Estrogen Replacement Therapy (ERT) in High-Risk Cancer Patients

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Menopausal estrogens are now being prescribed not only for symptom relief, but also to prevent the long-term sequelae of estrogen deficiency, namely osteoporosis and atherosclerotic disease. The well-established association between endometrial cancer and estrogen replacement therapy (ERT) has become less of a clinical concern due to the recognition of the protective effect of progestogens in this setting. A small literature has emerged suggesting that extending ERT to the woman with a history of endometrial carcinoma imposes no increased risk of recurrence and may improve survival. Candidates for ERT should be women with a better prognostic profile with reference to their cancer.

The relationship between ERT and breast cancer remains a topic of intense debate and investigation. Overall, the current literature finds no significant increase in risk among healthy women without a family history of breast cancer. There are no guidelines with reference to the woman with a history of breast cancer and the use of ERT. The most prudent approach with this population is to consider alternative treatments until more is known.

BACKGROUND

It has been over 15 years since the first retrospective, case-control studies were published which causally linked estrogen replacement therapy (ERT) with the development of endometrial cancer [1-3]. The ensuing publicity led to a significant decline in the use of such preparations. Fortunately, over the last decade, prodigious research into the menopause has elucidated much about the biology of the female climacteric and its clinical consequences. As the human life span lengthens, the full effect of ovarian hormonal decline is only beginning to be appreciated.

The available literature is replete with data supporting the use of menopausal estrogens. Relief of the menopausal syndrome (i.e., vasomotor instability, genitourinary atrophy, and so on) is a well-established benefit of ERT [4]. Moreover, the best anti-resorptive protocol for the treatment of post-menopausal osteoporosis is ERT [5-10]. The beneficial effect of such treatment is often unappreciated unless one considers the following: (1) 25 percent of women over 60 years of age have radiographic evidence of vertebral crush fractures; (2) women who suffer hip fractures have a mortality rate 20 times that expected for age; (3) during the 1980s the cost for proximal femur fractures in the U.S. exceeded $3 billion annually [11].

Abbreviations: CHD: coronary heart disease ERT: estrogen replacement therapy SHBG: sex hormone binding globulin

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Of even more staggering clinical significance is the burgeoning literature suggesting that ERT may be protective against coronary heart disease (CHD) [12–29]. Among these studies with considerable variability in design, population, definition of estrogen use, and end-point, the vast majority (greater than 80 percent) demonstrated a reduction in the risk of CHD among estrogen users of 30 to 50 percent or greater. Indeed, this beneficial effect is biologically plausible, inasmuch as estrogens have a marked anti-atherogenic effect on lipids and lipoproteins and do not adversely affect other risk factors for CHD, i.e., obesity, blood pressure, clotting factors.

The complex clinical picture which emerges in the older post-menopausal women combines menopausal changes with age-related disease processes. Is longevity—as well as quality of life—enhanced by ERT? Several investigators have looked at estrogen use and overall mortality [22,24,25,26,28,30,31,32]. Consistently estrogen use was associated with a substantial reduction in mortality, which generally reflected reduced deaths from acute and chronic sequelae of occlusive atherosclerotic vascular diseases. In a recent report by Henderson et al., 8,881 post-menopausal residents of a retirement community in southern California were followed for 7½ years: not only was estrogen use associated with protection from atherosclerotic disease, but mortality from cancer was also reduced, although not to a statistically significant degree [32].

Recognition of the benefits just outlined has resulted in a 43 percent increase in estrogen prescriptions dispensed in the United States, from 14 million in 1980 to 20 million in 1986. As women become more aggressive consumers of medical care, the interest in menopausal estrogens has increased dramatically. The lay press has consistently “followed” the medical literature regarding ERT and further intensified public debate. “Absolute contraindications” for the use of estrogens, a list which was historically of mammoth proportion, now include: (1) pregnancy; (2) history of estrogen-sensitive neoplasia; (3) active hepatic disease; (4) active thromboembolic disease; (5) undiagnosed genital bleeding. This review will focus on our current knowledge regarding the risks associated with ERT in a high-risk population—women with a history of endometrial or breast carcinoma. Many of these women are suffering from severe vasomotor symptoms and the sequelae of genitourinary atrophy. Moreover, among those with a good prognosis for survival, the long-term consequences of estrogen deprivation are as significant as those among women without a cancer history.

ENDOMETRIAL CANCER

Estrogens as Trophic Hormones

As early as 1923, Allen and Doisy characterized estrogens as primary trophic sex hormones [33]. There is currently abundant biochemical and morphological information available which clarifies the relationship between sex steroids and the endometrium.

