

Hormone Replacement Therapy in Cancer Survivors: A Con Opinion

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Introduction

Successful treatment of patients with cancer has resulted in an ever-increasing population of cancer survivors. With their cancer treatments behind them, these survivors are now facing the challenges of living a normal life. Following cancer therapy, women may experience menopausal symptoms, such as hot flashes, dyspareunia, atrophic vaginitis, and sleep disturbances. Menopause may be prematurely precipitated by the therapy or may naturally occur. Coronary artery disease and osteoporosis are potentially life-threatening conditions associated with aging and menopause. As in the general population, cardiovascular disease is currently the most common nonneoplastic cause of death in breast cancer survivors.¹ Estrogen replacement therapy has been shown to protect against heart disease and bone fractures. Thus, the issue of hormone replacement therapy in cancer survivors is a very real issue that needs to be addressed by practicing physicians. For women with breast cancer and uterine cancer, the issue of hormone replacement is quite complex with conflicting data and opinions.

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Breast Cancer

CELLULAR EFFECTS OF HORMONES

Available data are consistent with the idea that endocrine factors are involved in either the induction and/or promotion of breast cancer. Hormones act by increasing cell proliferation. Cellular DNA may be more susceptible to carcinogens during division. Mutations that occur spontaneously or from carcinogens are more likely to occur in rapidly dividing cells. Cell proliferation increases the risk of tumorigenesis by accelerating the accumulation of stochastic somatic genetic errors, including mutations, translocations, and reduction to homozygosity of tumor suppressor genes.²

Estrogen stimulates growth of normal and malignant breast cells in tissue culture.³ Progesterone also has proliferative actions in the breast. In mice, progesterone stimulates DNA synthesis in the epithelium of the terminal bud and ductal epithelium. In epithelial cells of the breast during the normal menstrual cycle and in women taking oral contraceptives, the highest thymidine labeling indices occur during the progestin-dominated secretory phase of the menstrual cycle.⁴

The epithelial cells of the terminal duct lobular units, from which the vast majority of breast cancers arise, undergo significant changes during the menstrual cycle. Cell proliferation of the terminal

duct lobular units is lowest during the follicular phase, then increases some four-fold to peak in the mid to late luteal phase. However, some research suggests that progestins induce only one round of cell replication, after which cells differentiate and cease proliferating, as opposed to estrogen, which appears to induce multiple replications.^{4,5} The conflicting data in the literature with respect to progesterone may be a result of experimental conditions, dose of progesterone used, and the animal model studied.⁴ Local growth factors may be either stimulatory or inhibitory for cell growth depending on the relative concentrations of estrogen and progesterone.

EPIDEMIOLOGY

Role of Endogenous Hormones

Epidemiologic data support a role for hormones in the development of breast cancer. The incidence of breast, ovary, and endometrial cancer show a sharp

relative risk of .30 when compared with a natural menopause at age 50 (i.e., fifteen years of ovarian failure is associated with a 70 percent reduction in breast cancer risk).²

The Cancer and Steroid Hormone Study Group reported that hysterectomy with bilateral salpingo-oophorectomy decreases the risk of breast cancer in women younger than 55 years, possibly by curtailing ovarian function at a critical period.⁶

It has been argued that premenopausal women with breast cancer who maintain their ovarian function have a prognosis and survival equal to that of postmenopausal women and, thus, provide indirect evidence for the safety of hormonal therapy. Recent data from several large studies, however, question the validity of this logic. The Scottish Cancer Trial's Breast Group and ICRF Breast Unit in London in a randomized, prospective trial with long-term follow-up demonstrated that oophorectomy in premenopausal women was as effective as

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slowing of the rate of rise of these cancers at the age of menopause (Figure). The simplest interpretation of this phenomenon is that the key etiologic elements are present in premenopausal women. Ovarian steroid hormones may be the key factors. Low serum levels of estrogens in women in China and Japan may partially explain the large differences in breast cancer risk between these Asian countries and the West.

Numerous reports have documented the protective effect of late menarche and early menopause on breast cancer risk.^{6,7} It is estimated that bilateral oophorectomy at 35 years of age is associated with a

standard chemotherapy.⁸ The Early Breast Cancer Trialists reported ovarian ablation in women younger than 50 was associated with a 26 percent reduction in recurrence and a 25 percent reduction in mortality.⁹ Similarly, Bianco et al¹⁰ found that those women who experience either temporary or permanent amenorrhea during chemotherapy for breast cancer had a significantly better survival.

