Established Breast Cancer Risk Factors

Various risk factors for breast cancer have been recognized for many years. Table 1 lists these established breast cancer risk factors together with the approximate magnitude of the increase in risk associated with them (1). Among the demographic variables, breast cancer incidence rates increase with age throughout the life span in Western countries, although the rate of increase is greater up to age 50 years than after 50 years. Breast cancer is more common among women in upper social classes than among women in lower social classes, among women who have never been married than in women who have been married, among women living in urban areas than in rural areas, among women living in the Northern United States than in the Southern United States, and among whites than blacks, at least among those over 50 years of age.

Women in North American and Northern European countries have the highest risk for breast cancer; women in Southern European and Latin American countries are at intermediate risk, and women in African and Asian countries have the lowest risk. However, rapid rates of increase in incidence rates have been noted in recent years in many Asian, Central European, and some South American countries. Most of the increase thus far has occurred in women under the age of 50 years, but it is likely that the increase will persist throughout life as the younger generation ages. If the increases in incidence rates in young women in these previously low-risk countries continue throughout their life span, then it is predicted that the annual worldwide incidence of breast cancer will be over 1,000,000 cases by the year 2000 (2).

Among reproductive variables, the later the age at which a woman has her first full-term pregnancy, the higher is her risk for breast cancer; the earlier the age at menarche and the later the age at menopause the higher is the risk; and, among women who have a premenopausal oophorectomy, the earlier the age at which this occurs the lower is the risk. Also, among postmenopausal women, obesity is associated with an increase in risk, probably because of the greater rate of conversion of androstenedione to estrone in the adipose tissue of obese women and the lower levels of sex hormone-binding globulin in obese than in nonobese women.

Evidence from many studies over the years has indicated that lactation is negatively associated with subsequent breast cancer risk only because the length of lactation is associated with the number of full-term pregnancies, which is in turn associated with age at first full-term pregnancy (1). However, a few recent studies (3, 4) have suggested that lactation may have an independent protective effect against breast cancer in premenopausal women when effects of other risk factors are taken into account in the statistical analysis. These recent findings merit further study. Some studies (5–8), but not others (9–11), have reported that a history of induced or spontaneous abortions is associated with an increased risk for breast cancer. Occasional reports that age at last pregnancy (12) or total number of pregnancies (8, 10, 11, 13, 14) have independent effects on breast cancer risk need to be evaluated in additional studies.

Other factors known to increase the risk for breast cancer include a family history of breast cancer, especially if it is premenopausal or bilateral in a first-degree relative, a history of cancer in one breast, a history of fibrocystic breast disease, a history of a primary cancer in the ovary or endometrium, and a history of radiation to the chest in relatively large doses.

It may be noted in Table 1 that most of the established risk factors for breast cancer are associated with only a modest increase in risk. In fact, the American Cancer Society (15) has estimated that only about one-fourth of breast cancer cases can be accounted for by known risk factors. Thus, much of the etiology is still unexplained, and hitherto unidentified risk factors remain to be identified. Also, the mechanisms by which most of the established risk factors have their effects have not yet been elucidated. To what extent, then, is current research filling these gaps? What are the areas of greatest research interest at present?

Areas of Current Research Interest

Some current research is considering potential risk factors that have not been well studied in the past, including alcohol consumption, cigarette smoking, caffeine consumption, exposure to DES, emotional stress, exposure to electric power, and lack of physical activity. Other research seeks to obtain more detailed knowledge about risk factors previously identified, such as a family history of breast cancer, a history of hormones or other substances, and other factors known to increase the risk for breast cancer. Still other epidemiological research seeks to clarify the role of agents strongly suspected from animals or other types of evidence to be etiologically involved, but for which the human epidemiological evidence is weak or inconsistent. Included in this category are a high-fat diet, use of oral contraceptives, use of estrogen replacement therapy, and endogenous hormones.

