Hormone replacement therapy and the risk of breast cancer

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Abstract | Hormone replacement therapy (HRT) is given to relieve the climacteric symptoms of menopause. Use of HRT reduced after a report from the Women's Health Initiative linked it to an increased risk of breast cancer. This association has been confirmed in several other studies, including the Million Women Study. The risk of breast cancer is greater for formulations that contain both estrogen and progesterone, compared with estrogen alone. The breast cancer risk associated with HRT is higher for estrogen receptor-positive cancers than for estrogen receptor-negative cancers, and for low-grade cancers compared with high-grade cancers. After cessation of HRT the increased risk of breast cancer dissipates within 2 years. The rapidity of the decline suggests that a proportion of breast cancers that are hormone dependent will regress if the hormonal stimulation is removed. In evaluating a woman who is considering HRT, factors that have been associated with an increased risk include the initiation of hormone use immediately after menopause, a lean body mass and high mammographic breast density.

Introduction

Hormone replacement therapy (HRT) is often prescribed to women to alleviate the climacteric symptoms associated with menopause. In addition, it has been proposed that HRT might have beneficial long-term effects, including preventing heart disease, stroke and age-related cognitive decline.[1] Estrogen monotherapy is associated with an increased risk of endometrial cancer;[2] therefore, women with an intact uterus are usually prescribed a combination of estrogen and progesterone, which is not associated with endometrial cancer.[2] In some cases, progesterone monotherapy is prescribed, in particular for the treatment of hot flashes.[3]

Decline in breast cancer: 2002–2003

In 2007, Peter Ravdin and colleagues expressed the opinion that an observed 6.7% decline in the incidence of breast cancer in the USA from 2002 to 2003 was likely the result of a precipitous drop in the use of HRT by American women.[4–6] The decline in incidence was particularly steep for estrogen receptor (ER)-positive cancers in women over 50 years of age.[4] The drop in HRT use was widely believed to have been the consequence of the publication in 2002 of the first findings of the Women's Health Initiative (WHI).[4] In that landmark study, the risk of breast cancer was higher in women randomized to a combination of estrogen and progesterone than in women receiving placebo. Prior to the WHI study, data regarding HRT use were from case-controlled studies and observational prospective studies, which have been reviewed previously.[7] The results of the WHI study were widely accepted, but many clinicians were initially skeptical of the connection proposed by Ravdin; it seemed counterintuitive that a drop in the cancer rate should follow so quickly after a cessation in exposure to a carcinogen. Surely, breast cancers develop slowly and years would elapse before exposure to a carcinogen would result in a palpable breast mass.

The Women's Health Initiative

The question is straightforward: if, on reaching menopause, a woman begins a regimen of HRT, does this increase her risk of breast cancer? In the WHI study, 27,347 women were randomized to receive either estrogen (0.625 mg/day of conjugated equine estrogens [CEE]) for 5 years or a placebo. In addition, 16,608 of the 27,347 women (those who had not had a hysterectomy) were randomized to receive CEE in combination with progesterone (2.5 mg/day of medroxyprogesterone acetate) or placebo. At 5 years of follow-up, the risk of breast cancer was 26% higher in women receiving combination HRT than in women given placebo.[8] A similar increase in risk was not observed in women receiving CEE alone.[9]

The WHI study is intrinsically complex and the results were published in installments over a period of 8 years.[8–16] Not all the women who took part in the WHI study had just entered menopause. In the subgroup of 16,608 women randomized to combination HRT or placebo, the average age at study entry was 63.3 years (range 50–79 years) and approximately 80% of the women were ≥5 years beyond their menopause.[9] Women who had previously received estrogen-based HRT were not excluded if they had stopped taking it more than 3 months before study initiation; 26% had previously received estrogen.[11]

Competing interests
The author declares no competing interests.