Estrogen diffuses across cell membranes and is bound in the cytoplasm to a specific receptor protein [34,35]. As discussed by Peterson et al., estrogenic activity at the cellular level is dependent upon the relative affinity of the hormone for estrogen-receptor protein [36]. Estradiol appears to be the most potent stimulator of cell biosynthesis, although stimulatory effects are noted with estrone. The most impor-
TABLE 1
Risk Estimates from Case-Control Studies of Estrogen Replacement Therapy and Endometrial Cancer

| Study | Relative Risks* |
|-------|-----------------|
|       | Ever Users | Long-Term Users |
| Smith | 1975 | 4.5 | — |
| Ziel  | 1975 | 7.6 | 13.9 |
| Mack  | 1976 | 5.6 | 8.8 |
| Gray  | 1977 | 3.1 | 11.6 |
| McDonald | 1977 | 2.0 | 7.9 |
| Wigle | 1978 | 2.2 | 5.2 |
| Horwitz | 1978 | 12.0 | — |
| Hoogerland | 1978 | 2.2 | 6.7 |
| Antunes | 1979 | 6.0 | 15.0 |
| Weiss | 1979 | 7.5 | 8.2 |
| Hulka | 1980 | — | 4.2 |
| Shapiro | 1980 | 3.9 | 6.0 |
| Jelovsek | 1980 | 2.4 | 4.8 |
| Spengler | 1981 | 3.2 | 8.6 |
| Stavraky | 1981 | 4.2 | 14.4 |
| Kelsey | 1982 | — | 8.2 |
| LaVecchia | 1982 | 2.7 | — |
| Henderson | 1983 | 1.4 | 3.1 |

*Risk relative to never-users
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Tant direct clinical consequence of estrogen stimulation of cell biosynthesis/ proliferation is the potential for endometrial hyperplasia.

The risk of developing endometrial hyperplasia increases with increasing dosages of estrogen. Moreover, hyperplasia can progress to adenomatous hyperplasia and then atypical adenomatous hyperplasia. The latter has been reported to be a pre-malignant lesion [37,38]. Nearly 50 percent of 115 women with hyperplasia studied by Wentz developed adenocarcinoma during a two- to eight-year follow-up [39]. Of the 75 women with adenomatous hyperplasia, 76.7 percent developed adenocarcinoma. Of 22 women who had atypical adenomatous hyperplasia, 81.8 percent developed cancer.

Menopausal Estrogens and Endometrial Carcinoma

Endometrial cancer rates did not change significantly in the U.S. from the 1930s until about 1970 [40]. Several epidemiologic studies have demonstrated, however, that as the sale of non-contraceptive estrogens increased in the early 1970s, so did the incidence of endometrial carcinoma [41–45]. Moreover, in three of these reports the converse was also reported: as sales declined, fewer cases of endometrial cancer were identified [41,44,45].

Needless to say, these observed trends do not verify a causal relationship. Case-control studies abound on this topic, however, and the results have supported similar conclusions (Table 1). The majority were conducted in the U.S. and employed unopposed conjugated estrogens as the estrogen treatment schedule. Estrogen use (compared to non-use) was associated with a twofold to fifteenfold increased
risk of developing endometrial cancer. Higher risk was observed with higher dosages and longer duration of treatment [1–3,46–61].

The value of case-control studies in measuring the association between exposure and disease has been questioned due to the inherent biases found in these designs [36]. Fortunately, Hulka et al. [53] and Shapiro et al. [54] selected cases and controls in a fashion designed to limit selection bias. They found that selection bias does not entirely account for the observed association between estrogen use and endometrial cancer. Moreover, these authors also controlled for confounding (i.e., factors associated with both estrogen administration and endometrial cancer are distributed equally between cases and controls) variables. In addition, most of the studies listed in Table 1 included large enough sample sizes to make it unlikely that the increased relative-risk estimates are secondary to chance.

Several cohort studies have evaluated the effect of non-contraceptive estrogen use on the risk of developing endometrial cancer [12,37,44,61]. Although most of these studies include a relatively small number of women with endometrial cancer, they generally concur with the findings of the case-control studies.

