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Risk of Cancer With Hormone Replacement Therapy: A Narrative Review

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ABSTRACT

Hormone replacement therapy (HRT) remains the cornerstone of menopausal symptom management, effectively alleviating vasomotor symptoms and genitourinary syndrome, whilst mitigating long-term risks such as osteoporosis. However, despite an increasing body of evidence on the relative safety of HRT, earlier studies that demonstrated an increased cancer risk have resulted in decades of controversy and reshaped clinical practice and public perception. Concerns around HRT are heightened in cancer survivors or those with strong family histories and genetic risks, and many clinicians remain reluctant to consider HRT due to the potential for promoting cancer. Globally, around 9 million women and an estimated 60 000 women in the UK under the age of 50 are diagnosed with cancer and will receive treatment that results in iatrogenic premature or early menopause or develop hormone-related, menopause-like, side effects, even if not rendered menopausal. Improvements in oncological management have resulted in significant benefits in cancer survivorship, and importantly, an increasing focus on quality of life. This article aims to comprehensively review the evidence and provide an overview for clinicians that can help guide discussions with patients regarding HRT risks and benefits, and promote shared, informed decision making.

1 | Introduction

Menopausal symptoms persist for an average of 7 years [1], but can continue for much longer [2], having a significant impact on a woman's quality of life. The most common symptoms are vasomotor (hot flushes, night sweats), sleep disturbance, changes in mood and genitourinary syndrome of menopause (GSM). Since their introduction in the 1960s, hormone replacement therapy (HRT) and hormone analogues such as tibolone continue to be the most effective treatment for managing symptoms and improving menopause related quality of life for many women. Although non-hormonal treatments are available, all are less effective than HRT, particularly for vasomotor symptoms (VMS) and have their own side effects. However, the association of HRT with an increased risk of some cancers has been a subject of extensive research and ongoing debate. This literature review examines the evidence linking HRT with cancer risk.

1.1 | Hormone Replacement Therapy

HRT consists of oestrogen ± a progestogen/progesterone and more recently testosterone. Oestrogen replacement aims to ameliorate menopausal symptoms due to hypoestrogenaemia in peri-and post-menopausal women. It can be given systemically or as local topical therapy for GSM. Meanwhile, progesterone is essential to provide endometrial protection in those with a remaining uterus and can either be given continuously in post-menopausal women, sequentially (usually 12–14 days/month) in peri-menopausal women, or as an intrauterine system for both peri- and post-menopausal women.

Natural progesterone is also associated with a sleep-inducing effect. Lastly, testosterone can be prescribed off licence for patients with hypoactive sexual desire disorder (HSDD) despite adequate oestrogenic HRT and is administered transdermally.

1.2 | Interpreting HRT Literature

HRT is not a singular entity but a heterogeneous prescription that can vary in dose, formulation, route of administration, and regimen. Consequently, careful interpretation of the literature is required, recognising that conclusions can be only drawn for the specific type of HRT detailed in the methodology and to be cautious about extrapolating it to other forms. Additionally, many of the large studies pre-date current HRT prescribing practice, further limiting the evidence that will be presented. Risk of HRT use also correlates to duration of exposure and then subsequent time since exposure. It remains best practice to use the lowest dose of HRT for the shortest duration required to manage symptoms, whilst minimising associated risks in line with the 2024 NICE menopause guideline [3].

A literature search was performed in PubMed/MEDLINE, Embase, the Cochrane Library and Web of Science from their inception to 6 May 2025. Search terms included combinations of the key terms: "hormone replacement therapy", "menopausal hormone therapy", "oestrogen", "progestogen", "micronised progesterone", "Tibolone", "vaginal oestrogen", "BRCA", "Lynch syndrome", "cancer" and specific cancer types. Only studies written in English were included.

2 | Average Population Risk

2.1 | Breast Cancer

The risk association between HRT and breast cancer has received significant consideration over the last 2–3 decades, particularly due to the media attention that surrounded two landmark studies, the Women's Health Initiative (WHI) and the Million Women Study (MWS), both summarised in Table 1.

The WHI was terminated 3 years prematurely as the rates of invasive breast cancers (and other complications) reported in combined oestrogen-progestin HRT arm exceeded the stopping boundary compared to placebo after a mean follow-up of 5.2 years [6]. Subsequent analysis that considered confounding factors and subset analysis of different age groups found results to be less concerning. The long-term outcomes, published in 2020 [7], reported that oestrogen alone (conjugated equine oestrogen – CEE) was associated with a lower breast cancer risk (hazard ratio (HR) 95% confidence interval (CI) 0.65–0.93, $p = 0.005$) and lower breast cancer mortality (HR 0.60; 95% CI 0.37–0.97; $p = 0.04$). Additionally, whilst combined CEE and medroxyprogesterone acetate (MPA) did confer an increased risk of breast cancer (HR 1.28, 95% CI 1.13–1.45, $p < 0.001$), there was no significant difference in breast cancer mortality (HR 1.35, 95% CI 0.94–1.95, $p = 0.11$). Criticisms of the WHI study included that only a single dose and type of HRT was examined and that the dosages were higher than what would ordinarily have been offered to older women. Unlike the UK's MWS, WHI participants were also older and overweight (average BMI 28.5), and consequently had a higher background risk of breast cancer and other complications.

The MWS reported that current users of combined HRT had a relative risk (RR) of 2.00 (95% CI 1.88–2.12) for breast cancer compared to never-users [5] whilst treatment with Tibolone or oestrogen only was associated with an attenuated risk (RR 1.45, 95% CI 1.25–1.68, $p < 0.0001$; RR 1.30, 95% CI 1.21–1.40, $p < 0.0001$, respectively). Yet the methodology of the MWS has also faced scrutiny. MWS was an observational study that relied on self-selected, self-reporting HRT users. Participants were women already scheduled for mammograms, potentially indicating a higher baseline cancer risk or greater awareness of cancer risks associated with HRT. Follow-up depended on national cancer registry reports rather than subsequent questionnaires, leaving changes in HRT use post-enrolment untracked.

TABLE 1 | Summary of the key points of the Women's Health Initiative and Million Women Study with regards to breast cancer risk.

	Women's health initiative [4]		
	Oestrogen + progestin trial	**Oestrogen alone trial**	**Million women study [5]**
Study design	Randomised control study—HRT vs. Placebo	Randomised control study—oestrogen alone vs. Placebo in hysterectomised women	Observational Cohort of women attending breast screening clinics. Women were self-selecting and self-reporting HRT users
Population size	16 600	10 700	1 084 110
Country	United States of America	United States of America	United Kingdom
Year	1993–2002	1993–2004	1996–2001
Average Age	63.2 years	63.2 years	55.9 years
Type of HRT	CEE 0.625 mg + MPA 2.5 mg/day	CEE 0.625 mg	All-observational study
Risk of breast cancer	HR, 1.24; 95% CI, 1.01–1.53	HR, 0.79; 95% CI, 0.61–1.02	RR 1.66; 95% CI 1.58–1.75, $p < 0.0001$

Abbreviations: CEE, conjugated equine oestrogen; HR, hazard ratio; MPA, medroxyprogesterone acetate; RR, relative risk.

In 2019, The Collaborative Group on Hormonal Factors in Breast Cancer produced a meta-analysis of prospective studies totalling 108, 647 postmenopausal women [8]. They reported that 5 years of HRT initiated at age 50 in the average woman would increase breast cancer incidence between ages 50 and 69 by approximately one additional case per 50 users of continuous combined HRT, one per 70 users of sequential HRT, and one per 200 users of oestrogen-only regimens. Extending HRT use to 10 years would approximately double these excess risks. However, whilst this analysis included MWS data, it did not include WHI and it only involved limited data on micronised progesterone.

