for time dependent analysis. To calculate expected cancers, we multiplied the person years at risk by corresponding national incidence rates (by 5 year age band and individual calendar year) for the general female population of England and Wales.

Standardised incidence ratios were calculated by the comparison of observed values with expected values. We calculated 95% confidence intervals, two sided P values, and trends assuming a Poisson distribution.[26] Sensitivity analyses excluded the first 12 months of follow-up, to investigate potential surveillance bias in the period immediately following assisted reproductive treatment (which could arise as a result of treatment and or after-care; supplementary appendix). Absolute excess risks represent an estimate of the increased risk in the study group as compared with the general population and gives a direct measure of excess risk. They are presented per 100 000 person years, with corresponding 95% confidence intervals, based on exact confidence intervals for Poisson counts. Analyses were performed using Stata, version 12.[27]

Patient involvement and study approval

Representatives from patient support groups were consulted on the original research question, design, and planning of this study. Approval of the study and waiver of the requirement for individual consent were obtained from the UK Health Research Authority Confidentiality Advisory Group and London Research

Ethics Committee (references 5.04(b)/10 and 10/H0720/18, respectively). Given the anonymous nature of the final dataset, it is not possible to disseminate results to individual study participants; instead results will be shared with fertility practitioners and clinics through the Human Fertility and Embryology Authority networks.

Results

Characteristics of study participants

In total, 255 786 women contributed 2 257 789 person years' follow-up. Average follow-up was 8.8 years (range 1-19 years), with 105 436 (41%) followed for at least 10 years. Average age at first treatment was 34.5 years. Infertility cause involved at least one female factor in 111 658 women (44%; including endometriosis, ovulatory disorders (predominantly polycystic ovary disease), and tubal disease). Infertility was unexplained in 47 757 (19%) women, and was due only to male factors in 84 871 (33%). Average infertility duration was 4.9 years. Women had 1.8 stimulated cycles on average, with only 20% (n=50 485) having more than two stimulated cycles. About half the study population had at least one live birth after treatment completion (table 1).

Breast cancer

There was no overall increased risk of breast cancer (2578 observed *v* 2641.2 expected cancers; standardised incidence ratio 0.98 (95% confidence interval 0.94 to 1.01); absolute excess risk −2.8 cases per 100 000 person years (95% confidence interval −7.1 to 1.8); table 2). More than three quarters (76%) of tumours were ductal carcinomas (n=1963), 9% lobular (n=228), 12% other epithelial tumours (n=319), and 3% non-epithelial or unspecified (n=68). There were no significantly raised risks in groups by age at first treatment, infertility duration, number of stimulated cycles, number of live births, and number of multiple births (table 3).

We found significant risk reductions with increasing duration since treatment completion (P=0.01; table 3), and in women with any female factor or only male factor infertility (table 3), but no difference between risks at premenopausal and postmenopausal ages separately (age <50 years, standardised incidence ratio 0.98 (95% confidence interval 0.94 to 1.02); ≥50 years, 0.97 (0.89 to 1.06); data not shown). After exclusion of the first 12 months of follow-up, breast cancer risk was significantly reduced compared with age standardised expectation (standardised incidence ratio 0.95 (0.92 to 0.99), P=0.02; supplementary appendix). There was no increased risk of invasive breast cancer (standardised incidence ratio 0.96 (0.92 to 1.00); absolute excess risk −4.4 cases per 100 000 person years (95% confidence interval −8.5 to −0.2); table 4), but a small increased risk of in situ breast cancer (291 cancers observed *v* 253.5 cancers

Table 1 | Characteristics of 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010

Characteristic	Total cohort (n=255 786)	Women who developed ovarian, breast, and corpus uteri cancer (n=3155)	Women who did not develop ovarian, breast, and corpus uteri cancer (n=252 631)
Age at first treatment (years; mean (SD))	34.5 (4.8)	36.3 (4.7)	34.5 (4.8)
Age at first treatment (No (%))			
<25 years	5671 (2)	20 (1)	5651 (2)
25-29 years	39 932 (16)	259 (8)	39 673 (16)
30-34 years	92 788 (36)	961 (31)	91 827 (36)
35-39 years	85 868 (34)	1244 (39)	84 624 (34)
40-44 years	28 174 (11)	563 (18)	27 611 (11)
≥45 years	3353 (1)	108 (3)	3245 (1)
Cause of infertility (No (%))			
Any female factor	111 658 (44)	1626 (52)	110 032 (44)
Male factor only	84 871 (33)	915 (29)	83 956 (33)
Unexplained	47 757 (19)	474 (15)	47 283 (19)
Unrecorded	11 500 (5)	140 (4)	11 360 (5)
History of endometriosis (No (%))	18 630 (7)	281 (9)	18 349 (7)
History of tubal disease (No (%))	66 370 (26)	1045 (33)	65 325 (26)
History of ovulatory disorder (No (%))	36 016 (14)	451 (14)	35 565 (14)
Duration of infertility reported at completion of last cycle (years; mean (SD))	4.9 (3.3)	5.6 (3.9)	4.8 (3.3)
No of stimulated cycles (mean (SD))	1.8 (1.2)	1.8 (1.3)	1.8 (1.2)
No of live births at completion of last cycle (mean (SD))	0.6 (0.7)	0.6 (0.7)	0.6 (0.7)
No of live births at completion of last cycle (No (%))			
0	129 217 (51)	1775 (56)	127 442 (50)
1	96 839 (38)	1011 (32)	95 828 (38)
≥2	29 645 (12)	368 (12)	29 277 (11)
Unrecorded	85 (0)	1 (0)	84 (0)
Any multiple birth recorded at completion of last cycle (No (%))	29 366 (11)	304 (10)	29 062 (12)

SD=standard deviation.