What emerges from the cohort studies is the effect of progestogens in modulating the growth-promoting effect of estrogen on the endometrium. For example, Gambrell et al. found that estrogen-progestogen users had an incidence of endometrial cancer of 56 per 100,000 women-years, much lower than the incidence of 359 per 100,000 women-years among estrogen users alone and even less than that observed in women not receiving any ERT (248 per 100,000 women-years) [37]. The biologic plausibility of these clinical observations is substantiated by extensive work showing that progestogens reduce the number of available estrogen receptors and promote the conversion of estradiol to the weaker steroid, estrone, through induction of 17-beta estradiol dehydrogenase [62,63]. The addition of progestogens to the treatment schedules of post-menopausal women on estrogen lowers the nuclear estradiol-to-estrone ratio relative to that observed in women treated with unopposed estrogen [64]. Moreover, Nordqvist has shown that endometrial cells exposed to progesterone in vitro have reduced synthesis of DNA and RNA [65]. Finally, Whitehead and colleagues have shown that in vivo stimulation of post-menopausal endometrium by estrogens cannot only be modified by progestogen treatment but that the progestogen effect is dependent upon dose and duration [63].

These observations form the framework upon which current clinical practice is based regarding the use of progestogens with menopausal ERT. This topic has recently been extensively reviewed by Whitehead et al. [66].

Substantial evidence suggests that women with adenocarcinoma of the endometrium associated with estrogen use have a considerably better long-term prognosis compared to non-users with this malignancy. The data which support this observation come from separate areas of investigation. To begin with, numerous published reports indicate that endometrial cancer in a setting of estrogen use is generally of low stage, low grade, and demonstrates less myometrial invasion [3,47,51,53,59,67]. In addition, several investigators have demonstrated that women with endometrial cancer who have used menopausal estrogens prior to their diagnosis have a survival advantage from all causes of death [67–70]. As noted by Schwartzbaum et al. in their recent investigation, the survival advantage of estrogen use is not solely due to selection bias (i.e., women selected to use estrogen are healthier and would have lived longer regardless of estrogen consumption) [70]. In this report, as well as one by
Collins et al., the risk of death from all causes was two to three times greater for women who did not use estrogen (Fig. 1) [69,70]. In contrast, Robboy and Bradley [71] and Smith et al. [72] found that when histologic grade was added to the model, the survival advantage for estrogen users was nullified. As addressed by Schwartzbaum et al., however, the studies by Robboy and Bradley and Smith dealt with a small number of deaths, and therefore these reports may not have the statistical power to detect survival advantage among estrogen users after histological grade was controlled. Moreover, an argument for not adjusting for this variable is that estrogen is responsible for the development of a less aggressive cancer. If early stage and lower grade are the results of a biologic process leading to a more curable disease, then stage and grade are intervening variables and should not be controlled [70]. Schwartzbaum et al. also point out that estrogen use might cause a women to be examined earlier and therefore have her neoplasia diagnosed at a more treatable point [70]. This possibility would make stage and grade confounding variables to be controlled for in the design model. These authors exercise extreme caution in their study and control for stage and grade. Regardless, they found a survival advantage for estrogen users which becomes more pronounced as estrogen use is extended beyond 3.5 years.

Estrogen Replacement Therapy (ERT) and Endometrial Cancer Recurrence

Compared to the voluminous literature just summarized, the available "data" on the use of ERT in women with previous endometrial carcinoma stands in sharp contrast (Table 2). The therapeutic dictum that estrogen is contraindicated in this population is not based on any investigative work regarding the biological effects of ERT on endometrial carcinoma. Indeed, the initial clinical data suggest that there is no increase in recurrence or mortality. Treatment of this patient population exemplifies the complexities often faced in clinical practice regarding risk:benefit ratio considerations.

Table 2 summarizes published reports to date which have attempted to investigate the relationship between ERT and endometrial cancer recurrence. These observa-
### Table 2
Effect of Estrogen Replacement Therapy on Endometrial Cancer Recurrence

| Investigator          | Subjects (n) | Stage IA | Stage IB | Stage II | Grade I | Grade II | Grade III | Myometrial Invasion | Interval to Treatment Post-Surgery (months) | Duration Follow-Up on ERT (months) | Recurrence |
|-----------------------|-------------|----------|----------|----------|---------|----------|-----------|-------------------|--------------------------------|----------------------------------|------------|
| Baker [73]            | 31          | —        | —        | —        | —       | —        | —         | —                 | 0-120                           | —                                | 0          |
| Bryant [74]           | 20          | 19       | 1        | 13       | 7       | 0        | —         | —                 | 18-24                           | 42-168                           | 0          |
| Creasman et al. [75]  | 47          | 30       | 17       | 0        | 29      | 13       | 5         | —                 | 0-81                            | 25-150                           | 0          |
| Lee et al. [76]       | 44          | 24       | 20       | 0        | 33      | 11       | 0         | —                 | 1- > 60                          | 24-84                            | 1          |
tional studies lend credence to the consideration of ERT in an individualized setting [73–76].

