Fertility Treatment and Female-Specific Cancers - The Eternal Conundrum:

A Systematic Review and Meta-Analysis

Does Fertility Treatment Increase the Incidence of Gynaecological Cancers?

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J Barcroft was the main contributor in preparation, writing and revision of the manuscript and gathering of data. *N Galazis, BP Jones, T Bracewell-Milnes* & *KJ Grewal* were involved in preparation of the manuscript, collecting the data and preparing the tables. *J Yazbek, K Lathouras, JR Smith & S Ghaem-Maghami (focus: gynaecological oncology)* were responsible for providing important intellectual input into the work and the preparation, drafting and final approval of the manuscript. *N Getreu, P Hardiman, MY Thum, and J Ben-Nagi (focus: reproductive medicine)* were responsible for providing important intellectual input into fertility-related issues within the manuscript. *S Saso* was responsible for the original manuscript design, drafting and revision for important intellectual content. In addition, he is also the guarantor for this paper and accepts full responsibility for the work and/or the conduct of the study.

Key Words Fertility treatment, In Vitro Fertilisation, Breast Cancer, Endometrial Cancer, Ovarian Cancer, Cervical Cancer, Infertility, Assisted Reproductive Technology, Clomiphene, Ovulation induction

Word Count -

The authors have no financial, personal, or professional conflicts of interest to declare

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Abstract

Background

Infertility affects more than 1 in 7 couples and is on the rise, driving an ongoing demand for fertility treatment. Infertility and nulliparity are established risk factors for endometrial, ovarian and breast cancer. The link between fertility treatment and cancer is contentious. Infertility, whilst an important, emotive issue for couples, is not a condition that necessitates treatment, hence the need to be cautious and ensure there are no deleterious treatment effects.

Objectives

To identify whether exposure to fertility treatment significantly increased the risk of developing breast, ovarian, endometrial or cervical cancer.

Methods

A literature search was carried out using EMBASE, Medline and Google Scholar up to July 2019. Studies comparing cancer incidence (breast, ovarian, endometrial or cervical) in defined patient groups: fertility treatment vs non-fertility treatment were included. The primary outcome of interest was breast, ovarian, endometrial and cervical cancer incidence in 'fertility treatment' compared to 'non-fertility treatment' group. Secondary outcomes focused on the cancer incidence in groups exposed to specific fertility drugs, including human menopausal gonadotrophin (hMG), gonadotrophins and clomiphene citrate (CC) compared to non-fertility treatment group. Treatment effect was expressed in odds ratios. The consistency of the treatment effect was assessed using the random effect model.

The primary analysis included 29 studies: Cervical (n=13), Endometrial (n=15), Breast (n=19) and Ovarian (n=19). Studies which contained multiple cancers (n=17) were included in each specific cancer analysis.

Outcomes

The study population included 21,070,337 women, 875,956 in 'fertility treatment' group and 20,194,381 in 'non-fertility treatment' group. Overall cancer incidence was 0.40% (3,467 of 875,956) in the 'fertility-treatment' group and 0.58% (116,807 of 20,194,381) in the 'non-fertility treatment' group. When a random effect model was used to analyse the cancer incidence, the difference was not shown to be statistically significant: OR 0.95 (95% CI 0.82-1.10).

On analysis of individual cancer types: Cervical cancer incidence was 0.36% (603 of 165,266) in the 'fertility treatment' group and 1.24% (52752 of 4,252,264) in the 'non-fertility treatment' group and this difference was statistically significant, although with wide confidence intervals: OR 0.68 (95% CI, 0.46-0.99). There were no significant differences in the incidence of breast: OR 0.86 (95% CI 0.73-1.01), ovarian: OR 1.19 (95% CI 0.98-1.46) or endometrial cancers: OR 1.28 (95% CI 0.92-1.79) between the 'fertility-treatment' and 'non-fertility treatment' groups.

Wider Implications

Whilst women embarking on fertility treatment may be inherently more at risk of gynaecological cancer, given infertility and nulliparity are known risk factors, our findings do not appear to suggest an additional deleterious effect from undergoing fertility treatment.

Fertility treatment, whilst it does not appear to significantly increase the risk of developing breast, endometrial and ovarian cancer, our data does suggest a possible reduced risk of developing cervical cancer. Additional work is needed to further define the relationship between fertility treatment and malignancy, particularly relating to at-risk patient sub-groups (obese, refractory to treatment), and the impact of treatment outcome on cancer incidence.

Word Count 480

Introduction

Infertility is becoming an increasing issue, affecting 1 in 7 couples (NICE, 2013). Age-related decline in fertility rates for both men and women, coupled with the tendency to delay starting a family, has increased demand for fertility treatment (Harper et al., 2017). Contributing factors include declining sperm counts amongst men and rising incidence of obesity (Wilkes and Murdoch, 2009). The demand on fertility services is driving the annual increase (4%) in the number of in vitro fertilisation (IVF) cycles performed year on year since 1991 (Human Fertilisation and Embryology Authority 2018).

Infertility is an important health economic issue, as it represents the second commonest reason why women present to their GP (second only to pregnancy) (NICE, 2013). The demand for fertility services, is driving a research into the development and improvement of existing treatment strategies, with the global aim of achieving a live birth, in the safest, most effective and efficient manner. It is estimated that 50% of couples affected by infertility pursue fertility treatment (Datta et al., 2016), and the age of initiation of treatment continues to rise (Human Fertilisation and Embryology Authority, 2018).

There have been some conflicting results on the long-term sequelae of fertility treatment on women and the children conceived as a result of fertility treatment (Kroener et al., 2017). With increasing use of fertility treatment, it is paramount that women and their prospective offspring are not put at potential risk from the process of undergoing treatment. Infertility, whilst an important, emotive issue, is not a condition that necessitates treatment, therefore it is difficult to justify significant complications associated with fertility treatment.

It is well known that nulliparity is a risk factor for certain malignancies, including ovarian, breast and endometrial cancer (Hanson et al., 2017). The prevalence and risk factors are specific to the individual cancers, but there are a number of similarities, notably an association with hormonal changes (Hanson et al., 2017). Women who choose to pursue fertility treatment, are more likely to be nulliparous and thus, have a higher inherent risk of cancer compared to the general population.

The aim of this meta-analysis is to determine whether a significant association exists between breast, endometrial, cervical and ovarian cancer incidence and fertility treatment. Fertility treatment is an umbrella term and incorporates ovulation induction, ovarian stimulation and IVF and involves exposure to a wide range of medications including selective oestrogen receptor modulators (SERMS) (such as clomiphene citrate, CC), gonadotrophins (FSH, LH or human menopausal gonadotrophin, hMG), gonadotrophin releasing hormone (GnRH) and human chorionic gonadotropin (hCG). The medications can be used in isolation such as in ovulation induction or in combination, as in IVF treatment.