Key points

- Hormone replacement therapy (HRT) is associated with an increase in the risk of breast cancer, and the risk increases with duration of use
- The risk associated with HRT is greater for estrogen–progesterone combination than for estrogen alone
- The risk of breast cancer dissipates within 2 years of cessation of treatment
- Cancers associated with HRT tend to be low grade and estrogen receptor positive
- Women with a lean body mass or high breast density face a higher risk of HRT-associated breast cancer than other women

Table 1 | HRT use and risk of breast cancer in the WHI[11]

Duration of combination HRT use prior to randomization (years)	HR (95% CI)
No past use	1.09 (0.86–1.39)
1–5	2.34 (1.07–5.11)
5–10	2.04 (0.77–5.39)

Abbreviations: HR, hazard ratio; HRT, hormone replacement therapy; WHI, Women's Health Initiative.

Study participants received the trial drug for up to 5 years and were followed up for a further 3 years. During the intervention period, 199 women in the HRT group developed breast cancer, compared with 150 women in the placebo group (hazard ratio [HR] = 1.26; 95% CI 1.02–1.55).[8] An excess risk was not apparent until 2 years after randomization (from year 2 to year 5 the HR was 1.7), and after HRT therapy was withdrawn the excess risk dissipated within 2 years.[8] The small number of incident cancers makes it difficult to estimate precisely the annual cancer risk. Furthermore, about 40% of the women who were randomized to HRT stopped treatment prematurely.[11] The investigators analyzed the data as intention-to-treat (as is correct practice); however, this raises problems because some women who were described as 'current users' in the analysis had actually stopped taking HRT.[11] This could introduce misclassification bias if current use, but not past use, is associated with breast cancer risk.

Many of the women in the WHI who used HRT started HRT ≥10 years after menopause (referred to as 'gap time').[13] Almost all of the increased breast cancer risk was associated with the approximately 26% of study participants who had used estrogen before entering the study (HR = 1.96; 95% CI 1.17–3).[13] Among women with no prior estrogen exposure, the HR associated with breast cancer was 1.02 (95% CI 0.77–1.36).[13] Therefore, if the WHI study had been limited to women with no past exposure to HRT then the early results would have been reassuring. The risk of cancer also increased with duration of total use (Table 1).[13]

Results from the 12% of women assigned to the treatment arm with no prior HRT exposure and who initiated HRT within 5 years of the menopause (952 out of 7,779 women) more closely address the key question.[15] In this subgroup, the HR for combination HRT use and breast cancer was 1.77 (95% CI 1.07–2.93), which was similar to the women with prior HRT use (HR = 2.06; 95% CI 1.30–3.27). Therefore, if we eliminate women with a gap time of ≥5 years then the increased risk associated with combined therapy is no longer restricted to women with past HRT use. The WHI investigators conclude that "women who initiate treatment soon after menopause and continue for many years appear to be at particularly high risk".[15] However, this conclusion was based on only 22 incidences of breast cancer and this is too few to subdivide by duration of exposure.

The results comparing women given estrogen alone with those receiving placebo are also of interest. In none of the WHI reports is there evidence that CEE monotherapy raised the risk of breast cancer; indeed, there is a suggestion that it might have been protective. When analyzed as intention-to-treat, the breast cancer HR in the CEE arm was 0.80 (95% CI 0.62–1.04; $P = 0.09$).[14] However, by the end of the study, 54% of the women were no longer adherent to their assigned medication. Interestingly, when the women who stopped taking CEE were censored at the time they stopped the drug, the HR indicated protection against breast cancer (HR = 0.67; 95% CI 0.47–0.97; $P = 0.03$).[14]

The Million Women Study

The Million Women Study (MWS) is a follow-up study of 1,129,025 women between the ages of 50 and 64 years.[17,18] Women in the UK completed a questionnaire at the time of mammographic screening and were followed up for a mean of 3.4 years through mailed questionnaires and linkage to the cancer registry and national mortality statistics. During the follow-up period, 15,759 breast cancers were diagnosed. For current users of HRT, the breast cancer odds ratio was 1.68 (95% CI 1.64–1.72) and for past users the odds ratio was 1.08 (95% CI 1.04–1.12); the effect of combination HRT increased with duration of use (Table 2). Therefore, as far as recent versus past use, the results of the MWS and the WHI are consistent. The principal difference is that in the MWS, a modest but significant increase in risk was associated with estrogen alone.[17,18] For current users of estrogen alone, the odds ratio was 1.4 (95% CI 1.32–1.44) and for current users of combination HRT, the odds ratio was 2.0 (95% CI 1.90–2.02). A theory to explain why estrogen was a risk factor in the MWS, but protective in the WHI is that breast cancers diagnosed in women after a long period of estrogen deprivation (that is, a long gap time) often undergo regression when exposed to estrogen.[19] In the MWS, combination HRT within 5 years of menopause was associated with a breast cancer HR of 1.43 (95% CI 1.36–1.49), but starting therapy thereafter did not significantly increase breast cancer risk (HR = 1.05; 95% CI 0.89–1.23).[18]