Creasman et al. studied 221 patients with stage I adenocarcinoma of the endometrium at the Duke University Medical Center [75]. Forty-seven women were placed on ERT in a non-randomized fashion. The entire group was followed for at least two years after cancer therapy or until death. Seventy-two percent of the ERT users were prescribed vaginal conjugated estrogens (0.625 or 1.25 mg every day for one month and then three times per week thereafter). The patients in this group received at least three months of estrogen and up to 84 months, with a median of 26 months. ERT was initiated 0 to 81 months after definitive cancer therapy (median interval, 18 months).

There was no statistically significant difference in the distribution of prognostic factors between the two groups: i.e., stage, grade, depth of invasion, nodal metastasis, peritoneal cytology, hormone receptor status. The authors note, however, that the “trends for several factors were toward more favorable disease status in the estrogen subgroup” [75].

There were 26 recurrences among the 174 (14.9 percent) non-users of estrogen whereas there was only one (2.1 percent) recurrence in the user population. Sixteen of the 27 recurrences among the non-estrogen users died from their disease. Ten patients in this group died of “intercurrent disease”: no further elaboration is provided by the authors. The single patient from the estrogen-treated group who succumbed from her disease recurred at 22 months. Her exposure to estrogen was brief (three months), approximately 18 months before her recurrence.

The authors of this report were clearly cognizant of the inherent weakness of their retrospective analysis compared to a prospective, randomized trial. Selection bias may well have influenced their findings; i.e., the length of time from primary treatment of the cancer to the initiation of ERT (median, 18 months) may have eliminated some women who would develop a recurrence. Given these methodological flaws, the authors employed statistical analysis to adjust for differences in the two groups based on prognostic factors associated with disease course and survival.

In summary, although this report deals with stage I disease only and may reflect results primarily in a population treated with estrogen after a specific disease-free interval from cancer therapy, their results have far-reaching implications. The significance, if any, of the predominant type of estrogen vehicle (vaginal cream) employed is unknown.

Recently, Lee et al. followed 144 patients with stage I disease over an 11-year period at Madigan Army Medical Center and Brook Army Medical Center [76]. Only patients considered at low risk for recurrence based on tumor grade (grades 1 or 2), myometrial invasion (less than one-half myometrial invasion), and metastatic disease (absent) were offered treatment. Forty-four selected patients were placed on oral estrogen therapy and followed for a minimum of two years. Twenty-five of these patients began ERT “within the first postoperative year”: no further details are available in terms of the time from surgery to initiation of estrogen. Fifteen were prescribed “a progestin” at some time during the observation; scheduling details (i.e., sequential versus continuous use) were not provided.

Among the estrogen users, there were no recurrences. This finding contrasts with the eight recurrences (8 percent) which occurred among the 99 non-estrogen users. What is quite noteworthy, however, is that the vast majority of the recurrences in this
group (seven out of eight) was found in a subgroup of 37 women with high-risk factors. Indeed, no significant difference was found between estrogen users and low-risk non-users. Eight deaths occurred from other diseases among the non-users: five of those were from myocardial infarction.

In summary, this report is in agreement with the previously discussed study of Creasman et al. [75]. Women with a low-risk profile for recurrence of endometrial carcinoma appear not to incur any increased risk from the addition of menopausal estrogens. This study takes note of the predominant non-malignant cause of death among non-users—myocardial infarction. Despite the very small number of patients in this subgroup, the clinical implications are overwhelmingly apparent. Twenty-five patients in the ERT group were treated less than one year after definitive cancer treatment. Again, this number is too small to make broad conclusions, but the suggestion that low-risk women may be early candidates for estrogen is inherent. In addition, these investigators studied women on oral therapy, which reflects the more general clinical practice.

Two other purely observational reports have also been published [73,74]. Baker followed 31 women with “an excellent prognosis for cure” who chose ERT due to menopausal symptoms and concerns about osteoporosis risks [73]. Ten of these women with “more advanced” disease, status post-surgery and radiation therapy, waited an average of 4½ years before commencing ERT. The remainder (21) began estrogen within 1.8 years of surgical treatment. The majority (23 out of 31) were prescribed oral estrogen. There have not been any recurrences among the estrogen users.

Between 1975 and 1988, Bryant followed 20 women who were treated with oral estrogen after definitive surgery for endometrial carcinoma [74]. Conjugated equine estrogen, 0.625 mg, every day was begun 18 to 24 months post-operatively. One to 11 years after initiating ERT, cancer recurrence has not occurred. Of note is the fact that, within this small population, seven women had grade II lesions and four women had invasion involving greater than one-third of the myometrium.

