Hormone Replacement Therapy in the Gynecologic and Breast Cancer Patient

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Hormone replacement therapy has increased in use as a result of its well-established benefits as an effective tool against such consequences as osteoporosis and ischemic heart disease and in the management of menopausal symptoms. However, its possible negative impact on the survival of patients with a previous diagnosis of breast, uterine, or ovarian cancer remains controversial. The risk:benefit analysis of hormone replacement therapy in this setting warrants further investigation. In the meantime, patients should be counseled on the risks, benefits, and contraindications of hormone replacement therapy before embarking on its use.

Introduction

Over the past three decades, several international medical publications have discussed the use of hormone replacement therapy (HRT) and cancer incidence in the "hormonally sensitive neoplasms." This article deals primarily with the safety of HRT in patients with a previous diagnosis of breast, uterine, or ovarian cancer. Do physiologic (not pharmacologic) doses of HRT have a negative impact on the disease-free and overall survival of these patients? Is there any credibility to the "fuel on the fire" theory, which suggests that estrogen preparations may activate quiescent disease and induce tumor regrowth? The benefits of HRT in preventing osteoporosis, postponing the onset of ischemic heart disease, maintaining a favorable lipid profile, and improving quality of life are well documented in the literature of the last two decades.

Breast Cancer Survivors

A prospective, randomized study has not been conducted in which breast cancer survivors were randomly assigned to receive either HRT or placebo and monitored for a period of five to 10 years. However, some indirect evidence can be extracted from the serendipitous exposure of an occult or subclinical breast cancer to high levels of endogenous or exogenous estrogen. Among these exposures are breast cancer coincident with pregnancy, pregnancy following therapy for breast cancer, the use of oral contraceptives, or HRT in patients with subclinical malignant lesions.

Pregnancy and Breast Cancer

Approximately 10% to 20% of breast cancers occur in women 15 through 44 years of age, and 0.5% to 4% are diagnosed during pregnancy or lactation. Because the average breast cancer lies occultly in the breast for five to eight years before diagnosis, many authors include in this category those patients for whom the diagnosis has been made within 12 months of delivery. Although the association of breast cancer in pregnancy is laden with both ethical and therapeutic uncertainties, little evidence suggests that pregnancy worsens the prognosis. A substantial amount of evidence has accumulated since the initial report of Haagensen et al.[1] in 1943, in which breast cancer associated with pregnancy was considered inoperable. Fifteen years later, Treves et al.[2] stated that pregnancy does not confer inoperability and that pregnant patients with breast cancer do not present a worse prognosis when compared with nonpregnant breast cancer patients of similar age and stage of disease. Pregnant women younger than 35 years of age have a higher likelihood of positive axillary nodes, but their survival is similar to that of nonpregnant women. Physicians have traditionally advised pregnancy termination in the first and second trimesters when breast cancer was diagnosed; the fetus is allowed to achieve viability only when the diagnosis was made during the last trimester. Several studies now conclude that neither spontaneous nor therapeutic abortion appears to favorably influence the course of breast cancer in these patients. Some suggest an unfavorable outcome in those undergoing termination and discourage termination in favor of treating the cancer directly.[2-4] Nevertheless, this group of patients does not support the "fuel on the fire" theory.

Pregnancy After Breast Cancer

Obviously, women of reproductive age may become pregnant after breast cancer treatment. As more women choose to postpone childbearing, pregnancy subsequent to breast cancer treatment will become more common. Many physicians recommend against subsequent pregnancy because of the fear that it might activate dormant cancer cells. Until recently, the trend was to advise the patient to avoid pregnancy for at least two years so that the placental estrogen would not activate the disease during the highest risk period for recurrence. However, Mignot et al.[5] reported that the survival of women who conceived within six months of breast cancer treatment was the same as that of controls. Breast cancer patients who subsequently became pregnant appeared to survive longer than comparable patients who did not become pregnant, even after eliminating biases for women with poor prognoses who are advised not to conceive and for those who are unlikely to become pregnant due to recurrences. In summary, the few studies on this subject have reported no adverse effect on survival from breast cancer when subsequent pregnancies occur.