The million women in the MWS represent a large proportion of the women in the UK who take HRT.[18] Another strength of the MWS is that, given the very large number of study participants, it is possible to do subanalyses by route of administration, formulation, tumor type and duration of use. This was a nonrandomized observational trial and so the exposure categories were based on reported HRT use and, therefore, if the results

are to be compared to the WHI study, they are analogous to the results for adherent women.

Collaborative Study

The Collaborative Study was an impressive meta-analysis combining data from 51 cohort and case-control studies and included 17,949 cases of breast cancer and 35,916 controls.[20] This study also supports the model that recent use (within 5 years), but not past use, of HRT is a risk factor for breast cancer. Similar to the MWS, the increase in risk correlated with the duration of use (Table 2) but the risk did not increase much for HRT use <5 years. The majority of women in the Collaborative Study who used estrogen used estrogen alone (85% of hormone users). The breast cancer odds ratio for combination therapy was greater than for estrogen alone but the difference was not large (1.53 versus 1.26 for women with duration of use >5 years).[20] The odds ratios associated with recent use of combination therapy in the Collaborative Group Study were notably smaller than those reported in the WHI or MWS. The WHI and MWS excluded women who stopped HRT 1–5 years previously from the current-use group; in the Collaborative Study, current users were combined with women with any HRT use in the past 5 years. The authors of the Collaborative Study speculate that the size of the increase in the risk of breast cancer associated with a year of HRT is similar to the increase in risk for each year in delaying menopause.[20] This is interesting, and the analogy is logical. At any given age, a postmenopausal woman has a lower risk of breast cancer than a premenopausal women and the difference is profound for women under 40 years.[21]

Other HRT and breast cancer studies

There are many published studies of HRT and breast cancer risk (for a systematic review see Collins *et al.*[7]). In a large case-control study by Ross *et al.*[22] the relative risk of breast cancer increased with duration of use for users of combination HRT, with an odds ratio of 1.1 for 1 month to 5 years of use and 1.5 for ≥5 years of use. No significant increase in risk was seen with estrogen-replacement therapy.

The California Teachers Study followed 133,479 women from 1995 to 2006; 2,857 women were diagnosed with breast cancer in the follow-up period.[23] Outcomes were ascertained through linkage to state statistics and cancer registries. The study confirmed previous reports that current, but not past, use of combination HRT, and duration of use are predictors of risk. There was no significant increase in breast cancer risk associated with past use of either formulation. Hormone use was measured at baseline using a questionnaire; therefore, current use was defined at the time of the baseline questionnaire and not at the time of cancer diagnosis. As a result, it is difficult to distinguish the effects of current versus past use. However, the study does have several strengths, including detailed information on hormone preparation and on cancer phenotype. In a second large prospective study conducted by Calle *et al.*,[24] HRT exposure status was updated every 2 years. This study confirms

Duration of prior HRT use (years)	Associated risk by study	
	MWS (OR [95% CI])[17,*]	Collaborative study (OR [SE])[20,‡]
<1	1.45 (1.19–1.78)	0.99 (0.085)
1–4	1.74 (1.60–1.89)	1.08 (0.060)
5–9	2.17 (2.03–2.33)	1.31 (0.079)
≥10	2.31 (2.08–2.56)	NA
10–14	NA	1.24 (0.108)
≥15	NA	1.56 (0.128)

Table 2 | HRT use and risk of breast cancer in the MWS and Collaborative Study

*Current users of HRT only. ‡Only recent users included; recent users defined as any HRT use in the past 5 years. Abbreviations: HRT, hormone replacement therapy; MWS, Million Women Study; NA, not available; OR, odds ratio; SE, standard error.

