Hormones and Breast and Endometrial Cancers: Preventive Strategies and Future Research

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A number of hormonal approaches for prevention of endometrial and breast cancers have been proposed. Because of the hormonal responsiveness of both tumors, much attention has focused on effects of exogenous hormone use. Although estrogens in hormone replacement therapy increase the risk of endometrial cancer, the disease is substantially reduced by long-term use of oral contraceptives. The issues with breast cancer are more complex, mainly because of a variety of unresolved effects. Long-term estrogen use is associated with some increase in breast cancer risk, and certain patterns of oral contraceptives appear to predispose to early-onset disease. With respect to estrogens, preventive approaches for both tumors would include use for as limited periods of time as possible. Addition of a progestin appears to lower estrogen-associated endometrial disease, but its effect on breast cancer risk remains less clear. Additional studies on effects of detailed usage parameters should provide useful insights into etiologic mechanisms. Other preventive approaches for endometrial cancer that may work through hormonal mechanisms include staying thin, being physically active, and maintaining a vegetarian diet. Breast cancer risk may possibly be reduced by extended periods of breastfeeding, restriction of intake of alcoholic beverages, remaining thin later in life, and being physically active. Additional research is needed to clarify the biologic mechanisms of these associations. The bridging of epidemiology with the biologic sciences should clarify many unresolved issues and lead to better preventive approaches. — Environ Health Perspect 103(Suppl 8):185–189 (1995)

Key words: prevention, hormones, neoplasms, endometrium, breast

Introduction

Both endometrial cancer and breast cancer have been shown to be hormonally responsive tumors. It is not surprising therefore that these tumors are affected by both hormone replacement therapy and oral contraceptive usage. Thus, a major focus of the present paper is on defining exogenous hormonal relationships for these tumors. Although much is known about their effects, a number of unresolved issues remain. Further information on effects would be useful in terms of promoting better recommendations for usage and clarifying etiologic mechanisms. Prevention has also been approached through alterations in lifestyle factors, most of which are thought to affect risk through hormonal mechanisms. Ultimately, however, prevention will depend on better understanding the biology of the tumors. Therefore, the final section of this paper will focus on future research priorities, which should integrate epidemiology with biochemical approaches.

Hormone replacement therapy consists of either estrogen alone or estrogen combined with a progestin. In the United States, the most commonly used menopausal hormones are conjugated equine estrogens and medroxyprogesterone acetate. Their use may be either short-term or long-term. Short-term use is for the relief of symptoms at the time of the menopause and may be for a few months or years. Long-term use is intended to prevent osteoporosis and fractures and cardiovascular diseases. To achieve maximum preventive benefit, hormone use should be, essentially, life-long. However, such usage may be associated with some adverse effects, including increased risk of both endometrial and breast cancers.

Oral contraceptives are for the most part combination products of an estrogen plus a progestin. The estrogen is either ethinyl estradiol or mestranol (the latter is metabolized in the body to the former), but the progestins are more varied. They are derived from either the 17-hydroxyprogesterone compounds (norethindrone is a prototype) or the 19-nor testosterone compounds. The latter have greater androgenic activity than the former.

Since the relationship of hormones to risk of ovarian and cervical cancers has been addressed elsewhere (M Pike, personal communication), the present review will focus on cancers of the breast and endometrium. However, it is worth noting that the risk of ovarian cancer can be substantially reduced by long-term use of oral contraceptives (*1*). Effects of hormones on cervical cancer remain less clear (*2*) because little research has been conducted on menopausal hormone relationships. More research has been conducted on the etiologic role of oral contraceptives, and some studies show that long-term use increases the risk of invasive cervical cancer. However, in the United States, where cervical cytology is commonly used, the precursor lesions are usually identified and treated well before invasive cancer develops. The possible risk of cervical cancer from oral contraceptives (or from any other cause) can essentially be eliminated with regular (every 1 to 3 years) cervical cytologic screening.

