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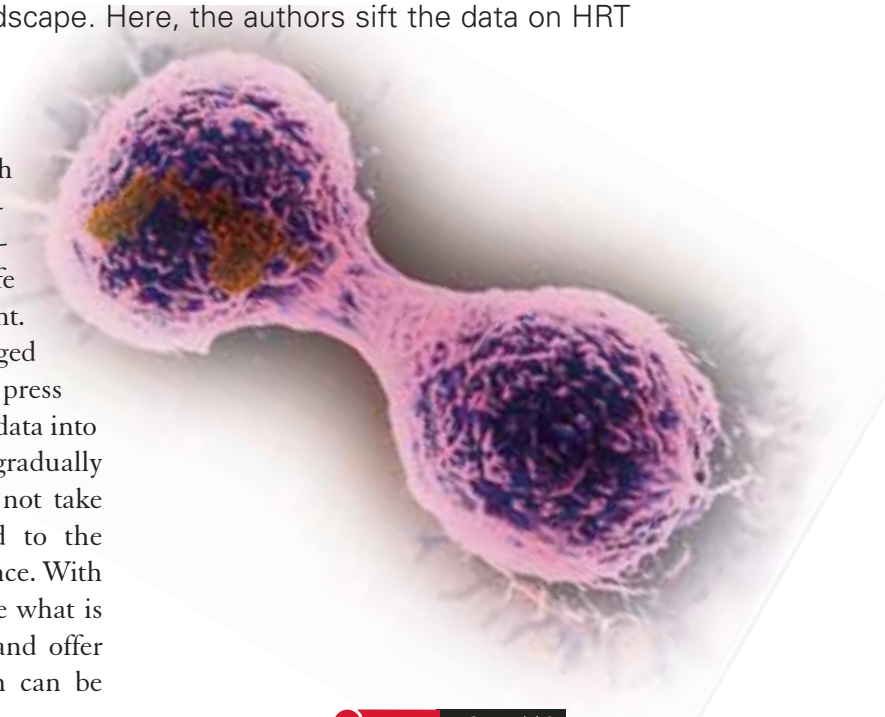
HRT and cancer: quantifying the risk

Until recently, hormone replacement therapy was hailed for its many benefits in postmenopausal women, but findings from the Women's Health Initiative and other trials have altered the landscape. Here, the authors sift the data on HRT and the risk of various cancers.



To say that the body of research on hormone replacement therapy (HRT) and the risk of cancer in postmenopausal women is rife with ambiguity is an understatement. Not only have recent studies challenged earlier findings, but the popular press often has generalized highly specific data into ubiquitous truths. Even so, we are gradually discerning who should and should not take the therapy, particularly in regard to the increased risk of cancer or its recurrence. With this article, we aim to objectively cite what is known about HRT in menopause and offer guidelines on how this information can be individualized to patients.

HRT and breast cancer

The most controversial risk associated with HRT is developing or aggravating breast cancer. Estrogen therapy—alone or in combination with progesterone—has been shown to increase production of the estrogen and progesterone receptors in breast tissue.[1] When acti-

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KEY POINTS

- Hormone replacement therapy (HRT) may be associated with an increased risk of breast cancer.
- Although the increased risk of breast cancer with HRT use is minimal, it may be advisable for some women to avoid this therapy altogether, especially those at high risk of breast cancer.
- The long-term use of unopposed estrogen is associated with epithelial ovarian cancer.
- The data on the risk of colorectal cancer with HRT use demonstrate a protective effect.
- Unopposed estrogen use is associated with the development of endometrial carcinoma.

vated, these receptors enhance breast density. In fact, a relationship between increasing breast density and breast cancer has been detected in several studies.[2,3]

Endogenous hormones also may heighten the risk of breast cancer. Risk factors such as early menarche, late menopause, and high postmenopausal serum estradiol levels appear to be significantly associated with the development of breast cancer, as does obesity that persists after menopause (with presumed high estrogen levels secondary to peripheral androgen conversion to estrogen).[4] In addition, an *in vitro* study suggests that breast-cell growth is stimulated with low doses of estrogen (but restricted at high doses).[5]

A recent prospective study found a significantly higher risk of invasive breast carcinoma among women who had ever used HRT (5 or more years).[6] No association was noted between use of HRT and ductal carcinoma in situ (DCIS) or invasive ductal or lobular carcinoma. Nor was any association found between current HRT use and DCIS or invasive ductal or lobular carcinoma, regardless of the duration of use. Holli and colleagues corroborate these findings.[7]

In the Nurses' Health Study, Colditz et al detected a significant association between breast cancer and the use of unopposed estrogen, estrogen in combination with progesterone, or progesterone alone.[8] Current HRT users who were 55 to 59 years of age had a significantly increased risk of breast cancer, as did women age 60 to 64 who had taken HRT more than 5 years. The authors recommended that the use of any form of HRT be considered carefully, on a patient-by-patient basis, especially after 55 years of age.