the results of earlier studies *vis a vis* the importance of current versus past use and duration of use. Cases were subdivided by BMI; estrogen alone was associated with a modest increase in risk of breast cancer for women with a BMI of ≤25 (HR = 1.26; 95% CI 1.05–1.50).[24]

Pathologic features

The association between HRT and breast cancer has been categorized by histopathology using broad criteria and is stronger for lobular and tubular cancers than for the more frequently occurring ductal cancers.[18,24] In the MWS, the strength of the association was inversely associated with tumor grade, in particular for combination HRT.[18] For women who took combination HRT, the HR was 1.0 for grade III (95% CI 0.9–1.2), 1.7 for grade II (95% CI 1.5–1.8) and 2.4 for grade I (95% CI 2.2–2.7) breast cancers. The association was also stronger for cancers that were ER positive compared with ER negative.[18,23,24] The majority of ER-positive breast cancers are also positive for progesterone receptor (PR).[23,24] In the California Teachers cohort, the breast cancer risks were evaluated separately for ER-positive and PR-positive breast cancers; the risk associated with current use of combination HRT was significant for PR-positive cancers.[23] The risk associated with combination HRT was not elevated to the same extent for PR-negative breast cancer, even if they were ER positive (although the latter subgroup was quite small [*n* = 388]).[24] In the Calle *et al.*[24] study, the effect of combination HRT on breast cancer risk was limited to women with ER-positive and PR-positive tumors.

Type of formulation

In general, combination HRT is associated with a greater risk of breast cancer than estrogen alone. The types of estrogen formulations in common use vary by year and by country. One advantage of a randomized trial is that all participants are exposed to the same drug at the same dose, whereas in observational trials the choice of drug is at the discretion of the participant and many different preparations are reported. In the WHI, all participants who received estrogen were treated with CEE;[8,9] in other studies, some participants received other forms of estrogen, including estradiol and estriol.[7] In an early prospective study from Sweden, Bergkvist *et al.*[25] found an elevation in risk associated with long-term use (≥3 years)

of estradiol, but not with CEE. In the MWS, the effects of recent use of estrogen on breast cancer risk were similar for CEE and estradiol.[17]

In terms of combination HRT, for some formulations both drugs are given throughout the month (continuous therapy) and for others estrogen alone is followed by estrogen and progesterone (sequential therapy). The women in the WHI study were treated with continuous therapy.[8] In the MWS, the HRs for current use were similar for users of sequential therapy (HR = 1.77; 95% CI 1.59–1.97) and continuous therapy (HR = 1.57, 95% CI 1.37–1.79).[17]

Modifying factors
Age of first use
A high proportion of women with early menopause (<45 years) will have undergone surgical oophorectomy. In cohort studies of young women, it is important to consider whether women in the comparison group were premenopausal or had undergone early menopause without receiving HRT. Ewertz et al.[26] reported that the HR of breast cancer following exposure to HRT increased with age at first use. For women who used HRT before they were 50, the observed number of breast cancers was fewer than expected, but the difference was not significant. Perhaps this is not surprising, because most women in the comparison group would be premenopausal.

Time from menopause to first use
In the WHI study, women initiated HRT at various times following menopause.[15] The breast cancer risk declined with increase in gap time; for women who started combination HRT within 5 years of menopause the HR was 1.77 (95% CI 1.07–2.93) whereas for those with a gap time of ≥5 years the HR was 0.99 (95% CI 0.74–1.31).[15] In the MWS, the odds ratio for combination HRT was 2.04 (95% CI 1.95–2.14) for women who started therapy within 5 years of menopause and 1.53 (95% CI 1.38–1.69) for women who started thereafter.[17]

