

## MENOPAUSAL ESTROGENS AND BREAST CANCER

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**Abstract** 1891 women given conjugated estrogens for the menopause were followed for 12 years (mean) for incidence of breast cancer. Overall, 49 cases were observed; 39.1 were expected on the basis of rates in the general population (relative risk = 1.3,  $P = 0.06$ ). The relative risk increased with follow-up duration, progressing to 2.0 after 15 years (13/6.6,  $P = 0.01$ ). The excess risk after 10 years was not due simply to prolonged estrogen use, since there was no clear dose-response relation to accumulated years of use. How-

ever, higher risk accrued to women using higher-dose tablets and those taking the medication on an other than daily basis. In addition, after 10 years of follow-up observation, two factors related to low risk of breast cancer, multiparity and oophorectomy, were no longer so related. Finally, estrogen use was related to an especially high risk of breast cancer among women in whom benign disease developed after they had started the drug. (*N Engl J Med* 295:401-405, 1976)

**R**EPRODUCTIVE factors and ovarian hormones have long been implicated in the origin of breast cancer.<sup>1-4</sup> As a result, the giving of estrogens to healthy women is controversial.<sup>5,6</sup> This question has led to intensive epidemiologic evaluation of users of oral contraceptives.<sup>7-10</sup> However, the long-term effects of a practice in existence for 40 years — estrogen treatment of menopausal women<sup>6</sup> — have not been adequately evaluated.

Much laboratory evidence supports the idea that estrogens are harmful, but observations on women suggest protection against breast cancer.<sup>11-18</sup> Indeed, several reports suggest protection against many cancers and other diseases as well.<sup>21,22</sup> The association either of increased risk or of protection against breast cancer with use of the fifth most frequently prescribed drug in this country<sup>20</sup> obviously requires evaluation. Recent reports<sup>21,22</sup> that estrogens may cause endometrial cancer add to the need for assessment of their other long-term effects.

### METHODS

The record of every woman seen in one private practice in Louisville, Kentucky, since 1939, was reviewed. Almost all these women were white, so that this study was restricted to whites. All such women treated with conjugated estrogen by mouth, for at least six months, were included. The initial medical history was abstracted, as was a detailed record of hormone treatment and a record of each woman's continuing health.

All women known to have died and those seen in the practice af-

ter December 31, 1969, were considered to have been followed. Efforts were made to bring all additional women into the office to obtain the relevant interval medical history. Women who had left the area or who declined the office visit were sent a questionnaire regarding this history. Efforts were made to communicate with persistent nonrespondents by telephone. Follow-up attempts culminated in a search of the death records both of Kentucky and of Indiana from the year the patient was last known to be alive. We originally intended to make the end of 1969 the closing date for the study. However, attempts at follow-up contact extended well into the early 1970's, and we had information on a number of breast cancers that occurred after 1969. To use these data, we redefined the closing date of the study as December 31, 1972. When calculating expected values, we assumed that all women who were alive at their last follow-up examination after 1969 lived through the end of 1972. This method overestimates the expected number of cases of breast cancer. Therefore, it minimizes any positive differences between observed and expected numbers. All information on exposure — e.g., usual strength and months of use, and information on diagnoses of benign disease — is that as of the end of 1969.

We derived the numbers of cases of breast cancer expected to occur in the study group by applying five-year age-specific incidence rates for the general population, in several periods, to the corresponding person-years accrued by the study group. Initially, two sets of rates were used: those for whites from the Second (1947) and Third (1969-1971) National Cancer Surveys, all areas combined, and those from the same surveys but restricted to centers in the southern United States.<sup>23,24</sup> Rates from the Second Survey were used for 1940-44 and 1945-49. Interpolations using the Second and Third Surveys were employed for the periods 1950-54, 1955-59, 1960-64 and 1965-72. For the initial analysis, the rates from the southern centers were used since they seemed the more appropriate for this study group. However, for detailed analyses, rates from all areas in the National Surveys were selected because they produced slightly higher expected values and, therefore, minimized the differences between observed and expected numbers. A standard computer program was used to accumulate person-years and to generate expected numbers.<sup>25</sup>

The measure of association used is the ratio of observed to expected numbers of cases, referred to as the relative risk. The 95 per cent confidence intervals of the relative risk were estimated on the assumption of an underlying Poisson distribution.<sup>26</sup> When the 95 per cent confidence interval does not include unity the relative risk is statistically significant, with a  $P$  value  $< 0.05$ . However, interpretations of statistical significance in this study merit caution, since

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Supported by a specialized center grant 5(PO1 CA06373) (Dr. Cole is the recipient of an award [PRA 115] from the American Cancer Society).