Cigarette Smoking, Caffeine, Emotional Stress, Electric Power Use, and Physical Activity

Among the agents upon which interest has only recently been focused, cigarette smoking and caffeine consumption do not appear promising as potential etiological agents. Evidence for a protective effect of cigarette smoking (16), possibly mediated through smoking-related changes in estrogen metabolism and age at menopause, has been contradictory and inconclusive (17–20), and at most the effect is small. Caffeine consumption does not appear to be related to breast cancer risk (21–25),
consistent (42, 46–48). Unreliable reporting, inconsistent measurements of alcohol intake, and the difficulty of accurately quantifying alcohol consumption represent the most likely explanations for the varied results. Inappropriate control groups and lack of assessment for the possible confounding effects of other dietary factors in some studies may also have contributed to the inconsistent findings (50).

While future studies are unlikely to eliminate misclassification with respect to exposure, the use of standardized questions for measuring alcohol intake and consistent assessment of potentially confounding variables would help to resolve some of the conflicting findings. Other issues that merit attention include the timing and duration of alcohol exposure. Drinking before the age of 30, regardless of later consumption, was found to increase the risk of breast cancer in one recent study (47). Further confirmation of this finding is needed to determine whether the age at which drinking began is an important factor.

Whether it is the alcohol or some other characteristics of women who drink alcoholic beverages that brings about the reported increase in risk remains uncertain. Knowledge of the mechanism by which alcohol has its effect would make the association easier to interpret. Possible mechanisms that have been suggested include interference with cell membrane permeability in breast tissue (51), exposure to circulating cytotoxic products of ethanol (52), and altered hepatic function, which in turn could affect hormone metabolism (53). Furthermore, if a specific component of alcohol can be implicated, this might suggest other agents with similar biochemical properties that might also be risk factors.

Use of Diethylstilbestrol during Pregnancy

Several studies (54–57) have reported that women who used DES during pregnancy subsequently have an elevated risk for breast cancer (see Table 3). The magnitude of the relative risks in these studies has been around 1.5 and generally increases with increasing estimated dose of the DES. Although it was not possible in some of the studies to separate out the effect of DES from an effect related to the reason DES was prescribed (in most cases, to prevent spontaneous abortion), the evidence is suggestive of a causal association. Some would argue that this is of little significance because DES is no longer used for the purpose of preventing spontaneous abortions. However, this observation may be important in that it suggests that exposure to high doses of certain agents over a short but critical time period (e.g., during a period of rapid growth of breast tissue during pregnancy) may increase the risk for breast cancer. This would suggest that epidemiological research into breast cancer etiology should pay more attention to potentially critical times of exposure, even though the exposure may have been of limited duration.

Genetic Studies

The extent to which the increased breast cancer risk among women with an affected first-degree relative (58–67) is attrib-

### Table 1 Risk factors for breast cancer in females

<table>
<thead>
<tr>
<th>Factor</th>
<th>High risk</th>
<th>Low risk</th>
<th>Magnitude of risk differential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Old</td>
<td>Young</td>
<td>&gt;&gt;&gt;</td>
</tr>
<tr>
<td>Country of birth</td>
<td>North America, Northern Europe</td>
<td>Asia, Africa</td>
<td>&gt;&gt;&gt;</td>
</tr>
<tr>
<td>Socioeconomic class</td>
<td>Upper</td>
<td>Lower</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>Marital status</td>
<td>Never married</td>
<td>Ever married</td>
<td>&gt;</td>
</tr>
<tr>
<td>Place of residence</td>
<td>Urban</td>
<td>Rural</td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td>Northern U.S.</td>
<td>Southern U.S.</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Black</td>
<td></td>
</tr>
<tr>
<td>Age at first full-term pregnancy</td>
<td>Older than 30</td>
<td>Younger than 20</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Body build, postmenopausal</td>
<td>Obese</td>
<td>Thin</td>
<td></td>
</tr>
<tr>
<td>Age at menarche</td>
<td>Early</td>
<td>Late</td>
<td></td>
</tr>
<tr>
<td>Age at menopause</td>
<td>Late</td>
<td>Early</td>
<td></td>
</tr>
<tr>
<td>Family history of premenopausal bilateral breast cancer</td>
<td>Yes</td>
<td>No</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>History of cancer in one breast</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>History of fibrocystic disease</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Any first-degree relative with breast cancer</td>
<td>Yes</td>
<td>No</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>History of primary cancer in ovary or endometrium</td>
<td>Yes</td>
<td>No</td>
<td>&gt;&gt;</td>
</tr>
<tr>
<td>Radiation to chest</td>
<td>Large doses</td>
<td>Minimal exposure</td>
<td>&gt;&gt;</td>
</tr>
</tbody>
</table>