Fertility treatment in simplified terms, involves stimulation of ovaries, to encourage multiple follicles to mature and develop simultaneously. Ovulation of multiple follicles is then triggered, and the oocytes are then collected. The oocytes are fertilised in vitro or via intra-cytoplasmic sperm injection (ICSI). The embryos are then replaced within the uterine cavity. This differs to the process of follicle development that occurs in a natural cycle where a single dominant follicle releases an oocyte mid-cycle, under the influence of a LH surge.

The link between fertility treatment and cancer risk is thought to be in part related to the 'supra-physiological' hormonal changes that occur during fertility treatment, related to the development of multiple follicles. The process encourages 'super-ovulation' by trying to circumvent the normal physiological mechanisms for regulating ovulation in order to maximise yield from treatment (Kroener et al., 2017).

The process of identifying women affected by malignancy in association with fertility treatment is inherently difficult for a number of reasons: firstly, unlike other fertility treatment complications, such as ovarian hyper-stimulation syndrome (OHSS) and multiple pregnancy, there is not a robust reporting system for cancer diagnoses, secondly, the incidence of cancer remains relatively low and thirdly, the cancer can develop several years post completion of treatment (Kroener et al., 2017).

Breast

Breast Cancer affects 1 in 7 women in their lifetime and represents the commonest female cancer diagnosed worldwide (UK, 2018 ; Kroener et al., 2017). Risk factors for development of breast cancer, include genetic predisposition (BRCA1/2), family history, hormone replacement therapy (HRT) use and late age of menopause (Cancer, 2012).

Similar to the pathogenesis of endometrial cancer, oestrogen is thought to play an important role in the pathogenesis of breast cancer (Cancer, 2012). This is based upon a robust association between oestrogen exposure and breast cancer; exogenously, in the context of HRT use and endogenously, in women who are obese, have polycystic ovary syndrome (PCOS), experience an early menarche or a later onset of menopause (Cancer, 2012). It has been suggested that the supra-physiological oestradiol environment associated with the repeated process of ovarian stimulation may have a role in the pathogenesis of breast cancer (Kroener et al., 2017).

Ovary

Women have a 1 in 50 lifetime risk of developing ovarian cancer (UK, 2018). Risk factors for the development of ovarian cancer, include nulliparity, infertility, combined oral contraceptive (COCP) use, genetic predisposition (BRCA 1/2), family history and endometriosis. Protective factors against the development of ovarian cancer, include breast feeding, pregnancy and salpingectomy/hysterectomy (Titus-Ernstoff et al., 2001).

The 'incessant ovulation theory', referring to the repeated process of ovulation, is thought to be important in the development of ovarian cancer (Titus-Ernstoff et al., 2001; Casagrande et al., 1979). The mechanism of ovulation involves disruption of the ovarian epithelium, with associated micro-trauma. The micro-trauma increases the number of epithelial inclusions within the ovary, which are thought to be important in the pathogenesis of ovarian cancer (Titus-Ernstoff et al., 2001). Fertility

treatment is associated with elevated gonadotropin levels (Mandai et al., 2007) and 'multi-follicular' ovulation (Tung et al., 2005), both of which are postulated to play a role in the pathophysiology of ovarian cancer.

Endometrium

Endometrial cancer is the commonest female reproductive tract cancer, with a lifetime risk of 1 in 36 and represents the fourth commonest diagnosed cancer within women (Cancer Research UK, 2018). Risk factors for the development of endometrial cancer, include anovulatory cycles such as PCOS, raised body mass index (BMI), genetic predisposition (including BRCA1/2, hereditary nonpolyposis colorectal cancer, HNPCC), HRT and tamoxifen use (Saso et al., 2011).

The supra-physiological hormone levels, notably oestradiol, associated with undergoing fertility treatment is thought to predispose to aberrant proliferation of the endometrium, known as endometrial hyperplasia, a process which can progress to the development of endometrial cancer. The association between oestradiol and endometrial cancer is well established and supported by a higher incidence in women with anovulatory cycles, such as PCOS (Saso et al., 2011).

Cervix

Cervical cancer has a prevalence of 1 in 142 and is associated with infection of human papilloma virus (HPV) (UK, 2018). Risk factors for the development of cervical cancer, include young age at first intercourse, large number of sexual partners, smoking and immuno-compromised status (Berrington de Gonzalez et al., 2004). Women who undergo fertility treatment, tend to be older, therefore you could postulate that they are more likely to have a longer period of exposure to HPV (Kroener et al., 2017).

Aims

To our knowledge, there has yet to be a meta-analysis which has looked at the impact of fertility treatment (ovulation induction, ovarian stimulation and IVF) in relation to the risk of ovarian, endometrial, cervical and breast cancer. The aim of this meta-analysis was to identify whether exposure to fertility treatment, significantly increased the risk of developing breast, ovarian, endometrial or cervical cancer.

Methods

Institutional review board (IRB) approval was not necessary as this review did not require any patient identifying information. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used for this study (Moher et al., 2009). A search was performed up to July 2019 within several databases (Cochrane library, EMBASE, Google Scholar, Medline) to ensure all relevant comparative studies evaluating the impact of fertility treatment on the incidence of endometrial, cervical, ovarian and breast cancer in women were identified. The search was augmented by a snowball strategy, examining the references cited in primary sources and review manuscripts.

The principal aim of the search was to identify articles, which compared the incidence of endometrial, cervical, ovarian and breast cancer in infertility patients who have undergone fertility treatment to those who have not undergone treatment. The term ‘fertility treatment’ includes the full spectrum of assisted reproduction techniques such as IVF, ovulation induction and ovarian stimulation.

The MESH terms used within the search included ‘fertility treatment’, ‘in vitro fertilisation’ ‘IVF’, ‘clomiphene’, ‘ovarian stimulation’, ‘fertility’, ‘infertility’, ‘ovulation induction’, ‘female’, ‘gonadotrophins’, ‘gonadotrophin releasing hormone’, ‘GnRH’, ‘human chorionic gonadotropin’, ‘hCG’, ‘human menopausal gonadotrophin’, ‘hMG’, ‘tamoxifen’ AND ‘cervical carcinoma/cancer’, 'endometrial cancer’, ‘uterine carcinoma/cancer’, ‘breast carcinoma/cancer’, ‘ovarian carcinoma/cancer’ and ‘borderline ovarian tumours.