More recently, in 2025, a Finnish nationwide cohort, including 357 928 HRT users and 351 735 age-matched non-users, reported that contemporary HRT formulations, exclusively using oestradiol rather than CEE, were still associated with an increased risk of breast cancer (oestrogen-only odds ratio (OR) 1.61, 95% CI 1.15–1.71), combined oestrogen-progestogen OR 1.82 (95% CI 1.76–1.88) [9]. Comparison of delivery routes showed that ever use of oral HRT for ≥ 10 years was associated with a higher risk (OR 1.87, 95% CI 1.80–1.95) than corresponding transdermal therapy (OR 1.63, 95% CI 1.51–1.75). Among combination regimens, those containing Norethisterone conferred the highest breast cancer risks (OR 2.16, 95% CI 2.03–2.30) whilst those containing Dydrogesterone carried the lowest risk (OR 1.32, 95% CI 1.12–1.55). Similarly, Tibolone use for ≤ 10 years conferred a relatively low increased risk of breast cancer as well (OR 1.30, 95% CI 1.12–1.55). Notably, no data was provided for micronised progesterone, limiting the study's applicability to body identical HRT formulations.

Interest has been focussed towards micronised progesterone as a safer option for reducing breast cancer risk. A meta-analysis [10] comparing synthetic progestogens and micronised progesterone reported that HRT, which combined either micronised progesterone or dydrogesterone, conferred no increased risk of breast cancer (OR 1.00, 95% CI 0.83–1.20; OR 1.10, 95% CI 0.89–1.36), respectively. Breast cancer risk was increased with the other synthetic progestogens: medroxyprogesterone (OR 1.19, 95% CI 1.07–1.33), levonorgestrel (OR 1.47, 95% CI 1.17–1.85), and norethisterone (OR 1.44, 95% CI 1.26–1.65). However, all nine studies included were observational and not all declared the duration of HRT use. More robust data is required to confirm the impacts of micronised progesterone and dydrogesterone on breast tissue.

2.2 | Endometrial Cancer

In the 1970s, it became evident that endometrial cancer risk was strongly associated with unopposed exogenous oestrogen exposure. A meta-analysis of 30 observational studies reported a relative risk (RR) of 2.3, which increased to RR 9.5 when unopposed oestrogen use was over 10 years [11].

Subsequently, the addition of progestins to HRT regimens was introduced for women with intact uteri to inhibit oestrogen-driven endometrial hyperplasia. The Women's Health Initiative (WHI) double blinded, placebo-controlled trial of 16 608 postmenopausal women with a uterus found that women taking combined 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate for a median of 5.6 years had a lower risk of endometrial cancer than the placebo group (HR 0.65, 95% CI 0.48–0.89, $p = 0.07$) with this difference being more significant in the post-intervention time period [12]. Similar findings were also demonstrated with the continuous use of micronised progesterone in the Postmenopausal Oestrogen/Progestin Interventions (PEPI) randomised control trial (RCT) [13].

However, the use of sequential combined HRT regimens for more than 5 years may confer a modest increased risk of endometrial cancer. This risk is inversely proportional to the number of days the progestogen is given. A meta-analysis of 11 studies demonstrated that the use of progestins for fewer than 10 days/month provides a RR of 1.76 (95% CI 1.51–2.05), due to insufficient endometrial protection [14].

For women, who are highly sensitive to the side effects of progestogens, the off-licence use of micronised progesterone administered vaginally could be considered, providing they have been cautioned on the limited safety data and the potential for variable absorption. One RCT of 100 women who were given 50 mcg oestradiol patches over 12 months was randomised to either oral or vaginal micronised progesterone [15]. This study found no difference in endometrial thickness between the groups, but they did not assess the endometrium histologically. The Early versus Late Intervention Trial with Oestradiol (ELITE) [16], in which women used 1 mg oral oestradiol per day with vaginal progesterone, assessed the endometrium histologically and reported an increased rate of endometrial hyperplasia; however, it must be noted that in this study lower doses of progesterone were used (4% vaginal micronised gel 45 mg/day) and for only 10 days per month. On this basis, if women are considering the use of vaginal micronised progesterone, they should be advised to use similar doses and durations as recommended with oral administration.

From a clinical perspective, the importance of balanced HRT regimens in women with a uterus must be highlighted. Adequate progestogen/progesterone should be prescribed to match oestradiol, particularly when using higher doses, to avoid endometrial pathology, as highlighted in the recently published unscheduled bleeding guideline by the British Menopause Society (BMS) [17]. The BMS also provides clear guidance on appropriate progestogen dosing [18]. Equally, as clinicians it is our duty to educate our patients about the importance of adherence and compliance with their HRT preparations, particularly when oestradiol and progestogen/progesterone are taken separately (as opposed to e.g., the combined patch).

2.3 | Ovarian Cancer

There may be a small increased risk in developing ovarian cancer with HRT use; however, the available studies are heterogeneous, limiting interpretation. A meta-analysis by the Collaborative Group on Epidemiological Studies of Ovarian Cancer combining data from 52 epidemiological studies of 12 110 postmenopausal women, 55% (6601) of whom had used hormone therapy, found that ever-use of HRT was associated with a 37% increased risk of ovarian cancer (RR 1.37, 95% CI 1.29–1.46), most commonly serous and endometrioid

subtypes [19]. This risk persisted for up to 5 years post HRT cessation but appeared to decline thereafter. They determined that women commencing HRT around age 50 and continuing for 5 years faced an increased ovarian cancer risk of approximately one additional case per 1000 users.

2.4 | Colorectal Cancer

In the WHI oestrogen plus progestin arm, HRT was associated with a lower rate of colorectal cancer (HR 0.56, 95% CI 0.38–0.81, $p = 0.003$) [20]. However, the number of events was low, 43 in the treatment group and 72 in the placebo. In the oestrogen arm, no difference in colorectal cancer rates was observed (HR 1.08, 95% CI 0.75–1.55) [21]. A meta-analysis, including four RCTs, concluded a similar reduction of colorectal cancers in combined HRT ever users (RR 0.74, 95% CI 0.68–0.81) and oestrogen only ever users (RR 0.79, 95% CI 0.69–0.91) [22].

2.5 | Other Cancers

Table 2 summarises the current literature on other HRT associated cancer risks not already discussed above.

TABLE 2 | Summary of the literature on other HRT associated cancer risks.

Gastric	In a meta-analysis of 11 studies, including 1 919 089 women, HRT was associated with a 28% reduction in gastric cancer [23]
Glioma	A meta-analysis of 17 studies including 2 995 082 glioma cases found the pooled risk of glioma in HRT uses (any duration) was significantly reduced [24]
Hepatocellular	2 case–control studies reported reduced risk of liver cancer in HRT users [25, 26], of which one reported increased overall survival in hepatocellular carcinoma patients [25]
Lung	A meta-analysis of 13 cohort studies suggested that HRT was associated with a decreased risk of lung cancer [27]
Melanoma	Melanocytes are known to respond to oestrogen stimulation. However, a 2012 meta-analysis of 36 observational studies, has shown no association between HRT use and melanoma [28]. Recent European studies have suggested an increased incidence of melanoma in women using unopposed oestrogen, but no increase risk in women using combined HRT formulations [29, 30]
Meningioma	Most meningiomas express progesterone receptors and some oestrogen receptors. Progesterone agonists, particularly cyproterone acetate, have been demonstrated to have a dose-dependent association with meningiomas [31]. There is conflicting evidence with regards to HRT with some studies demonstrating increased risk [32, 33] whilst others do not [34]. Absolute numbers are small with HRT use conferring a risk of less than 1 additional case per 10 000 women per year
Renal	A meta-analysis of cohort and case–control studies reported that HRT use was inversely associated with renal cancer risk [35]

3 | High Risk Women that is, Those Carrying Cancer Causing Genetic Mutations

3.1 | BRCA1/2 and Other Related Gene Mutation Carriers

In BRCA1 mutation carriers, the cumulative risk of developing breast and ovarian cancer by age 80 is approximately 72% and 44%, respectively, while for BRCA2 mutation carriers, it is 69% and 17% [36]. Risk-reducing salpingo-oophorectomy (RRSO) is recommended to reduce the risk of tubo-ovarian cancer, although there remains a 2%–4% risk of developing peritoneal cancer [37]. The National Comprehensive Cancer Network (NCCN) and Royal College of Obstetricians and Gynaecologists (RCOG) recommend RRSO between the ages of 35 and 40 for BRCA1 mutation carriers, whilst surgery can be reasonably delayed to age 40–45 years for BRCA2 mutation carriers [38, 39]. Other high-risk gene mutations, RAD51 C/D, BRIP, PALB2, are summarised below in Table 3.