In the Breast Cancer Detection Demonstration Project, Schairer et al found that the risk of breast cancer increased with the duration of HRT use among postmenopausal women.[9] With unopposed estrogen, the risk of breast cancer in nonobese women increased after 8 or more years of use. With estrogen-progesterone, the risk was elevated after 4 years of use. When Schairer and colleagues analyzed different types of breast cancer, they found estrogen-progesterone was associated with a significantly increased risk of ductal and/or lobular disease with 4 or more years of use. In contrast, unopposed estrogen was associated with an increase in ductal and/or lobular disease after 8 to 16 years of use. Pike and Ross also found a statistically significant association between the risk of breast cancer and the use of estrogen-progesterone, compared with the use of estrogen alone.[10]

Researchers found a significant association between HRT use of 5 to 10 years and the development of invasive breast cancer, but no significance for prior use exceeding 10 years.

We now have data from the estrogen-progestin arm of the Women's Health Initiative (WHI), which was halted after a mean follow-up of 5.2 years.[11] One reason this arm of the trial was interrupted was the emerging evidence that combination HRT is associated with invasive breast cancer. Researchers found a significant association between HRT use of 5 to 10 years and the development of invasive breast cancer (confidence interval [CI], 1.01-21.02). However, prior use exceeding 10 years was not significantly associated with breast cancer (CI, 0.60-5.43). This trial involved only 1 form and dose of HRT: conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg. It did not consider the use of lower doses of estrogen and progesterone or different formulations.

There are studies in which no association has been found between HRT and breast cancer—such as the National Health and Nutrition Examination Survey I (NHANES I) study[12] and a case-control trial of the use of estrogen or estrogen-progestin.[13] Interestingly, O'Meara et al recently determined that women

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previously diagnosed with breast cancer who used HRT (estrogen alone or in combination with progestin) had a reduction in cancer recurrence and mortality when compared with nonusers.[14] Similarly, in the Cancer Prevention Study II, Willis et al found that women who had ever used estrogen replacement therapy (ERT) had a significantly decreased risk of fatal breast cancer. Willis and colleagues also reported no association between HRT use and the risk of breast cancer.[15]

In a qualitative review of the literature, Bush et al found no relationship between the use of any form of ERT/HRT and the development of breast cancer.[16] The authors cite 2 overall findings: First, the general lack of agreement of studies (primarily observational) is consistent with no association (most estimates of risk converge at approximately 1.0). Second, women who use ERT/HRT are less likely to die from breast cancer than nonusers. This may be due to diagnosis at an earlier stage and/or better-differentiated or lower-grade neoplasms, both of which are more conducive to successful treatment.

Overall, however, the data on HRT use and breast cancer continue to suggest an increased risk, although that risk may be minimal. Therefore, it may be advisable for some women to avoid HRT altogether, especially those at high risk of breast cancer (i.e., women with 2 first-degree relatives who have had breast cancer or are BRCA-positive).[17,18] These women might be better treated with supportive medications, such as selective estrogen receptor modulators (SERMs), lipid-lowering agents, antihypertensives, afterload-reduction medications for cardiovascular protection, and bisphosphonates and/or calcium and vitamin D to preserve bone density.

In a collaborative analysis of 12 case-control studies, Whittemore et al detected no trend in increasing risk of ovarian cancer with duration of ERT use.

HRT and ovarian cancer

The risk for worsening disease with HRT may be greatest when it comes to ovarian cancer, which usually is diagnosed in its advanced stages. Although ovarian epithelium is responsive to gonadotropins, the association between endogenous or exogenous hormones and the development of epithelial ovarian cancer is unclear.