### Table 2 Adjusted relative risk for breast cancer according to level of daily alcohol intake

<table>
<thead>
<tr>
<th>Alcohol intake (g/day)</th>
<th>Adjusted relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>1.0</td>
<td>0.8–1.3</td>
</tr>
<tr>
<td>1.5–4.9</td>
<td>1.0</td>
<td>0.7–1.2</td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1.3</td>
<td>1.0–1.6</td>
</tr>
<tr>
<td>≥15.0</td>
<td>1.6</td>
<td>1.3–2.0</td>
</tr>
</tbody>
</table>

### Table 3 Relative risk for breast cancer according to time since exposure to diethylstilbestrol while pregnant

<table>
<thead>
<tr>
<th>Time since exposure (yr)</th>
<th>Relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>1.0</td>
<td>0.3–3.0</td>
</tr>
<tr>
<td>10–19</td>
<td>1.1</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>20–29</td>
<td>1.6</td>
<td>1.0–2.4</td>
</tr>
<tr>
<td>30–39</td>
<td>2.5</td>
<td>1.1–5.8</td>
</tr>
<tr>
<td>All exposed</td>
<td>1.4</td>
<td>1.1–1.9</td>
</tr>
</tbody>
</table>

* Adapted from Ref. 57.
utable to genetic as opposed to environmental factors is not known. Heredity has been found to be important in at least some families, however. In a few pedigrees, predisposition to breast cancer development appears to be inherited in a dominant fashion (68). The recently reported finding that families with ataxia-telangiectasia, an autosomal recessive syndrome, have an excess of breast cancer lends further credence to the hypothesis of a genetic component in some families (69). Linkage analysis showing that the glutamate-pyruvate transaminase locus may be linked to an allele that increases susceptibility to breast cancer (70, 71) has not been replicated in subsequent investigations (2, 72). However, the new DNA technology utilizing probes for possible marker genes may enable further elucidation of the role of genetics in breast cancer etiology.

Benign Breast Diseases

Since benign breast disease encompasses a broad spectrum of histological changes, breast cancer risk has been further evaluated according to the histopathological characteristics of the biopsy specimens (73–80). Growing evidence indicates that the elevation in breast cancer risk may be limited to women with proliferative disease (73, 76–80), particularly the small proportion of women with atypical hyperplasia who have been estimated to have approximately a 5-fold increased risk of breast cancer (76–80). Calcification in the biopsy specimens (73, 80) and possibly large breast size (81) may further increase the risk in women with proliferative disease. A family history of breast cancer and late age at first birth (or nulliparity) have also been suggested to be more important risk factors in women with proliferative disease than in those who have nonproliferative lesions (80, 81).

Additional studies are needed to confirm the finding that the risk of breast cancer among women with benign breast diseases is largely confined to the subgroups with proliferative disease. In addition, further assessment of interactions among breast cancer risk, proliferative disease status, and other established risk factors may not only improve identification of high-risk groups but also provide clues regarding underlying mechanisms.

Mammographic Parenchymal Patterns

Wolfe (82, 83) proposed that mammographic parenchymal patterns are highly predictive of subsequent breast cancer. Four patterns (N1, P1, P2 and DY) were described on the basis of the relative amounts of fat, ducts, and densities seen on xeromammograms. Although subsequent studies of Wolfe's classification have not yielded consistent results (84–92), sufficient evidence exists to indicate that the most dense patterns (P2 and DY) are associated with relative risks of approximately the same magnitude as well-established risk factors for breast cancer (93). The associations between parenchymal patterns and recognized breast cancer risk factors have also been explored. Several studies have shown an inverse association with parity (87, 89, 94–96, 98, 99), a positive association with age at first birth (84, 94–96, 98, 99), and an inverse association with body weight (92, 95, 99–101), but no consistent results have been observed for other established breast cancer risk factors.

