Estrogens and breast cancer
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Abstract
In this review, we summarize the epidemiologic evidence for the associations of oral contraceptives and postmenopausal hormones with risk of breast cancer. We also describe the biologic plausibility of these relationships. Overall, there appears to be little, if any, increase in risk with oral contraceptive use in general, even among users for 10 or more years. However, compared to never users, current oral contraceptive users appear to have a modest elevation in risk that subsides within about 10 years after cessation of use. For postmenopausal hormones, the weight of the evidence suggests little or no increase in risk among users of short duration, or for use in the past. However, current longer term use is associated with an increased risk of breast cancer that increases with duration. This increase in risk is large enough, and well enough supported, to be considered along with the other risks and benefits of postmenopausal hormone therapy.

Key words: breast neoplasms; estrogens; menopause; review

Biologic plausibility of an association of hormones with breast cancer risk
Several lines of evidence support the hypothesis that exogenous estrogens play an important role in the etiology of breast cancer. Rates of breast cancer increase rapidly in the premenopausal years, but the rate of increase slows sharply at menopause, when endogenous estrogens decline rapidly (Figure 1). Several reproductive variables that alter estrogen status also affect risk of breast cancer (Table I). For example, early age at menarche, and late age at menopause (reflecting prolonged ovarian function and estrogen production) are associated with increased risk of breast cancer.5,6 Dur-
Any use of oral contraceptives

In the pooled analysis, ever use of OCs was associated with a very modest increase in risk (RR = 1.07; 95% CI 1.04-1.11). Although this finding of only a very small increase in risk is reassuring, defining OC use this way is misleading because women in the “ever” use category include women with long and short-term use, so that any true relationship with one particular aspect of OC use may be missed.

Duration of use

Overall. Most studies have observed no significant increase in breast cancer risk with long durations of use (>5 years). In one meta-analysis where results from 10 studies were combined, the relative risk associated with 10 or more years of use was 1.14 (95% CI= 0.90-1.42). In a second meta-analysis, the relative risk was 1.1 for greater than five years of use when results were combined for either nine case-control studies (95% CI= 0.9-1.2) or four cohort studies (95% CI= 0.9-1.4). These results were from analyses where women of all ages were combined and provide considerable evidence against any material adverse effect of long-term OC use overall. Similar findings have generally been observed when long-term use was evaluated among either postmenopausal women or women over the age of 45 years.

Duration of use among young women. In several studies an elevated relative risk was observed among young women (generally less than 45 years) who used OCs for extended durations. In two meta-analyses, summary relative risks for long durations of use in young women were 1.5 and 1.4 (95% CI= 1.3-1.6). The greatest increase tended to be observed in the youngest women, generally women less than 35 years of age; this observation also was noted in several more recent case-control studies.

Several cohort studies also have evaluated these relationships. In the Oxford Family Planning Asso-
association study, over 17,000 women ages 25-39 years were followed for up to 19 years. No association was observed with increasing duration of use among women 25-44 years, although only 14 cases were <35 years of age. In the Royal College of General Practitioners cohort, 23,000 women who used OCs and 23,000 non-users were enrolled in 1968 and followed to 1985. Although little if any increase in risk was noted with increasing duration of use overall, a substantial increased risk was observed among women ages 30-34 years (e.g., relative risk of 10.2 for OC use of 10+ years relative to never use). However, these results must be interpreted cautiously as only 24 cases of breast cancer occurred among women ages 30-34 years, the follow-up rate in this cohort was low (as of 1985, less than 60% of the total possible number of person-years of follow-up was accounted for) and the incidence rate among the 30 to 34 year old women who did not use OCs was considerably lower than the age-specific national breast cancer rates. The largest prospective study of this association was the Nurses’ Health Study cohort. 121,700 women were enrolled in 1976 and have been followed every two years since that time. From 1976 to 1992 (during which time 3383 breast cancers were confirmed), no significant association was noted between duration of use and breast cancer risk either over, or among premenopausal women or women over 35 years of age. Similarly, in the pooled analysis, no substantial increase in risk with long-term OC use was noted among women 30 years of age and older.