Conclusion

The evidence is quite clear that the benefits of estrogen use in terms of the prevention of osteoporosis and cardiovascular disease far outweigh the risk of endometrial carcinoma. The question raised by the previously discussed reports is whether ERT is contraindicated in the woman who has been treated for endometrial cancer. Clearly, the definitive study has not been done, i.e., a larger, randomized prospective design. The clinical data to date, however, appear to argue strongly against a pervasive clinical practice of eliminating these patients from treatment consideration.

Therapy needs to be individualized, based on the patient’s needs, her history as well as her course on ERT. The best candidate appears to be a woman with a profile suggestive of a better prognosis with reference to her cancer. Whether or not the risk for recurrence is reduced by waiting to initiate ERT for 12 to 24 months after definitive therapy is unclear—but such scheduling should further clarify a treatment candidate’s risk profile. The role of the progestogens in this setting cannot be clarified from the current literature. There is no data that these agents would reduce the risk for recurrent disease, and their effect on lipids and lipoproteins must be
considered seriously so as not to reduce the cardioprotective benefit afforded by ERT.

BREAST CANCER

Endocrine Considerations in Breast Growth and Development

The endocrine requirements for breast development and function are complex with varied interactions among active and passive hormones [77]. Breast growth at puberty is primarily dependent upon estrogen. The initial response in most young girls to increasing levels of estrogen is an increase in size and pigmentation of the areola and the formation of a subareolar mass of breast tissue. Estrogen is bound in the breast in a manner similar to that in the uterus and vagina [78]. Prolactin is required for the optimal development of estrogen receptors. In subprimate mammals, estrogen replacement stimulates ductal growth, whereas progesterone is necessary for adequate alveolar growth; however, full differentiation of the gland requires insulin, cortisol, thyroxin, prolactin, and growth hormone [78]. Mammary changes occur routinely in response to the estrogen-progesterone sequence of the normal ovarian cycle.

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. Minimal quantities of thyroid hormone are necessary to complete this development. As noted above, numerous hormones are required for appropriate breast growth, but mild deficiencies in any of these can be compensated for by excess prolactin.

Endocrine Considerations in Breast Cancer

Although the pathogenesis of breast cancer remains enigmatic, there is considerable evidence that endocrine factors play a critical role. The main indications for a hormonal contribution to the etiology of breast cancer in humans comes from epidemiologic studies showing a protective effect of early first pregnancy and early castration, and the negative effect of early menarche, late menopause, and nulliparity. It has also been postulated that normal estrogen stimulation and luteal inadequacy, characterized by diminished progesterone secretion, could explain the main epidemiologic features of the etiology of breast cancer [79]. Unfortunately, a causal relationship between hormones and breast cancer risk has been sought—but not found [80,81]. Many of the epidemiologic findings did not persist in cross-culture or single-culture studies, and population bias has been a persistent problem. Luteal phase inadequacy has not been found in young women at high genetic risk for breast cancer or in pre-menopausal women with breast cancer [82–84].

With advances in technology, numerous investigators have specifically attempted to understand and quantify the role of estrogen further. The only significant report on plasma estrogen levels in post-menopausal breast cancer was by England et al. [85]. Twenty-five breast cancer patients and 25 controls were studied, and it was found that estrogen levels were 30 percent higher in the former population. There have been at least five case-control studies investigating urinary estrogens in post-menopausal women with breast cancer [86–90]. These studies support the findings of increasing levels of estrogen in this patient population.
Recent work by Siiteri et al. [91] and Moore et al. [92] emphasize the theoretical importance of bioavailable estrogen fractions in the pathogenesis of breast cancer. Siiteri et al. investigated a small group of breast cancer cases and controls matched for age, weight, height, and menstrual status [91]. In both groups, they found that the known association between obesity, reduced sex hormone binding globulin (SHBG), and increased free estradiol (E$_2$) held. More important, they found that some "normal weight" breast cancer patients with normal SHBG levels had an elevated percentage of free E$_2$. These results, based on a small number of patients, suggest that, in the breast cancer population, serum-free E$_2$ may be elevated by factors unrelated to SHBG concentration.

Moore et al., looking at 38 post-menopausal women with breast cancer and 38 controls of similar age and weight, compared total and non-protein bound E$_2$ levels [92]. Breast cancer cases had significant higher levels of E$_2$ and non-protein bound E$_2$ than controls as well as significantly less SHBG. Indeed, the level of non-protein bound E$_2$ among the cases was nearly four times that of controls. Unfortunately, the interpretation of these results is difficult due to the fact that cases and controls were drawn from different populations.

