The management of menopausal symptoms in women following treatment for cancer in a specialist menopause service

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Abstract

Objective

The aim of this study was to identify prescribing patterns at a specialist menopause service in a Central London teaching hospital for women following treatment for a malignancy.

Study design

This was a prospective cohort study with data collected over a seven month period from December 2019 to June 2020. All women reviewed at the specialist menopause services following treatment of a malignancy, BRCA carriers and Lynch syndrome were included in the study, with management options divided into three categories: hormonal, Non-hormonal and no treatment.

Main outcome measures

The primary outcome of this study was to identify prescribing patterns for all women reviewed following a diagnosis of a malignancy, as well as those with genetic mutations necessitating risk reducing prophylactic bilateral salpingo-oopherectomy (BSO).

Results

Altogether seventy-one women were included in this study, with the majority of women post management of a non-gynaecological malignancy (51/71, 72%), of which breast cancer was the most common (37/71, 52%). While non-hormonal treatment was the most popular among those treated for breast cancer, for all other malignancies, hormonal treatment was more widespread. Fourteen women also had genetic mutations, with all of these women commencing hormonal treatment post risk reducing surgery.

Conclusion

With the exception of those with a previous history of hormone sensitive breast cancer, the use of hormonal treatment for menopausal symptoms remained widespread. While this was a relatively small study, the need for long-term follow up across specialist menopause services, to assess the risk of recurrence is vital.

Introduction

The advice and management of women with menopausal symptoms secondary to malignancy remains an area of concern especially for Health Care Professionals (HCP's) without specialist menopause management experience. The importance of 'Quality of life' (Daly 1993) concerns is often overlooked or ignored by many HCPs despite being of utmost importance to most women. (Gupta 2006, Hunter 1986, McVeigh 2005)

The evidence surrounding the use of Hormone Replacement Therapy (HRT) and malignancies is scanty and mainly observational (Creasman 2005), with few Randomised Controlled Studies (RCT) (Genazzani 2001) available to provide concrete advice. While HRT is generally avoided in those recovering from breast cancer, the appropriate treatment for those with other gynaecological or non-gynaecological malignancies is less clear. As a result, prescribing patterns of HRT in these patients varies significantly. The relative uncertainty among many HCP's means that often women are left facing the debilitating, often severe symptoms of the menopause, after an already tumultuous journey of cancer treatment and recovery.

The main concern when initiating HRT in this population concerns the risk of recurrence of the cancer. With the limited and often conflicting data available, it remains a difficult area to navigate. Moreover, many of the misconceptions regarding the safety of HRT, stemming from the WHI study in 2002 continue to propagate (WHI 2002). This is despite more recent studies (Welton 2008) highlighting the importance of HRT in reducing the incidence of menopausal symptoms (Santoro 2015), osteoporosis (Wells 2002), cardiovascular disease (Hu, 1999. Zhu, 2019) as well as numerous other important benefits such as improving sexual function, sleep, general well-being and mood (Fluker 2001, Morgan 2005, Wren 1985). It also has to be noted that many of the concerns regarding the use of HRT relate to studies that used oral preparations, at high doses, which are well-known to have a completely different risk profile compared to transdermal preparations (D'Alonzo 2019). Moreover, many of the findings regarding the use of HRT looked at the incidence of new malignancy between HRT users versus non-users (WHI 2002), which is of minimal relevance for women who are more concerned regarding the risk of recurrence post treatment of their malignancy. Such research is of vital importance, in order to guide the discussion on how best to manage menopausal symptoms in this group of women and a number of studies have been published attempting to tackle this issue (Creasman 2005). However, given the average age of diagnosis, as well as the increasing disease-free survival time, it is an area that requires greater clarity for these women and those responsible in their care.

Gynaecological Malignancy

Endometrial

There is no evidence to suggest that HRT increases the risks of recurrence in patients with early stage (FIGO Stage I/II) endometrial cancer (Barakat 2006). Due to the potential theorised risk of residual disease being activated, some advocate the concurrent use of progestogens rather than estrogen only HRT following surgical intervention. However, the evidence to recommend one form of HRT over another in this situation remains scanty and has to be balanced with the increased risk of breast cancer in combinational therapy (Edey 2018). Although, the recommendations for stages III-IV endometrial cancer remains less clear, HRT is contraindicated in low grade endometrial sarcomas (Hinds 2010).