Role of Exogenous Hormones

Since 1970, at least 39 epidemiologic studies have examined the association of exogenous estrogen treatment and risk of

breast cancer. The findings of these studies are not consistent. A recent analysis that pooled duration response slopes from 16 case-control studies reported a relative risk of 1.3 (95 percent confidence interval, 1.2-1.6) for women who had used estrogens more than 15 years, as compared with nonusers.¹¹ Grady et al¹² calculated a risk of breast cancer of 1.25 in women who used estrogen for more than eight years, from pooled estimates of case-control and cohort studies. However, the authors caution that this risk may be too high due to a surveillance bias for those women who took estrogen or too low if estrogen treatment had been withheld from women at high risk for breast cancer.¹² Hemminki and Sihvo¹³ reviewed recommendations for postmenopausal hormone therapy. Their report suggests that until the 1990s, physicians in the United States tended to select healthier women for long-term estrogen therapy. Thus, exclusion from hormone therapy of women with an increased risk, history of, or current breast or gynecologic cancer from hormone therapy may have biased published surveys toward underestimating the real risk of breast cancer.

Further data implicating a role for estrogen in breast cancer were recently reported by Colditz et al¹⁴ in a meta-analysis of 31 studies. Current users of hormone replacement therapy had a significantly elevated relative risk of breast cancer as compared with never-users, with a 40 percent increased risk of breast cancer (relative risk, 1.40; 95 percent confidence interval, 1.2-1.63).

In the Nurses Health Study, these same authors observed that the risk of breast cancer was significantly elevated among current users (relative risk, 1.36; 95 percent confidence interval, 1.41-1.667).¹⁵ Similarly, Hunt et al¹⁶ observed an increased risk of breast cancer in current users of estrogen replacement therapy among women attending a menopause clinic in Great Britain. Mills et al¹⁷ found that current estrogen use was associated

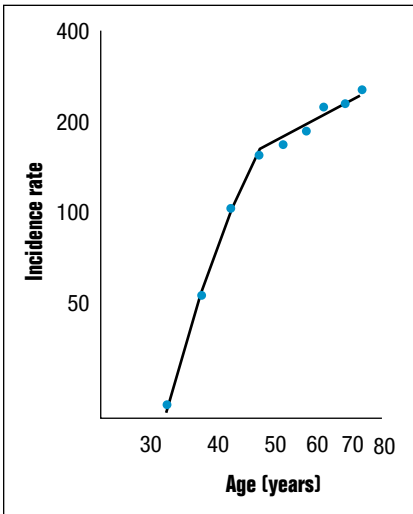
with a significant increase in breast cancer risk. These data taken together with other epidemiologic data and laboratory evidence suggest that estrogen is a promoter of mammary tumors. The widespread use of estrogen replacement therapy and hormone replacement therapy and the incidence of breast cancer combine to make even a small increase in relative risk (25 to 30 percent) an important public health issue.

More evidence implicating hormones in the pathogenesis of breast cancer is evident in studies evaluating diethylstilbestrol in the mothers who took this drug during pregnancy. There is an increased relative risk of breast cancer in the mothers of about 1.35.¹⁸ These data suggest a long latency effect. This phenomenon has also been observed in women who used the oral contraceptive pill. There is evidence of a modest increase in breast cancer risk in women diagnosed under the age of 45 years who took the birth control pill following

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menarche and in those who took the oral contraceptive pill for long periods of time prior to the first full-term pregnancy.¹⁹ These cancers did not become apparent until 10 to 20 years following cessation of the oral contraceptive pill.

Pre-menopausal women who are given tamoxifen may have increased levels of serum estradiol. Proponents for hormone replacement therapy argue that this has not appeared to affect their prognosis. However, the difficulty with this logic is that not all pre-menopausal patients demonstrate an increase in serum estradiol, and sufficiently large numbers



Age incidence curve of breast cancer. Adapted from Spicer and Pike.²

of premenopausal patients have not received long-term tamoxifen to justify a secure position of no effect on prognosis. It also appears that there is an increase in steroid hormone binding globulin, and thus the estradiol may be bound and not free.

Proponents of estrogen replacement therapy for breast cancer survivors bolster their arguments by stating that estrogen has been and is currently used as a treatment for breast cancer.²⁰ However, the dose is pharmacologic, not physiologic, and in-vitro studies demonstrate that low doses of estrogens can stimulate, while high doses of estrogen inhibit breast cancer growth.²¹

GENETICS

A personal history of breast cancer is a strong risk factor for the subsequent development of another primary breast tumor. The annual incidence of new primary breast cancers among breast cancer

survivors is 14 per 1,000 women compared with an incidence of two per 1,000 women in the general population. The risk of breast cancer is also increased in women with cancers of the corpus uteri and ovary, with a relative risk of about 1.5 from one to four years after the diagnosis of the first cancer.²² Follow-up surveys of patients with ovarian cancer reveal an increased risk of second primary cancers of the uterine corpus, colon, bladder, breast, and hematopoietic system.²³

PREGNANCY

Proponents of hormone replacement therapy argue that if pregnancy is safe following breast cancer, then hormone replacement therapy should also be safe. However, this intuitive logic is too simplistic. The levels of hormones in pregnancy cannot be compared with levels achieved with hormone replacement therapy. In addition to estrogen and progesterone, corticosteroid, growth hormone, insulin, and prolactin are increased in pregnancy. The interaction of these hormones and the elevated levels do not provide an analogous situation to hormone replacement therapy.