associations were sought in a number of subgroups of the data. Whenever such multiple comparisons are made, the possibility that some may be significant on a chance basis alone should be kept in mind. A discriminant-function analysis was also done. This multivariate technic evaluates the capacity of variables to contribute significantly and independently to a score for each subject that will discriminate those who acquired breast cancer from those who did not.<sup>27</sup>

## RESULTS

A total of 1891 women were studied. The average age at the start of estrogen therapy was 49 years, and the average year at which observation was begun was 1958. At the close of the study 1573 women were alive, 132 were dead, and 186 (9.8 per cent) were lost. If the lost are removed from consideration in the year in which they were last known to be alive, and the dead in the year in which they died, the study population accrued 22,717 person-years of follow-up duration, an average of 12 years per woman; 620 women were followed for longer than 15 years, including 285 for 20 or more years.

In 49 women breast cancer developed during the period of observation, as compared with 39.1 expected on the basis of rates among southern white women, a relative risk of 1.3 (1.0 to 1.7, 95 per cent confidence interval). The relative risk increased with increasing follow-up duration (Table 1). The figure was 0.9 in the first five years after the starting of estrogens, 1.2 from five to nine years and 1.3 and 2.0 in the intervals 10 to 14 and 15+ years. With standard regression technics, this trend was statistically significant ( $P = 0.02$ ). Finer subdivisions of the data according to follow-up periods of less than 10 years yield relative risks consistently close to 1.0. A finer breakdown of the follow-up duration after 10 years indicated that the excess becomes manifest after about 12 years. If the expected value accrued between 10 and 24 years of follow-up observation is divided into three groups, relative risks are  $6.0/4.9 = 1.2$  for 10 to 12 years,  $9.0/4.8 = 1.9$  for 13 to 16 years, and  $8.0/4.1 = 2.0$  for 17 to 24 years. Among women followed for 25 or more years no case was observed, but the expected number was only 0.3. Similar risks and trends are present if the rates from all areas in the National Cancer Surveys are used, although the expected values in this instance are somewhat higher. The overall relative risk is 1.2 on the basis of an expected value of 41.8, and the relative risk in the interval of 17

Table 1. Observed and Expected Numbers of Cases of Breast Cancer According to Follow-up Duration.

| FOLLOW-UP DURATION (YR) | CASES OF BREAST CANCER |          | RELATIVE RISK | 95% CONFIDENCE INTERVAL |
|-------------------------|------------------------|----------|---------------|-------------------------|
|                         | OBSERVED               | EXPECTED |               |                         |
| <5                      | 13                     | 13.9     | 0.9           | 0.5 - 1.5               |
| 5-9                     | 13                     | 11.1     | 1.2           | 0.6 - 2.0               |
| 10-14                   | 10                     | 7.5      | 1.3           | 0.6 - 2.4               |
| 15+                     | 13                     | 6.6      | 2.0           | 1.1 - 3.4               |
| Totals                  | 49                     | 39.1     | 1.3           | 1.0 - 1.7               |

Table 2. Observed and Expected Numbers of Cases of Breast Cancer According to Parity and Follow-up Duration.

| PARITY*             | FOLLOW-UP DURATION (YR) |      | TOTALS |
|---------------------|-------------------------|------|--------|
|                     | <10                     | 10+  |        |
| Nulliparous (515)†: |                         |      |        |
| Observed            | 9.0                     | 5.0  | 14.0   |
| Expected            | 6.6                     | 4.5  | 11.1   |
| Relative risk       | 1.4                     | 1.1  | 1.3    |
| 1,2 (890):          |                         |      |        |
| Observed            | 13.0                    | 13.0 | 26.0   |
| Expected            | 12.5                    | 7.1  | 19.6   |
| Relative risk       | 1.0                     | 1.8  | 1.3    |
| 3+ (426):           |                         |      |        |
| Observed            | 3.0                     | 4.0  | 7.0    |
| Expected            | 6.3                     | 2.9  | 9.2    |
| Relative risk       | 0.5                     | 1.4  | 0.8    |

\*Unknown parity (60) observed = 2; expected = 1.8.

†Figures in parentheses denote no. of women.

to 24 years is 1.7 on the basis of an expected value of 4.6.

After standardization for the increasing relative risk with increasing follow-up duration, there was no variation in relative risk by age at start of estrogens, year of first exposure, age at diagnosis or year of diagnosis.