The clinician attempting to treat post-menopausal women with estrogen is left with a contradictory literature regarding breast cancer pathogenesis, with only a modest potential for practical applications. The most useful information available involves the effect of exogenous as well as endogenous estrogens on breast cancer risk/recurrence. The following discussion summarizes current data which can be utilized in the context of management strategy.

*Pregnancy and Breast Cancer*

During pregnancy, the diagnosis of breast cancer becomes difficult due to the physiologic enlargement which tends to obscure the presence of new breast masses. Moreover, patients and physicians often incorrectly identify a new mass in the breast as a normal consequence of pregnancy, thereby delaying timely medical intervention. Mammography becomes almost useless due to the changes in breast parenchyma. All of these factors contribute to the observation that pregnant patients tend to present with more advanced disease than non-pregnant patients with breast cancer [93,94]. Yet despite these seemingly deleterious factors, it was recognized over 50 years ago that pregnant patients without histologic axillary node involvement have a favorable prognosis and were responsive to conventional therapy [95]. More recent work comparing pregnant patients with breast cancer to non-pregnant breast cancer patients of similar age and stage has found that the additional factor of pregnancy did not adversely affect prognosis [96–98]. The independent variable of youth—a factor associated with more aggressive disease—now appears to explain the unfavorable prognosis in many pregnant breast cancer patients [98].

Enough women have now become pregnant after treatment for breast cancer to allow for a limited literature regarding recurrence of disease. Several authors have noted that breast cancer patients who subsequently became pregnant have done better than comparable non-pregnant patients [96,99,100]. Unfortunately, a selection bias was probably introduced in these investigations, as women with a poor prognosis were generally counseled against subsequent pregnancy. In addition, women with recurrent cancer were unlikely to become pregnant. Misleading conclusions have also stemmed from the fact that women surviving long enough to become
pregnant were compared against women who succumbed to breast cancer early after diagnosis. Fortunately, this methodological flaw has been eliminated by using careful case matching. Indeed, Cooper and Butterfield compared women with a history of breast cancer who became pregnant to similar breast cancer patients who did not become pregnant and found a significant prolongation in survival in the former group [101].

Recommendations regarding pregnancy and breast cancer should be guided by the knowledge that recurrence is always possible. Wyle and DiSaia cautiously suggest that pregnancy may offer a benefit similar to additive hormonal therapy (i.e., tamoxifen) in women with receptor-positive tumors [77]. Considerably more investigative work, employing careful case matching, is required before management strategies can be generalized.

**Oral Contraceptives and Breast Cancer**

Oral contraceptives have been used widely since the early 1960s. A substantial body of literature currently exists on the relationship between oral contraceptive use and the risk of breast cancer. Numerous studies have failed to identify any increase in the incidence of breast cancer in this population [102-104]. Indeed, after an 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 [105].

In the context of considering estrogen use in high-risk populations, it becomes important to consider the record of oral contraceptive use in such groups of women. As discussed by Henderson et al., breast tissue mitotic rate, which increases during the luteal phase, is a significant determinant of a woman's breast cancer risk [106]. Theoretically, therefore, combination oral contraceptives, which stimulate the luteal phase of the cycle, may under certain circumstances increase the risk of breast cancer.

The "circumstances" of greatest significance would be those in which the woman's average breast tissue mitotic activity on combination oral contraceptives exceeds her "normal" activity. Specifically, late adolescence and the perimenopause have come under scrutiny because both periods are hallmarked by anovulatory cycles—just the right setting in which to identify an increased risk from the combination type of pill.

Five studies have specifically reported on the use of combination oral contraceptives in the perimenopausal population [107-111]. Although the range of reported relative risks was wide, all of these studies found some evidence of an elevated risk of breast cancer with such use. In the majority of these reports, the excess risk was seen in women age 46-60 [107-110]. In only one report was the excess risk observed in women over 50 [111]. Unfortunately, none of these studies dealt with the possible risk-modifying effect of specific oral contraceptive formulations. In fact, the significance of different formulations of combination oral contraceptives on breast tissue mitotic activity is not known. On a theoretical basis only, it can be presumed that those preparations with higher dosages of both estrogen and progestogen will have the greatest effect.

The other key period of consideration is late adolescence. Pike et al. recently found that long-term oral contraceptive use during this time carried with it a substantial increase in breast cancer risk [112]. Even more recent data, however, suggested that the greatest risk is imparted with oral contraceptive use before first full-term pregnancy [113].
Menopausal Estrogens and Breast Cancer

Although the risk of endometrial cancer associated with ERT is well established, the relationship between menopausal estrogen use and breast cancer is far less clear. Numerous studies have attempted to evaluate this issue and, overall, have failed to demonstrate any significant increase in breast cancer with ERT [114–140]. Unfortunately, the vast majority of these reports have dealt with small numbers of women, thereby limiting their statistical power to detect a difference between users and non-users of menopausal estrogen preparations.

