Hormones and Breast Cancer

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Patients with successfully managed breast cancer have generally been denied subsequent exposure to increased levels of estrogen (endogenous or exogenous) based on the belief that exacerbation of the cancer would occur. The advent of oral contraceptives, the trend toward childbearing later in life, and the demonstration of the protective value of menopausal estrogen replacement therapy against osteoporosis and cardiovascular disease requires that this issue be reexamined. New information bearing on this subject includes the recognition of estrogen receptors, the isolation of youth rather than pregnancy as the factor resulting in poor prognosis, epidemiologic studies showing no increased risk of breast cancer in women using oral contraceptives or taking hormonal replacement therapy, the beneficial effect of pregnancy subsequent to successfully managed breast cancer, and the absence of an adverse effect of oral contraceptives upon established breast cancer. In view of the lack of evidence relating estrogen to exacerbation of existing breast cancer, it may be in the best interest of our patients to liberalize our attitude to renewed hormonal exposure in patients with successfully managed breast cancer.

The potential relationship between hormones and breast cancer was first realized by Beatson [*1*] in 1896 when regressions were induced in advanced cancer after oophorectomy. The relationship was further strengthened with the observation that breast cancer in pregnant women carried an especially bad prognosis [*2*]. This poor outcome was felt to be due to enhanced growth of breast cancer as a result of increased levels of endogenous hormones during pregnancy. In 1943, Haagensen and Stout [*3*] enumerated criteria of operability in breast cancer. As a consequence of his failure to cure pregnant patients with breast cancer, Haagensen considered breast cancer during pregnancy to be "categorically inoperable" and recommended only palliative radiation therapy.

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However, early studies regarding hormones and breast cancer were not carefully controlled with respect to patient age and eventual outcome, lacked information regarding estrogen receptor status, and introduced personal bias into recommendations regarding management of breast cancer as related to hormonal exposure. In light of the advent of oral contraceptives, demonstration of the protective value of estrogen replacement therapy against postmenopausal osteoporosis and cardiovascular disease, and the current trend toward childbearing later in life, the issue of breast cancer as it relates to hormonal exposure needs to be reassessed [*4*].

Under ideal circumstances physicians would choose to base recommendations to their patients upon results of prospective studies. Ethical and logistic considerations render randomized studies relating to pregnancy and breast cancer incapable of being performed. Other studies of the relationship of prolonged hormonal exposure and risk of exacerbating a preexisting breast cancer would yield results only after long periods of observation. An expedient that may be used is to review those situations in which patients with and without breast cancer are exposed to high levels of estrogen. If no increased risk of developing breast cancer were observed or no adverse effect upon prognosis of established breast cancer were demonstrated, then we may decide to liberalize our recommendations to patients regarding hormonal exposure subsequent to successfully managed breast cancer. Those situations in which patients are exposed to high levels of female hormones are (1) pregnancy coincident with breast cancer, (2) pregnancy subsequent to breast cancer, (3) breast cancer in both previous and current users of oral contraceptives, and (4) breast cancer in postmenopausal women receiving estrogen replacement therapy.

ENDOCRINE PHYSIOLOGY OF THE BREAST

Prior to embarking upon a consideration of the relation of hormones to breast cancer, a review of the endocrine physiology of the normal breast is in order. The human female breast, at full development, consists of a series of alveolae from which a ductal network extends to the nipple with interspersed fatty tissue and fibrous ligaments. The alveolae are lined by cuboidal or low columnar cells that enlarge greatly and discharge their contents into the ductal system during lactation. Small groups of alveolae are found enmeshed in fatty tissue with such clusters representing lobules. The ducts from several lobules combine into a larger duct that terminates in the nipple. Each secretory duct, of which there are about 20, with its secondary and tertiary ducts and accompanying alveolae represents a lobe.