BMI
Several studies show that the increase in relative risk for breast cancer among HRT users is attenuated in obese women;[8,18,23,24] however, because obesity is a risk factor for breast cancer in postmenopausal women,[27] the absolute increase in risk may not be different than for women with a normal BMI. It is possible that in obese women, the higher levels of circulating estrogen due to aromatization of androgen in fatty tissues[28] might offset the effect of exogenous estrogen. In the MWS, BMI was a risk factor for breast cancer among women who did not take HRT.[18] In the California Teachers study,[23] the magnitude of risk diminished as BMI increased, but a modest association between HRT and breast cancer was still observed in women with a BMI >30 (HR = 1.11; 95% CI 0.73–1.70, for >15 years of HRT). Similarly, in the Calle et al.[24] cohort study, the effect of combination HRT was diminished in women as BMI increased. An effect of estrogen alone was seen for women with a BMI of <25 (HR = 1.26; 95% CI 1.05–1.50) but not in women

with a BMI of 25–30 (HR = 0.89; 95% CI 0.71–1.11). In general, women in the USA studies had a higher BMI than women enrolled in studies in Europe and we might, therefore, expect the global effect size of receiving HRT to be greater in Europe.

Benign breast disease
Few studies have looked at the effect of HRT in women with a history of benign breast disease. Dupont et al.[29] followed a cohort of women who had received a diagnosis of benign breast disease by virtue of a negative breast biopsy, and found that breast cancer risk was not different for women who did, and did not use HRT. The investigators concluded that benign breast disease is not a contraindication to the use of HRT.[24]

Breast density
Kerlikowske et al.[30] studied the association between HRT and breast cancer risk for women aged 55–59 years with different breast densities. For women with low breast density, the 5-year risk was 0.8% for non-users of HRT and 0.9% for users of combination HRT. Among women with high breast density, the 5-year risk was 2.4% for non-users of HRT and 4.2% for users of combination HRT. This implies that the risk of breast cancer attributable to HRT might be restricted to women in the higher categories of breast density.

BRCA status
Women with a *BRCA1* or *BRCA2* mutation have a baseline risk of breast cancer that is approximately 10-fold higher than in the general population.[31] Many of these women undergo surgically-induced (oophorectomy) menopause at a young age to reduce their breast cancer risk and will experience moderate to severe menopause-related symptoms.[32] In a case-control study, Eisen et al.[33] assessed the effect of HRT in postmenopausal women with a *BRCA1* mutation. The adjusted odds ratio for ever use of HRT was 0.58 (95% CI 0.35–0.96) and no difference was seen for estrogen alone and combination HRT.

The basic model
In the 4 years since the publication of the Ravdin paper,[1] it has been observed in many countries that a decline in the use of HRT is quickly followed by a decline in annual breast cancer incidence.[34] Studies of national trends complement the epidemiology studies in that current, but not past, use of combination HRT is a risk factor for breast cancer.[17,18,20] Based on these observations and the other studies reviewed here, a basic model can be constructed. Once combination HRT is initiated, the HR for breast cancer risk increases throughout the period of exposure; at 10 years, the HR is between 1.5 and 2.5. When exposure is terminated, the HR returns to unity within approximately 2 years.

It is not clear if the risk increase is immediate upon exposure to HRT. In the WHI study, no increase in risk was noted within the first 2 years after exposure.[10] In the MWS, the rise in risk was apparent in the first year.[18] Finally, in the Collaborative Study, no substantial effect

on risk was observed in the first 5 years of exposure.[20] It is not clear what the exact shape of the curve that relates time from first exposure to the HR is, because the various studies differ substantially in this regard. Lee *et al.*[35] propose that the odds ratio increases linearly, by 7.6% for each additional year of combination HRT use.