The existing data suggest that parenchymal patterns represent an additional risk factor but not a major marker for future occurrence of breast carcinoma. Since some of the inconsistent results may reflect lack of standardized methods for classifying mammograms (93), more rigorous adherence to Wolfe's system may clarify some of the discrepancies. Additional studies of the relationship between parenchymal patterns and other breast cancer risk factors, including the histopathological features of benign breast lesions, may further our understanding of the role of mammographic patterns in breast cancer development.

Radiation

It is widely accepted that relatively high doses of ionizing radiation can cause breast cancer, but questions have remained regarding the shape of the dose-response curve, the importance of age at exposure, and the length of the latency period. Past estimates have suggested a straight-line relation between dose and radiation-induced breast cancer (102–106) but, apart from the studies on atomic bomb survivors (107), empirical data demonstrating a breast cancer excess at low doses are lacking (108–110). With respect to age at exposure, it was traditionally believed that the susceptibility of the breast to the carcinogenic effects of radiation was maximal between the ages of 10 and 20 years while breast tissue is rapidly developing and decreased after age 30 with little or no risk before age 10 or after age 40 (102–104, 106, 111, 112). However, two groups of investigators have recently reported excess breast cancer risks among women who were below the age of 10 at the time of the exposure (113–115). Since the excess risk was not apparent until the women had reached the age at which breast cancer rates normally increase, these data also support the previous observation that younger women may have a longer latency period than older women (106). Questions about the risk of low-dose exposure, age of exposure, and latency periods are of considerable interest in light of the frequent use of diagnostic radiography and the growing use of mammography for breast cancer screening. While current estimates suggest that diagnostic radiography has a small effect on the occurrence of breast cancer (116) and substantial evidence indicates that mammography screening programs reduce breast cancer deaths in women age 50 or older (117–121), further research needs to refine the risks of routine radiography as well as establish the risk-benefit ratio for mammography in younger women.

Diet

Dietary fat has long been suspected of playing a role in the etiology of breast cancer. This suspicion stems from animal data (122, 123), marked international correlations between per capita fat "disappearance" data and breast cancer incidence and mortality rates (124), migrant studies (125), and temporal increases in breast cancer incidence paralleling higher rates of fat intake (126, 127). However, many other factors could explain these differences in breast cancer incidence rates over time and geographic area, and the applicability of animal studies to human studies is uncertain. Thus, the results of these positive studies should at most be considered suggestive.

In contrast, Table 4 shows results from one of the recent prospective cohort studies in which fat intake is slightly negatively associated with breast cancer risk. In general, epidemiological data suggest that a high intake of dietary fat is associated with an increased risk of breast cancer while a low intake is associated with a decreased risk.

<table>
<thead>
<tr>
<th>Quantile of intake</th>
<th>Age-adjusted relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (low)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.6–1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.6–1.1</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.6–1.0</td>
</tr>
<tr>
<td>5 (high)</td>
<td>0.8</td>
<td>0.6–1.1</td>
</tr>
</tbody>
</table>

* Adapted from Ref. 138.
logical case-control and cohort investigations have found either weak associations (either positive or negative) or no association between fat intake and breast cancer risk (128–138). In these studies, however, measurement of diet may be so inadequate that a real association may be missed. A study of vegetarian nuns in the United Kingdom found that the nuns did not have lower breast cancer mortality rates than single women in the general population (139), although perhaps other pertinent differences existed between the nuns and other women. In summary, the role of a high fat diet in breast cancer etiology is uncertain, but if it is a risk factor, it is unlikely to be a strong one.

The effect of diet on endogenous hormones that may be involved in the pathogenesis of breast cancer has been explored, but the results thus far are either inconsistent or need further confirmation (140–145). Recent studies (146, 147) have similarly failed to support the hypothesis that low dietary selenium intake is associated with an increased risk of breast cancer (148).

It is also plausible that total calories consumed is the most important dietary characteristic. Some animal evidence supports this possibility, and in humans total calories could influence breast cancer risk through its effect on obesity and age at menarche (50).