Table 2 | Relative and absolute excess risks of cancers of breast, ovary, and corpus uteri among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, including and excluding the first year after the start of treatment

Type of cancer	Follow-up (No of person years)	No of observed cancers	No of expected cancers	Standardised incidence ratio (95% CI)	Absolute excess risk (95% CI) per 100 000 person years at risk
Including first year of follow-up					
Breast*	2 257 789	2578	2641.2	0.98 (0.94 to 1.01)	−2.8 (−7.1 to 1.8)
Corpus uteri†	2 257 789	164	146.9	1.12 (0.95 to 1.30)	0.8 (−0.3 to 2.0)
Ovary‡	2 257 789	405	291.82	1.39 (1.26 to 1.53)	5.0 (3.3 to 6.9)
Excluding first year of follow-up					
Breast*	2 004 121	2384	2501.6	0.95 (0.92 to 0.99)	−5.9 (−10.6 to −1.0)
Corpus uteri†	2 004 121	157	141.79	1.11 (0.94 to 1.30)	0.8 (−0.4 to 2.1)
Ovary‡	2 004 121	356	271.9	1.31 (1.18 to 1.45)	4.2 (2.44 to 6.10)

*Breast cancer=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486.
†Corpus uteri cancer=ICD-9 codes 1820-1828 and ICD-10 code C54.
‡Ovarian cancer=ICD-9 codes 1830-1839 and 2362; ICD-10 codes C56, C570-C574, C481, C482, and D391.

expected, standardised incidence ratio 1.15 (1.02 to 1.29); absolute excess risk 1.7 cases per 100 000 person years (0.2 to 3.2); table 4), which was associated with the number of treatment cycles (P=0.03). Exclusion of the first 12 months of follow-up did not substantially change results for in situ breast cancer risk (table S5, supplementary appendix).

Carcinoma of the corpus uteri

Risk of corpus uteri cancer was not significantly raised (standardised incidence ratio 1.12 (95% confidence interval 0.95 to 1.30); absolute excess risk 0.8 cases per 100 000 person years (95% confidence interval −0.3 to 2.0); table 2). Over 92% (n=152) of corpus uteri tumours were epithelial, 70% (n=107) of which were endometrioid; 8% were non-epithelial or unspecified (n=12). We found a significantly increased risk of corpus uteri cancer in women with an ovulatory disorder (standardised incidence ratio 1.59 (1.13 to 2.17); table 3). There was a highly significant trend of increasing risk with decreased parity (P<0.001), and a significantly decreased risk with women having a multiple birth (standardised incidence ratio 0.42 (0.14 to 0.99); table 3). No significant variation in risk was noted with number of cycles (P=0.93), age at first treatment (P=0.28) or duration since treatment completion (P=0.12). Exclusion of the first 12 months of follow-up did not substantially change results (table S3, supplementary appendix).

Ovarian cancer

An overall increased risk of ovarian cancer was observed in our study population (standardised incidence ratio 1.39 (95% confidence interval 1.26 to 1.53); absolute excess risk 5.0 cases per 100 000 person years (95% confidence interval 3.3 to 6.9); table 2). Increased risks were seen across most age groups at first treatment, but there was a highly significant trend of increasing risk with decreasing age at first treatment (P<0.001; table 3). Significantly increased risks were found in women who had any diagnosis of female factor infertility (standardised incidence ratio 1.66 (1.46 to 1.88)), particularly endometriosis (2.31 (1.74 to 3.01)) or tubal disease (1.68 (1.43 to 1.97); table 3). No increased risk was seen where infertility was male factor only (standardised incidence ratio 1.05 (0.85 to 1.27)) or unexplained (0.96 (0.69 to 1.31); table 3). There was a significant trend of decreasing risk with increasing number of live births (P=0.001), and women remaining nulliparous after treatment completion conferred the highest risk (standardised incidence ratio 1.57 (1.37 to 1.79); table 3). No increased risk was seen with increasing infertility duration (P=0.15), number of cycles (P=0.86), or duration since treatment completion (P=0.74). Exclusion of the first 12 months of follow-up did not substantially change results (table S3, supplementary appendix).

When tumours were classified as invasive or borderline, significant excesses of both were noted (264 observed *v* 188.1expected cancers, standardised incidence ratio 1.40 (95% confidence interval 1.24 to 1.58), absolute excess risk 3.4 cases per 100 000 person years (95% confidence interval 2.0 to 4.9) and 141 *v* 103.7, 1.36 (1.15 to 1.60), 1.7 cases per 100 000 person years (0.7 to 2.8), respectively; table 4).

Invasive ovarian tumours

There was a significant trend of increasing risk of invasive ovarian tumours with decreasing age at first treatment (P=0.02; table 4). Significantly increased risks were detected in women who had any diagnosis of female factor infertility (standardised incidence ratio 1.66 (95% confidence interval 1.41 to 1.94)), particularly endometriosis (2.47 (1.75 to 3.39)) or tubal disease (1.71 (1.40 to 2.08); table 4). Risk significantly decreased with increasing parity (P=0.001), and women nulliparous after treatment completion were at greatest risk (1.67 (1.42 to 1.95); table 4). We saw no significant variation in risk with number of cycles (P=0.29), infertility duration (P=0.25), or duration since treatment completion (P=0.44), nor was risk raised in women treated for male factor only infertility (1.09 (0.84 to 1.39); table 4). A third of invasive ovarian tumours were serous (n=87), 25% endometrioid (n=66), 8% mucinous (n=22), 17% other or unspecified epithelial tumours (n=45), and 17% non-epithelial or unspecified (n=44). Exclusion of the first 12 months of follow-up did not substantially change results (table S4, supplementary appendix).