Ovarian Cancer

The lack of large multi-centre randomised studies regarding the use of HRT following cytoreductive surgery in ovarian malignancy has meant that many have remained cautious over its use. However, based on the small number of studies to date there have been no difference in the disease free survival time following surgery between HRT and non-HRT users for those with Stage I to III, epithelial, borderline and germ cell tumours (Bebar S 2000, Mascarenhas C 2006, Ursic-Vrscaj M 2001). This was similarly replicated in a small RCT, which followed 130 patients up to four years post-surgery for Stage 1-IV Epithelial ovarian cancer (Guidozzi 1999). A more recent prospective study following 112 patients, aged between 20-50 years, following a diagnosis of serous ovarian cancer similarly found no difference in disease free survival time between users and non-users of HRT (Zhang 2016). The benefit however can be immense with a substantial increase in physical and emotional function in HRT users compared to non-users (Li 2012). However, the difficulty with interpreting these studies relates to the small number of patients recruited, as well as the relatively short follow up time ranging from 24 to 48months. Due to the theorised risk of residual disease being stimulated by estrogen in women diagnosed with granulosa cell tumours, HRT is generally avoided in these patients.

Fallopian Tube cancer

Primary fallopian tube cancers are relatively rare and are often grouped under epithelial ovarian cancer, which also includes primary peritoneal disease (Marina 2019). With the origin of many high grade serous epithelial ovarian cancer been shown to be from the fimbrial end of the fallopian tube (Leeper 2002) and with limited studies published on the management of primary fallopian tube cancers, the advice on the use of HRT typically that given for epithelial ovarian cancers. (Saeaib 2017).

Cervical cancer

Cervical cancer is the third most common gynaecological cancer and can be differentiated into squamous cell and adenocarcinoma. Due to the association of the combined oral contraceptive pill in the development of adenocarcinomas (Smith 2003), concerns have been raised on the use of HRT for survivors of cervical cancer. While one multicentre case-control study demonstrated a positive but not a significant association between the use of estrogen only HRT with adenocarcinoma but not with squamous carcinoma (Lacey 2000), there is limited data beyond this study. Similarly, for those diagnosed with cervical cancer, the only data available is from a prospective cohort study in 1987, which followed 120 patients over five years following a diagnosis of Stage 1-II squamous and adenocarcinoma. This showed no difference in survival or incidence of cancer recurrence among HRT users versus non-users over five years (Ploch 1987). Due to the lack of definitive data, HRT has not been contraindicated for those diagnosed with cervical cancer.

<u>Non-Gynaecological malignancies</u>

Breast cancer

The publication of the WHI study in 2002 (WHI 2002) demonstrating the increased risk of breast cancer in HRT users led to some of the most dramatic changes in how HRT was prescribed at the start of the new Millenia. Unfortunately, the inextricable damage created by

this study and by subsequent publications echoing these results continue to dominate the media (Collaborators 2003, Cancer 2019). The difficulty with these studies is that they focus on the risk of breast cancer for women aged 50 years or over, whom we already know have a higher risk of hormone sensitive breast cancer (Wang 2017). While the aetiology of breast cancer has been associated with defective estrogen receptor signalling pathways, there is evidence to suggest that there are variations in the biological mechanisms governing the different sub-types (Suba 2014). However, with more women being diagnosed and surviving longer disease free from breast cancer, it leaves many in a difficult position on how best to manage their symptoms. While a number of observational studies appeared to contradict an increased risk of recurrence following HRT use, comparing these studies were extremely difficult due to inherent differences in study design (Col 2005). As a result, the HABITs (HRT After Breast Cancer-Is it Safe?) trial was established in order to identify if HRT was safe for women treated for breast cancer. This followed women for five years who had been diagnosed with Stage I-II breast cancer. Based in Sweden, it openly allocated women to a 2 year program of either HRT or alternative therapy (Holmberg 2004). Unfortunately, the trial was closed prematurely, due to the findings suggesting an unacceptable risk of recurrence in HRT users compared to non-users. However, the findings of the HABITs trial appear to contradict another RCT which ran concurrently, the Stockholm study, which did not demonstrate increased risk of recurrence between HRT versus non-users (VonSchoultz 2005). Drawing firm conclusions from both these studies are difficult though, as different regimes of HRT were used, with women in the Stockholm study receiving either estrogen alone or a longer 'spacing out' regime, where they received estrogen for 14 days every 3months. It was also noted that adjuvant tamoxifen use was higher in the Stockholm study. Interestingly, the incidence of contralateral breast cancer was higher in the Stockholm study, raising the question of whether this was a recurrence or a new primary malignancy (Fahlen 2013).