To broaden the search, the 'related articles' tool was utilised, and the citations generated were reviewed according to pre-defined criteria as to their relevance. Review articles were utilised to ensure all relevant citations were identified and included. Literature search and study screening were independently performed by two of the co-authors (J.B. and S.S.).

Data Extraction

A data extraction spread sheet was developed and agreed between the authors. The selected studies were comprehensively examined and relevant data were extracted for each paper and inputted to the spread sheet by the first author (J.B.) then cross-checked by the second author (N.G.). The information selected included author details, year of publication and country of the study, study aim, sample size, methodology, sample characteristics, outcome measures and conclusions. Disagreements regarding extracted data were resolved by discussion and deliberated on by the most senior author (S.S.). Tables 1-8 list the main characteristics of the selected studies.

Inclusion and Exclusion criteria *(Table 9)*

Inclusion criteria required the incidence of malignancy (breast, endometrial, cervical and ovarian) to be stated in both the defined treatment group (ovarian stimulation and/or IVF) and the control group (no fertility treatment). Fertility treatment included the use of CC, gonadotrophins, hCG, HMG, GnRH and progestogens in various combinations. Only original studies published in English, in peer-reviewed journals were considered. Studies in which the control group was not clearly defined were excluded from this meta-analysis. Abstracts or incomplete data sets were also excluded from the analysis.

Cancers included:

Breast: Invasive breast carcinoma (IDC- ductal) and (ILC- lobular) and ductal carcinoma in situ (DCIS).

Ovarian: Borderline and invasive ovarian tumour.

Uterine: Cancer of uterine body, uterine sarcoma and endometrial cancer. Endometrial hyperplasia was excluded.

Cervical: Cervical intra-epithelial neoplasia (CIN), carcinoma in situ (CIS), invasive squamous cell carcinoma and adenocarcinoma.

Outcome measures

The primary outcome of interest was the incidence of cancer, overall and per origin (breast, ovarian, endometrial and cervical cancer) in the 'fertility treatment' (exposed) group compared to the 'non-fertility treatment' group (control) (Figure 1). Secondary outcomes included the incidence of malignancy related to specific fertility drugs (in isolation and combination) in particular CC, hMG, GnRH, FSH, LH and hCG (Tables 2, 4, 6, 8 and 10).

Sub-group analyses were also performed, whereby the follow types of studies were excluded: (a) Smaller studies; (b) Outliers; (c) Duplicates (where studies included overlapping patient cohorts) and (d) Non-infertile comparative controls.

Statistical Analysis

The meta-analysis was performed according to recommendations outlined in the MOOSE (Meta-analysis of observational studies in epidemiology) and PRISMA guidelines (Stroup et al., 2000; Moher et al., 2009). Odds ratios (OR) were used as the summary statistic for binary variables. The Mantel-Haenszel method was used to combine the overall rates of the specific outcomes of interest (in this case, cancer incidence) (Mantel and Haenszel, 1959). The I^2 statistic was used to assess heterogeneity of treatment effects between studies. The degree of heterogeneity was categorised into low (I^2< 25%), moderate (I^2 between 25-75%) and high (I^2 >75%). Heterogeneity of treatment effects, relates to the amount of variation observed between studies included in the analysis that can be attributed to the

inherent differences between the trials, as opposed to the influence of chance or a sampling error. To assess the significance of treatment effects demonstrated in this meta-analysis, a random effects model was used. In essence, a random effects model acknowledges that variation exists between studies and the combined treatment effect represents the mean of the population of treatment effects (DerSimonian and Laird, 2015; Higgins et al., 2003). This type of analysis is useful in the applicability of the results and its clinical relevance to the general population, rather than just the population from within the study.

Results

The initial literature search identified 128 studies. After reviewing the abstracts, 49 studies were excluded leaving 79 studies for closer assessment. 53 of these met the pre-defined inclusion criteria. On further review of the study design, treatment and control groups, 24 studies were excluded for further analysis. Reasons for exclusion included the use of non-comparable data sets, a case-control design, the absence of a clearly defined treatment and control group or the inclusion of women with pre-defined risk for cancer i.e. BRCA1/2 gene carriers. The final meta-analysis included 29 retrospective studies, which were divided into individual cancer meta-analyses; Breast n=19, Ovarian n=19, Endometrial n=15 and Cervical n=13. Seventeen of the selected studies involved multiple cancer types and were included in each individual cancer meta-analysis. An overview of the search results and screening process is summarized in the study flow diagram (**Figure 1**).

Meta-analysis: Primary outcomes *(Figure 2)*

Breast Cancer

The study population consisted of 7,769,980 women: 301199 in the fertility treatment group and 7,468,781 in the non-fertility treatment group (control). Nineteen studies were included in the meta-analysis (**Tables 1 and 2**) (Yli-Kuha et al., 2012; Venn et al., 1999; Reigstad et al., 2015; Reigstad et al., 2017; Lerner-Geva et al., 2006; Potashnik et al., 1999; Modan et al., 1998; Lundberg et al., 2017;

Lerner-Geva et al., 2012, (Lerner-Geva, 2006 #8; Kristiansson et al., 2007; Kessous et al., 2016; Kallen et al., 2011; Gauthier et al., 2004; Doyle et al., 2002; Silva Idos et al., 2009; Calderon-Margalit et al., 2009; Brinton et al., 2014; Brinton, Trabert, et al., 2013; Brinton, Scoccia, et al., 2004).

Three studies demonstrated a significantly higher incidence of breast cancer in the fertility treatment group, compared to the non-fertility treatment group: Calderon-Margalit et al. (2009): OR 1.68 (95% CI 1.16-2.42), Silva Idos et al. (2009): OR 1.78 (95% CI 1.31-2.42) and Reigstad et *al.* (2017): OR 1.28 (95% CI 1.06-1.55) (Calderon-Margalit et al. 2009; Silva Idos et al. 2009; Reigstad et al. 2017). Conversely, five studies demonstrated a significantly lower incidence of breast cancer in fertility treatment group compared to non-fertility treatment group: Brinton et al. (2014): OR 0.71 (95% CI 0.61-0.83), Kallen et al. (2011): OR 0.39 (95% CI 0.32-0.48), Kristiansson et al. (2007):OR 0.62 (95% CI 0.43-0.89), Lundberg et al. (2017): OR 0.68 (95% CI 0.60-0.77) and Venn et al. (1999): OR 0.68 (95% CI 0.48-0.95) (Brinton et al., 2014; Kallen et al., 2011; Kristiansson et al., 2007; Lundberg et al., 2017; Venn et al., 1999).