Most women undergoing RRSO will experience early or premature menopause. The largest prospective observational study of premenopausal women undergoing RRSO, What Happens After Menopause 'WHAM', reported that VMS significantly increased after RRSO, affecting approximately 80% of non-HRT users at 3 months, with symptoms persisting and not returning to baseline by 12 months [40]. Furthermore, bone density was also significantly decreased at 24 months with 5.8% loss in the lumbar spine and 6.0% at the femoral neck among non-HRT users [41].

As discussed earlier in this review, combined progestin HRT regimens have repeatedly been shown to increase the risk of breast cancer whilst oestrogen only regimens have not. Although micronised progesterone has been heralded as 'breast neutral' in low-risk women, this is based on limited data and further research is required to confirm or refute this.

The Prevention and Observation of Surgical Endpoints (PROSE) prospective cohort study tracked 462 women with BRCA mutations and no prior breast cancer for an average of 3.6 years [42]. The mean age at RRSO was 42.7 years (range 21.5–73.9) and 93 (60%) used HRT, predominantly oestrogen-only. RRSO significantly reduced breast cancer risk (HR 0.40, 95% CI 0.18–0.92), and HRT use did not increase risk (HR 0.37, 95% CI 0.14–0.96). Similarly, Eisen et al.'s matched case–control study including

TABLE 3 | Recommendations for non-BRCA indications for risk-reducing oophorectomy [39].

Risk/Mutation	Age of RRSO	Breast cancer risk
RAD51C/RAD51D	40–50 years	20%–21%
PALB2	> 45–50 years	53%
BRIP 1	> 45–50 years	No increased risk
Family history with unknown BRCA mutation status	Approx. 50 years	No increased risk
Family history with negative BRCA mutation status	RRSO not recommended	No increased risk

189 women with BRCA 1 mutations reported an inverse relationship between breast cancer and oestrogen-only HRT use (OR 0.51, 95% CI 0.27 to 0.98, $p = 0.04$) and with combined HRT (OR 0.66, 95% CI 0.34 to 1.27; $p = 0.21$) [43]. However, in this study only 28 (14.8%) of the participants used oestrogen only HRT and 19 (10.1%) used combined HRT. A larger prospective longitudinal cohort study of 377 BRCA1 mutation carriers using HRT (259 received oestrogen-only) and 495 not on HRT found no association with breast cancer (HR 0.97, 95% CI 0.62–1.52, $p = 0.89$) [44].

This combined evidence, demonstrating no significant increase in breast cancer risk with HRT following RRSO, underpins the recommendation for HRT until the average age of natural menopause, 51 years [45]. However, it is important to note that there are a number of limitations with the detailed studies, including small sample size (particularly with regards to the number using combined HRT), short follow-up period (3.6–7.5 years), lack of RCTs and any data specifically on the impact of HRT in BRCA2 mutation carriers.

Oophorectomy in premenopausal women has been shown to decrease the free androgen index by 50% [46] and so, testosterone can be particularly effective in women who experience surgical menopause. Replacement may improve low energy as well as libido [47]. Although testosterone's short-term safety has been demonstrated when prescribed at doses within physiological pre-menopausal levels [48], its oncological safety in high risk women and its impact on breast tissue still remain unknown.

3.2 | Lynch Syndrome

Women with Lynch syndrome have defective mismatch repair genes (MLH1, MSH2 or MSH6). Mutation carriers have a 40%–60% lifetime risk of endometrial cancer and are advised to undergo hysterectomy and RRSO, after appropriate counselling, from age 35–40 years [39, 49]. The oncological safety of HRT has not been specifically studied in the Lynch Syndrome population. The recommendation for HRT use is based on extrapolation of evidence with regards to oestrogen only HRT and its neutral or even protective effect against colorectal cancer in the low-risk populations.

3.3 | Other Mutations/Indications for RRSO

Table 3 summarises other high-risk ovarian cancer mutations and high-risk family history that may be indications for RRSO [39]. There is no specific data on HRT safety in these cases. As RAD51C, RAD51D, and PALB2 carry an additional breast cancer risk, similar advice should be given as for BRCA1/2 mutation carriers.

4 | Women with a Personal History of Cancer

4.1 | Breast Cancer

A fundamental aim of breast cancer management is to reduce exogenous oestrogen to minimise growth of breast cancer cells and reduce the risk of recurrence. Many breast cancer survivors struggle with treatment-induced and worsening menopausal symptoms, as the international general consensus guidance is to avoid HRT.

The safety of HRT replacement in breast cancer survivors was examined in two independent Scandinavian prospective RCTs, 'The Hormonal Replacement Therapy After Breast Cancer—Is It Safe?' (HABITS) and Stockholm trials that commenced concurrently in 1997 [50, 51].

HABITS was a randomised, non-placebo-controlled, study comparing HRT against no HRT in 442 women with menopausal symptoms previously treated for stage I or II breast cancer, allowing concomitant tamoxifen but not aromatase inhibitors. HRT primarily involved 2 mg oral oestradiol-based products, excluding tibolone. Recruitment to the study closed early, after a median follow up of just 2.1 years, as the interim safety analysis revealed an unacceptably high breast cancer recurrence rate in the HRT group (HR 3.5, 95% CI 1.5–7.4). However, there were significant differences in patient characteristics between the two arms of the study, for example, the HRT cohort had a higher proportion of hormone receptor-positive cancers (62.3% vs. 54.5%). Additionally, analysis was on an intent-to-treat basis and 11 HRT-assigned women never received HRT and 43 in the non-HRT arm received HRT.

Meanwhile, the Stockholm trial ($n = 378$) was prematurely closed due to the findings of the HABITS study, despite showing no increase in recurrence risk with HRT (HR 0.82, 95% CI 0.35–1.9) after 4.1 years of follow up [51]. Although under-powered due to early closure, long-term follow up after 10 years, published in 2013, continued to show no additional risks from HRT in terms of breast cancer recurrence [52]. Neither study demonstrated excess mortality from breast cancer or other causes in the HRT group. The increased recurrence risk seen in HABITS has been attributed to higher doses

of progesterone and greater numbers of higher risk, node-positive patients. There were also higher rates of tamoxifen use in the Stockholm trial, which may have had a protective effect as it is an oestrogen receptor antagonist. Unfortunately, due to the early cancellation of these trials, other similar trials at the time were also terminated, preventing a definitive answer.

Tibolone has also been assessed in breast cancer survivors, due to the observation that Tibolone had a reduced stimulatory effect on breast tissue and may therefore be safer than other preparations in breast cancer survivors. Increased breast density is associated with a greater breast cancer risk [53], and whilst standard HRT results in an increase in mammographic breast density, Tibolone does not. The Long-Term Intervention on Fractures with Tibolone (LIFT) study reported that low dose Tibolone (1.25 mg per day) was associated with a significantly reduced invasive breast cancer risk (relative hazard 0.32, 95% CI 0.13–0.80, $p = 0.02$) in women without a personal history of breast cancer [54]. However the Livial Intervention Following Breast Cancer: Efficacy, Recurrence, and Tolerability Endpoints (LIBERATE) trial, which evaluated the safety of 2.5 mg daily of Tibolone use in breast cancer survivors was also terminated early due to an excess of breast cancers in the HRT group [55]. Findings reported after a median follow-up of 3.1 years, 237 of 1556 (15.2%) women on Tibolone developed cancer recurrence, in comparison to 165 of 1542 (10.7%) on placebo (HR 1.40, 95% CI 1.14–1.70, $p = 0.001$) [55]. In the sub analysis, those on aromatase inhibitors had a much higher risk of recurrence whilst using tibolone than those on tamoxifen (HR 2.42, 95% CI 1.01–5.79; HR 1.25, 95% CI = 0.981.59, respectively).