The studies agree on the lack of risk associated with past use, that is, the risk seems to dissipate within 2 years. This observation has interesting implications. If we assume, as Lee *et al.*[35] suggest, that the odds ratio was 1.8 for a woman with 10 years of exposure to combination HRT and that if a woman stops treatment, the odds ratio declines to 1.4 in 1 year and 1.0 in 2 years, a theoretical cohort of women who stop HRT treatment after 10 years will experience approximately 20% fewer clinically-apparent breast cancers over the next 3 years than a cohort of women who continue HRT. So, where do the breast cancers go? It is theoretically possible that the HRT was the initial cause of the breast cancer, but the time frame seems far too short for the removal of the precipitating event to manifest in a decreased risk of cancer within a year. Indeed, it has been estimated that it would take ≥5 years for a new breast cancer to be detectable clinically.[19] The alternate explanation is that breast cancers were present, but were subclinical, when HRT was stopped, and that the withdrawal of HRT slowed the growth of the cancer (or caused it to regress). A study that examined women who were taking HRT at the time of a breast cancer diagnosis is informative in this regard; cell proliferation in breast cancers (measured by Ki-67 expression) declined after the withdrawal of HRT.[36] If a breast cancer continues to grow, albeit at a slower rate, after HRT withdrawal, then we would expect it to manifest eventually and therefore we would anticipate a rebound in the incidence rate to occur a few years after the initial decline in a population that stopped using HRT. Similarly, a rebound in the annual risk of cancer should occur in a follow-up study within a few years of HRT cessation. In neither situation has a rebound been observed and, therefore, we assume that the cancers regressed completely or entered a prolonged state of dormancy. This is equivalent to saying that a proportion of the breast cancers are critically dependent on estrogen. In a therapeutic context, these cancers may be similar to those that respond dramatically to antiestrogen therapy.[37] The response to HRT withdrawal would be analogous to experiencing a complete pathologic response (or a prolonged clinical response) to an antiestrogen therapy in the neoadjuvant setting. Antiestrogen therapy has only rarely been studied in the neoadjuvant setting, but in a small study from Barcelona, a complete pathologic response was achieved in 19% of 74 patients with post-menopausal breast cancer treated with anastrozole alone.[37] The idea that a breast cancer can regress in the absence of surgery or cytotoxic chemotherapy is not without precedent. A small proportion of breast cancers will disappear entirely with antiestrogen therapy.[37] For example, three women with metastatic breast cancer had a prolonged response to withdrawal of CEE and no other treatment.[38]

The term 'over-diagnosis' is used to describe the (theoretical) proportion of breast cancers that are identified through mammography, but otherwise would not become clinically apparent over the lifespan of the woman.[39] For example, in the Malmo screening trial, there was an excess of 150 breast cancers in the mammography arm at the end of the screening period; 15 years later, there remained an excess of 115 cancers.[40] The interpretation here is that 35 cancers were the result of early diagnosis and 115 cancers were the result of over-diagnosis. It has been estimated that up to 35% of non-palpable, mammographically detectable invasive breast cancers fall into this over-diagnosis category,[39] and this finding provides support for the model that not all breast cancers progress.

In the MWS,[17] the odds ratio of 1.45 for women with only 1 year of HRT exposure indicates that in many of these women a subclinical cancer was present before HRT exposure.[19] If these cancers are completely dependent on estrogen and/or progesterone, one must explain how they arose in the first place—perhaps the low level of circulating hormones in postmenopausal women is sufficient (the therapeutic benefit of aromatase inhibitors in post-menopausal women suggests that this is the case for most cancers).[41] Perhaps the cancer in its earliest stages was supported by estrogen and/or progesterone when the woman was ovulating and then became dormant when she entered menopause, only to be reactivated with the introduction of HRT.

It is also interesting to speculate on the basis for the slow increase in the risk over the duration of HRT. Consider two current users of combination HRT—the woman who has used it longer is at higher risk of breast cancer. This relationship is true for many cancers and for many carcinogens; for example, among current smokers the risk increases with duration of smoking.[42] Conventional wisdom states that this is due to the accumulation of mutations, and, in some cases, these may be quantified by measuring adducts or counting chromosome breaks.[43] It is not clear why the effects of estrogen and/or progesterone are cumulative; the hormones do not accumulate in the body and evidence that they are directly mutagenic is limited.[44] To my knowledge, no study has correlated the concentration of mutations in normal breast tissue with the duration of estrogen exposure. Perhaps hormones act through an epigenetic mechanism; an alternate theory is that hormones are mitogenic, that is, the size of the at-risk precursor cell population expands with exposure.[21] An analogous model is that HRT might slowly increase the number of discrete microscopic preneoplastic lesions in the breast,[45] and that cancer occurs when a cell in a preneoplastic lesion gains a secondary mutation that confers a growth advantage.