Animal and laboratory data suggest that pharmacologic doses of estrogen and progesterone can inhibit the growth of breast cancer. At high doses, progesterone appears to be antiproliferative in breast cancers.⁴ The estrogen and progesterone levels observed in pregnancy cause cells to differentiate and the breast tissue in animals becomes more resistant to the stimulatory effects of estrogen.⁴ The mammary gland of different species responds differently to estrogens, depending on the dose and whether it is administered alone or in combination with progesterone.²⁴

Recent data suggest that concurrent or recent pregnancy adversely affects survival of young women (aged 20 to 29 years) with breast cancer. Adjustment for number of axillary nodes and stage of dis-

ease reduced the relative risk only slightly (relative risk, 2.83; 95 percent confidence interval, 1.24-6.45, $P=0.023$).²⁵ Another study observed a dual effect of pregnancy on the risk of breast cancer. There was a transient increase in breast cancer following childbirth, but a reduction in later years. These authors suggest that pregnancy results in an initial increase in risk by stimulating the growth of cells that have undergone the early stages of malignant transformation and results in long-term protection by inducing the differentiation of normal mammary stem cells that have the potential for neoplastic change.²⁶

There have been several reports (which together total about 500 patients) following patients who have had pregnancies following breast cancer. This information is of importance to patients

to ten years. The actual annual risk is relatively linear over the first ten to twelve years after therapy. Few of the published studies have a follow-up of ten years.

METHODOLOGIC LIMITATIONS OF HUMAN STUDIES OF HORMONE REPLACEMENT THERAPY IN BREAST CANCER SURVIVORS

There have been several small studies that have reported estrogen replacement therapy or estrogen and progesterone replacement therapy in patients with breast cancer. The published trials to date have been anecdotal and not formal clinical trials with clearly defined objectives, eligibility criteria, and end points. Stoll²⁷ administered daily doses of 0.625 milligrams of conjugated equine estrogens and 0.15 milligram norgestrel to symptomatic post-

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with breast cancer who wish to address this issue. Although the reported cases do not seem to contraindicate pregnancy following breast cancer, this data must be viewed with caution. The reported series are small, and represent a naturally selected group of survivors. Most reports have an interval of several years from the time of breast cancer to the time of conception. More worrisome is that most reports do not have adequate follow-up and report median follow-up periods of only two to three years. A significant percentage of patients who undergo treatment of breast cancer have occult metastasis, and even those with small tumors and negative nodes have a ten-year survival rate of 70 percent. Recurrence rates of five percent per year have been reported for up

menopausal woman with a history of breast cancer, but clinically free of recurrence. Treatment was given continuously for three months and if symptoms improved was continued for an additional three months. The patients were followed for at least two years. The authors did not report any tumor reactivation during that period of observation. This clinical trial is difficult to analyze as it is reported in summary form, without a clear definition of the patient population. The treatment interval and follow-up period was too short to provide reassuring data that hormone replacement is safe to administer.

Wile et al²⁸ conducted a case-control study of 25 breast cancer survivors who received estrogen replacement therapy. The mean duration of treatment was 35.2

months, with a range of six to 78 months. The study is a small, retrospective study with different regimens of hormone replacement therapy and different doses. The authors conclude that the study does not have the power to demonstrate an adverse affect of hormone replacement therapy on breast cancer.

The American College of Obstetricians and Gynecologists in their Committee Opinion in April 1994 reevaluated the use of estrogen replacement therapy in women with previously treated breast cancer. In this Committee Opinion, they conclude that in postmenopausal women with previously treated breast cancer, consideration of estrogen replacement therapy is an option but must be viewed with caution. The opinion further states that any possible benefit must be balanced by a thorough explanation of current knowledge, which by necessity will entail consultation with the patient's oncologist.²⁹ The American College of

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Physicians in their guidelines for hormone replacement therapy concluded the risks of hormone therapy may outweigh its benefits in women who are at increased risk for breast cancer.³⁰

Endometrial Cancer

ROLE OF EXOGENOUS HORMONES

Women with a uterus receiving estrogen therapy have about a 20 percent lifetime probability of having a hysterectomy because of endometrial hyperplasia or cancer due to the therapy.^{12,30} There does not

seem to be an increased risk when the estrogen is combined with progesterone therapy. The lifetime risk for developing endometrial cancer is increased about eightfold in women with a uterus who take unopposed estrogen for 10 to 20 years. Long-term estrogen replacement therapy is associated with an increased risk of developing endometrial cancer, which persists for up to 10 years following cessation of estrogen therapy, again suggesting a long latency effect.³¹