Two more nuanced scenarios with regards to considering systemic HRT are in women with oestrogen (ER) ± progesterone (PR) receptor negative breast cancer and in women who have had ductal (DCIS) or lobular (LCIS) carcinoma in situ. During extended follow-up of the HABITS study, HRT use in women with hormone receptor negative tumours was associated with a non-significant increase of a new breast cancer events (HR 1.80, 95% CI 0.7–4.8, $p = 0.205$) [56]. A meta-analysis of four RCTs of 4050 participants demonstrated an increased recurrence in those with hormone positive breast cancer (HR 1.80, 95% CI 1.15–2.82) but not in hormone negative disease (HR 1.19, 95% CI 0.80–1.77) [57]. Additionally, another meta-analysis also found no difference in all-cause mortality between HRT users and non-users in breast cancer survivors (RR 0.91, 95% CI 0.38–2.19) [58]. Yet concerns include the risk of HRT promoting a new breast cancer: in the minority of patients who do develop a second, contralateral breast primary, up to 30% will be ER positive [59]. This risk of local recurrence or a second primary is theoretically reduced in the context of bilateral mastectomy (a reduction of 34–43 cases of a second breast cancer per 10 000 person-years) [60] and this may shift the balance of risk when considering the use of HRT. However, there are currently no studies to guide decision-making in this scenario. Overall, the current guidance generally favours non-HRT options even in hormone negative disease as further research is required before HRT can be actively recommended. Similarly, some clinicians may be less reluctant to prescribe HRT following breast carcinoma in situ given it is generally less aggressive and better prognosis; however, there are no studies to support or refute the use of HRT.

Topical vaginal oestrogen is effective in treating GSM, however there are concerns over its use in breast cancer survivors, particularly as there is dose dependent systemic absorption [61]. A 2022 Danish data linkage study, in postmenopausal women treated for early-stage oestrogen receptor-positive breast cancer, reported a slight increase in breast cancer recurrence (HR 1.39, 95% CI 1.04–1.85) only among patients using adjuvant aromatase inhibitors (AI) alongside vaginal oestrogen, but no impact on survival was observed [62]. The efficacy of AIs is linked to minimising systemic oestrogen, and an HRT associated increase in exogeneous oestrogen could impact their effectiveness. In contrast, vaginal oestrogen did not appear to increase recurrence in Tamoxifen users (HR 0.64, 95% CI 0.39–1.06) [62], most likely as this agent inhibits oestrogen binding. Similarly, a UK registry-based study of 49 237 breast cancer patients found no association between vaginal oestrogen use and increased breast cancer mortality [63].

In addition to standard oestrogen and progestogen replacement, there has been increased use of testosterone for managing menopausal symptoms beyond sexual function, such as fatigue, cognition, brain fog and quality of life. However, its utility and oncological safety remains to be determined. Limited data suggests that testosterone does not have an adverse impact on breast health and that it does not increase breast density in low risk women [47], however caution is advised in high risk women as testosterone is aromatised to oestradiol. A single- arm intervention pilot study of 29 premenopausal women with hormone-positive breast cancer being managed with ovarian suppression and aromatase inhibitor therapy were additionally treated with low-dose topical testosterone to improve sexual function and impact on oestradiol levels. Although none of the women experienced an increase from their baseline oestradiol during the 3-month treatment protocol, this is a very small non-randomised study and further research is required to confirm the safety of testosterone use in breast cancer survivors using aromatase inhibitors [64].

4.2 | Endometrial Cancer

Endometrial cancers tend to express oestrogen receptors, and so historically there has been concern regarding the use of HRT. To date, only one RCT has evaluated the safety of hormone replacement therapy (HRT) in endometrial cancer patients [65]. Barakat et al. randomised 1236 women with histologically confirmed stage I or II endometrial cancer to receive either oestrogen-only HRT (post-hysterectomy) or placebo following surgery. Tumour recurrence rates were 2.3% in the HRT group and 1.9% in the placebo group (RR 1.17, 95% CI 0.54–2.50). However, this study did not report overall survival (OS), progression-free survival (PFS), or time to recurrence. The trial was also underpowered due to early termination prompted by concerning findings from the WHI study in non-cancer cohorts.

However, other studies offer reassurance: a systematic review and meta-analysis by Shim et al. collated data from five non-randomised studies together with Bakarat et al.'s randomised controlled trial [66], and reported no increased risk of endometrial cancer recurrence in HRT users. Furthermore, as ovarian conservation is considered in pre-menopausal women with a

low risk of endometrial cancer, the BGCS-BMS guidance [67] states that HRT can be considered in those with early stage endometrial cancer, following discussion of risks and benefits. However, the safety of HRT in patients with advanced endometrial cancer remains unstudied, and its use is therefore not recommended in this population due to the risk of cancer progression. There is limited data regarding the benefit of combined progestogen and oestrogen HRT in hysterectomized women with endometrial cancer. However, some specialists consider the use of combined continuous HRT in this group, extrapolating from the evidence that combined HRT reduces the risk of developing endometrial cancer in women with an intact uterus [12]. However, this decision needs to be balanced against the additional breast cancer risk with combined HRT regimens.

4.3 | Ovarian Cancer

Ovarian cancer is a heterogeneous disease, encompassing several different subtypes, the most common being epithelial ovarian cancers. Three RCTs, collectively involving 350 participants, have evaluated overall survival (OS) in women with epithelial ovarian cancer using HRT [68–70]. A Cochrane meta-analysis of these trials reported a pooled OS favouring the HRT arms (HR 0.71, 95% CI 0.54–0.93), with progression-free survival (PFS) showing minimal impact (HR 0.76, 95% CI 0.57–1.01) [71]. However, these studies are constrained by several limitations including small sample sizes, heterogeneous populations, substantial HRT discontinuation rates (3.6%–65.5%) and high non-compliance rates (31.1%–65.3%) [68, 69].

Low-grade serous ovarian cancer (LGSOC) is a less common subtype of epithelial ovarian cancer and oestrogen receptors are highly expressed and are a significant driver of cancer growth. LGSOC is responsive to anti-oestrogen therapies and therefore HRT is generally not recommended, particularly for stage II to IV disease. As the RCTs generally did not distinguish between high- and low-grade serous subtypes, there is no additional trial data to support the safety of HRT in this patient group.

Due to the rarity, there are no studies on the safety of HRT in germ cell and sex-cord stromal tumours; therefore, any guidance is pragmatic and theory based. For example, as the majority of germ cell tumours occur in women under the age of 20 and treatment is aimed at preserving ovarian function, HRT is given to those who have not been able to have ovarian conservation [67]. Or as granulosa cell tumours are strongly oestrogen dependent and respond to anti-oestrogen treatment, HRT should be avoided until more evidence is available [67].

4.4 | Cervical Cancer

Squamous cell carcinoma (SCC), accounting for 90% of cervical cancers, is not hormonally driven, and ovarian conservation is considered for premenopausal patients with early-stage disease. A prospective study of 120 patients with early-stage cervical cancer treated with surgery or radiation found no difference in five-year recurrence rates or overall survival between those receiving oestrogen-only or oestrogen-progestin HRT versus placebo [72].

Although cervical adenocarcinomas frequently express oestrogen and progesterone receptors, multiple studies indicate that their expression does not correlate with other prognostic factors, recurrence, or survival outcomes [73, 74]. Two small retrospective studies have reported no adverse effects with HRT and Tibolone use post-treatment [75, 76].

Women with more advanced disease will often experience menopause due to radiotherapy rather than surgery, and those with an intact uterus should have combined oestrogen and progestogen HRT.

4.5 | Vulval and Vaginal Cancers

Although there are no studies of HRT use in vulval and vaginal cancers, as these are not considered hormone dependent, HRT can generally be used to manage menopausal symptoms.