Two recent studies have attempted to overcome this methodological issue and clarify conflicting epidemiologic observations by combining data from several reports using meta-analysis [141,142]. The latter is a systematic, quantitative means of combining data across studies to increase statistical power and to generalize results [143].

Dupont and Page, in their review, subdivided the literature based on type of endogenous estrogen prescribed, duration of use, and dosage [141]. They found a limited amount of data comparing types of menopausal estrogen. There is some suggestion, however, that estradiol products may be associated with an increased risk of breast cancer [125,131,144]. This risk was noted with estradiol valerate [144] and injectable estradiol [125] and therefore has little clinical applicability for most U.S. practitioners.

Dupont and Page found that several authors noted a modest, but persistent and statistically significant, trend of increasing risk with increasing duration of treatment [122,132,144]. Other authors, however, have failed to demonstrate any evidence of a positive duration-risk relationship [119,120,129,131–133,135,136,138], or they have found that breast cancer risk fluctuates inconsistently with increasing duration of treatment [125,140]. Key and Pike [145], noting that several negative studies employed hospital control groups, suggested that these reports may be affected by unknown biases. Two large, well-controlled studies have used population-based control groups, however, and failed to find an increased risk of breast cancer with increasing duration of estrogen use [135,136]. In the meta-analysis of Steinburg et al., breast cancer relative risk was increased to an estimated 1.3 (CI, 1.2–1.6) after 15 years of estrogen use [142]. These reviewers did not find an increased risk with five years or less of ERT. No report to date has been able to separate clearly the critical issue of latency of effect of menopausal estrogen use from the effect of duration of use. Thus, the current literature does not permit a definite conclusion to be made regarding the presence or absence of a positive duration-risk relationship. The contradictory results may be due, in part, to differences in dosages and types of treatment found among the studies.

In terms of the relationship between daily dosages of estrogen and breast cancer risk, the only worthwhile literature available concerns conjugated equine estrogen preparations [115,120–122,129,131,134,136,144]. Dupont and Page found that the combined relative risk for women who took 0.625 mg per day or less was 1.08 (CI, 0.96–1.2) [141]. Indeed, the results of all the relevant studies were mutually consistent [115,120–122,129,131,134,136,144]. The combined relative risk for women using 1.25 mg per day was also low. The individual relative risks from the latter studies differed significantly from each other, however, indicating that factors other than high-dose conjugated equine estrogen may affect cancer risk in some of these reports.
[141]. Although none of the estimated relative risks exceeded 2.0, the current literature does not permit confident conclusions regarding this treatment dose.

There are several other important issues which are worthy of note when considering menopausal estrogen use and breast cancer. In all instances discussed, however, the reader should remember that any conclusions based on the current literature reflect a myriad of patients, estrogen preparations, and treatment schedules.

Several studies have looked at breast cancer risks associated with ERT among women with histologic evidence of benign breast disease [121,134,136,138,139]. Four of these five studies found relative risks which did not differ significantly from 1.0 [134,136,138,139]. The study by Ross et al. [121] found an increased risk—but was based on only 14 women with breast cancer who had taken conjugated equine estrogens and also had a history of benign breast disease. Dupont and Page found that the combined relative risk of breast cancer from these studies was 1.16 (CI, 0.89–1.5). Moreover, the relative risks of the individual studies, overall, did not differ significantly from each other. Therefore, this meta-analysis provided considerable evidence that the elevation in breast cancer risk among women with benign breast disease is not greater than 50 percent. As concluded by Dupont and Page, a history of benign breast disease does not constitute grounds for denying women ERT [141].

Steinburg et al. found in their meta-analysis that the effect of ERT on breast cancer risk was enhanced among women with a family history of breast cancer (RR risk, 3.4; CI, 2.0–6.0) [129,132,134,147]. This finding is a critical point which requires further clarification, although, based on the current literature, these candidates for ERT should be considered high-risk for long-term therapy (greater than 15 years).

Colditz et al. recently reported on data collected from the Nurses' Health Study [150]. Female registered nurses were followed prospectively for ten years, thereby greatly reducing the potential for bias. Past use of estrogens, regardless of duration, was not associated with an increased risk of breast cancer; however, risk was elevated among current users (RR, 1.36; CI, 1.1–1.7). Of interest is the observation that current users of ERT who did not consume alcohol did not have an increased risk of breast cancer (RR, 0.99; CI, 0.62–1.60). Whether or not this finding is due to chance or a true interaction remains to be clarified. There is no strong evidence, to date, that estrogen users should be counselled against alcohol consumption.