If diet is related to breast cancer, not only will it be important to identify the specific etiological components of diet but also the age at which such dietary constituents have their effect. If the effect of diet is mediated by age at menarche, then little is to be gained (with respect to breast cancer risk) by changing the diet of older women. If the role of diet is primarily as a late stage promoter, then young women may indulge to their hearts’ content and alter their diet when they reach middle age. Designing epidemiological studies to test dietary hypotheses is exceedingly difficult. Given the likely extent of measurement error, observational studies are likely to be inconclusive. Given the probably small or moderate association at most between diet and breast cancer, randomized trials require such large sample sizes as to be almost prohibitively expensive. Thus, it is difficult to suggest what directions epidemiological studies should take. Further research elucidating biochemical and metabolic mechanisms may provide additional information about the likelihood that a high-fat diet affects breast cancer risk.

Oral Contraceptives

Perhaps the greatest interest and greatest controversy in breast cancer epidemiology has surrounded the questions of whether use of oral contraceptives and use of estrogen replacement therapy affect risk for breast cancer. Regarding oral contraceptive use, almost all studies find that in the vast majority of women, oral contraceptive use neither increases nor decreases the risk for breast cancer (5, 10, 149–169). However, whether certain subgroups of women have their risk increased if they use oral contraceptives is controversial. Among the subgroups for which evidence is at least suggestive, but nevertheless inconsistent, are women with a history of biopsy-proved benign breast disease (7, 149, 150, 160, 162, 170), women who use oral contraceptives at an especially late age (46–55 years of age) (166), and women who use oral contraceptives at an especially early age (<20 years of age) and/or before their first pregnancy (7, 10, 170–174). It is difficult to separate effects of use at an early age from use before the first pregnancy because these two variables are so highly correlated.

Particular concern (and controversy) has been focused on the subgroup of women who use oral contraceptives very early in their reproductive years. Some studies have shown an adverse effect from use at an early age or use before the first pregnancy (7, 10, 170–174) (see Table 5, for instance), while others have not (164, 175–178). In both camps, some studies have been well designed, while others have had methodological deficiencies. Various possible reasons for these discrepant results have been proposed, such as varying patterns of oral contraceptive use in different geographic regions (179, 180), different calendar years of introduction of oral contraceptives in various geographic regions and thus limitations of the possible latency period in some areas (180–182), inadequate methods of analysis (179, 183–186), different oral contraceptive formulations in different time periods and places (179), differential response rates (187), greater surveillance for breast disease in oral contraceptive users (185), different methods of interviewing cases and controls (188, 189), and inappropriate control groups (183). However, in our view, none of these explanations is likely to account for the differences among at least some of the better designed studies, yet we are unable to suggest any better explanations. Recently, McPherson et al. (173) have presented data suggesting that long-term use at an early age of compounds with ethinylestradiol as the estrogen may be associated with an increase in risk and that a latent period of 15–20 years is needed before the increase in risk is seen. This hypothesis needs to be evaluated in other sets of data that include sufficient numbers of women who have used oral contraceptives for relatively long periods of time at a young age.

In addition, a recent Scandinavian study has reported an association with long-term use (>12 years) of oral contraceptives regardless of whether oral contraceptives were used before the first pregnancy (180). It has been suggested that oral contraceptive use began on a large scale earlier in Sweden than elsewhere and that other geographic areas will show this increase in risk with long-term use when more time has elapsed. However, data from New Zealand, in which oral contraceptive use began earlier than in Sweden, do not show this increase in risk with long-term use (178).

It appears to us that at least three important questions remained unresolved with regard to oral contraceptives and breast cancer: (a) Does very long-term use (for instance, 15 years or more) increase the risk? (b) Does use at a very young age increase the risk? (c) Do the specific constituents of the oral contraceptives make a difference? To answer these questions, more time is needed to allow assessment of risk in a large enough number of women who have used specific oral contraceptives for very long periods of time or who started use at very young ages. Use at very young ages could represent one of the critical time periods mentioned above.