Breast growth is largely dependent upon estrogen and progesterone. As indicated in studies utilizing oophorectomized animals, estrogen replacement stimulates ductal growth whereas progesterone is necessary for adequate

alveolar growth [5]. However, neither hormone alone or in combination is capable of yielding optimum breast growth and development. Full differentiation of the gland requires insulin, cortisol, thyroxine, prolactin, and growth hormone [6]. Changes occur routinely in response to the estrogen-progesterone sequence of a normal menstrual cycle. The rapid mammary growth during pregnancy is due to placental hormone-induced ductal proliferation associated with an increase in number and size of the alveoli. This glandular tissue displaces the connective-tissue stroma, so the total increase in functional breast tissue is far greater than external measurements would imply. This growth in preparation for milk production is largely secondary to increased circulating levels of estrogen, progesterone, and prolactin. The precise role of placental lactogen in pregnancy-induced mammary growth is at present unknown.

The estrogen-induced impetus to mammary epithelial stem cell division requires the presence of insulin. Final differentiation of the alveolar epithelial cell into a mature milk cell is accomplished in the presence of prolactin, but only after prior exposure to cortisol and insulin. The complete reaction depends on the availability of minimal quantities of thyroid hormone. Thus, the endocrinologically intact person in whom estrogen, progesterone, thyroxine, cortisol, insulin, prolactin, and growth hormone are available can have appropriate breast growth. Mild deficiencies in any of these hormones, short of severe restrictions or total absence, can be compensated for by excess prolactin. Furthermore, the growth of the breast and breast function can be incited by an excess of prolactin.

Milk production normally occurs only after parturition, in spite of the fact that all hormonal components necessary for lactation are present in the prenatal period. Apparently, high levels of sex steroids present during pregnancy block the action of prolactin on breast tissue. Thus, with the rapid fall of estrogen and progesterone at delivery, the blockade is lifted and milk production is stimulated. The maintenance of elevated prolactin levels requires intermittent suckling activity. Prolactin levels rise rapidly during routine suckling, thus stimulating additional milk production or secretion. The afferent limb of this reflex is neural and the efferent is hormonal. In the absence of suckling, prolactin levels return to normal nonpregnant state within 7 days after delivery. In summary, the hormonal requirements for breast development and function are complex, with varied interactions among active and permissive hormones.

PREGNANCY COINCIDENT WITH BREAST CANCER

Breast cancer is difficult to detect during pregnancy because physiologic enlargement tends to obscure the presence of new breast masses. In addition, patients and physicians often mistake a new mass in the breast as a normal consequence of pregnancy and delay medical intervention. Furthermore, the breast parenchyma increases in density during pregnancy, rendering mammography nearly useless. It should not be surprising that pregnant patients tend to present with more advanced disease than the average patient with breast cancer [7,8]. Yet early on it was recognized that pregnant patients without histologic axillary node involvement had a favorable prognosis and therefore were responsive to conventional therapy [9]. When pregnant patients with breast cancer have been compared with breast cancer patients of similar age and stage of disease, it was discovered that the additional factor of pregnancy did not confer a worse prognosis [10–12]. It is now recognized that the independent variable of youth results in an unfavorable prognosis in breast cancer patients presumably as a result of a more aggressive tumor in these young women [12]. Previously only young breast cancer patients have had the opportunity of having breast cancer coincident with pregnancy, although as women postpone childbearing the situation of pregnancy coincident with breast cancer will become more common. Physicians should treat pregnant patients with breast cancer aggressively and with curative intent. Primary care physicians should carefully monitor the breasts of their pregnant patients and obtain histologic information should a dominant mass appear.

In the past early pregnancy complicated by breast cancer was often terminated in the belief that there would be patient benefit. In fact, blood loss during radical mastectomy was less in the postpregnant breast when compared with the gravid state. It has recently been demonstrated that the majority of breast cancers developing during pregnancy are estrogen-receptor negative [12]. Therefore, very little long-term benefit could be expected by performing therapeutic abortion aimed at eliminating placental hormones. It was also hoped that prophylactic oophorectomy would benefit breast cancer patients. Women were offered castration and therapeutic abortion to minimize sources of endogenous estrogen. However, prospective controlled studies have failed to document benefit of prophylactic oophorectomy in breast cancer patients [13]. Therefore, termination of pregnancy in a patient with breast cancer should not be performed solely to improve patient outcome. Primary breast cancer may be well managed throughout the course of pregnancy by standard techniques. A patient close to term may wish to delay therapy of breast cancer until a healthy child can be delivered without risk of significant tumor dissemination in the interim.