Use before a first full-term pregnancy

Any influence of OCs on the breast was hypothesized to be greatest prior to the cellular differentiation that occurs with a full-term pregnancy. In two meta-analyses, the summary relative risk indicated a modest increase in risk with long-term use (RR= 1.7; RR= 1.4). However, results of the individual studies tended to vary substantially and in few of the studies was a relation noted between exposure duration and disease risk. Additionally, in several more recent studies, and in the large Nurses’ Health Study cohort, no increase in risk was observed specifically in relation to use prior to a first pregnancy.

Recency of use

Few studies have specifically evaluated the relationship between current or very recent use of OCs and breast cancer risk, but they generally have noted at least a modest increased risk relative to never users, suggesting that OCs may act as late stage promoters. In the Nurses’ Health Study cohort, current

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Table I

**Established hormonally-related risk factors for breast cancer**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comparison category</th>
<th>Risk category</th>
<th>Typical relative risk</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche</td>
<td>&lt;12</td>
<td>12 yr</td>
<td>0.9</td>
<td>Brinton et al., 1988</td>
</tr>
<tr>
<td></td>
<td>13 yr</td>
<td></td>
<td>0.8</td>
<td></td>
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<tr>
<td></td>
<td>14 yr</td>
<td></td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥15 yr</td>
<td></td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Age at birth of 1st. child</td>
<td>Before 20 yr</td>
<td>20-24 yr</td>
<td>1.3</td>
<td>White, 1987</td>
</tr>
<tr>
<td></td>
<td>25-29 yr</td>
<td></td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥30 yr</td>
<td></td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Age at menopause</td>
<td>45-54 yr</td>
<td>After 55 yr</td>
<td>1.5</td>
<td>Trichopoulos et al., 1972</td>
</tr>
<tr>
<td></td>
<td>Before 45 yr</td>
<td></td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Oophorectomy before 35 yr</td>
<td>BMI ≤21*</td>
<td>BMI ≥28</td>
<td>1.6</td>
<td>Huang et al., 1997 (in press)</td>
</tr>
</tbody>
</table>

*BMI= kg/m²; relative risks given are among never users of postmenopausal hormones.
users had a 50% higher risk than never users. This increased risk was not attributable to increased disease detection among current OC users.

In the pooled analysis, current and recent users of oral contraceptives had an increased risk of breast cancer (RR for current vs never users = 1.24; 95% CI = 1.16-1.34) which subsided within 10 years of stopping OC use (Figure 2). Importantly, the authors observed a modest increased risk of breast cancer only among current and recent OC users, and did not observe any independent effect of long durations of use on risk of breast cancer even among very young women. Thus, the increased risk of breast cancer observed among young (<35 yrs), long-term OC users in past individual studies was possibly due to recency of OC use rather than duration of use.

Type and dose of OC

Although the specific formulation of the OC might be important in determining cancer risk, studies of this issue are difficult because study participants may not be able to remember specific formulations; very large studies are needed to have enough statistical power to examine individual brands and, finally, no satisfactory classification system exists to categorize specific OC formulations by their effect on breast tissue. For these reasons, few studies have evaluated specific OC formulations in relation to breast cancer risk. The pooled analysis found no significant variation in risk between the specific types of OCs or with dose.

Progestin-only contraceptives

These contraceptives include progestin-only pills (“mini-pill”), depot-medroxyprogesterone (DMPA) and implantable levonorgestrel (Norplant). Although the progestin-only pill has been evaluated in few studies, to date, no increase in breast cancer risk has been observed for ever users (≥10 years of use) and, in the two studies where duration of use was evaluated (≥15 years), longer term users were observed to have a similar or lower risk of breast cancer compared to never users.

In the most comprehensive of DMPA, no significant increase in risk was observed with increasing duration of use, although both long-term users who began use before age 25, and users under age 35 overall were observed to have a modest increase in breast cancer risk. Norplant, a long-acting contraceptive which is implanted sub-dermally, was introduced in the United States in 1990. No epidemiologic data have been published on Norplant’s influence, if any, on breast cancer risk.