Table 3 | Standardised incidence ratios (SIRs) for ovarian, breast, and corpus uteri cancer among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors*

Factor	Follow-up (No of person years)	Breast cancer†		Corpus uteri cancer‡		Ovarian cancer§	
		No of observed cancers	SIR (95% CI)	No of observed cancers	SIR (95% CI)	No of observed cancers	SIR (95% CI)
Age at first treatment (years)							
<25	48 187	14	1.32 (0.72 to 2.21)	0	0.00 (0.00 to 6.97)	6	2.21 (0.81 to 4.80)
25-29	381 964	185	0.92 (0.79 to 1.06)	10	1.24 (0.60 to 2.29)	64	2.16 (1.67 to 2.76)
30-34	866 351	774	0.95 (0.89 to 1.02)	43	1.19 (0.86 to 1.60)	142	1.52 (1.28 to 1.80)
35-39	714 056	1033	0.97 (0.91 to 1.03)	72	1.22 (0.96 to 1.54)	134	1.23 (1.03 to 1.45)
40-44	218 767	479	1.02 (0.93 to 1.12)	33	0.96 (0.66 to 1.35)	50	1.05 (0.78 to 1.38)
≥45	28 463	93	1.09 (0.89 to 1.34)	6	0.68 (0.25 to 1.48)	9	0.97 (0.45 to 1.85)
Trend across categories	—	P=0.13		P=0.28		P<0.001	
Infertility cause							
Any female factor	1 109 593	1279	0.95 (0.90 to 1.00)	97	1.25 (1.02 to 1.53)	246	1.66 (1.46 to 1.88)
Male factor only	757 063	774	0.92 (0.86 to 0.99)	41	0.91 (0.65 to 1.24)	98	1.05 (0.85 to 1.27)
Unexplained	326 495	416	1.10 (1.00 to 1.21)	16	0.78 (0.45 to 1.27)	40	0.96 (0.69 to 1.31)
Unrecorded	64 638	109	1.49 (1.24 to 1.80)	10	2.53 (1.21 to 4.66)	21	2.59 (1.60 to 3.95)
History of endometriosis							
Yes	181 279	214	0.98 (0.86 to 1.12)	9	0.75 (0.35 to 1.43)	55	2.31 (1.74 to 3.01)
No	2 076 509	2364	0.98 (0.94 to 1.02)	155	1.15 (0.98 to 1.34)	350	1.31 (1.17 to 1.45)
History of tubal disease							
Yes	710 522	826	0.96 (0.90 to 1.03)	59	1.23 (0.93 to 1.58)	158	1.68 (1.43 to 1.97)
No	1 547 266	1752	0.98 (0.94 to 1.03)	105	1.06 (0.87 to 1.29)	247	1.25 (1.10 to 1.41)
History of ovulatory problems							
Yes	311 523	357	0.92 (0.83 to 1.02)	39	1.59 (1.13 to 2.17)	55	1.28 (0.97 to 1.67)
No	1 946 265	2221	0.99 (0.95 to 1.03)	125	1.02 (0.85 to 1.21)	350	1.41 (1.26 to 1.56)
Duration of infertility at last cycle (years)							
<2	133 067	171	0.95 (0.82 to 1.11)	6	0.55 (0.20 to 1.20)	28	1.44 (0.96 to 2.09)
2-3	439 560	527	1.05 (0.96 to 1.14)	23	0.82 (0.52 to 1.23)	73	1.30 (1.02 to 1.64)
4-5	447 739	520	0.99 (0.90 to 1.07)	30	1.03 (0.70 to 1.47)	74	1.27 (1.00 to 1.60)
6-7	271 583	316	0.91 (0.82 to 1.02)	27	1.38 (0.91 to 2.01)	60	1.61 (1.23 to 2.07)
8-9	151 580	197	0.95 (0.83 to 1.10)	16	1.34 (0.77 to 2.18)	36	1.64 (1.15 to 2.27)
≥10	209 751	322	0.95 (0.85 to 1.05)	37	1.68 (1.18 to 2.31)	57	1.60 (1.21 to 2.08)
Unrecorded	324 953	404	1.07 (0.97 to 1.18)	18	0.92 (0.54 to 1.45)	42	1.02 (0.74 to 1.38)
Trend across categories	—	P=0.20		P<0.001		P=0.15	
Total No of stimulated cycles							
0 ("natural cycle" only)	90 973	142	0.88 (0.74 to 1.04)	8	0.66 (0.28 to 1.29)	17	0.99 (0.58 to 1.59)
1	1 041 791	1203	0.98 (0.92 to 1.03)	89	1.29 (1.04 to 1.59)	196	1.44 (1.25 to 1.66)
2	473 125	585	1.01 (0.93 to 1.09)	29	0.91 (0.61 to 1.30)	87	1.38 (1.10 to 1.70)
3-4	306 137	420	1.03 (0.93 to 1.13)	24	1.06 (0.68 to 1.58)	53	1.23 (0.92 to 1.60)
≥5	66 149	107	1.08 (0.89 to 1.31)	7	1.24 (0.50 to 2.55)	17	1.67 (0.97 to 2.67)
Trend across categories	—	P=0.07		P=0.93		P=0.86	
Total number of live births at last cycle completion							
0	1 009 134	1299	0.99 (0.93 to 1.04)	122	1.61 (1.34 to 1.92)	222	1.57 (1.37 to 1.79)
1	718 998	843	1.03 (0.96 to 1.10)	24	0.53 (0.34 to 0.79)	114	1.25 (1.03 to 1.50)
≥2	249 685	314	0.92 (0.82 to 1.03)	11	0.54 (0.27 to 0.96)	34	0.93 (0.64 to 1.30)
Unrecorded	414	1	1.82 (0.05 to 10.13)	0	0.00 (0.00 to 99.86)	0	0.00 (0.00 to 49.93)
Trend across categories	—	P=0.56		P<0.001		P=0.001	
Any multiple birth as recorded at last cycle completion							
Yes	232 824	258	1.10 (0.97 to 1.24)	5	0.42 (0.14 to 0.99)	33	1.23 (0.85 to 1.73)
No	1 745 409	2199	0.98 (0.94 to 1.02)	152	1.17 (1.00 to 1.38)	337	1.39 (1.24 to 1.54)
Time since last treatment (years)							
0-3	687 180	525	1.04 (0.95 to 1.13)	28	1.39 (0.92 to 2.00)	99	1.54 (1.25 to 1.88)
3-6	486 191	529	1.04 (0.95 to 1.13)	29	1.28 (0.85 to 1.83)	73	1.27 (1.00 to 1.60)
6-10	444 324	657	1.00 (0.93 to 1.08)	38	1.07 (0.76 to 1.47)	84	1.24 (0.99 to 1.53)
10-15	296 445	590	0.93 (0.86 to 1.01)	45	0.99 (0.72 to 1.33)	86	1.39 (1.11 to 1.71)
≥15	64 091	156	0.86 (0.73 to 1.01)	17	0.98 (0.57 to 1.57)	28	1.57 (1.05 to 2.27)
Trend across categories	—	P=0.01		P=0.12		P=0.74	