4.6 | Other Cancers

There is limited and often conflicting evidence regarding the safety of HRT following a cancer diagnosis, leading to reluctance among clinicians to prescribe HRT due to concerns of promoting disease recurrence. However, for many cancer survivors withholding HRT may unnecessarily reduce quality of life without any clear evidence of oncological harm. Table 4 summarises the available literature for other malignancies not covered above.

A recent cohort study of female cancer survivors in the United Kingdom was conducted to attempt to address this issue [79]. This study assessed cancer-specific mortality in HRT users versus non-HRT users in survivors of the 17 most common cancers (excluding breast cancer as it is considered a definite contraindication to HRT). 182 589 patients were included, of which only 7% used systemic HRT after their cancer diagnosis. The study concluded that there was no evidence that HRT users had increased cancer-specific mortality compared with non-users at any of the cancer sites. Although this provides some useful insight, the authors themselves acknowledge that the retrospective nature of the study meant it was impossible to adjust for all possible confounders and variables that may have impacted HRT prescribing and oncological outcomes such as non-oncological contraindications for HRT or family history. Furthermore, HRT is likely to have been prescribed to patients with fewer comorbidities and better oncological prognosis.

5 | Managing HRT and Cancer in Clinical Practice

Patients with cancer related menopause should be managed within multidisciplinary teams, including menopause specialists and oncologists/surgeons, considering available guidance, menopausal symptoms, risks of disease recurrence, long-term implications of menopause and balancing this with patient preference in a shared decision-making model. In order to provide comprehensive oncological care, access to additional specialist

TABLE 4 | Summary of literature on HRT use in those with a personal history of cancer.

Bladder	12%–18% of bladder cancers are oestrogen receptor positive [77] and oestrogen has been shown in preclinical studies to play a role in tumour progression [78]. However, Cardwell et al.'s cohort study did not demonstrate a negative impact of HRT in bladder cancer survivor outcomes (HR 0.82, 95% CI 0.65–1.04) [79]
Colorectal	A meta-analysis of ten cohort studies demonstrated that HRT was inversely associated with the risk of colorectal cancer mortality (HR 0.77, 95% CI 0.68–0.87) with a linear-dose response of 3% decrease in mortality for each additional year of HRT use [80]
Gastric	Preclinical mouse models have reported oestrogen-stimulated tumour growth and gastric cancer cell apoptosis with Tamoxifen [81]. However, in the cohort study by Cardwell et al. HRT use was not associated with reduced outcome (HR 0.81, 95% CI 0.47–1.42)
Haematological	One cohort study of 130 women with POI secondary to their myeloablative chemotherapy for haematological cancer. Although the follow up was short, there was no increased rate of recurrence [82]. Cardwell et al. found no increased risk of cancer specific mortality in non-Hodgkin lymphoma (HR 0.79, 95% CI 0.66–0.95), myeloma (HR 1.02, 95% CI 0.72–1.45) and leukaemia (HR 0.77, 95% CI 0.57–1.05) patients
Hepatocellular	Preclinical studies have shown that oestrogen prevents fibrosis and hepatocellular cancer development [83]. HRT appears to reduce the risk of liver cancer, and Cardwell et al. reported no detrimental effect of HRT on OS (HR 1.11, 95% CI 0.74–1.66) [79]
Lung	Oestrogen receptors are expressed in both normal cancerous lung tissues and preclinical studies in mouse models have demonstrated tumour growth is simulated by oestrogen [84]. Clinical cohort studies are mixed, with the WHI reporting poorer survival [85] with HRT use whilst more recent studies show improved survival [79, 86]
Melanoma	A small non-randomised study with 83 stage 1 or 2 melanoma survivors using HRT and 123 survivors not using HRT reported a favourable OS in the HRT group (HR 0.173, 95% CI 0.048– 0.621) [87]. No study has investigated HRT use in more advanced melanoma
Meningioma	Epidemiological studies generally suggest an increased meningioma risk in patients receiving HRT (including MWS) [88]. Majority of evidence is based on use of older progestogens; impacts of newer treatments—Levonorgestrel intrauterine system and micronised Progesterone require further study. A recent study found no increased meningioma growth in patients treated with HRT compared to untreated controls [89]
Renal	A meta-analysis of six cohort and 8 case–control studies including 648 107 women found that HRT was not associated with an increased risk of kidney cancer (pooled RR 1.08, 95% CI 0.96–1.22) [35] with a non-linear dose–response relationship ($p = 0.0021$). Furthermore, oestrogen was found to increase apoptosis and reduced cell progression in human renal cell carcinoma cell lines [90]
Thyroid	A meta-analysis of nine prospective cohort studies no association between HRT use and the development of thyroid cancer (RR 1.11, 95% CI 0.98–1.26) [91]

input may also be required, for example, to optimise bone and cardiovascular health.

6 | Strengths and Limitations

This review provides an integrated synthesis of the current evidence on HRT and cancer risk across multiple tumour types, drawing on randomised trials and large-scale prospective cohort studies where available. By examining differences in risk according to hormone formulation, it offers a nuanced overview relevant to current clinical practice. However, the evidence base remains limited by substantial heterogeneity between studies, changes in HRT formulations over time, early termination of several key trials and incomplete reporting of important risk modifiers such as receptor status, genetic susceptibility, and lifestyle factors. Many of the trials are observational, with limited information on HRT type, dose, duration, and patient comorbidities. The majority of studies used older forms of HRT. Long-term data reflecting contemporary HRT formulations, including choice of progestogen, route of oestrogen administration (oral or transdermal), low-dose regimens, and intrauterine or vaginal delivery of progestogens is needed. Moreover, most studies predominantly include participants of Caucasian origin, leaving the generalisability to diverse ethnic groups unclear. These limitations underline the need for caution when presenting the evidence to patients during shared decision making and the need for the development of individualised risk prediction tools.

7 | Future Research

Despite decades of research, there remains controversy over the cancer risks associated with HRT due to conflicting evidence

and limited randomised trial data. This gap was highlighted by the recent NIHR James Lind Alliance priority setting partnership for menopause. Clinicians and respondents with lived experience identified 'How long can people with a personal risk of heart disease or cancer safely take hormone therapy? If they can, which type and what dose of hormone therapy is best?' as a top 10 research priority [92]. Further studies are required using more contemporary HRT formulations as well as other hormones such as testosterone. The interplay between HRT and pre-existing cancer risk factors (e.g., BRCA mutations) and personal cancer history also warrants further investigation.

Assessing the role and safety of HRT in those with an increased cancer risk or with a personal cancer history is complex, and varies depending on cancer type, HRT regimen and individual patient characteristics. Current evidence supports a generally favourable safety profile for low dose, contemporary HRT preparations in women at average cancer risk, while highlighting specific higher risk populations, for example, those with genetic cancer risks such as a BRCA mutation or a strong family history of hormone-sensitive cancers, cancer where more complex individualised assessment is required, considering tumour biology, time from diagnosis and treatment, recurrence risk, comorbidities, symptom burden and patient choice. Expert multidisciplinary team discussion and a shared- patient decision making pathway should be the standard of care when managing menopause in this cohort of women. Overall, the evidence emphasises the importance of personalised, risk-stratified management and underscores the need for high-quality studies evaluating contemporary HRT formulations across different cancer survivorship groups.

7.1 | Future Research

- The differential impact of progestogens on breast cancer risk warrants rigorous investigation, particularly for micronised progesterone and dydrogesterone for which there is some evidence that they may be 'breast neutral'.
- Nuances of HRT after breast cancer such as in hormone receptor negative disease, ductal carcinoma in situ (DCIS), and women who have had bilateral mastectomy.
- Oncological safety of testosterone.
- Use of web/app-based clinical decision aids, such as the MENO.pause app.

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References

1. N. E. Avis, S. L. Crawford, G. Greendale, et al., "Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition," *JAMA Internal Medicine* 175, no. 4 (2015): 531–539.