Endometrial Cancer

It has been well demonstrated that estrogens cause endometrial cancer at the doses normally consumed for either acute symptoms or long-term prevention. The effect is

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7–8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

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Abbreviation used: DNA, deoxyribonucleic acid.

duration dependent; i.e., longer use confers greater risk (*3–5*). Ten years of use can produce an 8- to 10-fold increase in risk. In some studies, cessation of use appears to be associated with a relatively rapid decrease in risk, although other studies suggest that elevated risk may continue for some time after discontinuation (*3–5*). In general, the disease produced is not an extremely aggressive cancer (*6,7*), but mortality, nonetheless, appears elevated (*8*).

Progestins have been shown to produce regressive changes in endometrial hyperplasia, a presumed precursor of endometrial cancer (*9*). This has led to widespread enthusiasm for combining estrogen therapy with progestins to combat carcinogenic effects. Although lower rates of endometrial hyperplasia have been seen among those receiving combined therapy than among women receiving estrogens alone, effects on endometrial cancer remain less clear. In one recent study (*10*), the addition of a progestin for 10 or more days each month considerably reduced endometrial cancer risk. Whether or not the risk associated with estrogens may be completely obliterated by the addition of progestins remains unresolved.

The situation with oral contraceptives and endometrial cancer is quite clear. Oral contraceptives reduce the risk of endometrial cancer, with the greatest benefit occurring among long-term users, whose risk is reduced by approximately half that of nonusers (*11–14*). Some studies have shown that this risk reduction persists for at least 5 years after cessation of pill usage (*13*), although other studies have found that the protective effect wanes within 3 years (*14*).

Breast Cancer

The issues with breast cancer are much more complex, since contradictory relationships have been derived from a number of diverse studies. Resolution of effects is especially important, since breast cancer is a very common disease and the mortality is high.

Because of the conflicting results, it is difficult to determine precise relationships with hormone use. However, it would appear from several studies that use of oral contraceptives may be associated with a relative risk of about 1.5 for breast cancers diagnosed at an early age (i.e., before age 45) (*15–18*). This excess risk appears to result from high risks among recent users and among women who either start using oral contraceptives at young ages (e.g., before age 20) or who use them for long periods (e.g., 8 years or more). Other oral contraceptive use characteristics and use by older women do not produce this increased risk as best as can be determined from available data.

Although there is contradictory evidence regarding the effect of estrogens on breast cancer risk, a number of studies suggest that long-term use (10 years or more) may result in increased relative risks of the magnitude of 1.4 to 1.8 (*19–24*). Some data suggest that current use may also be adverse (*24–26*), but many studies do not support such an effect. The effect of combined estrogen/progestin therapy is less certain because the experience in the United States with that regimen has not been sufficiently long (*27*). Data in this country are just now accumulating. However, unlike the endometrium, where progestins counteract the proliferative effects of estrogens, there is evidence that progestins cause mitogenic activity in breast tissue. Thus, there is reason to suspect that combined therapy may have very different effects on breast cancer risk than on endometrial cancer risk. In support of this are data from a Swedish study, in which the combined therapy was associated with more adverse effects than with estrogens alone (*28*). Additional studies in this country are needed to confirm the effects of this mode of therapy, which has become increasingly popular in recent times.

Prevention

Much attention has focused on preventing these cancers. More is known about preventing endometrial cancer than breast cancer, mainly because of the recognized importance of estrogens in the etiology of endometrial disease.

For endometrial cancer, one recommendation is quite straightforward; namely, menopausal estrogens should not be used. If hormones must be used, they should be used with at least 10 days of a progestin each month; up to 13 days may be better. Data are just beginning to emerge on the currently popular regimen of continuous, daily, low-dose estrogen plus progestin (*29*), but effects on either endometrial or breast cancer remain unresolved.