Patients may choose to terminate an early pregnancy in the event of discovery of breast cancer. The majority of pregnant patients with breast cancer will have axillary node involvement. These node-positive patients will benefit from cytotoxic chemotherapy after primary therapy [14–17]. The chemotherapeutic agents are teratogenic to the embryo and may be harmful to the fetus [18]. The patient may elect breast conservation incorporating radiotherapy. Modeling of radiation exposure at our facility using phantoms with a target dose to the breast of 5,000 cGy reveals a dose to the uterus of 16 cGy ± 10 percent. Although the dose to the uterus is not large, it is teratogenic in the embryo and leukemogenic in the fetus. Other considerations in the decision whether or not to abort are philosophic issues relating to the care of the child by a

chronically ill mother or by a family in which the mother has died from breast cancer. Regardless of other considerations, therapeutic abortion should not be undertaken solely to eliminate placental estrogen, since pregnancy as an isolated factor does not appear to adversely affect prognosis of breast cancer.

PREGNANCY SUBSEQUENT TO BREAST CANCER

Haagensen [3] believed that pregnancy subsequent to breast cancer would have no unfavorable prognostic significance. He reasoned that if the cancer were completely removed, pregnancy would have no effect and that a residual focus of cancer would eventually doom the patient anyway. Modern concepts in oncology do not embrace such an all or none phenomenon and hold that small residue of cancer may be kept in check by host defense mechanisms. These mechanisms in breast cancer may be altered by changes in hormonal status, prompting physicians to recommend against subsequent pregnancy.

Enough women have become pregnant after treatment for breast cancer to allow several observations to be made. It has been generally noted that breast cancer patients who subsequently became pregnant have fared better than comparable patients who did not become pregnant [10,19,20]. A bias was likely introduced as women with poor prognosis were generally counseled against subsequent pregnancy. Women with recurrent breast cancer were unlikely to become pregnant. Women who succumbed to breast cancer early after their diagnosis have been compared with those women surviving long enough to become pregnant, suggesting that pregnancy was the cause of the prolonged survival rather than the result. This issue has been studied by eliminating these biases using careful case matching. These studies have demonstrated significant prolongation in survival in those women with breast cancer who became pregnant when compared with similar breast cancer patients who did not become pregnant [21].

At this point it is of value to review the hormonal therapy of breast cancer. It is relatively easy to conceive of a mechanism by which breast cancer arising from hormonally sensitive tissue may be influenced by deprivation of hormone (ablative hormonal therapy). This may be accomplished by castration, adrenalectomy, or hypophysectomy. Paradoxically, breast cancer has been found to regress after administration of estrogens, androgens, and progestational agents (additive hormonal therapy). The initial observation occurred after patients with breast cancer received hormones for treatment of unrelated, nonmalignant conditions. The mechanism of action of additive hormonal therapy is still not known. The best understanding is in the case of the weak estrogen, tamoxifen, which binds to a cytoplasmic estrogen receptor. The tamoxifen-receptor complex is unable to interact properly with nuclear DNA, resulting in the inability of the cell to produce vital molecules [22].

Current knowledge regarding estrogen receptors would suggest that an alteration in hormonal status in a patient whose tumor was receptor negative would not affect patient outcome. The correlation between positive estrogen receptor status and good prognosis would result in a larger proportion of estrogen receptor-positive patients with tumor surviving to a subsequent pregnancy [12]. The benefit of additive hormonal therapy in receptor positive breast cancer may be duplicated by pregnancy, accounting for the observed benefit. In any event, no harm has been documented to those breast cancer patients who subsequently became pregnant. Our recommendations regarding pregnancy and breast cancer should be guided by the knowledge that recurrence is always possible and that the well-being of a family whose mother has breast cancer should be considered.