Progesterone versus estrogen

The combination of progesterone and estrogen increases the risk of breast cancer to a greater extent than estrogen alone; however, there is no consensus on whether or not estrogen on its own increases the breast cancer risk. The

observations regarding combination HRT are consistent with two alternate theories: progesterone alone is harmful, or both hormones act together to increase risk. It is assumed that both progesterone and estrogen act through binding to their receptors.[46] The observed decline in cancer incidence after 2002 was predominantly ER-positive breast cancers, but most ER-positive cancers are also PR positive. Furthermore, there is evidence that the risk associated with combination HRT is much greater for ER-positive than for ER-negative breast cancers. In the California Teachers study, the excess risk was statistically significant for ER-positive and PR-positive cancers but not for ER-positive and PR-negative cancers.[23] This suggests that the presence of the PR is necessary to mediate the risk; unfortunately, the category of ER-negative and PR-positive breast cancers was too small to evaluate. Similarly, data on the risk of exposure to progesterone alone would be helpful, but is lacking. Therefore, it is not possible to distinguish between the two models based on the results of epidemiology studies alone and we are reliant on model systems.

If the carcinogenic effects of progesterone and/or estrogen were due to the induction of mutations, then we might expect oral contraceptives to be carcinogenic, but the effects of the pill (which contain similar hormones) on breast cancer risk is minimal.[47] That the age of exposure to exogenous hormones seems to be a critical factor (and the short latent period) suggests a different mechanism, one that acts on small, pre-existent lesions (which are probably rare in young women). Horwitz and Sartorius propose that exposure to progestins generates a population of ER-negative, PR-negative, CK5^{+} cells (that probably derive from more differentiated receptor-positive cells), which are precursors to breast cancer.[48,49] The progenitor cells multiply later under exposure to estrogen. This model is appealing in that it separates the effects of progesterone and estrogen and does not depend on the generation of mutations (that is not to say that mutations are unimportant in breast cancer etiology, or that carcinogens are irrelevant). Further data from Joshi et al.[50] show that the mammary stem-cell pool expands during exposure to progesterone during the luteal phase of the menstrual cycle, or after exposure to exogenous estrogen and progesterone in combination. Asselin-Labat et al.[51] demonstrated that the mammary stem-cell pool shrinks in ovariectomized mice and expands under the influence of estrogen and progesterone. This finding suggests that the action of estrogen may be permissive, rather than direct, in that it upregulates the PR. However, Schramek et al.[52] provide evidence that the effect of progesterone is direct, acting through the receptor activator of nuclear factor κB ligand (RANKL) and its receptor RANK. Treatment of mice with medroxyprogesterone acetate resulted in a dramatic upregulation of RANKL in mammary epithelial cells, which, in the presence of a DNA-damaging agent, correlated with the induction of in situ and invasive carcinomas. Furthermore, the loss of RANK expression impaired the self-renewal capacities of the putative cancer stem cells. An antibody that blocks the binding of RANKL to RANK (denosumab) is an effective treatment for the prevention of osteoporotic fractures,[53] and it is of interest to see if the benefits of the drug extend to prevention of breast cancer.

Cancer incidence versus mortality

Cancer incidence is the usual end point in epidemiologic studies; incidence is easier to measure than mortality because fewer study participants are needed and follow-up time is shorter. The number of cancers detected in a cohort under observation reflects their size distribution, their palpability and the frequency and sensitivity of the screening measures employed. A change in incidence is important, but it is more important to reduce mortality. Approximately 15% of women who have surgery for early-stage breast cancer will eventually succumb to the disease because of latent metastases.[54] It is possible that the doubling time of the cells in the metastatic compartment is not constant, but rather that metastases can regress, become dormant or their growth rate can accelerate. Unfortunately, tools to measure and follow the growth of small metastases are not available and, therefore, cancer incidence is used as a surrogate. If a risk factor were to act differently on the primary cancer and the metastasis, the HRs for cancer incidence and cancer mortality might be discordant. Epidemiologists often describe new breast cancers as being more or less 'advanced'. To diagnose an advanced-stage cancer the relevant question is whether or not latent distant metastases are present; however, the presence of small metastases at diagnosis is inferred from the experience of a distant recurrence years later. Distant recurrence is the ultimate measure of cancer aggressiveness but, in cross-sectional studies, epidemiologists and clinical researchers often employ surrogate measures, such as tumor size and node status. It is of interest to consider estrogen-replacement therapy in this light.