Similarly, the use of tibolone remains divided in these patients, despite previous evidence suggesting its risk being comparable to estrogen only HRT (Erel 2006). The LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) trial was designed to assess the use of Tibolone in breast cancer survivors (Kenemans 2009) but again closed prematurely due to an increased risk of recurrence. The effects of tibolone on breast tissue density though has been shown to be minimal compared to combined HRT (Kubista 2007, Bruce 2004)

With all RCTs closing prematurely, it offers little hope to women suffering with severe menopausal symptoms secondary to their treatment for breast cancer (Cusack 2013). While NICE (National Institute for Clinical Excellence) advises against the use of HRT for women with a history of breast cancer, it also recognises that there may be exceptional circumstances where this may be necessary (NICE, 2009). More recently, many clinicians have recognised this and have moved towards an individualised risk-benefit approach, to enable women to make an informed decision rather being faced with ongoing debilitating symptoms (Xydakis 2006). However, difficulties remain on how best to navigate this discussion with the lack of consistent evidence and the relative uncertainties on prescribing patterns. Prescribing HRT with the lowest possible risk of stimulating residual disease would be advised but for those with an intact uterus this presents a challenge due to the need to ensure endometrial protection. While combined HRT has been shown to confer the highest risk of breast cancer compared to estrogen only HRT, there remains uncertainty on the risk profile on alternative methods of progestogen

administration (Collaborators 2003). Similarly, although there have been no RCTs on the use of vaginal estrogen therapy, an increased risk of recurrence has not been demonstrated in a number of studies (Le Ray 2012, Durna 2002). However, these studies have typically looked at women with Stage I and II breast cancer, whose risk of recurrence is suspected to lower than those diagnosed initially with more advanced disease.

Unsurprisingly, the use of complementary and alternative therapy has been shown to be higher among breast cancer survivors (Harris 2002) and these can be broadly categorised into

- Mind-Body- Cognitive behavioural therapy (CBT), aromatherapy
- Natural products- Black cohosh, Vitamin E, phytoestrogen
- Whole body approaches- Acupuncture, reflexology

While varying levels of efficacy and success have been demonstrated in a number of studies for the wide range of therapies available (Newton 2002, Kim 2015), this was not replicated in a meta-analysis comparing over 70 RCTs (Nedrow 2006). More recently, a critical review based in the UK suggested more favourable outcomes for managing menopausal symptoms through the mind and whole-body approach (Johnson 2019). Although the consumption of phytoestrogens in breast cancer survivors is not recommended (NICE 2018), the overall efficacy of natural products on menopausal symptoms remains mixed (Pachman 2010).

Other alternatives for managing menopausal symptoms in breast cancer survivors are non-HRT based medications. However, specific guidance by NICE recommends avoiding Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Noradrenaline Reuptake Inhibitors (SNRIs) that are known potent inhibitors of cytochrome 450 in tamoxifen users (UKMi 2018, NICE 2018). Typically, venlafaxine remains the premier choice due to its efficacy, although citalopram, escitalopram and sertraline are equally safe in this group (Stubbs 2017). Typically used as a neuroleptic or for managing neuropathic pain, gabapentin has also shown to be effective for managing hot flushes (Guttuso 2003) and are suitable for breast cancer survivors, although women need to be counselled on potential side effects that can lead to their discontinuation. Similarly, side effects from the centrally acting alpha-adrenergic receptor, clonidine, can be intolerable for many women (Goldberg 1994, Pandya 2000)

Other malignancies

It is important not to overlook the management of menopausal symptoms for women treated for other less common malignancies.