*See supplementary appendix for results excluding the first 12 months of follow-up.
†Breast cancer=ICD-9 codes 1740-1749, 2330, and 2383; ICD-10 codes C500-C509, D050-D059, and D486.
‡Corpus uteri cancer=ICD-9 codes 1820-1828 and ICD-10 code C54.
§Ovarian cancer=ICD-9 codes 1830-1839 and 2362; ICD-10 codes C56, C570-C574, C481, C482, and D391.

Table 4 | Standardised incidence ratios (SIRs) for invasive and in situ breast cancer and invasive and borderline tumours of the ovary among 255 786 women who underwent assisted reproduction in Great Britain, 1991-2010, stratified by various factors*

		Invasive breast cancer†		In situ breast cancer‡		Invasive ovarian tumours§		Borderline ovarian tumours¶	
Factor	Follow-up (No of person years)	No of observed cancers	SIR (95% CI)	No of observed cancers	SIR (95% CI)	No of observed cancers	SIR (95% CI)	No of observed cancers	SIR (95% CI)
Overall	2 257 789	2272	0.96 (0.92 to 1.00)	291	1.15 (1.02 to 1.29)	264	1.40 (1.24 to 1.58)	141	1.36 (1.15 to 1.60)
Age at first treatment (years)									
<25	48 187	14	1.43 (0.78 to 2.39)	0	0.00 (0.00 to 4.34)	<5	**	<5	**
25-29	38 964	168	0.91 (0.78 to 1.06)	16	1.10 (0.63 to 1.78)	35	2.33 (1.63 to 3.25)	29	1.98 (1.33 to 2.85)
30-34	866 351	685	0.92 (0.86 to 1.00)	85	1.27 (1.02 to 1.57)	81	1.46 (1.16 to 1.82)	61	1.61 (1.23 to 2.07)
35-39	714 056	925	0.97 (0.91 to 1.04)	100	0.94 (0.77 to 1.15)	97	1.32 (1.07 to 1.61)	37	1.04 (0.73 to 1.43)
40-44	218 767	411	1.00 0.90 to 1.10)	66	1.23 (0.95 to 1.56)	40	1.13 (0.80 to 1.53)	10	0.82 (0.39 to 1.50)
≥45	28 463	69	0.94 (0.73 to 1.19)	24	2.12 (1.36 to 3.15)	<10	**	<5	**
Trend across categories	—	P=0.30		P=0.47		P=0.02		P<0.001	
Infertility cause									
Any female factor	1 109 593	1118	0.92 (0.87 to 0.98)	151	1.14 (0.97 to 1.34)	161	1.66 (1.41 to 1.94)	85	1.66 (1.33 to 2.05)
Male factor only	757 063	676	0.89 (0.83 to 0.96)	93	1.18 (0.95 to 1.44)	65	1.09 (0.84 to 1.39)	33	0.96 (0.66 to 1.35)
Unexplained	326 495	374	1.10 (0.99 to 1.22)	42	1.18 (0.85 to 1.59)	26	0.98 (0.64 to 1.44)	14	0.92 (0.50 to 1.55)
Unrecorded	64 638	104	1.58 (1.30 to 1.92)	5	0.73 (0.24 to 1.70)	12	2.35 (1.21 to 4.10)	9	3.00 (1.37 to 5.70)
History of endometriosis									
Yes	181 279	186	0.95 (0.82 to 1.10)	26	1.25 (0.81 to 1.83)	38	2.47 (1.75 to 3.39)	17	2.03 (1.18 to 3.25)
No	2 076 509	2086	0.96 (0.92 to 1.00)	265	1.14 (1.01 to 1.28)	226	1.31 (1.14 to 1.49)	124	1.30 (1.08 to 1.55)
History of tubal disease									
Yes	710 522	725	0.94 (0.87 to 1.01)	92	1.11 (0.89 to 1.36)	105	1.71 (1.40 to 2.08)	53	1.62 (1.21 to 2.12)
No	1 547 266	1547	0.97 (0.92 to 1.01)	199	1.17 (1.01 to 1.34)	159	1.25 (1.07 to 1.46)	88	1.24 (0.99 to 1.53)
History of ovulatory problems									
Yes	311 523	315	0.91 (0.81 to 1.02)	41	1.05 (0.75 to 1.42)	33	1.16 (0.80 to 1.63)	22	1.52 (0.96 to 2.31)
No	1 946 265	1957	0.97 (0.92 to 1.01)	250	1.17 (1.03 to 1.32)	231	1.45 (1.27 to 1.65)	119	1.33 (1.11 to 1.60)
Duration of infertility at last cycle (years)									
<2	133 067	156	0.97 (0.83 to 1.14)	15	0.82 (0.46 to 1.35)	16	1.23 (0.70 to 1.99)	12	1.89 (0.98 to 3.30)
2-3	439 560	464	1.03 (0.94 to 1.13)	61	1.26 (0.97 to 1.62)	53	1.48 (1.11 to 1.93)	20	0.99 (0.61 to 1.53)
4-5	447 739	461	0.97 (0.89 to 1.07)	52	1.03 (0.77 to 1.35)	53	1.42 (1.06 to 1.85)	21	1.02 (0.63 to 1.55)
6-7	271 583	278	0.90 (0.79 to 1.01)	35	1.03 (0.72 to 1.44)	40	1.63 (1.16 to 2.21)	20	1.57 (0.96 to 2.42)
8-9	151 580	169	0.92 (0.78 to 1.06)	27	1.31 (0.86 to 1.91)	27	1.84 (1.21 to 2.67)	9	1.24 (0.57 to 2.36)
≥10	209 751	279	0.92 (0.82 to 1.04)	42	1.15 (0.83 to 1.56)	40	1.60 (1.14 to 2.18)	17	1.61 (0.94 to 2.58)
Unrecorded	324 953	355	1.05 (0.94 to 1.16)	48	1.37 (1.01 to 1.82)	25	0.97 (0.63 to 1.43)	17	1.12 (0.65 to 1.79)
Trend across categories	—	P=0.11		P=0.58		P=0.25		P=0.42	
Total number of stimulated cycles									
0 ("natural cycle" only)	90 973	121	0.85 (0.71 to 1.02)	21	1.14 (0.71 to 1.74)	13	1.04 (0.55 to 1.78)	<5	**
1	1 041 791	1073	0.97 (0.91 to 1.03)	121	1.02 (0.85 to 1.22)	129	1.47 (1.23 to 1.75)	67	1.39 (1.08 to 1.77)
2	473 125	512	0.98 (0.90 to 1.07)	70	1.25 (0.97 to 1.58)	56	1.37 (1.03 to 1.78)	31	1.40 (0.95 to 1.98)
3-4	306 137	371	1.01 (0.92 to 1.12)	47	1.18 (0.87 to 1.57)	42	1.48 (1.06 to 1.99)	11	0.75 (0.37 to 1.33)
≥5	66 149	85	0.96 (0.77 to 1.91)	21	2.11 (1.31 to 3.23)	14	2.04 (1.11 to 3.42)	<5	**
Trend across categories	—	P=0.27		P=0.03		P=0.29		P=0.18	
Total number of live births after last treatment									
0	1 009 134	1154	0.98 (0.92 to 1.04)	135	1.04 (0.87 to 1.23)	156	1.67 (1.42 to 1.95)	66	1.38 (1.07 to 1.75)
1	718 998	732	0.99 (0.92 to 1.07)	107	1.37 (1.12 to 1.65)	78	1.34 (1.06 to 1.67)	36	1.09 (0.76 to 1.51)
≥2	249 685	276	0.90 (0.80 to 1.02)	37	1.07 (0.76 to 1.48)	20	0.81 (0.50 to 1.26)	14	1.16 (0.63 to 1.95)
Unrecorded	414	0	0.00	1	20.00 (0.51 to 111.43)	0	0.00 (0.00 to 74.89)	0	0.0 (0.0 to 149.79)
Trend across categories	—	P=0.37		P=0.32		P=0.001		P=0.34	
Any multiple birth recorded									
Yes	232 824	234	1.10 (0.97 to 1.25)	22	1.05 (0.66 to 1.58)	22	1.34 (0.84 to 2.03)	11	1.06 (0.53 to 1.90)
No	1 745 409	1928	0.96 (0.92 to 1.00)	258	1.16 (1.02 to 1.31)	232	1.45 (1.27 to 1.65)	105	1.27 (1.04 to 1.54)
Time since last treatment (years)									
0-3	687 180	488	1.05 (0.96 to 1.15)	37	1.06 (0.71 to 1.39)	62	1.73 (1.33 to 2.22)	37	1.30 (0.92 to 1.79)
3-6	486 191	476	1.03 (0.94 to 1.12)	51	1.24 (0.93 to 1.63)	45	1.27 (0.93 to 1.71)	28	1.27 (0.85 to 1.84)
6-10	444 324	556	0.94 (0.87 to 1.02)	95	1.52 (1.23 to 1.85)	63	1.37 (1.05 to 1.75)	21	0.96 (0.59 to 1.46)