Estrogen Replacement Therapy

Likewise, the literature on use of estrogen replacement therapy and risk for breast cancer is inconsistent, and again the

<table>
<thead>
<tr>
<th>Duration of use (mo)</th>
<th>Adjusted relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neve</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1–12</td>
<td>1.0</td>
<td>0.5–1.9</td>
</tr>
<tr>
<td>23–48</td>
<td>2.0</td>
<td>1.0–3.8</td>
</tr>
<tr>
<td>≥48</td>
<td>2.6</td>
<td>1.3–5.4</td>
</tr>
</tbody>
</table>

* Adapted from Ref. 173.

* Adjusted for age at first term birth, age at menarche, menopausal status, history of benign breast disease, and family history of breast cancer.
elapse of additional time may be the main hope for resolving the controversy. Most studies (5, 149, 152, 153, 156, 190–196) have reported that estrogen replacement therapy does not increase the risk for breast cancer. Until recently, among the studies that have noted an increased risk (197–201), the elevation in risk has for the most part been seen only in certain subgroups. For instance, some investigators have found the increased risk only among those who have had a bilateral oophorectomy (197, 199), while others have noted the increased risk only in women with ovaries intact (200, 201). Such inconsistencies suggest that these findings in specific subgroups are probably attributable to chance. A few studies (197, 199, 201, 202) have also noted that women with a history of biopsy-confirmed benign breast disease may be at particularly high risk if they also use estrogen, a finding difficult to interpret in light of the uncertainty as to what benign breast disease really is.

Two recent studies (202, 203) were based on large enough numbers of women who had used estrogen replacement therapy for 15 years or more that a possible effect in these very long-term users could be examined with some degree of power. One study (202) reported a relative risk of 1.5 among women who used estrogen for 20 years or more (see Table 6). The other study (203), based on case and controls of ages 20–54 years, found a relative risk of 1.7 in women with a bilateral oophorectomy who had used estrogen for 15 years or more and a relative risk of 2.0 in women who had undergone hysterectomy and had one or two ovaries intact and who had a similar duration of estrogen therapy. Numbers of very long-term users among women undergoing natural menopause were not sufficient for an effect to be studied. Although the former study found a significant trend with length of use, no such trend was apparent in the latter study. A trend with length of use was also noted in a case-control study from Italy (204), however. A few studies (195, 197, 201) have also suggested slightly increased risks with increasing doses of estrogen.

Current evidence thus indicates either that estrogen replacement therapy has no effect on breast cancer risk or that it has a modest effect (i.e., relative risk of less than 2.0) in women who have used estrogen for long periods of time or who have used estrogens at relatively high dosages. It is obviously important to determine whether or not risk is in fact somewhat elevated. Therefore, additional studies based on relatively large numbers of women who have used estrogen replacement therapy for 15 years or more are of highest priority. Whether addition of progesterin to estrogen has any effect on breast cancer risk also needs to be carefully monitored, inasmuch as studies to date have been inconclusive. Any effect of estrogen replacement therapy on breast cancer risk would have to be considered in conjunction with the established protective effect of replacement estrogen against osteoporotic fractures and the established increased risk for endometrial cancer, and the probably decreased risk for coronary artery disease.

### Table 6

<table>
<thead>
<tr>
<th>Yr of use</th>
<th>Adjusted relative risk</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>0.9</td>
<td>0.8–1.0</td>
</tr>
<tr>
<td>5–9</td>
<td>1.1</td>
<td>0.9–1.3</td>
</tr>
<tr>
<td>10–14</td>
<td>1.3</td>
<td>0.9–1.6</td>
</tr>
<tr>
<td>15–19</td>
<td>1.2</td>
<td>0.9–1.8</td>
</tr>
<tr>
<td>≥20</td>
<td>1.5</td>
<td>0.9–2.3</td>
</tr>
</tbody>
</table>

* Adapted from Ref. 202.