2. M. Hunter, A. Gentry-Maharaj, A. Ryan, et al., "Prevalence, Frequency and Problem Rating of Hot Flushes Persist in Older Postmenopausal Women: Impact of Age, Body Mass Index, Hysterectomy, Hormone Therapy Use, Lifestyle and Mood in a Cross-Sectional Cohort Study of 10 418 British Women Aged 54–65," *BJOG: An International Journal of Obstetrics & Gynaecology* 119, no. 1 (2012): 40–50.

3. National Institute for Health and Care Excellence, *Menopause: Identification and Management (2015) NICE Guideline NG23* (NICE, 2015).

4. R. T. Chlebowski, T. E. Rohan, J. E. Manson, et al., "Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials," *JAMA Oncology* 1, no. 3 (2015): 296–305.

5. V. Beral and Million Women Study Collaborators, "Breast Cancer and Hormone-Replacement Therapy in the Million Women Study," *Lancet (London, England)* 362, no. 9382 (2003): 419–427.

6. J. E. Rossouw, G. L. Anderson, R. L. Prentice, et al., "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial," *Journal of the American Medical Association* 288, no. 3 (2002): 321–333.

7. R. T. Chlebowski, G. L. Anderson, A. K. Aragaki, et al., "Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-Term Follow-Up of the Women's Health Initiative Randomized Clinical Trials," *Journal of the American Medical Association* 324, no. 4 (2020): 369–380.

8. Collaborative Group on Hormonal Factors in Breast Cancer, "Type and Timing of Menopausal Hormone Therapy and Breast Cancer Risk: Individual Participant Meta-Analysis of the Worldwide Epidemiological Evidence," *Lancet* 394, no. 10204 (2019): 1159–1168.

9. H. Siitonen, J. Joensuu, H. Savolainen-Peltonen, M. Gissler, O. Ylikorkala, and T. S. Mikkola, "Update of the Impact of Menopausal Hormone Therapy on Breast Cancer Risk," *European Journal of Cancer* 220 (2025): 115340.

10. Z. Yang, Y. Hu, J. Zhang, L. Xu, R. Zeng, and D. Kang, "Estradiol Therapy and Breast Cancer Risk in Perimenopausal and Postmenopausal Women: A Systematic Review and Meta-Analysis," *Gynecological Endocrinology* 33, no. 2 (2017): 87–92.

11. D. Grady, T. Gebretsadik, K. Kerlikowske, V. Ernster, and D. Petitti, "Hormone Replacement Therapy and Endometrial Cancer Risk: A Meta-Analysis," *Obstetrics and Gynecology* 85, no. 2 (1995): 304–313.

12. R. T. Chlebowski, G. L. Anderson, G. E. Sarto, et al., "Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial," *JNCI Journal of the National Cancer Institute* 108, no. 3 (2015): djv350.

13. H. L. Judd, I. Mebane-Sims, C. Legault, et al., "Effects of Hormone Replacement Therapy on Endometrial Histology in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," *Journal of the American Medical Association* 275, no. 5 (1996): 370–375.

14. L. A. Brinton and A. S. Felix, "Menopausal Hormone Therapy and Risk of Endometrial Cancer," *Journal of Steroid Biochemistry and Molecular Biology* 142 (2014): 83–89.

15. C. Di Carlo, G. A. Tommaselli, V. Gargano, F. Savoia, G. Bifulco, and C. Nappi, "Transdermal Estradiol and Oral or Vaginal Natural Progesterone: Bleeding Patterns," *Climacteric* 13, no. 5 (2010): 442–446.

16. I. Sriprasert, M. Mert, W. J. Mack, H. N. Hodis, and D. Shoupe, "Use of Oral Estradiol Plus Vaginal Progesterone in Healthy Postmenopausal Women," *Maturitas* 154 (2021): 13–19.

17. British Menopause Society (BMS), *British Menopause Society Guideline: Management of Unscheduled Bleeding on Hormone Replacement Therapy (HRT)* (British Menopause Society (BMS), 2024), https://thebms.org.uk/wp-content/uploads/2024/12/01-BMS-GUIDELINE-Management-of-unscheduled-bleeding-HRT-NOVEMBER2024-A.pdf.

18. British Menopase Society, *British Menopause Society Tool for Clinicians: Progestogens and Endometrial Protection* (British Menopause Society, 2021).

19. Collaborative Group on Epidemiological Studies of Ovarian Cancer, "Menopausal Hormone Use and Ovarian Cancer Risk: Individual Participant Meta-Analysis of 52 Epidemiological Studies," *Lancet* 385, no. 9980 (2015): 1835–1842.

20. R. T. Chlebowski, A. K. Aragaki, K. Pan, et al., "Estrogen Plus Progestin and Colorectal Cancer: Long-Term Findings From the Women's Health Initiative Randomized Clinical Trial," *Journal of Clinical Oncology* 42, no. 30 (2024): 3530–3536.

21. J. R. Johnson, J. V. Lacey, D. Lazovich, et al., "Menopausal Hormone Therapy and Risk of Colorectal Cancer," *Cancer Epidemiology, Biomarkers & Prevention* 18, no. 1 (2009): 196–203.

22. K. J. Lin, W. Y. Cheung, J. Y. C. Lai, and E. L. Giovannucci, "The Effect of Estrogen vs. Combined Estrogen-Progestogen Therapy on the Risk of Colorectal Cancer," *International Journal of Cancer* 130, no. 2 (2012): 419–430.

23. Y. C. Jang, C. Y. Leung, and H. L. Huang, "Association of Hormone Replacement Therapy With Risk of Gastric Cancer: A Systematic Review and Meta-Analysis," *Scientific Reports* 12, no. 1 (2022): 12997.

24. G. Alfuridy, R. Alghamdi, A. Alkhoshi, et al., "Does Exogenous Hormonal Therapy Affect the Risk of Glioma Among Females: A Systematic Review and Meta-Analysis," *Neuro-Oncology Advances* 6, no. 1 (2024): vdad167.

25. M. M. Hassan, G. Botrus, R. Abdel-Wahab, et al., "Estrogen Replacement Reduces Risk and Increases Survival Times of Women With Hepatocellular Carcinoma," *Clinical Gastroenterology and Hepatology* 15, no. 11 (2017): 1791–1799.

26. K. A. McGlynn, K. Hagberg, J. Chen, et al., "Menopausal Hormone Therapy Use and Risk of Primary Liver Cancer in the Clinical Practice Research Datalink," *International Journal of Cancer* 138, no. 9 (2016): 2146–2153.

27. C. Jin and B. Lang, "Hormone Replacement Therapy and Lung Cancer Risk in Women: A Meta-Analysis of Cohort Studies: Hormone Replacement Therapy and Lung Cancer Risk," *Medicine (Baltimore)* 98, no. 51 (2019): e17532.

28. S. Gandini, S. Iodice, E. Koomen, A. D. Pietro, F. Sera, and S. Caini, "Hormonal and Reproductive Factors in Relation to Melanoma in Women: Current Review and Meta-Analysis," *European Journal of Cancer* 47, no. 17 (2011): 2607–2617.

29. E. Botteri, N. C. Støer, S. Sakshaug, et al., "Menopausal Hormone Therapy and Risk of Melanoma: Do Estrogens and Progestins Have a Different Role?," *International Journal of Cancer* 141, no. 9 (2017): 1763–1770.

30. I. Cervenka, M. Al Rahmoun, Y. Mahamat-Saleh, et al., "Exogenous Hormone Use and Cutaneous Melanoma Risk in Women: The European Prospective Investigation Into Cancer and Nutrition," *International Journal of Cancer* 146, no. 12 (2020): 3267–3280.

31. A. Weill, P. Nguyen, M. Labidi, et al., "Use of High Dose Cyproterone Acetate and Risk of Intracranial Meningioma in Women: Cohort Study," *BMJ (Clinical Research Ed.)* 372 (2021): n37.