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Table 4 | Continued

Factor	Follow-up (No of person years)	Invasive breast cancer† No of observed cancers	Invasive breast cancer† SIR (95% CI)	In situ breast cancer‡ No of observed cancers	In situ breast cancer‡ SIR (95% CI)	Invasive ovarian tumours§ No of observed cancers	Invasive ovarian tumours§ SIR (95% CI)	Borderline ovarian tumours¶ No of observed cancers	Borderline ovarian tumours¶ SIR (95% CI)
≥10	296 445	510	0.93 (0.85 to 1.01)	75	0.98 (0.77 to 1.22)	63	1.38 (1.06 to 1.77)	23	1.39 (0.88 to 2.08)
≥15	64 091	132	0.86 (0.72 to 1.02)	22	0.85 (0.54 to 1.29)	21	1.52 (0.94 to 2.32)	7	1.75 (0.70 to 3.60)
Trend across categories	—	P=0.005		P=0.29		P=0.44		P=0.84	

*See supplementary appendix for results excluding the first 12 months of follow-up.
†Invasive breast cancer=ICD-9 codes 1740-1749 and ICD-10 codes C500-C509.
‡In situ breast cancer=ICD-9 code 2330 and ICD-10 code D050-D059.
§Invasive ovarian tumours=ICD-9 codes 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) and 2362; ICD-10 codes C56, C570-C574, C481, and C482 (excluding morphology codes 8442/8451/8462/8472/8473).
¶Borderline ovarian tumours=ICD-9 code 1830 (with morphology codes 8442/8451/8462/8472/8473) and ICD-10 codes D391 and C56 (with morphology codes 8442/8451/8462/8472/8473).
**Data suppressed to comply with data disclosure regulations where cells relate to small numbers of individuals. None of the standardised incidence ratios for affected cells approached significance.