The incidence of breast cancer was 0.76% (2294 of 301199) in the fertility treatment group and 0.75% (56258 of 7,468,781) in the non-fertility treatment group. A random effects model of analysis was used to analyse breast cancer incidence which did not demonstrate any statistical significance: OR 0.86 (95% CI 0.73-1.01). The degree of heterogeneity across the studies was high (I^2 = 89%).

Ovarian Cancer

The study population consisted of 5,819,588 women: 245,019 in the fertility treatment group and 5,574,569 in the non-fertility treatment group (control). Nineteen studies were included in the meta-analysis (Brinton, Lamb, et al., 2004; Brinton , Trabert, et al., 2013; Calderon-Margalit et al., 2009; Doyle et al., 2002; Kallen et al., 2011; Kessous et al., 2016; Kristiansson et al., 2007; Lerner-Geva et al., 2012; Lundberg et al., 2019; Modan et al., 1998; Potashnik et al., 1999; Reigstad et al., 2015; Reigstad et al., 2017; Sanner et al., 2009; Silva Idos et al., 2009; Trabert et al., 2013; van Leeuwen et

al., 2011; Venn et al., 1999; Yli-Kuha et al., 2012). Two studies demonstrated a significantly higher incidence of ovarian cancer in the fertility treatment group compared to the non-fertility treatment group: Reigstad et al. (2017): OR 2.19 (95% CI 1.58-3.06) and Lundberg et al. (2019): OR 1.35 (95% CI 1.06-1.73) (Lundberg et al., 2019; Reigstad et al., 2017) (**Tables 3-4**).

Ovarian cancer incidence was 0.15% (370 of 245,019) in the fertility treatment group and 0.11% (6289 of 5,574,569) in the non-fertility treatment group. Using the random effects model, this difference was not shown to be statistically significant: OR 1.19 (95% CI 0.98-1.46). A moderate degree of heterogeneity was calculated across these studies ($I^2 = 44\%$).

Endometrial Cancer

The study population consisted of 3,063,239 women: 164,472 in the fertility treatment group and 2,898,767 in the non-fertility treatment group. Fifteen studies were included in the meta-analysis (Althuis, Moghissi, et al., 2005; Brinton, Trabert, et al., 2013; Brinton, Westhoff, et al., 2013; Calderon-Margalit et al., 2009; Doyle et al., 2002; Kessous et al., 2016; Kristiansson et al., 2007; Lerner-Geva et al., 2012; Modan et al., 1998; Potashnik et al., 1999; Reigstad et al., 2015; Reigstad et al., 2017; Silva Idos et al., 2009; Venn et al., 1999; Yli-Kuha et al., 2012) . Two studies demonstrated a higher incidence of endometrial cancer in the fertility treatment group: Kessous et al. (2016): OR 3.02 (95% CI 1.38-6.65) and Calderon-Margalit et al. (2009): OR 3.29 (95% CI 1.29-8.38). Conversely, Venn et al. (1999), showed a significantly lower incidence of endometrial cancer in the fertility treatment group: OR 0.31 (95% CI 0.10-0.99), compared to the non-fertility treatment group (Calderon-Margalit et al., 2009; Kessous et al., 2016; Venn et al., 1999) (**Tables 5-6**) .

Endometrial cancer incidence was 0.12% (200 of 164,472) in the fertility treatment group and 0.05% (1508 of 2,898,767) in the non-fertility treatment group. A random effect model was used to analyse endometrial cancer incidence. This difference was not shown to be statistically significant: OR 1.28 (95% CI 0.92-1.79). A moderate degree of heterogeneity was found across the studies ($I^2 = 53\%$).

Our analysis suggests that women who have undergone fertility treatment do not have an increased risk of developing endometrial cancer, compared to those who have not undergone fertility treatment.

Cervical Cancer

The study population consisted of 4,417,530 women: 165,266 in the fertility treatment group and 4,252,264 in the non-fertility treatment group. Thirteen studies were included in the meta-analysis (Althuis, Scoccia, et al., 2005; Brinton, Trabert, et al., 2013; Calderon-Margalit et al., 2009; Doyle et al., 2002; Kallen et al., 2011; Kessous et al., 2016; Kristiansson et al., 2007; Potashnik et al., 1999; Reigstad et al., 2015; Reigstad et al., 2017; Silva Idos et al., 2009; Venn et al., 1995; Yli-Kuha et al., 2012; Lundberg et al., 2017) . Five studies demonstrated a significantly lower incidence of cervical cancer in the fertility treatment group compared to the non-fertility treatment group (Brinton, Trabert, et al., 2013; Kallen et al., 2011; Kristiansson et al., 2007; Reigstad et al., 2015; Yli-Kuha et al., 2012) (**Table 7-8**).

Cervical cancer incidence was 0.36% (603 of 165,266) in the fertility treatment group and 1.24% (52752 of 4,252,264) in the non-fertility treatment group. A random effects model was used to analyse cervical cancer incidence. This difference was found to be statistically significant: OR 0.68 (95% CI, 0.46-0.99). There was a high degree of heterogeneity across the studies ($I^2 = 90\%$).

Overall

The 29 studies were combined to generate an overall risk of cancer in women exposed to fertility treatment compared to those who did not (Althuis, Moghissi, et al., 2005; Althuis, Scoccia, et al., 2005; Brinton, Lamb, et al., 2004; Brinton, Scoccia, et al., 2004; Brinton et al., 2014; Brinton, Trabert, et al., 2013; Brinton, Westhoff, et al., 2013; Calderon-Margalit et al., 2009; Doyle et al., 2002; Gauthier et al., 2004; Kallen et al., 2011; Kessous et al., 2016; Kristiansson et al., 2007; Lerner-Geva et al., 2006;

Lerner-Geva et al., 2012; Lundberg et al., 2017; Lundberg et al., 2019; Modan et al., 1998; Potashnik et al., 1999; Reigstad et al., 2015; Reigstad et al., 2017; Sanner et al., 2009; Silva Idos et al., 2009; van Leeuwen et al., 2011; Venn et al., 1999; Venn et al., 1995; Yli-Kuha et al., 2012; Trabert et al., 2013). The study population included 21,070,337 women: 875,956 in fertility treatment group and 20,194,381 in non-fertility treatment group (**Table 10**).