ORAL CONTRACEPTIVES AND BREAST CANCER

If oral contraceptives were carcinogenic with respect to breast cancer, then breast cancer patients with a documented predisposition to develop the disease should not be offered these medications. Yet an ample number of studies have failed to point to any increase in incidence of breast cancer in users of oral contraceptives [23–25]. A single study suggested a relationship between the use of combination type oral contraceptives with a high progestogen content and an increased incidence of breast cancer, although questions about the methodology of the study have been raised [26]. After extensive review of the subject, the Food and Drug Administration has concluded that there is no increased risk of breast cancer in users of oral contraceptives [27].

Another question remains regarding the use of oral contraceptives in women with established breast cancer. With the realization that breast cancer may originate and remain occult for years before presentation as a mass, large numbers of women with primary breast cancer may have been exposed inadvertently to oral contraceptives during the inception and evolution of their tumors. When these women were examined and compared with breast cancer patients of similar age who had never used oral contraceptives, a trend towards earlier stage at presentation in users of oral contraceptives was observed [28,29]. This trend was attributed to surveillance bias by which women receiving regular medical care were scrutinized more carefully than women not using oral contraceptives. Women who had used oral contraceptives in the past were intermediate in terms of stage of presentation when compared with current users and women who had never used oral contraceptives. The trend towards earlier stage at detection did not generally translate into better survival for recent users of oral contraceptives.

A single retrospective review of the outcome of breast cancer patients who were recent users of oral contraceptives when compared with nonusers demonstrated a significant improvement in survival when matched by stage [30]. Although the numbers were small, the report undermines the possible significance of surveillance bias by citing data stating that 95 percent of breast cancers were discovered by the patient or her husband rather than by the physician [31]. Nonetheless, there has been no evidence to suggest that recent use of oral contraceptives by

patients discovered to have breast cancer has an adverse effect on outcome.

BREAST CANCER AND HORMONAL REPLACEMENT THERAPY

Noncontraceptive estrogens were first marketed in the United States in 1942. Since that time, there has been extensive use of these medications as estrogen replacement therapy for the relief of menopausal symptoms. Numerous studies have attempted to evaluate the risk of developing breast cancer in women using estrogen replacement therapy. The vast majority of these studies have failed to demonstrate any significant increase in incidence of breast cancer related to estrogen replacement therapy [*32–34*]. There has even been a suggestion that estrogen combined with progestational agents may afford a degree of protection against the development of breast cancer [*35*]. Some subgroups may be at slightly increased risk of developing breast cancer associated with estrogen replacement therapy. These are women who have undergone surgical menopause and then receive estrogen replacement therapy [*36–38*]. However, the increase in risk is slight and is of borderline significance. In those studies showing an increased risk in oophorectomized women receiving estrogen replacement therapy, the risk was elevated to about the same level as that of women entering menopause naturally [*39*]. The possible risk of developing breast cancer is probably outweighed by the improvement in quality and duration of life in women receiving hormonal replacement therapy [*33,38,39*].

In conclusion, there is no substantial evidence that there is any association between high levels of female hormones, whether endogenous or exogenous, with increased risk of development of breast cancer or exacerbation of preexisting breast cancer. Therefore, when women who have had breast cancer request information regarding the use of oral contraceptives, risk of subsequent pregnancy upon their disease, or the use of estrogen replacement therapy for relief of menopausal symptoms, the answer should be tempered by current available information as reviewed here. Since freedom from recurrent breast cancer can never be guaranteed, there will be breast cancer patients who will develop recurrence coincident with renewed hormonal exposure. In this era of excessive medical litigation, there will be the understandable reluctance to offer exogenous estrogens to women with a history of breast cancer based on traditional, albeit unfounded, information. Patient and physician education will be necessary to change these patterns of therapy. As long as breast cancer patients are informed that there is no evidence that estrogen has an adverse effect upon established breast cancer, it seems appropriate to allow these women to lead more normal lives as related to renewed hormonal exposure.

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