Interestingly, the use of HRT in certain malignancies has been shown to have a protective effect in reducing the risk of recurrence (Deli 2020). These include colorectal (Grodstein 1999), hepatocellular (Hassan 2017), local malignant melanoma (MacKie 2004) and haemopoietic malignancies (Yang 2017). Similarly, for thyroid cancers (Moleti 2017) and prolactinomas (Christin-Maître 2007), there are no contraindications to using HRT. However, with a positive estrogen receptor status being associated with a poorer prognosis in gastric and bladder tumours, some advise against the use of HRT, although there is a lack of clinical evidence to support the risk of recurrence (Zhao 2003, Fernandez 2003).

Specialist Menopause Services

Given the conflicting nature of the evidence available, specialist menopause services offer women the opportunity to explore their concerns and have a tailor-made management plan for their menopausal symptoms post treatment of their malignancy. It is vital that as part of this discussion, HCPs are transparent on the uncertainties and conflicting nature of the clinical evidence available and that this is balanced with women's own expectations of what is important to them. Equally, the implications of being hormonally deficient and the subsequent cardiovascular risks and effects on bone health and cognition must be discussed. Achieving this delicate balance is key to ensuring a holistic approach to women's health.

Therefore, the primary objective of this study was to identify the management of women referred to the specialist menopause services following treatment for a malignancy. This included hormonal, non-hormonal as well as no treatment for women. The secondary outcomes of this study were to identify the most common malignancy, menopausal symptoms and the age group of women referred to our services.

Methods

This was a prospective cohort study and included all women reviewed post treatment for a malignancy at the specialist menopause services. Women who had been referred for genetic mutations were also included in the study. Data was collected over a seven month period from December 2019 to June 2020 and included

- Age
- Primary malignancy and treatment
- Symptoms of menopause
- Management of symptoms

Management of menopausal symptoms was further divided into the,

- Hormonal- HRT (combined and sequential), Combined oral contraceptive pill (COCP), Progesterone only pill (POP) and Hormonal Intrauterine device (IUD)
- Non-hormonal- Gabapentin, Venlafaxine, Acupuncture, Cognitive Behavioural Therapy
- No medication

Results

Seventy-two women were referred to the specialist menopause services for management of their menopause symptoms following a diagnosis of a malignancy. We excluded 1 woman from this study, as she had a diagnosis of endometrial hyperplasia

Chart 1 shows the referrals by type of malignancy with the majority of women being reviewed for non-gynaecological malignancies (51/71), of which the most common was breast cancer (37/71,52%). 28% of women were reviewed following treatment of gynaecological malignancies, of which ovarian cancer (9/71, 13%) was the most common followed by cervical cancer (7/71, 10%).

Altogether fourteen women were identified as having underlying genetic mutations, of which thirteen were for BRCA gene defects. Only one woman was reviewed following a diagnosis of Lynch syndrome.