Overall, the incidence of cancer was 0.40% (3467 of 875,956) in the fertility treatment group and 0.58% (116,807 of 20,194,381) in the non-fertility treatment group. A random effects model was used to analyse the cancer incidence. Again, this difference was not shown to be statistically significant: OR 0.95 (0.82-1.10). Not deviating from the above findings, a high degree of heterogeneity was found across the studies ($I^2 = 88\%$).

Our analysis suggests that undergoing fertility treatment does not increase the overall risk of developing breast, endometrial, ovarian and cervical cancer, compared to those who have not undergone treatment.

Meta-analysis: Secondary outcomes

Fertility Drug Types

A number of studies reported the incidence of cancer for the specific drug used.

CC only (**Figure 3**)

Breast Cancer

Seven studies reported the incidence of breast cancer in women treated with CC only (Brinton, Scoccia, et al., 2004; Gauthier et al., 2004; Lerner-Geva et al., 2006; Lerner-Geva et al., 2012; Modan et al., 1998; Reigstad et al., 2017; Silva Idos et al., 2009). Breast cancer incidence was 1.41% (505 of 35900) in CC treatment (only) group and 0.67% (9338 of 1,396,765) in the non-fertility treatment group. A

random effectss model was used to analyse the breast cancer incidence. This difference was not found to be significantly significant: OR 1.08 (95% CI 0.89-1.30). A moderate degree of heterogeneity was found across the studies (I^2 = 66%).

One to Five Cycles

A random effect model was used to analyse the breast cancer incidence for those patients that underwent 1-5 cycles of IVF (n=3). This difference was not found to be statistically significant: OR 3.47 (95% CI 0.34-34.88). A high degree of heterogeneity was seen across the studies (I^2 = 99%).

Over Six Cycles

Similarly, a random effect model was used to analyse the breast cancer incidence for those patients that underwent >6 cycles of IVF (n=3). This difference was not found to be statistically significant: OR 1.34 (95% CI 0.10-17.46). A high degree of heterogeneity was seen across the studies (I^2 = 99%).

Ovarian Cancer

Six studies reported the incidence of ovarian cancer in women treated with CC only (Calderon-Margalit et al., 2009; Lerner-Geva et al., 2012; Modan et al., 1998; Reigstad et al., 2017; Trabert et al., 2013; Silva Idos et al., 2009). Ovarian cancer incidence was 0.28% (90 of 32344) in the CC treatment (only) group and 0.10% (1344 of 1,324,359) in the non-fertility treatment group. A random effects model was used to compare ovarian cancer incidence. This difference was found to be statistically significant: OR 1.40 (95% 1.10-1.77). The degree of heterogeneity was very low (I^2 = 0%).

Endometrial Cancer

Eight studies reported the incidence of endometrial cancer in women treated with CC only (Althuis, Moghissi, et al., 2005; Brinton, Westhoff, et al., 2013; Calderon-Margalit et al., 2009; Lerner-Geva et al., 2012; Modan et al., 1998; Reigstad et al., 2017; Silva Idos et al., 2009; Venn et al., 1999). Endometrial cancer incidence was 0.31% (110 of 36052) in the CC treatment group and 0.05% (713 of 1336699) in non-fertility treatment group (**Figure 3**). A random effects model was used to analyse

endometrial cancer incidence. This difference was not found to be statistically significant: OR 1.47 (95% 0.95-2.28). The degree of heterogeneity was moderate (I^2 = 63%).

Combined Cancer Risk

Collating the incidence of breast, ovarian and endometrial cancer in association with CC treatment compared to those women who did not receive fertility treatment, the cancer incidence was 0.68% (705 of 104296) in the treatment group, and 0.28% (11395 of 4057823) in the non-fertility treatment group (Brinton, Scoccia, et al., 2004; Gauthier et al., 2004; Lerner-Geva et al., 2006; Lerner-Geva et al., 2012; Modan et al., 1998; Reigstad et al., 2017; Silva Idos et al., 2009; Trabert et al., 2013; Brinton, Westhoff, et al., 2013; Venn et al., 1999). A random effect model was used to compare overall cancer incidence. The difference was shown to be statistically significant: OR 1.23 (95% CI 1.04-1.45). There was a moderate degree of heterogeneity across the studies (I^2 = 59%).

<u>CC and hMG</u>

Breast Cancer

Three studies reported the incidence of breast cancer in women treated with a combination of CC and hMG. A random effects model was used to analyse breast cancer incidence. This difference was not found to be statistically significant: OR 0.82 (95% 0.56-1.19). There was a very low degree of heterogeneity (I^2 = 0%).

Endometrial Cancer

Three studies reported the incidence of endometrial cancer in women treated with a combination of CC and hMG. A random effects model was used to analyse endometrial cancer incidence. This difference was not shown to be statistically significant: OR 1.11 (95% 0.65-1.87). There was a moderate degree of heterogeneity (I^2 = 56%).

<u>hMG only</u>

Breast Cancer

Three studies reported the incidence of breast cancer in women treated with hMG only. A random effect model demonstrated a statistically significant difference between those women that underwent treatment and those that did not: OR 0.44 (95% CI 0.20-0.98). There was a low degree of heterogeneity across the studies (I^2 = 21%).

Endometrial Cancer

Three studies reported the incidence of endometrial cancer in women treated with hMG only. When a random effects model was used to analyse endometrial cancer incidence, this difference was not found to be statistically significant: OR 1.51 (95% CI 0.60-3.82). The degree of heterogeneity was low (I^2 = 0%).

Gonadotrophins only

Breast Cancer

Three studies reported the incidence of breast cancer in women treated with Gonadotrophins only. Using a random effects model to analyse breast cancer incidence, this difference was not found to be statistically significant: OR 1.08 (95% CI 0.87-1.35). There was a very low degree of heterogeneity (I^2 = 0%).

Ovarian Cancer

Two studies reported the incidence of ovarian cancer in women treated with Gonadotrophins only. A random effects model was used to analyse ovarian cancer incidence, this difference was not found to be statistically significant: OR 1.10 (95% CI 0.53-2.27). The degree of heterogeneity was low (I^2 = 0%).

Endometrial Cancer

Three studies reported the incidence of endometrial cancer in women treated with Gonadotrophins only. A random effects model was used to analyse endometrial cancer incidence, this difference was not found to be statistically significant: OR 0.85 (95% CI 0.32-2.29). There was a low degree of heterogeneity (I^2 = 0%).

Sub Group Analysis

Exclusion of small studies

A sub-group analysis was performed for studies only with more than 800 women in each group for breast and ovarian cancer and more than 50 in each group for endometrial and cervical cancer.