Results of epidemiologic studies have provided considerable reassurance that there is little, if any, increase in risk with OC use in general, even among women who used OC for 10 or more years. Accumulating data also suggest that long-term OC use prior to a first full-term pregnancy does not appreciably increase risk.

The finding from case-control studies, of an increase in risk among young women who used OCs for extended durations has not been confirmed by the larger prospective studies. In the recent pooled analysis, which included nearly all published studies) long-term use among young women was not independently associated with an increase in breast cancer risk. Rather current users and recent users (<10 years since last use) were observed to have a modest elevation in risk compared to never users. This relationship most likely could not be discerned from the individual studies, as duration of use, rather than recency of use, was often reported. Among young women, the long-term users are much more likely to be recent users such that a very large data set (such as the pooled analysis) was needed to determine the independent effect of these variables.

It is important to note that current and recent users, the group that appears to have a modest increase in risk, are generally young (<45 years) and thus have a low absolute risk of breast cancer. Hence, a modest increase in their risk will result in few additional cases of breast cancer. Nevertheless, this apparent increased risk among current and recent users should be fac-

**Figure 2. Relative risk of breast cancer by time since last use of combined oral contraceptives**

*Relative risk to never-users stratified by study, age at diagnosis, parity, age at first birth, and age at which risk of conception ceased*
ored into the overall decision whether or not to use OC.

**Postmenopausal hormone use**

**Prevalence of postmenopausal hormone use**

Postmenopausal estrogens have been used for over half a century. By the mid 1970’s almost 30 million prescriptions were being filled annually in the US. Both the formulations prescribed, patterns of use and delivery systems have changed substantially over time.

**Epidemiologic findings**

Estrogen only

The possible relation between postmenopausal estrogen use and risk of breast cancer has been investigated in over three dozen epidemiologic studies over the past 20 years. Most of these studies have been summarized in six meta-analyses. A summary of these findings, plus a more detailed discussion of several of the most important and most recent studies is provided below.

**Ever use.** All of the meta-analyses have concluded that overall, ever users of postmenopausal estrogens have little or no increase in risk of breast cancer compared with women who have never used this therapy. Depending upon the inclusion criteria for the meta-analyses, the relative risk estimates across studies range from 1.01 to 1.07 with narrow confidence limits.

**Duration of use.** In a meta-analysis limited to case-control studies, Steinberg et al. reported a 30% increase in risk with more than five years of use (Table II), and a 45% increase in risk after 10 years of use when combining results from the follow-up studies. In another meta-analysis, Colditz et al. calculated a summary relative risk of 1.23 (95% confidence interval 1.08-1.40) for ten or more years of hormone use. Sillerro-Arenas et al. found the same overall estimate, but when stratified by menopause type, the relative risks were somewhat higher: for more than 12 years of use, among women with a natural menopause, the relative risk was 1.32 (1.08-1.40), and for those with a surgical menopause, 1.63 (95% CI: 1.26-2.12). Grady et al. also calculated a relative risk of 1.25 (95% CI: 1.04-1.51) for eight or more years of use.

Results of several large studies have become available since the publication of these meta-analyses. The largest of these, in terms of number of cases, was a population-based case-control study of 3,130 cases and 3,698 controls. In that study, Newcomb et al. observed no significant positive association between postmenopausal hormone use and breast cancer risk, even among long-term users. With >15 years of estrogen use, the relative risk was 1.11 (95% CI: 0.87-1.43).

In another recent population-based case-control study, Stanford et al. observed no increase in risk regardless of duration of postmenopausal hormone use. Compared to never users, women using hormones for 12 to 14, 15 to 19 and >20 years had relative risks of 1.0 (95% CI = 0.5-2.0), 0.5 (95% CI = 0.3-1.0) and 1.0 (95% CI = 0.5-2.0) respectively. However, as with the study by Newcomb et al., the 95% confidence intervals included the elevated relative risks observed in the meta-analyses.

One difficulty in interpreting the results of case-control studies is the impact of nonparticipation, particularly among the controls. For example, in the Stanford study, the response rate among controls was approximately 70%. In the general population, estrogen users tend to have a somewhat higher socio-economic status on average, and, typically, better educated individuals are more likely to participate as controls in health-related research studies. Thus, if the responding controls were more likely to be estrogen users than the nonresponding controls, the observed relative risk may have been biased towards 1.0 (no effect). As any true increase in risk is likely to be small, even a modest bias in control participation could obscure the results.