Chart 1- Referral by type of malignancy

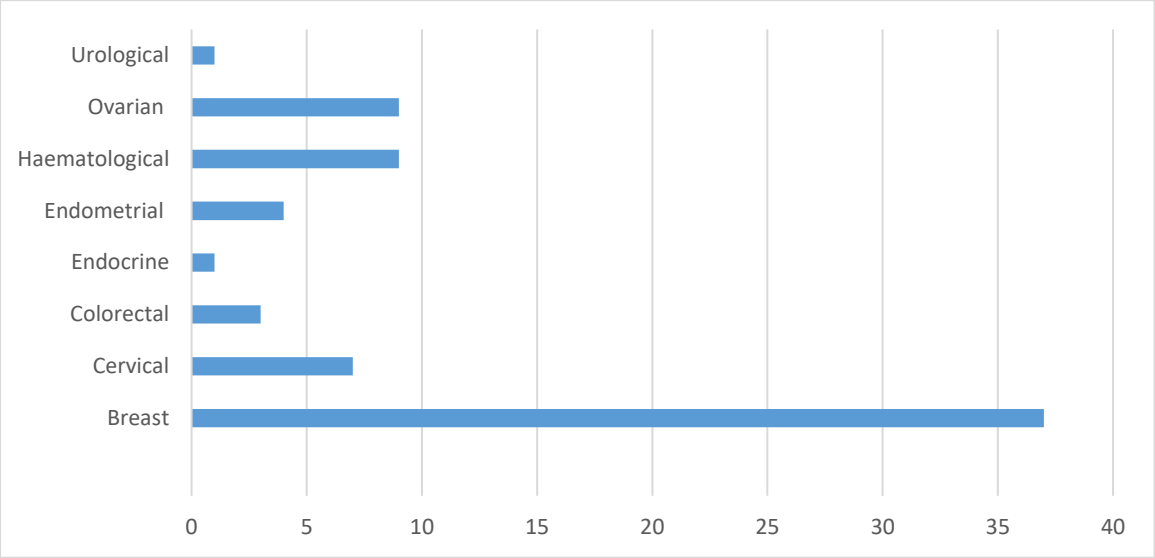


Chart 2 shows the breakdown by age and primary malignancy of the women referred to the menopause service, with the most women being aged between 40-49years. The most commonly reported menopausal symptoms (Chart 3) were hot flushes followed by 'other', which included a combination of dizziness, muscle and bone pain and reduced. Ten patients had no symptoms of menopause at the time of their review.

Chart 2- Age distribution of women referred to the menopause clinic

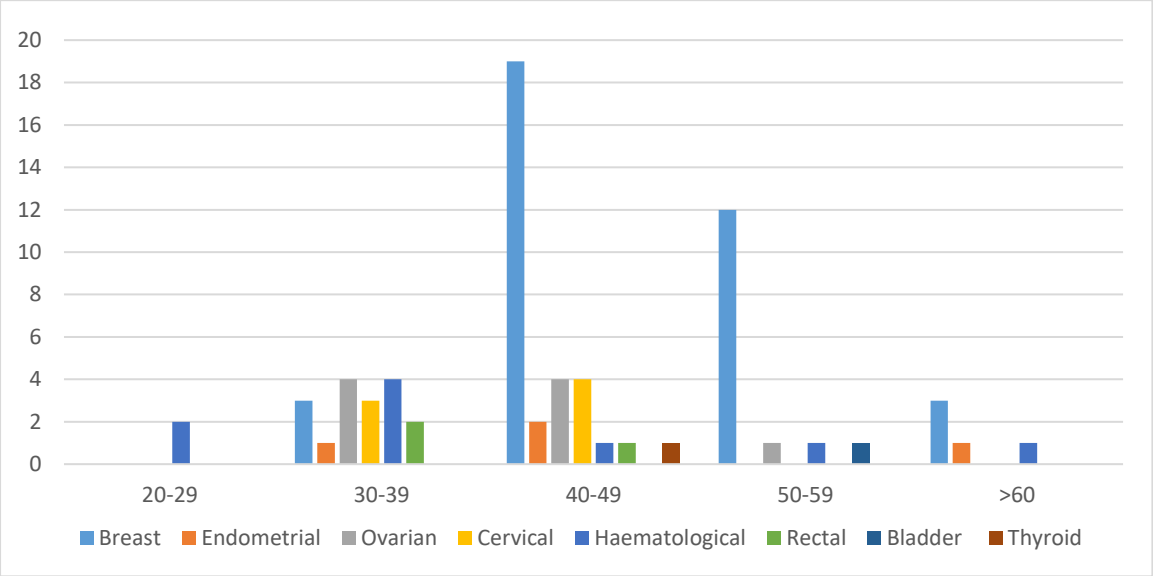
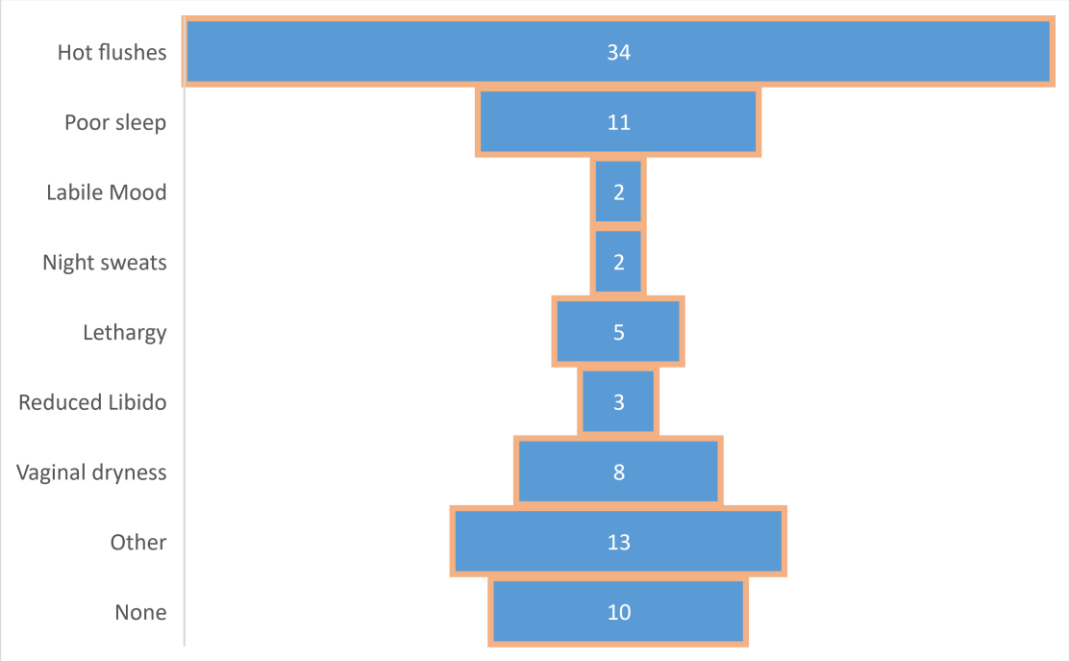