32. D. S. Michaud, V. Gallo, B. Schlehofer, et al., "Reproductive Factors and Exogenous Hormone Use in Relation to Risk of Glioma and Meningioma in a Large European Cohort Study," *Cancer Epidemiology, Biomarkers & Prevention* 19, no. 10 (2010): 2562–2569.

33. L. Andersen, S. Friis, J. Hallas, P. Ravn, H. D. Schrøder, and D. Gaist, "Hormone Replacement Therapy Increases the Risk of Cranial Meningioma," *European Journal of Cancer* 49, no. 15 (2013): 3303–3310.

34. E. B. Claus, L. Calvocoressi, M. L. Bondy, M. Wrensch, J. L. Wiemels, and J. M. Schildkraut, "Exogenous Hormone Use, Reproductive Factors, and Risk of Intracranial Meningioma in Females," *Journal of Neurosurgery* 118, no. 3 (2013): 649–656.

35. X. Zhang, Y. Du, X. Tan, et al., "The Relationship Between Hormone Replacement Therapy and Risk of Kidney Cancer in Women: A Meta-Analysis," *Cancer Control: Journal of Moffitt Cancer Center* 27, no. 2 (2020): 1073274820930194.

36. K. B. Kuchenbaecker, J. L. Hopper, D. R. Barnes, et al., "Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers," *Journal of the American Medical Association* 317, no. 23 (2017): 2402–2416.

37. A. P. M. Finch, J. Lubinski, P. Møller, et al., "Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a *BRCA1* or *BRCA2* Mutation," *Journal of Clinical Oncology* 32, no. 15 (2014): 1547–1553.

38. M. B. Daly, T. Pal, M. P. Berry, et al., "Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology," *Journal of the National Comprehensive Cancer Network* 19, no. 1 (2021): 77–102.

39. R. Manchanda, F. Gaba, V. Talaulikar, et al., "Risk-Reducing Salpingo-Oophorectomy and the Use of Hormone Replacement Therapy Below the Age of Natural Menopause," *BJOG: An International Journal of Obstetrics & Gynaecology* 129, no. 1 (2022): e16–e34.

40. M. Hickey, K. M. Moss, E. O. Krejany, et al., "What Happens After Menopause? (WHAM): A Prospective Controlled Study of Vasomotor Symptoms and Menopause-Related Quality of Life 12 Months After Premenopausal Risk-Reducing Salpingo-Oophorectomy," *Gynecologic Oncology* 163, no. 1 (2021): 148–154.

41. H. Jiang, D. L. Robinson, P. V. S. Lee, et al., "Loss of Bone Density and Bone Strength Following Premenopausal Risk-Reducing Bilateral Salpingo-Oophorectomy: A Prospective Controlled Study (WHAM Study)," *Osteoporosis International* 32, no. 1 (2021): 101–112.

42. N. D. Kauff, S. M. Domchek, T. M. Friebel, et al., "Risk-Reducing Salpingo-Oophorectomy for the Prevention of BRCA1- and BRCA2-Associated Breast and Gynecologic Cancer: A Multicenter, Prospective Study," *Journal of Clinical Oncology* 26, no. 8 (2008): 1331–1337.

43. A. Eisen, J. Lubinski, J. Gronwald, et al., "Hormone Therapy and the Risk of Breast Cancer in BRCA1 Mutation Carriers," *JNCI Journal of the National Cancer Institute* 100, no. 19 (2008): 1361–1367.

44. J. Kotsopoulos, "BRCA Mutations and Breast Cancer Prevention," *Cancers* 10, no. 12 (2018): 524.

45. National Institute for Health and Care Excellence (NICE), *Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People With a Family History of Breast Cancer* (Nice, 2013).

46. H. L. Judd, W. E. Lucas, and S. S. C. Yen, "Effect of Oophorectomy on Circulating Testosterone and Androstenedione Levels in Patients With Endometrial Cancer," *American Journal of Obstetrics and Gynecology* 118, no. 6 (1974): 793–798.

47. R. M. Islam, R. J. Bell, S. Green, M. J. Page, and S. R. Davis, "Safety and Efficacy of Testosterone for Women: A Systematic Review and Meta-Analysis of Randomised Controlled Trial Data," *Lancet Diabetes and Endocrinology* 7, no. 10 (2019): 754–766.

48. C. Achilli, J. Pundir, P. Ramanathan, L. Sabatini, H. Hamoda, and N. Panay, "Efficacy and Safety of Transdermal Testosterone in Postmenopausal Women With Hypoactive Sexual Desire Disorder: A Systematic Review and Meta-Analysis," *Fertility and Sterility* 107, no. 2 (2017): 475–482.e15.

49. E. Barrow, J. Hill, and D. G. Evans, "Cancer Risk in Lynch Syndrome," *Familial Cancer* 12, no. 2 (2013): 229–240.

50. L. Holmberg and H. Anderson, "HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?), A Randomised Comparison: Trial Stopped," *Lancet* 363, no. 9407 (2004): 453–455.

51. E. von Schoultz, L. E. Rutqvist, and the Stockholm Breast Cancer Study Group, "Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial," *JNCI Journal of the National Cancer Institute* 97, no. 7 (2005): 533–535.

52. M. Fahlén, T. Fornander, H. Johansson, et al., "Hormone Replacement Therapy After Breast Cancer: 10 Year Follow Up of the Stockholm Randomised Trial," *European Journal of Cancer* 49, no. 1 (2013): 52–59.

53. S. Azam, T. Lange, S. Huynh, et al., "Hormone Replacement Therapy, Mammographic Density, and Breast Cancer Risk: A Cohort Study," *Cancer Causes & Control* 29, no. 6 (2018): 495–505.

54. S. R. Cummings, P. D. Delmas, V. Stathopoulos, et al., "The Effects of Tibolone in Older Postmenopausal Women," *New England Journal of Medicine* 359 (2008): 697–708.

55. P. Kenemans, N. J. Bundred, J. M. Foidart, et al., "Safety and Efficacy of Tibolone in Breast-Cancer Patients With Vasomotor Symptoms: A Double-Blind, Randomised, Non-Inferiority Trial," *Lancet Oncology* 10, no. 2 (2009): 135–146.

56. L. Holmberg, O. E. Iversen, C. M. Rudenstam, et al., "Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors," *JNCI Journal of the National Cancer Institute* 100, no. 7 (2008): 475–482.

57. F. Poggio, L. Del Mastro, M. Bruzzone, et al., "Safety of Systemic Hormone Replacement Therapy in Breast Cancer Survivors: A Systematic Review and Meta-Analysis," *Breast Cancer Research and Treatment* 191, no. 2 (2022): 269–275.

58. P. J. Coronado, A. Gómez, E. Iglesias, et al., "Eligibility Criteria for Using Menopausal Hormone Therapy in Breast Cancer Survivors: A Safety Report Based on a Systematic Review and Meta-Analysis," *Menopause* 31, no. 3 (2024): 234–242.

59. S. M. Swain, J. W. Wilson, E. P. Mamounas, et al., "Estrogen Receptor Status of Primary Breast Cancer Is Predictive of Estrogen Receptor Status of Contralateral Breast Cancer," *JNCI Journal of the National Cancer Institute* 96, no. 7 (2004): 516–523.

60. A. W. Kurian, A. J. Canchola, C. S. Ma, C. A. Clarke, and S. L. Gomez, "Magnitude of Reduction in Risk of Second Contralateral Breast Cancer With Bilateral Mastectomy in Patients With Breast Cancer: Data From California, 1998 Through 2015," *Cancer* 126, no. 5 (2020): 958–970.

61. R. J. Santen, S. Mirkin, B. Bernick, and G. D. Constantine, "Systemic Estradiol Levels With Low-Dose Vaginal Estrogens," *Menopause* 27, no. 3 (2020): 361–370.

62. S. Cold, F. Cold, M. B. Jensen, D. Cronin-Fenton, P. Christiansen, and B. Ejlertsen, "Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study," *Journal of the National Cancer Institute* 114, no. 10 (2022): 1347–1354.