There does appear to be a link between treatment with unopposed estrogen and the development of epithelial ovarian cancer. When compared with women who had never used ERT, patients with more than 10 years of current use had a significantly increased risk of death from ovarian cancer.[19] An earlier investigation found an increased mortality risk with 11 or more years of HRT use.[20]

Purdie et al found an increased risk of endometrial and clear-cell ovarian cancer with unopposed estrogen use.[21] However, no overall association was noted between ERT use and ovarian cancer. With more than 5 years of ERT use, Risch found an increased risk of serous and endometrioid cancer (with no mucinous malignancy association).[22] However, Kaufman et al found no significantly increased risk in specific subtypes of ovarian cancer with ERT use.[23] Nor did Hempling and colleagues find any association between HRT use and the duration or development of subtypes of ovarian cancer.[24]

In a collaborative analysis of 12 case-control studies, Whittemore et al detected no trend in increasing risk of ovarian cancer with duration of ERT use.[25] In their population and hospital studies, there was ambiguity regarding ERT use, with the population studies demonstrating a statistically significant decreased risk with current ERT use, while the hospital studies showed no effect. Booth et al similarly found no significant risk of

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ovarian cancer with ever-use of ERT.[26]

However, in a meta-analysis, Garg et al demonstrated an increased risk of developing invasive ovarian cancer with ever-use of HRT.[27] Similarly, when Negri and colleagues reanalyzed several European studies, they found an overall effect of ever-use of HRT on the development of ovarian cancer.[28] However, among patients with previously diagnosed ovarian cancer, ERT does not appear to significantly affect the disease-free interval or overall survival.[29,30]

A large trial found a significant association between postmenopausal hormones and a decreased risk of colorectal cancer, although this effect is lost with discontinuation.

Thus, the data are inconclusive on an association between ovarian cancer and HRT. What can probably be generalized at this point is that long-term use (more than 5 to 10 years) of unopposed estrogen is strongly associated with epithelial ovarian cancer. Women with significant menopausal symptoms, and those at risk for fractures and other sequelae of menopause, may benefit from a short-term trial of HRT (less than 5 years). Further studies are needed to fully assess the relationship.

Colorectal cancer

HRT appears to slightly reduce the risk of colorectal cancer. Troisi et al found no association between the use of postmenopausal hormones and the development of colorectal cancer (although no distinction was made between dosing of estrogen and/or progesterone therapy).[31] However, they did detect a slight reduction in the distal colon and rectal cancer risk among recent users.

Another large, prospective, case-control trial found a significant association between current use of postmenopausal hormones (estrogen and/or progesterone) and a decreased colorectal cancer risk, although it appears that this protective effect is lost when use is discontinued.[32] Fernandez and colleagues found that unopposed estrogen had a protective effect with duration of use that was significant for trend[33]; ever-use of ERT was associated with a decreased risk of colorectal cancer.

Similarly, Kampman et al found that women who had recently used HRT had a decreased risk of colon cancer, and Chute and colleagues found a slightly decreased risk of colorectal cancer with past use of postmenopausal hormones.[34,35] However, Risch and Howe found no association between HRT and the risk of rectal cancer.[36]

Findings from the WHI trial on the risk of colorectal cancer were not statistically significant at 5 years follow-up (the adjusted CI includes 1.0), but were consistent with earlier studies reflecting a protective effect of HRT in postmenopausal women.[11]

At a minimum, the data on the risk of colorectal cancer with HRT use appear to demonstrate a slight protective effect.[11,37] For patients who have a genetic susceptibility to colorectal cancer (e.g., a family history of hereditary nonpolyposis colon cancer), HRT use may confer some prophylactic benefit. Continued research will help elucidate this relationship.

HRT and endometrial cancer

The relationship between unopposed estrogen and the endometrium has been thoroughly investigated. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial determined that the use of continuous unopposed estrogen in a postmenopausal woman with a uterus worsens endometrial hyperplasia.[38] When it is atypical and complex, this hyperplasia is associated with an approximately 23% higher risk of progression to endometrial carcinoma compared with hyperplasia without cytologic atypia.[39] When an estrogen-progestin combination is used

Investigations conducted in the past 5 years have also helped elucidate the relationship between hormone replacement therapy (HRT) and other aspects of women's health. Here are a few highlights.

Cardiovascular disease. At one time, HRT was believed to reduce cardiovascular sequelae in menopause.[1] It now appears that, when women with recent cardiac compromise use HRT, they face an increased risk of cardiac events such as recurrent nonfatal myocardial infarction (MI), unstable angina, or death, with no significant trend toward improved heart disease thereafter.[2-4] Among the reasons the estrogen-progestin arm of the Women's Health Initiative (WHI) trial was terminated was the apparent increased risk of coronary heart disease, stroke, and thromboembolic events associated with HRT use.[5] Although the only outcome that was statistically significant involved venous thromboembolic disease overall (CI, 1.26-3.55) and deep vein thrombosis specifically (CI, 1.14-3.74), a trend of mildly increased cardiovascular disease was noted.