Chart 3- Menopausal Symptoms reported



Gynaecological malignancies

Endometrial Cancer

There were 4 patients who were referred to the menopause services following surgery for endometrial malignancy. Three patients had Stage 1 disease and of them 2 had estrogen only HRT for their symptoms. The remaining patient was symptom-free and so was not commenced on HRT. One patient had endometrial sarcoma and was prescribed non-hormonal medication.

Ovarian Cancer

There were 9 patients who were referred for management discussions following surgery for ovarian malignancy.

Table 1 shows the breakdown of malignancy by staging with no patients having Stage Ib, IIb or IIc disease. Only one patient received combined HRT, as she had uterus preserving surgery.

Only 1 patient had Stage IV disease and she was also a BRCA2 gene carrier, she was also diagnosed with Breast cancer three years following her diagnosis of ovarian malignancy, which was triple negative.

Table 1- Ovarian Cancer

Stage	**Type**	**HRT**
Ia	- Granulosa cell - Granulosa cell - Granulosa cell - Brenner tumour	Evorel 50 Estrogel 2 pumps and Vagifem Estrogel 2pumps BD Estradot 75
Ib	X	
Ic	- Clear cell - Mucinous adenocarcinoma	4mg Estradiol and Tostran Estrogel 2pumps BD
IIa	- Borderline serous	Estradot 125 and Mirena
IIb	X	
IIc	X	
III	- Clear cell	Estradiol 3mg
IV	- Serous	Evorel 50

Cervical cancer

There were 7 patients referred to menopause clinic following a diagnosis of cervical cancer, all of whom had HRT prescribed following treatment. Six women had squamous cell carcinoma, 4 Stage 1b disease and 2 Stage 1b disease. They all had a combination of chemotherapy and brachytherapy and subsequently started combined HRT. One woman had adenocarcinoma of the cervix, Stage 1b, and subsequently started estrogen only HRT following a Total Hysterectomy and Bilateral Salpingo-Oophorectomy (TAH+BSO).

Non-gynaecological malignancies

Breast Cancer

There were 37 women referred to the menopause services for management of their menopausal symptoms following treatment for breast cancer.

Thirty-four women had been diagnosed with primary breast cancer in the last 10 years, with 2 patients diagnosed from 2000-2009. One patient was diagnosed with a primary breast cancer in 1999 and had a recurrence in 2019.

Table 2 shows the breakdown of breast cancer by hormone status and management and Table 3 shows the types of HRT used in these patients in more detail.