Borderline ovarian tumours

Significantly increased risks of borderline ovarian tumour was associated with decreasing age at first treatment (P<0.001) and any diagnosis of female factor infertility (standardised incidence ratio 1.66 (95% confidence interval 1.33 to 2.05)), particularly endometriosis (2.03 (1.18 to 3.25)) or tubal disease (1.62 (1.21 to 2.12); table 4). Risk did not change significantly with number of cycles (P=0.18), parity (P=0.34), infertility duration (P=0.42), or duration since treatment completion (P=0.84), nor was risk raised in women treated for male factor only infertility (0.96 (0.66 to 1.35); table 4). Close to half of borderline tumours were serous (n=64), 34% mucinous (n=48), less than 2% endometrioid (n<5), less than 2% other or unspecified epithelial tumours (n<5), and 18% non-epithelial or unspecified (n=25). Exclusion of the first 12 months of follow-up reduced the risk of borderline ovarian tumours (1.19 (0.98 to 1.43); table S4, supplementary appendix) and risk in relation to endometriosis (1.57 (0.81 to 2.73); table S4, supplementary appendix).

Ovarian cancer risk stratified by risk factors

Parous women who did not have a diagnosis of endometriosis did not have an increased risk of ovarian cancer overall (standardised incidence ratio 1.03 (95% confidence interval 0.86 to 1.22)), invasive tumours (1.03 (0.82 to 1.27)), or borderline tumours (1.02 (0.75 to 1.35); table 5). Risks of all types of ovarian cancer were raised in nulliparous women who did not have a diagnosis of endometriosis but to a lesser extent than in parous women with endometriosis (table 5). Women who were nulliparous with a diagnosis of endometriosis had greater risk of invasive ovarian tumour (2.64 (1.69 to 3.93); table 5) than women with just one of these risk factors. By contrast, nulliparous women with endometriosis had no significant risk of a borderline tumour (1.47 (0.59 to 3.04)), although nulliparity and endometriosis were each separately associated with increased risk (table 5). The significant association between decreasing age at first treatment and increasing risk of invasive ovarian tumour was present in women with at least one of endometriosis or nulliparity (P<0.001), but not in those without either

Table 5 | Standardised incidence ratios (SIRs) for all, invasive, and borderline ovarian cancers among 225 786 women who underwent assisted reproduction in Great Britain, 1991-2010, by presence or absence of known risk factors endometriosis and nulliparity

Factor	Follow-up (No of person years)	Type of ovarian cancer: All ovarian cancer* No of observed cancers	All ovarian cancer* SIR (95% CI)	Invasive cancer† No of observed cancers	Invasive cancer† SIR (95% CI)	Borderline tumours‡ No of observed cancers	Borderline tumours‡ SIR (95% CI)
No diagnosis of endometriosis and at least one birth recorded by treatment completion	1 036 996	133	1.03 (0.86 to 1.22)	85	1.03 (0.82 to 1.27)	48	1.02 (0.75 to 1.35)
No diagnosis of endometriosis and no births recorded by treatment completion	1 039 514	217	1.57 (1.37 to 1.79)	141	1.56 (1.32 to 1.84)	76	1.57 (1.24 to 1.97)
Diagnosis of endometriosis and at least one birth recorded by treatment completion	79 870	24	2.41 (1.55 to 3.59)	14	2.22 (1.21 to 3.72)	10	2.76 (1.33 to 5.08)
Diagnosis of endometriosis and no birth recorded by treatment completion	101 368	31	2.24 (1.52 to 3.18)	24	2.64 (1.69 to 3.93)	7	1.47 (0.59 to 3.04)

*Ovarian cancer=ICD-9 codes 1830-1839 and 2362; ICD-10 codes C56, C570-C574, C481, C482, and D391.
†Invasive ovarian tumours=ICD-9 codes 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) and 2362; ICD-10 codes C56, C570-C574, C481, and C482 (excluding morphology codes 8442/8451/8462/8472/8473).
‡Borderline ovarian tumours=ICD-9 code 1830 (with morphology codes 8442/8451/8462/8472/8473) and ICD-10 codes D391 and C56 (with morphology codes 8442/8451/8462/8472/8473).

(P=0.62); however, these analyses were based on small numbers (table S6, supplementary appendix).

Discussion

Assisted reproduction is practiced worldwide, and more than five million children have been born as a result.[28] It is important to establish related disease risks for affected individuals, public health systems, and for counselling of potential patients. In this large population based cohort, we found no overall increased risk of breast cancer associated with assisted reproduction, consistent with most[3-10] but not all[12] published studies. We found no significant association between the risk of breast cancer and age at first treatment, in contrast to a small number of earlier studies.[8 9 29] Reasons for significant decreases in breast cancer risk seen in some subanalyses—such as women who had assisted reproduction for female factor infertility—are unclear, but could reflect beneficial levels of lifestyle related risk factors for breast cancer.[30 31] However, details of these risk factors and also age at first birth were not available.

Menopausal status did not seem to account for the significant reduction in risk with increasing follow-up. Despite no increased risk of invasive breast tumours, there was a significant increase in in situ tumours which was significantly associated with increasing number of stimulated cycles. Interpretation of these findings is challenging: the significant association with increasing number of cycles suggests a causal association, yet there was no overall increased risk of breast cancer. Other potential explanations include surveillance bias, chance, and potential confounding by factors such as socioeconomic status, given that most cycles within our cohort were privately funded. To our knowledge, this study is the first to analyse risks of in situ and invasive breast cancers after assisted reproduction separately, so there are no previous data with which to compare.

Risk of corpus uteri cancer overall was not raised in our study. Women with the known risk factor of nulliparity[32] and those with a history of ovulatory problems (mainly the known risk factor polycystic ovary disease[33]) were found to have an increased risk of corpus uteri cancer. Most similar studies contained few events.[3 5 6] The largest studies included 15[4] and 49 cases[7] of endometrial cancer in women after assisted reproduction, and neither suggested an increased risk.