Although the evidence suggests that HRT use is beneficial in treating the vasomotor symptoms of perimenopause, its use in women at risk for cardiovascular events may be contraindicated; other supportive treatment may better serve the needs of these patients.

In women with no cardiovascular risk factors, HRT administration should include continued surveillance of the patient and the literature to determine the safest way to minimize risk. At the same time, careful attention should be devoted to other ways of protecting the patient's heart, bones, and overall health.

Bone mineral density. Estrogens have long been associated with improved bone mineral density (BMD).[6] However, the exact relationship between HRT and postmenopausal bone fracture is unclear. Trials exploring this relationship are under way. At present, it appears that HRT must be taken indefinitely in order to sustain BMD[7] and that adding calcium supplementation to the therapy helps minimize BMD loss.[8]

The WHI trial found HRT use to be significantly associated with reduced fractures overall (CI, 0.63-0.92), although the data were not statistically significant for hip and vertebral fractures alone.[5] While further corroborative findings will help to better define the efficacy of HRT against bone loss, it is reasonable at this time to consider it at least minimally beneficial in postmenopausal women.

Phytoestrogens. These compounds are another potential source of relief for postmenopausal patients. Although there is some evidence that these "natural" estrogens are beneficial, recent studies in animals and women suggest that they have a complex effect on the breast and elicit an uncertain response in the skeletal and cardiovascular systems.[9] These products may be considered for the relief of hot flushes and other perimenopausal symptoms in women who do not tolerate HRT use.[10] However, further studies are needed to determine their efficacy in the postmenopausal population.

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instead of estrogen alone, the rates of hyperplasia are similar to those among controls.[38]

In a meta-analysis, Grady et al found that the risk of endometrial cancer increased substantially with 10 or more years of unopposed estrogen use. The risk of death from endometrial carcinoma also was significantly increased with unopposed estrogen use.[40] With estrogen-progestin, no effect was observed.

Brinton and Hoover found that the risk of endometrial cancer increased significantly over time with unopposed estrogen use. In addition, endometrial cancers in estrogen users were detected at an earlier stage of disease.[41]

In a case-control study of postmenopausal women with endometrial cancer, Beresford et al found that long-term use of estrogen (5 or more years) with cyclic progesterone increased a woman's risk of endometrial cancer, compared with nonuse.[42] However, Pike and Ross found that continuous estrogen-progesterone therapy resulted in no increase in endometrial cancer; only when progestin was given for less than 7 days per month did the combined therapy show an increased risk.[10] Other studies have found no association between continuous HRT use and endometrial cancer.[43] In fact, many studies have demonstrated that combined estrogen-progesterone therapy usually elicits an atrophic response from the endometrium.[44-48]

The WHI also found no significant association between HRT and endometrial cancer.[11] However, since the estrogen-progestin arm of this trial was stopped after a mean follow-up of 5.2 years, data on the long-term use of HRT and endometrial cancer are lacking.

As for uterine sarcomas, there is evidence that they synthesize estrogen and estrogen and progesterone receptors.[49,50] However, there appears to be no strong association between ERT/HRT and development of these sarcomas.[51]

In summary, unopposed estrogen appears to be strongly associated with the subsequent development of endometrial carcinoma and should be avoided in women with uteri.[40] It also appears that continuous, combined HRT confers no elevated risk of endometrial carcinoma, and that women on HRT who develop endometrial carcinoma may have had some form of preexisting disease.[38,52] If a patient prefers sequential HRT, then progesterone should be given at least 10 consecutive days per month.[17,53]

Conclusion

Since its origination, the reported effectiveness of HRT has fluctuated widely. The therapy has long been appreciated for easing the vasomotor symptoms of menopause. However, its long-term good—or harm—has yet to be clearly defined. Still, HRT remains potentially beneficial to many women, even though the percentage of patients taking it as prescribed may be quite low.[54,55]

When the estrogen-progestin arm of the WHI trial was halted, investigators concluded that "there were more harmful than beneficial outcomes in the estrogen plus progestin group versus the placebo group."[11] While it is only 1 study addressing HRT use, the WHI trial may portend a global decline in the number of women and physicians willing to risk adverse events to improve quality of life.

One thing is clear: The ubiquitous treatment of postmenopausal women with HRT is no longer desired. Rather, the goal should be individualizing medical treatment based on each woman's specific needs and risk factors. Although HRT remains among the treatment options, other supportive medications also are available (e.g., bisphosphonates, SERMs). Clinicians should continue to follow the literature on the use of HRT in specific situations, and be aware of other ways of potentially enhancing longevity and improving the postmenopausal patient's quality of life. ■

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