Oral Contraceptives and Breast Cancer

Given the long natural history of this neoplasm, a large number of patients subsequently diagnosed with breast cancer used oral contraceptives (OC) during the promotion and progression of the disease. Although there is abundant literature on the incidence of breast cancer in OC users, there is a paucity of data on outcomes in
patients who may have been exposed to OCs while harboring a breast malignancy.[6,7] Rosner and Lane[8] studied 347 patients 50 years of age or younger with primary breast carcinoma who were treated from 1971 to 1981. Among the 112 OC users and the 235 nonusers, no significant differences were found in the disease-free survival, time to recurrence, or overall survival. Users for fewer than two years showed a similar result. Recent OC users (within one year of diagnosis) had a similar survival to that of those who stopped use more than one year prior to diagnosis. No significant differences were noted in survival between patients who began use 10 years or more before diagnosis and those beginning more recently. In summary, their data showed no adverse effect of OC use on the outcome of breast cancer, regardless of the duration of use or latency period.

HRT With Subclinical Malignant Lesions

Noncontraceptive estrogens were first marketed in the United States in 1942. Since then, these medications have been used extensively to relieve menopausal symptoms and, most recently, to prevent or retard the development of osteoporosis and ischemic heart disease in aging women. Numerous studies have attempted to evaluate the risk of developing breast cancer in women using estrogen replacement therapy (ERT), with the vast majority failing to demonstrate any significant increase in the incidence of breast cancer related to ERT. A study by Bergkvist et al[9] reported that estrogen use was associated with an overall slight increase in the risk of breast cancer (relative risk 1.1) and correlated with the duration of use (the relative risk reaching 1.7 after nine years). This increased risk was associated only with the use of estradiol; no increased risk was found with the use of conjugated estrogens or other types of estrogens. Another report by Bergkvist[10] compared 261 women who developed breast cancer in a population-based cohort of estrogen-treated women with 6,617 breast cancer patients who did not have recorded estrogen treatment. Complete follow-up was achieved during a period of up to nine years. The relative survival rate was significantly higher (approximately 10 percentage points at eight years) in patients who had received estrogen treatment corresponding to a reduction of approximately 40% in excess mortality. The time from the use of estrogen to diagnosis and the total duration of the use of estrogen medication were unrelated to survival when the effect of a recent use was taken into account in a multivariate analysis. This article and a more recent article by Strickland et al,[11] which demonstrated the same improved survival in patients diagnosed while taking ERT, strongly argue against the "fuel on the fire" theory proposed by those who prohibit ERT for breast cancer survivors.

Although the latest reports from the Nurses' Health Study suggest that women who used estrogen in the past were not at an increased risk of breast cancer, investigators found an increase in relative risk among current long-term (five or more years) users of estrogen.[12,13] Because of the large numbers in the Nurses' Health Study and the careful analysis by the investigators, reports from this study must be given credibility, though these findings are not definitive and are not free of all confounding variables. Detection bias is a major concern - current users had a 14% higher prevalence of mammography compared with nonusers. Also, current users differed from nonusers in several important aspects (eg, history of benign breast disease, number of births, age at menarche, body mass index). Although each factor alone would not explain the observed outcome, what is the additive effect of all factors? In the end, the size of the statistical risk is not outside the range of influence by biases.

In 1989, Dupont and colleagues[14] reported on the re-evaluation of 10,366 consecutive breast cancer biopsy specimens of benign lesions performed between 1950 and 1968. Follow-up information was obtained on 3,303 women for a median duration of 17 years. The sample contained 84% of the patients originally selected for follow-up. The relative risk of developing breast cancer was 0.98 for women who used exogenous estrogens compared with 1.8 for women who did not. Exogenous estrogens actually lowered the observed breast cancer risk in women with atypical hyperplasia (3.0 vs 4.5), with proliferative disease without atypia (0.92 vs 1.9), and without proliferative disease (0.69 vs 0.91). At the very least, this 1989 report demonstrated that even high-risk women with tissue proven hyperplasia were not at increased risk of developing breast cancer if they chose to use HRT.