We found an excess of ovarian cancer compared with age standardised expectation. Significant increases were observed for both invasive and borderline tumours, but were not seen in women without the known risk factors of endometriosis[34 35] and nulliparity.[35] Ovarian cancer risks were not associated with number of treatment cycles, time since treatment completion, or male factor or unexplained infertility, which argues against a causal role for assisted reproduction procedures. However, we did find a significant association between age at first treatment and risk of all, invasive, and borderline ovarian cancers. Previous studies investigating invasive ovarian tumour risk after assisted reproduction[3-7 11 13 15 16] have generally found increased risks in comparison with the general population when potential confounding effects of infertility have not been considered,[16] but not when such factors were taken into account.[3 4 11 16] While our study compared cancer incidence with that in the general population (standardised for age and calendar year), it had sufficient size to stratify by potential confounding factors and thereby to investigate characteristics of associations. We found an increased risk of borderline ovarian tumour in women having assisted reproduction compared with the general population. As with invasive ovarian tumours, this increased risk was not seen in parous women without endometriosis. Few studies have investigated the risk of borderline ovarian cancer in women after assisted reproduction,[6 13 14] but increased risks have been found in studies in the Netherlands[13] and Australia.[14]

Although the increased risk in borderline ovarian cancer in women with assisted reproduction could be genuine, it could also be due to surveillance bias. The frequency of borderline tumour diagnosis is increased in ovarian cancer screening studies using ultrasound,[36] and women who have undergone assisted reproduction might have more frequent ultrasound scans after treatment than the general population. This potential bias is supported by the reduction in overall risk after we excluded the first 12 months of follow-up. However, sensitivity analyses looking at time to diagnosis, age at diagnosis, diagnosis in women of high socioeconomic status, and clinical presentation in other studies suggested surveillance bias an unlikely cause of increased risks.[13 14] We are not able to further differentiate surveillance bias from a genuine increase in borderline tumours. Women with unrecorded cause of infertility had significantly increased rates of breast, ovarian, and corpus uteri cancers. Reasons are unclear but might include reverse causality (box S2, supplementary appendix).

Strengths and limitations of the study

Most studies investigating risks of cancer in women after assisted reproduction have been small,[6 8] with few events and short follow-up.[4 7] Two of the largest studies published so far include 67 608[4] and 113 226[7] women treated with assisted reproduction. Systematic reviews have included at most 70 753 treated women for analyses of breast cancer risk,[10] 79 143 for ovarian cancer risk,[16] and 118 320 for analysis of all gynaecological cancer risk.[37] Our study comprised over 250 000 treated women, including almost 65 000 person years of follow-up for at least 15 years beyond last treatment with an average follow-up of 8.8 years and a maximum follow-up of 19 years (table S2, supplementary appendix). However, we cannot exclude the possibility of different risk profiles for any studied cancer on longer follow-up, at ages when most reproductive related cancers occur.[35]

Women treated with assisted reproduction are likely to differ from the general population in their parity, age at first birth, age at menopause, and

the incidence of predisposing conditions such as endometriosis. More information on these and other factors (eg, socioeconomic status, oral contraceptive use, body mass index, and breastfeeding) would be useful. Comparison to women with untreated infertility problems might have been beneficial, although interpretational problems would remain because of potential selection factors for treatment. Although our study was not able to compare with such a group as some smaller studies have done,[4 13 14] large study size enabled us to stratify for some important potential confounders and draw inferences despite using general population rates as our comparator. While comparator rates do include cohort participants, less than 5% of the population of reproductive age women underwent assisted reproduction, and our standardised incidence ratios were generally lower than 2.0; therefore, resulting bias will have been minimal.[38]

Infertility diagnoses were reported by treating fertility clinics to the HFEA. No data were available about how such diagnoses were made. Further details of specific treatments could have enabled detailed analysis of risk by treatment type. However, over our 19 year study period, ovarian stimulation regimens as part of assisted reproductive cycles have been relatively constant, with the majority of advances leading to better success rates having occurred in assisted reproduction laboratories. Gonadotrophin injections have been used for ovarian stimulation and human chorionic gonadotropin for triggering ovulation throughout the study period, and while new highly purified and recombinant versions have been used in more recent years, they are essentially equivalent. Clomifene citrate was used as additional ovarian stimulation in the pioneering years of assisted reproduction treatment, but this was uncommon by 1991. Downregulated cycles using GnRH (gonadotrophin releasing hormone) agonists were standard by 1991 and not replaced by GnRH antagonists as standard until after the study period. Progesterone support was used throughout the study period. The number of ovarian punctures per cycle and information about fertility treatment before assisted reproduction were not available.

Conclusions and implications

In this large, national population based study of British women after assisted reproductive technology treatment, no increased risk of corpus uteri or invasive breast cancer was detected. There was an increased risk of in situ breast cancer associated with increasing number of treatment cycles. We also observed an excess of all types of ovarian cancer. However, our results suggest that this finding is more likely due to underlying patient characteristics, rather than assisted reproduction itself. We were not able to distinguish between a genuine increase in risk of borderline ovarian tumours and other explanations including surveillance bias. Further investigation of this and longer follow-up is warranted to continue monitoring these important outcomes in this ever growing population.

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Ethical approval: Approval of the study and waiver of the requirement for individual consent were obtained from the UK Health Research Authority Confidentiality Advisory Group and London Research Ethics Committee (references 5.04(b)/10 and 10/H07 20/18, respectively).

Data sharing: No additional data are available, in compliance with ethical and governance regulations under which this research was undertaken.