Data from several recent cohort studies, also not included in the meta-analyses, are available. Initial results from the prospective Netherlands Cohort study of 62,573 women were recently reported. However, long-term use was uncommon, with only 14 cases in the category of five or more years of use. The relative risk in this category was 0.9 (95% CI = 0.4-2.1); these broad confidence intervals are clearly compatible with a wide range of true effects. Similar null findings with broad confidence intervals were observed among the small number of recent users.

Colditz et al. recently reported updated results from the Nurses’ Health Study. This is the largest prospective study conducted to date on this topic, with 725,550 person-years of follow-up among post-menopausal women, and 1,935 cases of newly diagnosed invasive breast cancer. In this analysis, because of the similar findings for estrogen and estrogen plus progestin use, results were presented for all hormone use combined. An excess risk of breast cancer was limited to women with current or very recent use of postmenopausal hormones. The risk increased with increasing...
duration of use, and was statistically significant among current users of five or more years duration (compared to never users: RR for 5-9 years of use = 1.36, 95% CI = 1.15-1.61; RR for >10 years of use = 1.47, 95% CI = 1.22-1.76).

**Recency of use.** Data on recency of use are more sparse because many studies did not distinguish current from past users. The Sillero-Arenas meta-analysis calculated a relative risk for current use of 1.63 for women with natural menopause and 1.48 for women with surgical menopause. Colditz et al. estimated a summary relative risk of 1.40 (95% CI = 1.20-1.63) comparing current to never users.

In the Newcomb study, recent long-term use (at least 5 years use within two years of the cases’ date of diagnosis) was not associated with an increased risk, with a relative risk of 0.91 (0.72-1.14). Similarly, in the Stanford study no significant associations between postmenopausal hormone use and breast cancer risk were noted regardless of recency of use (RR for current use vs never use = 0.9; 95% CI = 0.7-1.3).

In the Nurses’ Health Study cohort, past users were not at increased risk regardless of duration of use. Among current users, only women with 5 or more years of use had a significantly increased risk of breast cancer (RR for 5-9 years of use = 1.36, 95% CI = 1.15-1.61; RR for >10 years of use = 1.47, 95% CI = 1.22-1.76 all compared to never users). In the Breast Cancer Detection Demonstration project cohort relative risks ranged from 1.0 to 1.4 among current users of 5 to >15 years duration.

Some investigators have suggested that the increased risk observed in many of the studies is an artifact of increased surveillance for breast cancer among women taking hormones. Consistent with such a possibility, both Colditz et al. and Schairer et al. reported a higher relative risk associated with in situ disease than invasive disease. However, in both of these studies a significant positive (although weaker) association was noted when only invasive breast cancer cases were considered. In addition, in the Nurses’ Health Study, mammography rates uniformly exceeded 90% even among women who never used hormones. Moreover, current hormone users of short duration did not have an elevated risk, despite slightly higher mammography rates than never users. Finally, higher breast cancer morbidity was observed among participants who were long-term current users at the time of diagnosis, further evidence that the association did not result simply from increased detection of early cancers among hormone users.

**Type and dose of estrogen.** Limited data are available regarding the effects of dose or type of estrogen on breast cancer risk. In the US, approximately three quarters of the hormone use has been conjugated equine estrogens, thus findings from most US studies represent use of conjugated estrogens only. Colditz et al.
served similar increases in breast cancer risk among current users of conjugated estrogen alone (RR= 1.32; 95% CI= 1.14-1.54), and other estrogen formulations (RR= 1.28; 95% CI= 0.97-1.71), all compared to never users. In the Swedish cohort, the relative risk of breast cancer appeared slightly higher among users of estrogen formulations than among women using conjugated estrogens although the estimates were imprecise. In a meta-analysis where published results from European (n= 3) and US studies (n= 9) were separately pooled, the relative risk for ever use was higher in Europe (1.31) than in the US (1.05) again suggesting that synthetic estrogens may confer a slightly higher breast cancer risk than use of conjugated estrogens. In several meta-analyses that examined the influence of dose on breast cancer risk (generally <1.25mg/day vs >1.25 mg/day), no substantial variation in effect was observed although the relative risks observed for higher doses tended to vary from study to study. Risk according to breast cancer risk factor profile. Several studies have evaluated the association between estrogen use and breast cancer risk within strata of other breast cancer risk factors, such as age, family history of breast cancer, adiposity, previous oral contraceptive use and alcohol intake. However, to date these analyses have generally been limited by the small number of participants in any one subgroup thus leading to the examination of ever versus never hormone use (instead of the preferred duration and recency of use) and to imprecise estimates of relative risk.