Additionally, since obesity is a well-recognized risk factor for endometrial cancer, staying thin is a preventive approach. This risk factor is also thought to operate through an estrogenic mechanism, since after menopause the primary source of estrogens is from conversion of androstenedione to estrone in adipose tissue. Obesity is also associated with higher conversion rates or elevated plasma levels of estrogen. Further, obesity is related to lower levels of sex hormone-binding globulin and more frequent anovulatory menstrual cycles (less progesterone). Dietary modification may also be effective in reducing the risk of endometrial cancer. Studies of vegetarians provide evidence that risk may be affected by modification in hormone metabolism. Thus, postmenopausal vegetarian women have been found to have lower urine levels of estriol and total estrogens, lower plasma prolactin levels, and higher serum values of sex hormone-binding globulin than nonvegetarian women (*30*). In line with evidence of effects on endometrial cancer risk of obesity and dietary patterns are recent data supporting a possible protective effect of physical activity (*31*). The relationship is biologically plausible, since physical inactivity is known to be involved in the development and maintenance of excess body weight. Further, inactive women have been shown to have higher serum estrogen levels than active women, even after taking differences in body weight into account (*32*). Finally, it is apparent that the risk of endometrial cancer can be lowered by certain childbearing patterns, since there are extensive data showing a low risk for women bearing many children and a high risk for nulliparous women. It is as yet unclear whether the biologic mechanism underlying the association with childbearing relates to changes in endogenous hormones.

The hormonally relevant strategies to prevent breast cancer are more complex than those for endometrial cancer. Although there are data to suggest that use of oral contraceptives at young ages or for long periods of time may be associated with some increase in risk, it appears that these usage characteristics may apply only to an increase in risk for a minority of breast cancers; namely, those occurring at young ages. Thus, these restricted risks must be weighed against recognized benefits of oral contraceptives in terms of pregnancy prevention and reduction of other diseases, including not only endometrial cancer but also ovarian cancer. Recommendations regarding the effects of use of estrogens are somewhat more clear and there is evidence that these agents should not be used for long periods of time. This recommendation results in the need to balance the risk of osteoporosis and cardiovascular diseases against breast cancer. There are many reviews evaluating the risk/benefit and cost effectiveness of

menopausal estrogen therapy (*33–36*). In all of these assessments, mortality from cardiovascular diseases outweighed the risk of death from breast cancer, although in some of the analyses the benefits may have been overstated because of selective use of estrogens by healthier women. Further, it is doubtful that these analyses fully describe the situation, since many women would rather not face an increase in breast cancer risk, even if it means increasing their risk of a heart attack on a larger scale.

Other therapeutic regimens that may alter breast cancer risk through hormonal mechanisms have received increasing enthusiasm. However, the proposed regimens are controversial and are currently being recommended as preventive agents in only very high-risk women. These include tamoxifen, which is currently being tested in a clinical trial among high-risk women (*37*). Tamoxifen is an antiestrogenic agent that has been shown in therapeutic trials to reduce the incidence of new primary cancers in the unaffected breast. Although the current status of this trial is uncertain because of observed increases in the occurrence of endometrial cancer among exposed women, the resolution of the preventive effect of this intervention on breast cancer risk is of great importance. Also of interest is the preventive effect of gonadotropin-releasing hormone agonists that are currently being tested as a possible preventive agent among younger women (*38*). The long-term effects of both of these agents, however, must be tested in large, randomized, controlled intervention trials before they can be introduced for general use.