AGS affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? *Lancet* 1971;2:163. doi:10.1016/S0140-6736(71)92335-X
2 Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture. *Cancer Res* 1988;48:246-53.
3 Vessa A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999;354:1586-90. doi:10.1016/S0140-6736(99)05203-4
4 Brinton LA, Trabert B, Shalev V, Lunenfeld E, Sella T, Chodick G. In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services. *Fertil Steril* 2013;99:1189-96. doi:10.1016/j.fertnstert.2012.12.029
5 Källén B, Finnström O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after in vitro fertilization. *Hum Reprod* 2011;26:253-8. doi:10.1093/humrep/deq307
6 Yli-Kuha AN, Gissler M, Klemetti R, Luoto R, Hemminki E. Cancer morbidity in a cohort of 9175 Finnish women treated for infertility. *Hum Reprod* 2012;27:1149-55. doi:10.1093/humrep/des031
7 Luke B, Brown MB, Spector LG, et al. Cancer in women after assisted reproductive technology. *Fertil Steril* 2015;104:1218-26. doi:10.1016/j.fertnstert.2015.07.1135
8 Pappo I, Lerner-Geva L, Halevy A, et al. The possible association between IVF and breast cancer incidence. *Ann Surg Oncol* 2008;15:1048-55. doi:10.1245/s10434-007-9800-2
9 Sergentanis TN, Diamantaras AA, Perlepe C, Kanavidis P, Skalkidou A, Petridou ET. IVF and breast cancer: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20:106-23. doi:10.1093/humupd/dmt034
10 Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Res Treat* 2015;150:405-13. doi:10.1007/s10549-015-3328-0
11 Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. *Cochrane Database Syst Rev* 2013;8:CD008215.
12 Reigstad MM, Larsen IK, Myklebust TA, et al. Risk of breast cancer following fertility treatment—a registry based cohort study of parous women in Norway. *Int J Cancer* 2015;136:1140-8. doi:10.1002/ijc.29069
13 van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011;26:3456-65. doi:10.1093/humrep/der322
14 Stewart LM, Holman CD, Finn JC, Preen DB, Hart R. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. *Gynecol Oncol* 2013;129:372-6. doi:10.1016/j.ygyno.2013.01.027
15 Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol* 2013;128:260-4. doi:10.1016/j.ygyno.2012.10.023
16 Siristatidis C, Sergentanis TN, Kanavidis P, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis. *Hum Reprod Update* 2013;19:105-23. doi:10.1093/humupd/dms051
17 Reigstad MM, Storeng R, Myklebust TA, et al. Cancer risk in women treated with fertility drugs according to parity status-a registry-based cohort study. *Cancer Epidemiol Biomarkers Prev* 2017;26:953-62. doi:10.1158/1055-9965.EPI-16-0809
18 Dor J, Lerner-Geva L, Rabinovici J, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. *Fertil Steril* 2002;77:324-7. doi:10.1016/S0015-0282(01)02986-7
19 Jensen A, Sharif H, Kjaer SK. Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study. *Am J Epidemiol* 2009;170:1408-14. doi:10.1093/aje/kwp290
20 Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771-6. doi:10.1056/NEJM199409223311204
21 Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study. *BMJ* 2009;338:b249. doi:10.1136/bmj.b249
22 Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertil Steril* 2017;108:393-406. doi:10.1016/j.fertnstert.2017.06.005
23 Scotland ISD. Scottish Cancer Registry: NHS National Services Scotland; 2010 [Available from: http://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry.asp
24 Statistics ON. Cancer Registrations, 1971 to 2011: Office for National Statistics; 2014 [updated 19th June 2014. Available from: http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations-england-series-mb1-/no-43-2012/stb-cancer-registrations-2012.html#tab-Cancer-registrations-1971-to-2011.
25 Parkin DMCV, Ferlay J, Galceran J, Storm HH, Whelan SL. Comparability and Quality Control in Cancer Registration. Lyon: International Agency for Research on Cancer; 1994. Contract No: technical report No 19.
26 Breslow NE, Day NE. *Statistical Methods in Cancer Research*. International Agency for Research on Cancer, 1987, Available from http://www.iarc.fr/en/publications/pdfs-online/stat/sp82/.
27 Stata Corp. *Stata Statistical Software: Release 12*. Stata Corp LP, 2013.
28 Adamson GD, Tabangin M, Macaluso M, de Mouzon J. The number of babies born globally after treatment with the assisted reproductive technologies (ART). *Fertil Steril* 2013;100:S42-S. doi:10.1016/j.fertnstert.2013.07.1807.
29 Stewart LM, Holman CD, Hart R, Bulsara MK, Preen DB, Finn JC. In vitro fertilization and breast cancer: is there cause for concern? *Fertil Steril* 2012;98:334-40. doi:10.1016/j.fertnstert.2012.04.019
30 Domar AD, Conboy L, Denardo-Ronay J, Rooney KL. Lifestyle behaviors in women undergoing in vitro fertilization: a prospective study. *Fertil Steril* 2012;97:697-701.e1. doi:10.1016/j.fertnstert.2011.12.012
31 Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001;2:133-40. doi:10.1016/S1470-2045(00)00254-0
32 Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. *Placenta* 2008;29(Suppl B):169-77. doi:10.1016/j.placenta.2008.08.007
33 Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20:748-58. doi:10.1093/humupd/dmu012
34 Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *J Clin Oncol* 2016;34:2888-98. doi:10.1200/JCO.2016.66.8178
35 Ovarian Cancer Research Fund Alliance (OCRFA). Ovarian Cancer Statisticshttps://ocrfa.org/patients/about-ovarian-cancer/statistics/2016/.
36 Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327-40. doi:10.1016/S1470-2045(09)70026-9
37 Schwarze JE, Valdebenito P, Ortega C, Villa S, Crosby J, Pommer R. Do women offered assisted reproduction technologies have a higher incidence of gynecologic cancer? A systematic review and meta-analysis. *JBRA Assist Reprod* 2017;21:115-9. doi:10.5935/1518-0557.20170026
38 Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *Am J Epidemiol* 1998;148:1012-7. doi:10.1093/oxfordjournals.aje.a009567

Supplementary appendix: figures S1 and S2, boxes S1 and S2, and tables S1-S6

b) Children's study

c) Children's study- donor