Breast Cancer: OR 0.71 (95% CI 0.54-0.95); I^2 = 94% (n=7)

Ovarian Cancer: OR 1.28 (95% CI 0.85-1.91); I^2 = 81% (n=4)

Endometrial Cancer: OR 1.10 (95% CI 0.58-2.12); I^2 = 75% (n=5)

Cervical Cancer: OR 0.63 (95% CI 0.42-0.94); I^2 =93% (n=8)

Exclusion of outliers

A sub-group analysis was performed whereby outliers outside the funnel plot were excluded.

Breast Cancer: OR 0.76 (95% CI 0.67-0.87); I^2 =64% (n=13)

Ovarian Cancer: OR 1.20 (95% CI 1.04-1.38); I^2 =0% (n=17)

Endometrial Cancer: OR 1.21 (95% CI 0.97-1.50); I^2 =0% (n=11)

Cervical Cancer: OR 0.48 (95% CI 0.36-0.63). I^2 =31% (n=7)

Removal of duplicates

A number of studies within the meta-analysis contained overlapping patient cohorts. To eliminate bias associated with over-representation of data from inclusion of the same cohort within two studies, a sub-group analysis was performed, removing the earlier study (containing the overlapping patient cohort) from the analysis.

Breast Cancer: OR 0.88 (95% CI 0.73-1.06); I^2 =89% (n=16)

Ovarian Cancer: OR 1.26 (95% CI 1.03-1.55); I^2 =38% (n=16)

Endometrial Cancer: OR 1.28 (95% CI 0.85-1.94); I^2 =63% (n=12)

Cervical Cancer: OR 0.74 (0.47-1.16); I^2 =90% (n=12)

Exclusion of studies with non-infertile controls

Recognising that infertility itself is a known risk factor for malignancy, a sub-group analysis was performed, excluding studies which compared infertile women undergoing fertility treatment to a non-infertile patient group, i.e. studies with matched population controls/parous women. A sub-group analysis was performed comparing cancer incidence in 'infertile women' who have been exposed to fertility treatment, to 'infertile women' that have not been exposed, 'non- fertility treatment' group.

Breast Cancer: OR 0.84 (95% CI 0.70-1.01); I^2=84% (n=11)

Ovarian Cancer: OR 1.13 (95% CI 0.91-1.40); I^2=20% (n=12)

Endometrial Cancer: OR 1.11 (95% CI 0.83-1.49); I^2=20% (n=9)

Cervical Cancer: OR 0.79 (0.43-1.45); I^2=56% (n=6)

Overall: OR 0.94 (0.81-1.08); I^2=73%

Meta-regression analysis

A meta-regression analysis (Weighted Least Squares model) found that as the weight, sample size and quality of the study increased, the effect of fertility treatment on cancer incidence remained non-

detrimental and for the case of breast, ovarian and endometrial cancers, non-significant. Hence, our primary outcome results remained the same, including the 'positive effect' of fertility treatment on cervical cancer.

Breast cancer: weight & quality - beta = -0.114, p=0.149; population size - beta = -1.04×10^8, p=0.171

Ovarian cancer: weight & quality - beta = -0.007, p=0.953; population size - beta = -2.01×10^7, p=0.111

Endometrial cancer: weight & quality - beta = -0.02, p=0.65; population size - beta = -7.4×10^8, p=0.55

Cervical cancer: weight & quality - beta = -0.089, **p=0.007**; population size - beta = -2.5×10^7, **p=0.002**

Discussion

The rise in the utilisation of fertility treatment as a consequence of more couples seeking assistance with conception, has prompted the need for a comprehensive meta-analysis with the objective of identifying whether a causal association exists between fertility treatment and cervical, endometrial, breast and ovarian cancer. Fertility treatment incorporates exposure to various medications (in isolation or combination), including CC, hCG, hMG, GnRH and Progestogens. It has been postulated that the association between fertility treatment and cancer incidence may be related to the profound hormonal changes that occur during treatment (Kroener et al., 2017).

Main findings

The impact of fertility treatment on cancer incidence appears to be cancer and fertility drug type-specific. We have demonstrated that undergoing fertility treatment is associated with a significant reduction in the incidence of cervical cancer: OR 0.68 (95% CI, 0.46-0.99), compared to those who have not undergone fertility treatment. Fertility treatment does not appear to significantly alter the incidence of breast, endometrial and ovarian cancers.

With regards to the impact of specific fertility drugs, CC treatment appears to significantly increase the overall combined risk of developing cancer (breast, ovarian, cervical and endometrial): OR 1.23 (95% CI 1.04-1.45). For individual cancers, CC treatment appears to increase the incidence of ovarian, breast and endometrial cancer when compared to the non-fertility treatment group, however this was only shown to be a statistically significant for ovarian: OR 1.40 (95% CI 1.10-1.77) but not for breast (OR 1.08) or endometrial cancer (OR 1.47).

Conversely, hMG treatment was associated with a significant decrease in the incidence of breast cancer, when compared to the non-treatment group: OR 0.44 (0.20-0.98). The remainder of the associations between individual fertility drugs and cancer incidence were not shown to be statistically significant.

Exclusion of outliers in the sub-analysis, resulted in a significantly lower incidence of breast cancer: OR 0.76 (95% CI 0.67-0.87) and a higher incidence of ovarian cancer: OR 1.20 (95% CI 1.04-1.38), in the fertility treatment group, which differs from a possible trend demonstrated in the primary analysis. For endometrial and cervical cancer, exclusion of outliers did not change the results of the primary outcome analysis.

Exclusion of duplicates, including overlapping patient cohorts, resulted in a change in the primary outcome analysis for ovarian and cervical cancer. For ovarian cancer, excluding data from three studies resulted in a stronger association, such that the sub-analysis demonstrated a significantly higher incidence of ovarian cancer in fertility treatment group, rather than the trend observed in the primary analysis: OR 1.26 (95% CI 1.03-1.55) (Brinton, Lamb, et al., 2004; Kristiansson et al., 2007; Modan et al., 1998). Conversely for cervical, excluding Kristiansson et al. (2007) from the analysis, meant the significant inverse relationship between cervical cancer and fertility treatment demonstrated in the primary analysis, was no longer found to be statistically significant: OR 0.74 (95% CI 0.47-1.16) (Kristiansson et al. 2007).

Infertility is an established risk factor for malignancy. In order to ensure we controlled for the influence of infertility, studies which compared infertile women undergoing fertility treatment, against a non-infertile group of controls were excluded. The 'infertile' sub-group analysis results were consistent with the primary outcome results for breast, ovarian and endometrial. For cervical cancer, whilst there remained a trend towards a lower incidence of cervical cancer in the 'fertility treatment' group, compared to the 'non-fertility treatment' group, the significant inverse relationship demonstrated in the primary outcome analysis was not maintained in the infertility sub-cohort: OR 0.79 (0.43-1.45).