The HABITS study was a prospective randomized trial designed to measure the impact of HRT on breast cancer survivors.[55] All of the women had completed surgical treatment for breast cancer and had no evidence of disease. In this trial, estrogen alone was associated with a significant increase in local recurrence or contralateral breast cancer (28 versus eight events; $P = 0.0005$) but not in distant recurrence (10 versus eight events).[55] This prompts the question 'if a woman develops breast cancer while on estrogen-based HRT, is that woman more likely to experience a distant recurrence than a woman with a cancer of similar size who does not take HRT?' There is no consensus on this issue. In the WHI study, breast cancers associated with combination HRT were more likely to be node positive than women assigned to placebo.[16] In addition, there were more deaths from breast cancer in the combination HRT group than in the placebo group (25 versus 12; HR = 1.96; 95% CI 1.0–4.0; $P = 0.05$).[16] Estrogen alone did not increase breast cancer mortality. In the MWS, the association with HRT was stronger for breast cancers that were ER positive than those that were ER negative, and with those that were low grade versus those that were high grade (ER positive and low grade are both factors that are associated with a good prognosis).[56] However, (as in the WHI) HRT was more

strongly associated with node-positive breast cancer and with cancers that were clinically detected rather than screen detected. It remains to be seen if the reduction in breast cancer incidence described by Radvin and others will be followed by a commensurate reduction in breast cancer mortality.

Clinical implications

In a meta-analysis, the odds ratio increased by 7.6% per year of use of combined HRT.[35] It is important to note that this does not imply that if a woman uses combination HRT for 10 years, she is 76% more likely than expected to get breast cancer during that 10-year period, because the odds ratio increases incrementally. Based on this linear model, the excess of observed to expected breast cancers would be 15% at 5 years and 34% at 10 years. These are not dramatic risks, but they are sufficiently large that combination HRT should not be prescribed without due consideration of the risks. If a woman has had a hysterectomy, estrogen therapy is a reasonable choice. It is not yet clear if the risks related to combination HRT are similar for women of all ethnic groups and genetic backgrounds. In women who undergo surgical oophorectomy because of a BRCA1 or BRCA2 mutation, short-term HRT seems to be safe,[34] but further studies in high-risk women and in women with surgically-induced menopause are needed. The absolute risk of breast cancer attributable to HRT is greater for lean women and women with high breast density than for women with high BMI[23,24] or low breast density[30] and these factors should be taken into account by the prescribing physician.

Conclusions

Much of our knowledge of the relationship between HRT and breast cancer risk comes from three large studies. A collaborative analysis of 51 individual studies from around the world provided strong evidence that current, but not past use of estrogen in combination with progesterone was associated with increased breast cancer risk. This was followed by the MWS, which included a very large number of study participants representative of HRT use in the underlying population. The WHI was a randomized trial that was probably the least informative, but it was the most influential. Within a year of publication of the first WHI results, the use of HRT was reduced around the world.

Taken as a whole, these and other studies suggest that, among women who use a combined estrogen–progesterone therapy, the annual risk of breast cancer increases with the duration of use and dissipates within 2 years of termination of therapy. Estrogen alone also increased breast cancer risk, but the absolute risk increase is much lower than for combination HRT. If a woman begins combination HRT at menopause, after 5 years of use she can expect to experience breast cancer 15% more than otherwise expected, and at 10 years, 34% more than expected. If she stops HRT, the risk will return to baseline in approximately 2 years. The rapid diminution in risk after HRT cessation suggests that some subclinical breast cancers will regress or become dormant when hormone exposure is withdrawn. After a rapid decline in the use of HRT in 2002 and 2003, many countries experienced a decline in the incidence of breast cancer, but it is not certain that this will lead to a reduction in mortality. The data on HRT suggest potential therapeutic applications and support the investigation of antihormonal therapies in the neoadjuvant breast cancer setting.

Review criteria

The articles in cited in this Review represent, from the author's point of view, the most significant and representative articles of their type published in the English literature from 1997 to 30 June 2011. Articles published prior to the publication of the Collaborative Study in 1997 are summarized in an earlier Review that is cited in this Review. All articles pertinent to hormone replacement therapy in the Women's Health Initiative and in the Million Women Study were reviewed. Other articles reviewed here were selected based on the quality of the study, according to the author's judgment.

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