Table 2- Breast Cancer

Hormone Status	**Management of Menopausal symptoms**			
	Hormonal	Non-Hormonal	None	TOTAL
ER+/PR+	0	6	5	11
ER+/PR-	0	11	2	14
ER-/PR+	1	0	1	2
ER-/PR-	X	X	X	NIL
HER2 + only	0	2	0	2
Triple Negative	5	2	1	8

Table 3- Types of hormonal treatment following Breast malignancy

Hormone status	**Type of HRT**	
	Combined HRT	Tibolone
ER-/PR+	0	1
Triple Negative	4	1

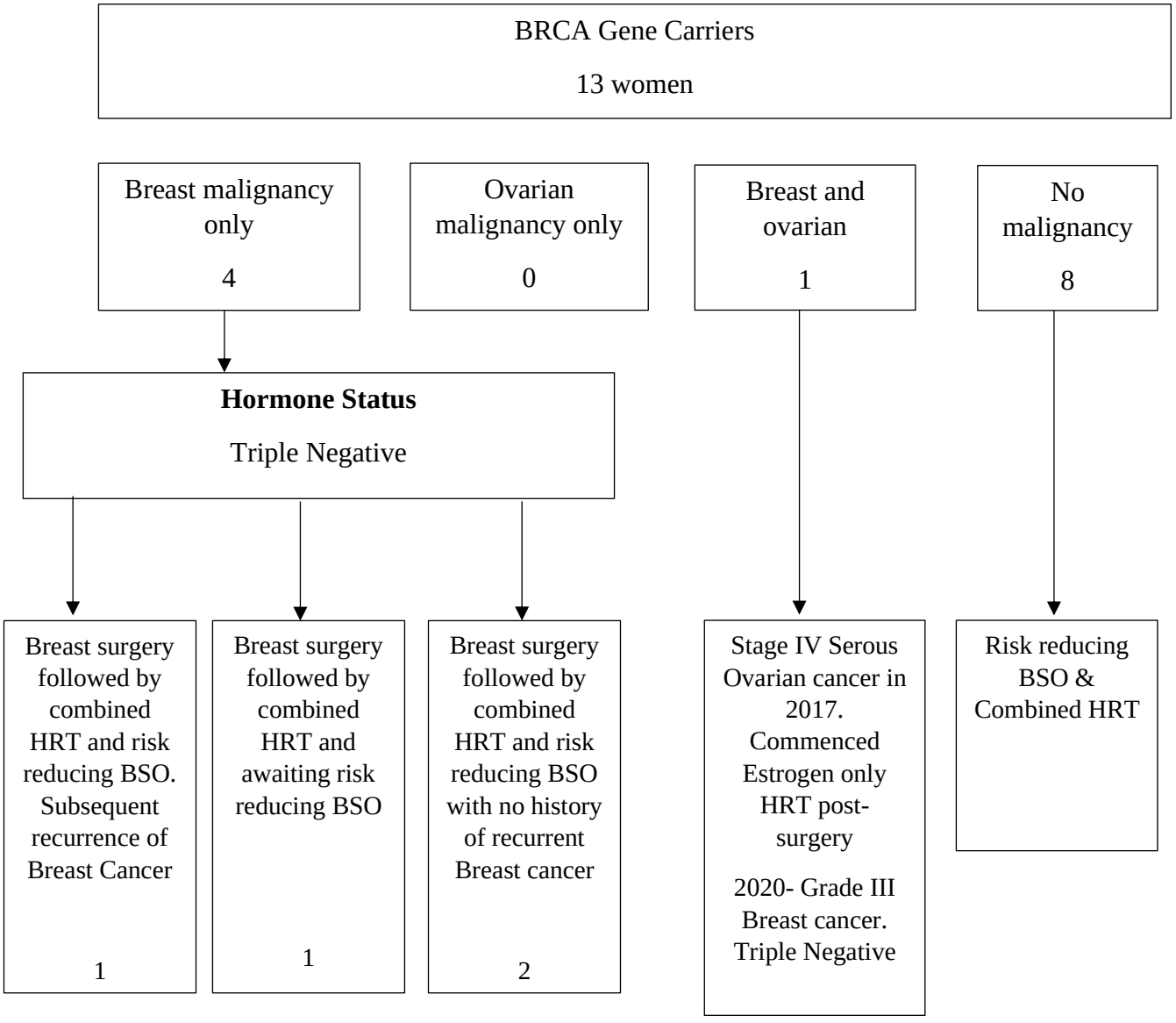
Genetic mutations

Fourteen women were identified as having underlying genetic mutations, of which 13 were due to BRCA gene mutations. Diagram 1 presents a flowchart of the management of these women.