Breast cancer

Breast cancer is a hormone-sensitive cancer and certain histological sub-types express oestrogen and progesterone receptors on their surface (Cancer, 2012). Overall, our lack of a significant association between breast cancer incidence and fertility treatment exposure, was consistent with two published recent meta-analyses (Gabriele et al., 2017; Sergentanis et al., 2014). Sergentanis et al. (2014) demonstrated that breast cancer incidence was not significantly increased in women treated with controlled ovarian stimulation as part of IVF treatment (Sergentanis et al. 2014). Similarly, Gabriele et al. (2017), showed no significant impact on breast cancer incidence related to ovulation induction (Gabriele et al. 2017).

Our data, whilst not statistically significant, did suggest a possible trend towards a protective effect of undergoing fertility treatment, on the subsequent chance of developing breast cancer, compared to those who did not undergo treatment: OR 0.86 (95% CI 0.73-1.01). Inclusion of two studies published after the meta-analyses mentioned (Gabriele et al. 2017; Sergentanis et al. 2014), notably Brinton et al. (2014) and Lundberg et al. (2017), both of which demonstrating a significant inverse relationship between ovarian stimulation (Lundberg et al., 2017) and ovulation induction (Brinton et al., 2014) on breast cancer incidence, is likely to explain the reason for the slight difference (albeit non-significant) between our findings and previous meta-analyses.

Looking at secondary outcomes, particularly the impact of specific fertility drugs on cancer incidence, the hMG treatment group demonstrated a significantly lower incidence of breast cancer, compared to the untreated group: OR 0.44 (95% CI 0.20-0.98). CC treatment was associated with a trend towards a higher breast cancer incidence, but this was not shown to be statistically significant: OR 1.08 (95% CI (0.89-1.30). Similarly, when the relationship between CC treatment duration was assessed, there was not a clear dose/duration response.

An observed trend towards a higher incidence of breast cancer, associated with CC use is consistent with a recent meta-analysis by *Gennari et al* (2015) where a similar trend towards an increased breast cancer risk in women treated with older treatment protocols (consisting predominantly of CC) was highlighted, but not in women treated with hormonal infertility treatment and IVF (Gennari et al., 2015). There is likely to be a significant degree of heterogeneity of data, given the nature of the data (older studies) and variation in protocols used, so results should be interpreted with caution.

CC is used predominantly in anovulatory cycles and increases follicle recruitment, through an increase in the release of GnRH, resulting in higher levels of circulating gonadotrophins (Sovino et al., 2002). hMG used widely in IVF treatment, contains FSH and LH. Both CC and hMG are associated with an increase in the circulating levels of oestradiol and progesterone and are important in ovulation induction (Fishel and Jackson 1989).

The drug selection for each specific patient depending on the type of infertility may help to allude as to the difference in the observed association between breast cancer incidence and hMG and CC treatment. It is possible that women treated with CC are more likely to have PCOS, therefore experience anovulatory cycles, associated with oestrogen predominance, translating to a higher risk of breast cancer (Sovino et al. 2002). Conversely hMG is a gonadotrophin, typically used for women who have hypogonadotrophic hypogonadism as a cause for infertility/anovulation, a condition known to be associated with a low oestrogen state, therefore may be inherently at a lower risk of hormone sensitive cancers, such as breast cancer. This postulates that the difference in breast cancer incidences in women

treated with hMG and CC, may relate to the different underlying hormone profiles of the patient populations, rather than the response to the specific drug.

Endometrial cancer

Our data suggests that undergoing fertility treatment does not significantly increase the incidence of endometrial cancer compared to women who did not undergo fertility treatment: OR 1.28 (95% 0.92-1.79). Overall, these findings are in line with those published in a recent meta-analysis by Saso et al. (2015) which showed no significant increase in endometrial cancer incidence in women treated with fertility treatment when compared to the 'non-fertility treatment' group (Saso et al., 2015).

Whilst our analysis, did not show a significant association, there was an observed trend towards an increased incidence of endometrial cancer in the fertility treatment group (OR 1.28, 95% CI 0.92-1.79), which was higher in the CC group (OR 1.47, 95% CI 0.95-2.28) when compared to the control group. Our overall trend differed to the possible protective effect of fertility treatment suggested in a previous meta-analysis: OR 0.78 (95% CI 0.39-1.57) (Saso et al., 2015). The reason for the difference is likely due to the inclusion of two recent studies (published since the meta-analysis) both of which demonstrated a significantly higher incidence of endometrial cancer in women treated with fertility treatment, compared to those who did not undergo fertility treatment (Kessous et al., 2016; Reigstad et al., 2017).

The link between endometrial cancer and CC use is supported by a recent Cochrane review, which identified a dose and duration dependent association in women treated with high CC doses (>2000mg) and multiple cycles of CC (>7 cycles) (Rizzuto et al., 2019). As postulated previously, women requiring repeated CC cycles/doses may be inherently more susceptible to endometrial cancer, due to persistent anovulatory cycles which are refractory to CC use, requiring repeated treatment cycles. Anovulatory cycles, are associated with high levels of circulating oestradiol, leading to endometrial proliferation, without the protective effect of progesterone on the endometrium. If left untreated this can lead to

endometrial hyperplasia and ultimately endometrial cancer (Sovino et al. 2002). In our data set, we did not have sufficient provision of data to support a sub-analysis regarding the impact of CC dose and duration on endometrial cancer incidence.

Ovarian Cancer

Our findings suggest a trend towards a higher incidence of ovarian cancer in women undergoing fertility treatment, but this result was not statistically significant: OR 1.19 (95% CI 0.98-1.46). Our findings are in keeping with a recent Cochrane review, which showed no increased risk in the ovarian cancer incidence in women who underwent fertility treatment (Rizzuto et al. 2019).

On exclusion of duplicates and outlier studies, the association between fertility treatment and ovarian cancer was strengthened, resulting in a significantly higher incidence of ovarian cancer observed within the treatment group; duplicates: OR 1.26 (95% CI 1.03-1.55) and outliers: OR 1.20 (95% CI 1.04-1.38).