63. L. McVicker, A. M. Labeit, C. A. C. Coupland, et al., "Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer," *JAMA Oncology* 10, no. 1 (2024): 103–108.

64. P. Taranto, D. de Brito Sales, F. C. Maluf, et al., "Safety and Efficacy of Topical Testosterone in Breast Cancer Patients Receiving Ovarian Suppression and Aromatase Inhibitor Therapy," *Breast Cancer Research* 26, no. 1 (2024): 133.

65. R. R. Barakat, B. N. Bundy, N. M. Spirtos, J. Bell, and R. S. Mannel, "Randomized Double-Blind Trial of Estrogen Replacement Therapy Versus Placebo in Stage I or II Endometrial Cancer: A Gynecologic Oncology Group Study," *Journal of Clinical Oncology* 24, no. 4 (2006): 587–592.

66. S. H. Shim, S. J. Lee, and S. N. Kim, "Effects of Hormone Replacement Therapy on the Rate of Recurrence in Endometrial Cancer Survivors: A Meta-Analysis," *European Journal of Cancer* 50, no. 9 (2014): 1628–1637.

67. British Gynaecological Cancer Society and British Menopause Society, *British Gynaecological Cancer Society and British Menopause Society Guidelines: Management of Menopausal Symptoms Following Treatment of Gynaecological Cancer* (British Gynaecological Cancer Society and British Menopause Society, 2024).

68. R. A. Eeles, J. P. Morden, M. Gore, et al., "Adjuvant Hormone Therapy May Improve Survival in Epithelial Ovarian Cancer: Results of the AHT Randomized Trial," *Journal of Clinical Oncology* 33, no. 35 (2015): 4138–4144.

69. F. Guidozzi and A. Daponte, "Estrogen Replacement Therapy for Ovarian Carcinoma Survivors: A Randomized Controlled Trial," *Cancer* 86, no. 6 (1999): 1013–1018.

70. L. Li, Z. Pan, K. Gao, et al., "Impact of Post-Operative Hormone Replacement Therapy on Life Quality and Prognosis in Patients With Ovarian Malignancy," *Oncology Letters* 3, no. 1 (2012): 244–249.

71. N. Saeaib, K. Peeyananjarassri, T. Liabsuetrakul, R. Buhachat, and E. Myriokefalitaki, "Hormone Replacement Therapy After Surgery for Epithelial Ovarian Cancer," *Cochrane Database of Systematic Reviews* 2020, no. 1 (2020): CD012559.

72. E. Ploch, "Hormonal Replacement Therapy in Patients After Cervical Cance Treatment," *Gynecologic Oncology* 26, no. 2 (1987): 169–177.

73. K. Bodner, P. Laubichler, O. Kimberger, K. Czerwenka, R. Zeillinger, and B. Bodner-Adler, "Oestrogen and Progesterone Receptor Expression in Patients With Adenocarcinoma of the Uterine Cervix and Correlation With Various Clinicopathological Parameters," *Anticancer Research* 30, no. 4 (2010): 1341–1345.

74. J. D. Martin, R. Hähnel, A. J. McCartney, and N. D. Klerk, "The Influence of Estrogen and Progesterone Receptors on Survival in Patients With Carcinoma of the Uterine Cervix," *Gynecologic Oncology* 23, no. 3 (1986): 329–335.

75. A. Richardson, L. Watson, M. Persic, and A. Phillips, "Safety of Hormone Replacement Therapy in Women With a History of Cervical Adenocarcinoma," *Post Reproductive Health* 27, no. 3 (2021): 167–173.

76. S. H. Lee, Y. J. Cho, K. J. Cho, et al., "Effect of Tibolone on the Survival of Early Stage Cervical Adenocarcinoma Patients," *Obstetrics & Gynecology Science* 61, no. 5 (2018): 584–589.

77. A. Basakci, Z. Kirkali, E. Tuzel, K. Yorukoglu, M. U. Mungan, and M. Sade, "Prognostic Significance of Estrogen Receptor Expression in

Superficial Transitional Cell Carcinoma of the Urinary Bladder," *European Urology* 41, no. 3 (2002): 342–345.

78. G. Godoy, G. Gakis, C. L. Smith, and O. Fahmy, "Effects of Androgen and Estrogen Receptor Signaling Pathways on Bladder Cancer Initiation and Progression," *Bladder Cancer* 2, no. 2 (2016): 127–137.

79. C. R. Cardwell, T. A. Ranger, A. M. Labeit, et al., "Hormone Replacement Therapy and Cancer Mortality in Women With 17 Site-Specific Cancers: A Cohort Study Using Linked Medical Records," *British Journal of Cancer* 131, no. 4 (2024): 737–746.

80. K. Liu, Y. He, Q. Li, S. Sun, Z. Mei, and J. Zhao, "Impact of Hormone Replacement Therapy on All-Cause and Cancer-Specific Mortality in Colorectal Cancer: A Systematic Review and Dose–Response Meta-Analysis of Observational Studies," *Journal of Evidence-Based Medicine* 17, no. 2 (2024): 377–389.

81. X. Wang, Q. Chen, X. Huang, et al., "Effects of 17β-Estradiol and Tamoxifen on Gastric Cancer Cell Proliferation and Apoptosis and ER-α36 Expression," *Oncology Letters* 13, no. 1 (2017): 57–62.

82. X. Yang, C. Wang, X. He, et al., "Hormone Therapy for Premature Ovarian Insufficiency Patients With Malignant Hematologic Diseases," *Climacteric* 20, no. 3 (2017): 268–273.

83. L. Shi, Y. Feng, H. Lin, R. Ma, and X. Cai, "Role of Estrogen in Hepatocellular Carcinoma: Is Inflammation the Key?," *Journal of Translational Medicine* 12 (2014): 93.

84. Z. Hammoud, B. Tan, S. Badve, and R. M. Bigsby, "Estrogen Promotes Tumor Progression in a Genetically Defined Mouse Model of Lung Adenocarcinoma," *Endocrine-Related Cancer* 15, no. 2 (2008): 475–483.

85. R. T. Chlebowski, A. G. Schwartz, H. Wakelee, et al., "Oestrogen Plus Progestin and Lung Cancer in Postmenopausal Women (Women's Health Initiative Trial): A Post-Hoc Analysis of a Randomised Controlled Trial," *Lancet (London, England)* 374, no. 9697 (2009): 1243–1251.

86. J. Clague, P. Reynolds, K. D. Henderson, et al., "Menopausal Hormone Therapy and Lung Cancer-Specific Mortality Following Diagnosis: The California Teachers Study," *PLoS One* 9, no. 7 (2014): e103735.

87. R. M. MacKie and C. A. Bray, "Hormone Replacement Therapy After Surgery for Stage 1 or 2 Cutaneous Melanoma," *British Journal of Cancer* 90, no. 4 (2004): 770–772.

88. V. S. Benson, K. Pirie, J. Green, et al., "Hormone Replacement Therapy and Incidence of Central Nervous System Tumours in the Million Women Study," *International Journal of Cancer* 127, no. 7 (2010): 1692–1698.

89. L. Dresser, C. A. Yuen, A. Wilmington, et al., "Estrogen Hormone Replacement Therapy in Incidental Intracranial Meningioma: A Growth-Rate Analysis," *Scientific Reports* 10, no. 1 (2020): 17960.

90. C. P. Yu, J. Y. Ho, Y. T. Huang, et al., "Estrogen Inhibits Renal Cell Carcinoma Cell Progression Through Estrogen Receptor-β Activation," *PLoS One* 8, no. 2 (2013): e56667.

91. J. M. Bae, "Hormonal Replacement Therapy and Risk of Thyroid Cancer in Women: A Meta-Epidemiological Analysis of Prospective Cohort Studies," *Journal of Menopausal Medicine* 27, no. 3 (2021): 141–145.

92. Z. Nash, M. Christmas, T. Gronlund, et al., "Top Ten Menopause Research Priorities," *Lancet* 404, no. 10471 (2024): 2535–2536.