METHODOLOGIC LIMITATIONS OF HUMAN STUDIES

There have been several retrospective, nonrandomized studies of patients given estrogen replacement therapy following treatment for endometrial cancer. Creasman et al³² reported 47 patients who were treated with estrogen replacement therapy after therapy for endometrial cancer. The patients were treated with a variety of estrogens including both oral and vaginal preparations. Estrogen therapy was given after a median interval from cancer therapy of 15 months. Thus, the study represents a selection bias, suggesting that the authors may have eliminated patients who developed recurrent disease in the initial 15 months following therapy. The groups were not evenly matched, and the patient numbers were too small to achieve a statistically significant difference. The authors do note a trend for several factors pointing to a more favorable disease status in the estrogen group. With larger numbers, this trend would have probably been of statistical significance.

Lee et al³³ reported on 44 patients placed on estrogen replacement therapy following treatment for endometrial cancer. The patients were at low risk for recurrence due to strict selection criteria that included well differentiated tumors, superficial invasion, and no evidence of metastatic disease. Treatment was started within the first year following therapy in 57 percent of the patients. The dose of

conjugated estrogen therapy ranged from 0.625 to 1.25 for 25 days each month and 15 patients also took progesterone (34 percent). This study suffers from the same deficiencies as the Creasman report.

In a letter to the editor, Bryant³⁴ reported treating 20 patients with oral estrogen after treatment for endometrial cancer, beginning 18 to 24 months after surgery using daily doses of 0.625 mg conjugated estrogens. Nine patients received medroxyprogesterone acetate suspension (DepoProvera) prior to starting estrogen therapy. No mean or medium follow-up is given. Because these data are presented only as correspondence to the editor, it cannot be given credence beyond that of an anecdote.

In a review article, Baker³⁵ reported a small series of 31 patients who received estrogen replacement therapy between 1972 and 1988. The patients received a variety of oral, oral and vaginal, or transdermal estrogen therapy. The strict selection criteria resulted in a group that was

sue of nonrespondents, which can substantially bias a survey outcome.

In a Committee Opinion in August 1993, The American College of Obstetricians and Gynecologists concluded that there are no definitive data to support specific recommendations regarding the use of estrogen in women previously treated for endometrial carcinoma. The opinion states that estrogens could be used for the same indications as for any other woman, except that the selection of appropriate candidates should be based on prognostic indicators and the risk the patient is willing to assume. The need for progestational agents in addition to estrogens could not be evaluated by the Gynecologic Practice Committee due to the paucity of data.³⁶

Summary

In patients with hormonally sensitive tumors, estrogen replacement therapy carries a theoretical risk of stimulating recurrent disease as well as contributing to an


Long-term estrogen replacement therapy is associated with an increased risk of developing endometrial cancer.

at a very low risk of recurrence. This preliminary data is presented in a summarized format.

A survey of members of the Society of Gynecologic Oncologists indicated that 83 percent of respondents approved of estrogen replacement therapy in stage I, grade 1 tumors; 56 percent favored using estrogen in the case of stage I, grade 2 tumors; and only 39 percent favored using estrogen in patients with stage I, grade 3 tumors. This survey has been used as a rationale for the safety of estrogen replacement therapy. However, it should be remembered that a survey is not a peer-reviewed mechanism of evaluating a treatment, and there is also the is-

increased risk of other hormonally related cancers. In women with hormone-related cancers, it is unknown if their inherently increased risk for other related cancers can be further increased by the administration of hormones. In genetically susceptible animal models, hormones have been shown to promote growth of hormonally sensitive cancers. The uncertainty and potential risk of hormone replacement therapy demonstrates the need for randomized, prospective trials to provide women with a reasonable basis for therapeutic alternatives. The most prudent approach with this population is to consider alternative treatments until the ongoing, randomized clinical trials

have been evaluated with adequate long-term follow-up. Until such time, nonhormonal alternatives to manage symptomatic patients should be employed. It is incumbent on physicians to educate

themselves and become adept in their use. Diet and exercise will have to be an essential component of the counseling provided to patients following cancer therapy. 

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UICC First International Meeting on Advances in the Knowledge of Cancer Management

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The International Union Against Cancer is organizing its first Cancer Management Meeting in Vienna from June 29 to July 1, 1997. The meeting will deal predominantly with selected topics where new knowledge has been acquired or progress made in understanding the molecular biology and/or treatment of the disease.

The program will offer important new information for clinicians and scientist working in oncology as well as for oncology nurses. It will provide an opportunity for direct interaction and exchange of ideas with lecturers of diverse professional backgrounds and for participation in workshops concentrating on breast, prostate, and colorectal cancers organized in parallel with the meeting.

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