Following a diagnosis of breast cancer, 4 women were identified as being BRCA carriers and they were all confirmed as having triple negative breast cancer. Of these 4 women, 1 had a recurrence of breast cancer following a risk reducing prophylactic bilateral salpingo-oopherectomy (BSO) and her combined HRT was discontinued following the recurrence. One woman in this group is awaiting her risk reducing BSO following management of breast cancer and is presently on combined HRT.

One woman with a BRCA gene mutation was originally managed for ovarian cancer in 2017 and following surgery, she commenced estrogen only HRT. In 2020, she was diagnosed with triple negative breast cancer and has since undergone a mastectomy. She remains on estrogen only HRT due to her ongoing symptoms.

<u>Diagram 1-</u> Management of women with BRCA gene mutation referred to the menopause clinic



One woman had risk reducing surgery following a diagnosis of Lynch Syndrome and she subsequently commenced Estrogen only HRT.

Other malignancies

There were 14 patients that were referred for other non-gynaecological malignancies excluding breast cancer. Table 4 shows the breakdown of their management by the type of primary malignancy. All 3 patients who had hormone replacement in the form of the COCP or POP were less than 40 years old. One woman with a history of rectal carcinoma declined HRT, as she had no symptoms and 2 women with anal and bladder carcinoma decided to watch and wait as their symptoms were minimal.

One woman had a Mirena IUD ® inserted prior to her diagnosis of a lymphoma due to heavy menstrual bleeding and this was due for removal, as she was now 60 years old. She was 58 years old when she had her primary diagnosis.

Table 4- Other malignancies

System	**Primary malignancy**	**Management**					
		Combined HRT	COCP	POP	IUD	Surveillance	Declined
Endocrine	Thyroid	1					
Colorectal	Rectal	1					1
	Anal					1	
Urological	Bladder					1	
Haematological	Lymphoma	5	1	1	1		
	Ewing's		1				

Discussion

It can be seen that the majority of women referred to the specialist menopause services were aged between 40-49years and following a diagnosis of breast cancer. Despite many suffering from severe symptoms, the use of non-hormonal preparations was more widely seen in this group of women and is likely a direct reflection of the relative uncertainty and also concern of the risk of recurrence in using HRT. Interestingly, it was also identified that these women were also less willing to consider HRT, as many felt that they had gone into the menopause only a few years earlier than what would have occurred 'naturally'.

In contrast, the use of the contraceptive pill was widespread among those with a history of a haematological malignancy, which formed the second largest group of women with a non-gynaecological malignancy. This is most likely due to the younger age group where the use of the contraceptive pill is generally more acceptable than HRT due to its association with menopause. Among those reviewed for a gynaecological malignancy, the use of HRT was widespread although it has to be noted that no women were reviewed for vulval or vaginal carcinoma.

While the primary outcome of this study was to identify the prescribing patterns for women referred for the management of menopause symptoms, it also provides scope for long term follow up. More specifically, gathering data on recurrence through such follow up will enable HCP's to be better informed when counselling women on the uncertainties around HRT, especially for those previously treated for breast cancer. It would also be of immense value for counselling women with BRCA gene mutations, who have no previous history of malignancy and do not undergo mastectomy but subsequently start combined HRT following risk reducing BSO. Understanding whether there is a greater risk of developing breast cancer in these women could help in guiding us on whether hysterectomy should be included as part of the risk-reducing surgery to avoid the use of combined HRT. Interestingly, all four of the women with BRCA gene mutations had triple negative breast cancer.

While it has to be acknowledged that small numbers of women were overall observed in this study, it nevertheless provides valuable insight into prescribing patterns and the concerns that many women have in regards to the management of their symptoms and the effects on their quality of life. Developing such studies over time and across specialist menopause services are vital in providing much-needed insight in an area that has undoubtedly suffered from media sensationalism. Our focus should remain however, on identifying the best route of managing menopausal symptoms that strives to achieve a reasonable quality of life for women who have been treated for a primary malignancy.

Acknowledgments

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