It has been suggested that progestogen use with ERT will reduce the risk of breast cancer [127]. As eloquently discussed by Ernster and Cummings [148], there is no substantial evidence to support this treatment approach. Based on only ten patients, Bergkvist et al. suggested that progestogen use may increase cancer risk [144]. On a practical level, it is useful to remember that breast cell division is predominantly in the latter part of the menstrual cycle, when progesterone levels are high [149]. Therefore, not only is there no theoretical reason to believe that progestogens should decrease breast cancer risk, but the potential for negatively affecting lipids and lipoproteins and reducing the cardioprotection afforded by estrogen should take precedence.

Based on the current and admittedly inconsistent literature, it appears unlikely that ERT significantly increases breast cancer risk in the majority of healthy women. Issues such as dosage and duration of treatment need to be considered cautiously. Minimal dosages to relieve symptoms and prevent long-term sequelae should be utilized. Duration of treatment must be weighed against the more prevalent conse-
quences of estrogen deficiency such as hip fracture and, most important, CHD. Treatment strategies for women with a family history of breast cancer should be individualized. There is no evidence that short-term therapy for symptom relief poses a significant risk to this latter population.

**ERT and Breast Cancer Recurrence**

When faced with the dilemma of considering menopausal estrogen use for women with a history of breast cancer, there is no data upon which to base clinical strategy. On a purely theoretical basis, the available literature on breast cancer recurrence after pregnancy may offer some evidence that menopausal estrogens pose no risk to women whose cancer has a positive prognostic profile. Here the argument could be made that typical estrogen schedules "mimic" the early follicular phase milieu, with reference to estrogen levels, and should be considered "safer" than the endocrine environment of pregnancy. The clinical decision to act upon such theory must be individualized.

There exists a very modest literature suggesting that survival after the diagnosis of breast cancer is improved in the setting of prior non-contraceptive estrogen use [151–153]. Bergkvist et al. found that relative survival rate was significantly higher in patients who had received ERT. The most favorable course occurred in women, 50 years old or more, who were recent users, and corresponded to a 40 percent reduction in excess mortality [151]. Although these authors entertain the notion that their findings might be explained by direct biologic effects of estrogen on tumor characteristics, the effect of a number of confounding variables (i.e., selection bias: healthier women are given ERT) is undoubtedly significant in this setting. Indeed, this type of report does little to assist the clinician in decision making.

**Conclusion**

The complexities surrounding breast disease and menopausal estrogen use need to be separated, once and for all, from clinical experience with the endometrium and ERT. The established management strategy with reference to preventing the emergence of endometrial carcinoma in the setting of ERT—the judicious use of progestogens—has no corollary when considering breast cancer risk in the menopausal population. The literature on the latter topic, however, suggests that the risk:benefit ratio for most healthy women favors estrogen use. There are no guidelines for the woman with a history of breast cancer. If there is a candidate for ERT in this population, she is clearly the woman whose cancer has a better prognostic profile, i.e., negative axillary nodes, positive estrogen receptor status, at least five years' survival after definitive cancer therapy. Clinicians should be prepared to deal with alternative treatment modalities to help with symptom relief and alleviate other known risks for osteoporosis and CHD.

**SUMMARY**

Treatment strategies for the woman with a history of endometrial or breast cancer experiencing menopausal symptoms, or interested in preventing the long-term consequences of estrogen deficiency, remain a controversial area in health care. There are no established guidelines. One plausible cornerstone of management is choosing the "right" candidate for treatment—the woman with a profile suggestive of a better prognosis with reference to her cancer.
While the definitive, methodologically sound study has not been conducted involving either endometrial cancer or breast cancer patients, there does exist a modest literature regarding the former. These reports suggest that ERT does not increase the risk for endometrial cancer recurrence; however, critical controversies such as when to start after cancer treatment, what estrogen vehicle to use, and the role of progestins remain to be clarified.

There are no reports in the English literature on the use of ERT and breast cancer recurrence. Inferential support for the use of post-menopausal estrogens comes from generally poorly designed studies showing that breast cancer recurrence does not increase after pregnancy. It has been argued that the estrogen exposure with post-menopausal preparations should be far less “worrisome” than that found in the pregnant state. There is no clinical applicability to this postulate, and management needs to be individualized. It is imperative that women with a history of breast cancer be fully appraised of alternative treatment modalities.

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