There are a number of well-established risk factors for breast cancer, but most are not readily amenable to preventive mechanisms. These include higher risks for women with early ages at menarche, late ages at menopause, late ages at first birth, a family history of breast cancer, and a history of benign breast disease. In terms of preventable factors, much attention has focused on possible dietary means of lowering risk, but most studies to date have yielded inconclusive findings (*39*). Restriction of alcoholic beverage consumption is generally viewed as beneficial, although controversy still exists regarding whether the association is causal. Further, the levels of consumption associated with risk remain to be elucidated. There is, however, fairly convincing evidence that obesity somewhat increases the risk of postmenopausal breast cancer. Despite this, there has been a surprising lack of attention on weight loss as an interventive technique for lowering breast cancer risk. This may result from the complexities associated with body mass as a predictor of breast cancer risk, since large body mass has actually been associated with a reduction in the risk of early-onset breast cancer, possibly due to high levels of progesterone in thin, premenopausal women. Further complicating the interpretation of the role of anthropometric factors in the etiology of breast cancer is that the timing of weight change as well as the distribution of fat on the body has been shown to be predictive of risk (*40,41*). Several studies have emphasized the importance of change in recent weight, possibly reflecting its role in adult adiposity. There is also accumulating evidence that fat distribution may predict breast cancer risk among postmenopausal women, with abdominal obesity being more hazardous than peripheral accumulation. Further, recent results support the possible importance of physical activity in preventing breast cancer (*42*). Adolescent physical activity has been shown to be particularly important in reducing risk, possibly through a delay in the onset of menarche. Thus, the interrelationships of body size, diet, and physical activity obviously merit further research. Finally, recent attention has focused on avoidance of certain environmental factors (most notably, pesticide residues) (*43*) as a means of breast cancer prevention, although much further research is needed to clarify how risk might be affected.

Like endometrial cancer, breast cancer has been shown to be influenced by reproductive patterns. The age at first birth has been shown in many studies to be an important determinant of risk. Since this is not a readily modifiable lifestyle factor, it is encouraging that recent studies are showing some consistency regarding a protective effect of breastfeeding on breast cancer risk (*44,45*). However, some studies support that breastfeeding may only protect against premenopausal breast cancer, and it remains unclear whether the limited durations of breastfeeding of most women in the United States will be sufficient to alter breast cancer risk. Nonetheless, given the widespread potential for this intervention, it is obvious that further exploration of its preventive mechanisms regarding breast cancer should be pursued.

Future Research

To be successful in gaining new information for prevention, our research strategies must change. We should increase our efforts in molecular/biochemical epidemiology. This field combines rigorous epidemiologic study designs with the technology and innovation of molecular biology. Molecular epidemiology allows for study of cellular and molecular alterations in somatic tissue (the target tissue for cancer) and in germline tissue. In somatic tissue, there are opportunities to study markers in precursor lesions or in cancer tissue. Precursor lesions are of particular interest in etiology and pathogenesis. Markers found in precursor lesions can be related to those identified in invasive cancers as well as to hormonal interventions and other risk factors identified through more traditional epidemiologic methods.

Endogenous hormones represent a biomarker that is being increasingly examined with respect to the etiology of endometrial and breast cancers. Endometrial cancer is a particularly appropriate cancer to approach from a biochemical/epidemiologic perspective, since there is such clear evidence of the influence of ovarian hormones on risk. A unified theory of how risk factors might operate through one common hormonal pathway has been suggested (Figure 1) (*46*). It is apparent, therefore, that many of the risk factors produce higher levels of estrogen exposure without the compensatory effects of progesterone. However, there are many important gaps in our knowledge that inhibit a full understanding of the proposed carcinogenic process. Integration of biochemical markers with epidemiologic risk factors may help to answer a number of important unresolved questions. For instance, mechanisms of action of dietary factors, body fat distribution, and physical activity may be better understood by correlating these risk factors with patterns of endogenous hormones.