A study was conducted of 77 breast cancer survivors who accepted HRT after breast cancer therapy and were followed over the past 15 years (Table).[15] The median age at diagnosis was 50 years, and the median interval between diagnosis and start of HRT was 23.8 months, with 37 patients starting within 24 months. The median duration of therapy was 27 months. All but 13 took progesterin with estrogen. Most received HRT as conjugated estrogen, and seven used estradiol patches. The median follow-up from diagnosis was 59 months, and the median disease-free survival was 53 months. Seven women had breast cancer recurrence after starting HRT, with the average interval from diagnosis to relapse at 45.3 months (20 to 106 months). Of these patients, five were still taking HRT at the time of recurrence, whereas two had stopped HRT before recurrence was diagnosed. Four of the five patients stopped HRT at the time of recurrence; one is alive with no evidence of disease, two are alive with disease, and one died of the disease. Of the 77 patients started on HRT, 71 (92%) have no evidence of disease. Three patients (4%) are alive with disease, and three died, one of complications from chemotherapy (at necropsy she was free of disease) and two of progressive disease. Among the 70 patients with no evidence of recurrence, only three have stopped taking HRT.

Although this study is not sufficient to ensure absolute safety of HRT in women previously treated for breast cancer, it strongly suggests that renewed hormonal exposure to HRT does not cause substantial recurrences as was anticipated by some. The authors are now evaluating disease recurrence, progression, and survival in those patients with ductal breast carcinoma who have taken HRT compared with a group of matched controls.

Endometrial Cancer Survivors

The association between unopposed exogenous estrogen therapy and endometrial cancer has been well established.[16,17] The tumors are primarily well differentiated and limited to the endometrium with minimal invasion. Several investigators have demonstrated that the addition of a progestin to the ERT reduces the relative risk of endometrial cancer from 4-8 to 1.0 or less. The standard of practice for patients treated for endometrial carcinoma has been to reject ERT because the growth-promoting effects of estrogen might stimulate growth of residual tumor cells. The treatment of menopausal symptoms in these patients has been with progestin-only therapy. Although this practice offers some relief from vasomotor symptoms, it has a poor effect on the prevention of osteoporosis or ischemic heart disease. Some data are now available supporting the use of ERT in survivors of endometrial carcinoma. A nonrandomized, retrospective report in 1985 involving 221 stage I endometrial cancer patients, 47 of whom received ERT, showed no difference between nontreated and estrogen-treated groups for known prognostic factors of tumor recurrence (eg, stage, grade, depth of invasion, node metastasis, peritoneal cytology, or hormone receptor status).[18] Among the 174 nontreated patients, 26 recurrences (14.9%) and 26 deaths (16 of disease and 10 of intercurrent disease) were noted, whereas among the 47 treated patients, there was one recurrence and one death (2.1%). This suggests a protective effect against recurrence in patients who receive ERT. In another retrospective series[19] in 1990 of 143 patients with stage I endometrial carcinoma considered at low risk for recurrence, 44 estrogen users had no recurrences or deaths after a mean follow-up of 87 months. In the 99 nonestrogen patients, eight recurrences and five deaths occurred from intercurrent myocardial infarction.

In a third retrospective study from the Department of Obstetrics and Gynecology at the University of California at Irvine (UCI), patients were treated at UCI Medical Center and Long Beach Memorial Women's Hospital between the years of 1986 and 1993. All patients with advanced disease (stage III or IV) and with history other than adenocarcinoma or multiple primaries were excluded. In an analysis of 132 patients with stage I or II adenocarcinoma of the endometrium, 65 (49%) patients received HRT some time after diagnosis and therapy, while 67 similar patients did not receive HRT or ERT and served as controls. The control patients were treated during the same period by the same physicians, but the patients were not interested in replacement therapy following initial treatment for their endometrial neoplasia. Of the 65 patients receiving HRT, 61 took 0.3-1.25 mg (82% received 0.625 mg) of conjugated estrogens, three received only vaginal estrogen cream, and one patient used an estrogen patch. All patients also received oral medroxyprogesterone 2.5 mg daily. The HRT was compared with the control group on several parameters. The mean age of diagnosis in the control group was 68.6 years (range 36-92) compared with 62.3 years in the HRT group (range 27-76). The mean parity was not significantly different (2.2 and 2.4 for the HRT and control groups, respectively). The mean duration of follow-up in the two groups was 58.2 and 31.1
months, with the HRT group having longer follow-up. One explanation for this observed difference is that the longer a patient was followed, the more likely that she would be placed on HRT and thus excluded from the control group. Follow-up ranged from two to 211 months in the HRT group and from two to 90 months in the control group. More than 95% of the HRT group was followed for at least 12 months; 77% had been followed for 24 months or more. This was considered important since 80% of the recurrences in endometrial cancer occur within 24 months of treatment. The mean duration of HRT was 36.3 months with a range of two to 127 months. The interval of treatment to initiation of HRT ranged from 0 to 162 months with a mean interval of 21.3 months.