**Adjusted for age, type of menopause, and interval since oophorectomy.**

---

**Endogenous Hormones**

Finally, epidemiological studies have also been concerned with the possible etiologial significance and usefulness as markers of risk of different patterns of circulating endogenous steroid hormones and their metabolites, including estrone, estradiol, 2-hydroxyestradiol, estriol, androstenedione, testosterone, and progesterone, as well as blood levels of sex hormone-binding globulin and prolactin. Some recent evidence (205, 206) suggests that studies of hormone levels in serum need to be supplemented by measurements of hormone levels in breast fluid, since breast fluid estrogen levels may be 5 to 45 times higher than serum levels, and the levels in these different tissues are not correlated. As more is learned about measurement and storage issues and of how these hormones interact with each other, it is hoped that a clearer picture of the role of endogenous hormones will emerge. Studies of levels and metabolism of endogenous hormones and blood-borne steroid-binding proteins should lead to a better understanding of the mechanisms underlying the relation of known risk factors, such as age at first birth, age of menarche, and age at menopause, to the development of breast cancer.

Some studies have sought to determine associations of risk factors with development of tumors of different degrees of differentiation and estrogen receptor status. Such studies could shed light on the role of endogenous hormones in breast cancer etiology. Results of studies through 1985 have been reviewed by Stanford *et al.* (207). Unfortunately, other than an increasing proportion of estrogen receptor-positive tumors with increasing age, a higher proportion of estrogen receptor-positive tumors in whites than in blacks, and possibly a higher proportion of estrogen receptor-positive tumors in postmenopausal women than in premenopausal women independent of age, results regarding other established and potential risk factors have been inconsistent (207–214). Why different results have been obtained in various studies is unclear, but to date these studies have not increased our understanding of the relationship between endogenous hormones and breast cancer or of the mechanisms of action of established risk factors. In fact, it remains to be determined whether the estrogen receptor status of a diagnosed tumor is in any way influenced by exposures before the tumor developed or during early stages of tumor development, and whether the receptor status of a tumor reflects the receptor status of the cells from which the tumor arose. Likewise, it is not known whether the estrogen receptor status of normal cells affects the likelihood of cancer following exposure to a carcinogenic agent.

The correlation between estrogen receptor status and progesterone receptor status is sufficiently high that it has been difficult to separate any independent associations they may have with breast cancer risk factors (208).

### Summary of Suggestions for Future Directions

This brief review of results of recent epidemiological investigations suggests some additional approaches for future studies. First, the studies of the DES-exposed women and of oral contraceptive users suggest that the timing of exposure may be critical, since the possible effect of both these hormonal agents may be limited to specific time periods of rapid breast development. Studies of other possible etiological agents should also try to focus more on exposures during critical time periods. On the other hand, if such a critical period does not exist in postmenopausal women, then there may be little effect of...
hormones used at this time. Instead, exposure to higher than average levels of estrogen from estrogen replacement therapy or through greater conversion to estrogen in adipose tissue in obese women may result in only a modest elevation in risk and only after prolonged exposure, because of the relative inactivity of the breast at the time of exposure. Also, the effect of radiation and the possible effects of estrogen replacement therapy and oral contraceptives remind us of the long latency period that may be necessary before an effect is seen for at least some agents. Thus, studies with long-term follow-up and that include long-term users are important in studies of effects of hormones and other exposures.

Among the newly hypothesized etiological agents, it would seem that the possible protective effect of physical activity merits further study. An effect of physical activity has not been well studied in the past, and possible biological mechanisms have been postulated. With regard to alcohol, assessment of the influence of age when consumption began and duration of exposure as well as the identification of plausible mechanisms of action would aid in clarifying the role of alcohol consumption in breast cancer etiology.

Ongoing studies of benign breast diseases are aimed at addressing the question of subgroups at particularly high risk, and ongoing studies of radiation are addressing such questions as the risks from low-dose exposures and the latency period following exposure. The results of these studies will be awaited with interest.

Since it is virtually certain that endogenous sex hormones play a role in breast cancer etiology, continued study of their role with new and improved measurement techniques is obviously of high priority. Likewise, in those cases of breast cancer in which marked familial aggregation is seen, newly developed probes for marker genes will be useful.

Finally, it is also likely that exposures not studied to date are involved in breast cancer etiology, since known risk factors by no means account for the entire risk of breast cancer. Thus, new ideas are needed, particularly regarding exposures at critical time periods.

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Jennifer L. Kelsey and Gertrud S. Berkowitz


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