Conversely, a meta-analysis by Kashyap et al. (2004), looking specifically at infertile women undergoing fertility treatment, observed a non-significant trend towards a reduction in ovarian cancer incidence in women who underwent fertility treatment compared to those who did not undergo treatment suggesting a possible protective role of fertility treatment (Kashyap et al., 2004). The difference in findings is attributed to the inclusion of two recent studies, both of which demonstrated a significantly higher incidence of ovarian cancer in women undergoing fertility treatment, compared to women in the non-fertility treatment group (Reigstad et al., 2017; Lundberg et al., 2019). It is important to highlight that these two studies used a non-infertile group as the control group (Lundberg et al. 2019; Reigstad et al. 2015).

Infertility in isolation, is an independent risk factor for ovarian cancer, possibly relating to the frequency of ovulation in a lifetime (Titus-Ernstoff et al., 2001). Fertile women are likely to ovulate less frequently, due to the anovulatory state associated with pregnancy/breastfeeding, both of which are

known to be protective factors for ovarian cancer (Tung et al. 2005). Women embarking on fertility treatment are inherently at a higher risk of ovarian cancer than a 'non-infertile woman'. To delineate this confounder further, success of fertility treatment is important as pregnancy is a known protective factor due to its associated quiescent state. Unfortunately, the provision of data for the outcome of fertility treatment was not sufficient to perform a meaningful sub-group analysis to explore this further.

Infertility, as a confounder was controlled for through a sub-group analysis. The infertile sub-cohort excluded studies which used non-infertile comparative controls in favour of those who compared infertile women receiving fertility treatment to those not receiving fertility treatment. The sub-group analysis did not significantly change the outcome of the primary analysis: OR 1.13 (95% CI 0.90-1.40).

The possible relationship between fertility treatment and ovarian cancer incidence, may also relate to the underlying process of fertility treatment. The process of super-ovulation is known to be associated with significant micro-trauma and formation of inclusion cysts within the ovary, which are known to be traumatic and may pre-dispose to ovarian cancer (Tung et al. 2005).

Cervical Cancer

Our findings have demonstrated a significantly lower incidence of cervical cancer in women undergoing fertility treatment (OR 0.68 (95% CI, 0.46-0.99). Recognising infertility as a potential confounder, a sub-group analysis was performed only including studies with untreated infertile women as the control group. The significant inverse relationship between fertility treatment and cervical cancer demonstrated in the primary analysis was curtailed in the infertile sub-group analysis, pointing towards a lower incidence of cervical cancer in the fertility treatment group.

There were no existing meta-analyses looking specifically at the association between cervical cancer incidence and fertility treatment, however a meta-analysis by Siristatidis et al. (2013) looking at gynaecological malignancies (including cervical cancer), demonstrated a reduced incidence of cervical

cancer and a higher incidence of breast and endometrial cancer in women undergoing controlled ovarian stimulation as part of IVF, when compared to the general population (Siristatidis et al., 2013).

When an infertile sub-group analysis was performed by Siristatidis et al. (2013), a reduction in the overall treatment effect was seen, once infertility was removed as a potential confounder. Our findings, supported by Siristatidis et al. (2013), do suggest that being 'infertile' puts you at a lower risk of cervical cancer, rather than exposure to fertility treatment itself (Siristatidis et al. 2013).

Significant risk factors for cervical cancer include, multiple sexual partners, nulliparity, early age of first intercourse, smoking and low socio-economic status (Parikh et al. 2003). There are a number of reasons why cervical cancer may be lower in women engaging in investigation for infertility, whether or not they actually receive treatment. Firstly, better access to healthcare and more frequent clinical examinations may result in early detection of a cervical abnormality, prompting timely intervention and prevention of progression. Secondly, infertile women being investigated/undergoing fertility treatment are more likely to be in a long-term monogamous relationship, based on the fact that infertility is defined as "an inability to conceive following one year of unprotected sexual intercourse with a regular partner" (NICE, 2013). Thirdly, undergoing investigations and fertility treatment is often costly, so women are likely to be of higher socio-economic status. Finally, women who are investigated or undergo fertility treatment may have better overall engagement in healthcare, which could be translated to better adherence to regular cervical screening.

Moreover, cervical cancer is not a hormone sensitive cancer, therefore, it is unlikely that a clear causal mechanism exists between hormonal fertility treatment and the pathogenesis of cervical cancer (Parikh et al. 2003).

Strengths and limitations

This study provides an up to date, comprehensive meta-analysis of the impact of exposure to fertility treatment on the development of breast, ovarian, cervical and endometrial cancer. The study incorporates evidence from 29 retrospective studies from centres across the world, providing large, varied data sets, strengthening the validity and applicability of the study outcomes.

We recognise that incorporating data from large number of data sets, derived from multiple studies from across the globe, introduces a significant degree of clinical heterogeneity. Inter-study variation was identified in a number of important areas including patient demographics, fertility drug type, duration of use, protocol used, study selection criteria, duration of follow up and cancer identification method. The variation in location of the studies, whilst it provides excellent validity and applicability of the outcomes derived from the dataset, does introduce a significant degree of variation, particularly in the patient demographics and standard protocols utilised. Similarly, the wide-span of the study (1963-2013) undoubtedly introduces significant variation in practice both within and between studies, affecting the consistency and validity of the data. The control groups varied between studies, which is likely to have contributed to the significant variation observed reflected in the significant degree of heterogeneity between studies. Recognising infertility as an important confounder and in attempt to reduce variation, studies which used non-infertile comparative controls were excluded from the sub-group analysis.

The highest degree of heterogeneity was seen in cervical and breast cancer (I^2 90% and 89% respectively). We therefore appreciate that the findings have to be interpreted with an element of caution, due to the significant variation that is likely to exist between studies. Furthermore, the retrospective nature of the study design introduces significant bias to the analysis, however the nature of the desired outcome (cancer incidence) is not conducive to a more robust study design, such as a randomised controlled trial, given its relatively rare occurrence.

Conclusion

The overall cancer incidence is not significantly higher in women undergoing fertility treatment, which is reassuring. Moreover, controlling for infertility in the sub-group analysis, did not significantly change the primary outcome analysis for breast, endometrial and ovarian cancer. Interestingly, fertility treatment may be associated with a lower incidence of cervical cancer, but the treatment effect was curtailed when infertility was removed as a potential confounder. Finally, CC use has been shown to increase the overall cancer incidence, particularly for ovarian cancer.

Future work should focus in improving the overall follow up process of women undertaking fertility treatment particularly focusing on overall outcome of fertility treatment and number of cycles required to achieve pregnancy (if applicable). Secondly, the development of robust systems for reporting new cancer diagnoses following fertility treatment will ensure a more accurate representation of the true cancer incidence on which to base future analyses.

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