In one of the meta-analysis, the estrogen/breast cancer relationship did not vary substantially by family history of breast cancer (evaluated in 10 studies), benign breast disease (12 studies), and type of menopause or number of ovaries. In some but not all studies, a higher relative risk has been observed among older women. Although the findings have not been entirely consistent, at least six studies have reported a modestly stronger association between estrogen use and breast cancer among leaner women.

Estrogen plus progestin use

The addition of a progestin to estrogen regimens has become increasingly common as it reduces or eliminates the increased risk of endometrial hyperplasia and cancer associated with using unopposed estrogens. In the US, by the mid-1980s, almost 30% of postmenopausal hormone prescriptions included a prescription for progestin. Two of the first studies to assess the impact of added progestin suggested that it could decrease breast cancer risk. However, these studies were small and potentially important confounders (e.g., age, parity) were not accounted for in the analysis. Since then, several additional studies have been published; taken together these studies indicate that a substantial protective effect of typical doses used in postmenopausal hormone therapy can be ruled out.

Findings from these latter studies have not been consistent however. In several case-control studies but not others an increased risk with use of estrogen plus progestin was suggested. Neither of the two most recent case-control studies has observed a significant increase in risk with estrogen plus progestin use.

Only two prospective studies have reported on this relationship and their findings were similar. Bergkvist et al. observed a relative risk of 4.4 (95% CI= 0.9-22.4) among women who used estrogen plus progestin for >6 years compared to never users. Women using hormones for shorter duration did not appear at an increased risk (relative risks varied from 0.5 to 0.9) but confidence intervals were wide; the type of progestin not specified. Colditz et al. recently reported findings from the Nurses’ Health Study where, among women using progestins, about two-thirds used 10 mg of medroxyprogesterone. The relative risk associated with current estrogen plus progestin use was 1.4 (95% CI= 1.2-1.7), very similar to that for estrogen alone. Thus overall, although the recently published papers differed in their findings, within each study, no material difference in risk was observed comparing those who used estrogen alone and those using estrogen plus progestin.

Widespread use of estrogen plus progestin is so recent that few data are available to evaluate the effect of different formulations, doses or schedules of use on risk of breast cancer.

Summary of data on postmenopausal hormone use and breast cancer risk

Although aspects of the relationship between PMH and breast cancer risk remain unresolved, several areas of agreement have emerged. The finding of no increase in risk comparing ever users or short-term users to never users is consistent and reassuring. Although not entirely consistent, overall, the findings also suggest an increased risk in two important subgroups of users: users of long duration and current users. In general, users of long duration are more likely to be current users, so in many studies these two groups overlap substantially. Part of the inconsistency in findings between studies likely stems from the limited number of cases in any given study in these two

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groups. From a biological perspective, these are the groups one would most expect to demonstrate a relation with breast cancer risk. Exogenous estrogens are well known to increase progression of mammary tumors in animal models, and appear to act in a very late stage, perhaps stimulating growth in tumors which are already present but undiagnosed.

Although better and more complete information will be forthcoming, it is unlikely that the current controversies will be fully settled in the foreseeable future. For now, the weight of the evidence suggests little or no increase in risk among users of short duration, or of past use. However, current longer term use appears to be associated with an increased risk of breast cancer. This increase in risk is large enough, and well enough supported, to be considered along with the other risks and benefits of postmenopausal hormone therapy.

References