Compared with the control population, the study population showed a trend toward tumors of lower grade. In patients receiving HRT, 38 (59.4%) had well-differentiated neoplasms. In contrast, only 26 (38.8%) of controls were well differentiated, a difference that was statistically significant (P<.05). Analysis of depth of invasion also was performed and again revealed a tendency toward less advanced cancers in the estrogen users vs controls. Whereas only 65% of the patients on HRT had myometrial invasion, 90% of the control patients had invasion. Differences in treatment methods also were analyzed. A simple total abdominal hysterectomy was the total treatment in 49.2% of the HRT group compared with only 31.3% of the controls. There were two (3.1%) recurrences in the HRT group vs six (8.9%) in the control group, a difference that was not statistically significant. The mean time to recurrence was nearly identical in both groups (27.5 months in the HRT group vs 28.2 months in the treatment group).

The disease status of patients on both HRT and controls also was assessed. In the HRT group, only one death occurred that was secondary to intercurrent disease, no deaths occurred from the endometrial disease, and no patients were alive with disease at the time of this study. By contrast, in the control group, three deaths (4.5%) occurred, all of which were secondary to intercurrent disease. No patients died of disease, and two patients (3.0%) were alive with disease at the time of the study.

Ovarian Cancer Survivors

Traditionally, a history of ovarian epithelial cancer has not been considered a contraindication for patients to be treated with HRT. However, there are some theoretical considerations. In some respects, the epidemiology of ovarian cancer parallels that of breast cancer.[20] The incidence increases with age and is higher in nulliparous patients. The relative risk of epithelial ovarian cancer is 1.8 in the infertile patient attempting pregnancy for 10 years or more.[21] Both pregnancy and OC use demonstrate a significant protective effect against epithelial ovarian cancer. A report from the Centers for Disease Control (CDC) stated that OC use reduced the risk of epithelial ovarian cancer by 40% for women of reproductive age.[22] The reduction in risk was directly related to the duration of OC use, but even short-term use conferred some protective effect, and the protection lasted for 10 years after OC use was discontinued. The data for HRT are less clear, and the few published studies are contradictory. However, most have shown no association with increased relative risk of ovarian cancer following the use of HRT or ERT. A recent association has been proposed between the use of fertility drugs and increased ovarian cancer risk.[23] This increased relative risk is reported to be independent of the known increased risk for infertile patients, but this study fails to distinguish between ovariolytic and anovulatory patients, does not differentiate among drugs and dosages used, and incorporates only a small number of exposed cases and controls.

Both estrogen and progesterone receptors have been detected in ovarian epithelial carcinomas with estrogen receptors and histologic type or prognosis, but some studies have shown an increased prevalence of receptor positivity in endometrioid ovarian carcinoma.[24,25] The presence or absence of receptors has not been shown to predict reliably which patients might respond to hormone therapy. Both antiestrogen therapy and high-dose estrogen and progestin therapy have been used to treat metastatic ovarian cancer, with variable percentage of patients responding.[26,27] No exacerbation of the neoplastic process induced by hormonal therapy has been shown.

Conclusions

While this format does not permit a discussion of the convincing data supporting the benefits of HRT, the data are well known. A prospective, randomized study evaluating the theoretical disadvantage of HRT in these cancer survivors is needed. In the interim, can we avoid thoroughly informing our patients of the benefits as well as the potential risks of HRT so they can decide the course of action? It is no longer appropriate to continue a posture of categorically prohibiting HRT in breast, uterine, and ovarian cancer survivors.

References


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