From cancer tissue, homogeneous case groups can be defined by specific alterations analogous to the concept of uniform histologic case groups and exposures of interest can be examined within each subgroup. This approach can provide means of identifying molecular signatures of many types of exposures and the definitive evidence needed to clarify cause-and-effect relationships. For instance, in breast cancer, one approach to differentiating disease has been to examine risk factors by estrogen receptor status. Most studies that have evaluated prior estrogen use by estrogen receptor status have found no significant differences, although several studies showed that estrogen users were more likely to have estrogen

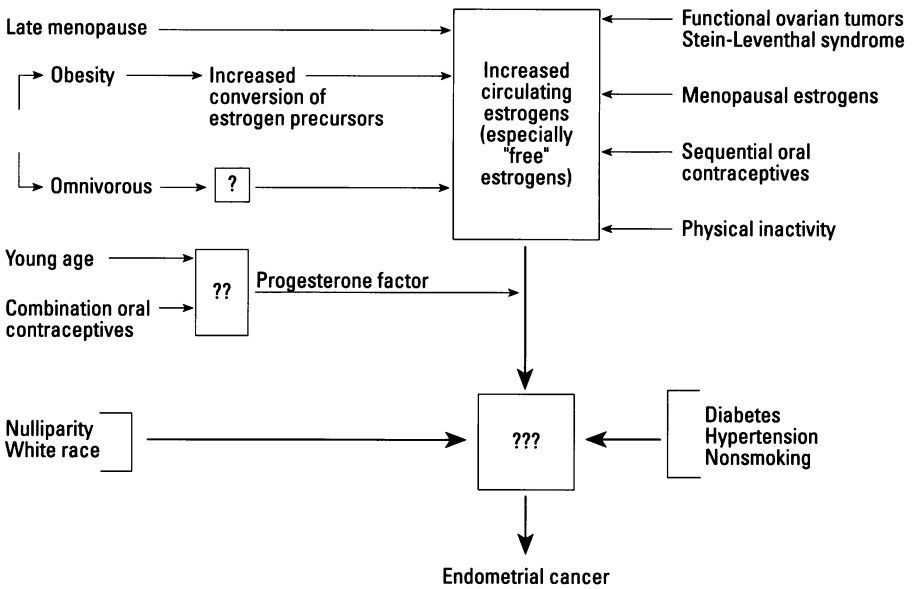

Figure 1. Risk factors for endometrial cancer and their possible modes of action.

receptor-negative tumors (*47–49*). These studies, however, by only considering estrogen receptor status and not also progesterone receptor status, may have missed distinctive relationships. Thus, future studies that precisely define breast cancer by a variety of biologic parameters may provide further insights into hormonal mechanisms of carcinogenesis.

Germline tissue provides a different kind of information and has a different import for epidemiologic studies. The DNA from germline tissue can provide evidence of genetic alterations that may enhance susceptibility to cancer or other diseases. White blood cells frequently are analyzed for susceptibility markers because they are reasonably accessible. Through analysis of cellular and molecular alterations in germline tissue, we can study the interaction of susceptibility markers and epidemiologic risk factors such as hormonal exposures for their combined effect on cancer risk. With respect to breast cancer, identification of the BRCA-1 and *p53* tumor suppressor genes holds promise as a potential modifier of other, more traditional risk factors.

For epidemiologists to join forces with laboratory scientists, a significant amount of bridging work is needed. This requires transitional epidemiologic studies that employ biochemical or molecular markers from human tissues or fluids and that bridge the gap between innovative laboratory technology and assays that can be used in population-based epidemiologic research. These studies address laboratory issues of quality control, assay accuracy and replicability within and across laboratories, feasibility, and standardization. The epidemiologic issues concern tissue collection acceptable to subjects, and specimen transport and storage consistent with the needs of the laboratory. Unless time is devoted to these types of studies, we will have many failures and waste significant amounts of scientific energy and resources.

Last, attention must be focused on translational research. The synthesis of knowledge from multiple scientific disciplines to develop and undertake a research agenda should bring us closer to solving problems than would be achieved merely by approaching issues through the vision of a singular discipline. It is also the rationale for and means by which the prevention trials of promising strategies and agents can be designed and operationalized. The potential for application of research findings to the reduction of human cancer incidence must be an important criterion for our research agenda.

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