### Breast-Cancer Risk Indicators

The data were assessed according to parity and follow-up duration (Table 2). The usual association of reduced risk with increased parity was present during the first 10 years of follow-up observation, but was absent thereafter. Most subjects had undergone hysterectomy and bilateral oophorectomy. Therefore, the results were evaluated according to ovarian status (Table 3). The person-years leading to the expected numbers for the oophorectomized group are only those accrued after both ovaries were removed. The association of increased breast-cancer risk with increased follow-up duration is unrelated to ovarian status. The trend in relative risk with follow-up duration is actually more prominent, and the relative risks larger, for the group with ovaries removed, but the two groups were not significantly different. The anticipated low relative risks for oophorectomized women were not seen, possibly because the onset of estrogen therapy coincided closely with the time of oophorectomy. Thus, as an oophorectomized woman reaches 10 years after oophorectomy, when the protection against breast cancer conferred by the operation should begin to appear,<sup>28</sup> she also passes the 10-year observation period in this study; beyond which excess risk of breast cancer is noted.

Women with a history of histologically confirmed benign breast disease showed the anticipated higher relative risk of breast cancer as compared to those with no such history. However, the relative risk was greater among women for whom the benign condition was diagnosed after than among those with diagnosis before estrogen was started ( $6.0/1.5 = 4.0$  vs.  $7.0/3.4 = 2.1$ ). (Two cases observed and 0.3 expected among women with benign breast disease diag-

**Table 3. Observed and Expected Numbers of Cases of Breast Cancer According to Ovarian Status and Follow-up Duration.**

| OVARIAN STATUS* | FOLLOW-UP DURATION (Yr) |     |       |     | TOTALS |
|-----------------|-------------------------|-----|-------|-----|--------|
|                 | <5                      | 5-9 | 10-14 | 15+ |        |
| Intact (906)†:  |                         |     |       |     |        |
| Observed        | 8.0                     | 4.0 | 4.0   | 7.0 | 23.0   |
| Expected        | 7.8                     | 6.0 | 4.3   | 3.8 | 21.8   |
| Relative risk   | 1.0                     | 0.7 | 0.9   | 1.8 | 1.1    |
| Removed (1028): |                         |     |       |     |        |
| Observed        | 5.0                     | 9.0 | 6.0   | 6.0 | 26.0   |
| Expected        | 6.9                     | 5.8 | 3.8   | 3.5 | 20.1   |
| Relative risk   | 0.7                     | 1.6 | 1.6   | 1.7 | 1.3    |

\*43 patients were eligible both before & after oophorectomy. The person-yr for these patients were divided appropriately between the 2 groups.

†Figures in parentheses denote no. of women.

nosed both before and after start of estrogen were counted in both groups.) This difference in risk was not due to the fact that the group with diagnosis after estrogen was begun had a higher proportion of their years at risk in later follow-up intervals. The relative risk among the group with benign disease after estrogen therapy was even greater if the expected number was limited to person-years accumulated after diagnosis of the benign disease (a prior diagnosis of breast cancer would have eliminated a woman from this group). With this modification the figure is 6.7 (6.0/0.9).

#### Type of Estrogen Use

Long-term replacement therapy was the usual goal in this group of women. Consequently, number of years of estrogen use and total follow-up duration are highly correlated. Therefore, separating the effect of duration of use (dose) from that of follow-up duration (latent period) is difficult because of the small numbers of observations in critical subgroups (e.g., women having taken the medication for a short time, but followed for a long time). However, to the extent to which we could evaluate this question, the follow-up effect appeared to be the more important: there was no evidence of a linear dose effect once follow-up duration had been controlled. Specifically, among women followed for less than 10 years, the relative risk was remarkably similar and close to 1.0 for every subgrouping of number of years of use (from one year or less to six to nine years of use). Among those followed for 15 or more years, the highest relative risk (2.3) was in the group taking the medication for more than 15 years. However, subdivisions of the data based on lesser categories of duration of use failed to give any evidence of a dose-response relation. Indeed, among those followed for 15 or more years, the data for the shortest duration of use grouping (five years or less) yielded a relative risk of 2.1, although this figure was based on only four observed cases.

The relation of risk of breast cancer to the strength of the medication used and to the frequency of use was examined in two ways: by "usual" mode of therapy and by "ever use" of a particular regimen. The results are similar for both classifications. Presented here are the results based on the "ever" classification

(Table 4). The lesser-strength tablets were those usually prescribed, and there was little difference in relative risk between women who used 0.3 mg and those who ever used 0.625 mg. However, the relative risk of 2.7 (1.2 to 5.3, 95 per cent confidence interval) was increased for women who ever used the 1.25-mg or 2.50-mg tablet. Most women used estrogen daily, and the remainder were on several different regimens. The different regimens were primarily every-other-day use, and to a lesser extent, use twice per week, cyclically (three weeks on, and one off) or other schedule. The relative risk was highest for women in the other-than-daily group, 2.3 (1.1 to 4.4). These associations of breast-cancer risk with strength of medication and frequency of use were the same both for women who did and for women who did not have a history of benign breast disease. Strength and frequency appear to have independent effects (Table 5), progressing to a risk of 4.7 (1.9 to 9.7) for women who ever used the stronger medication and ever took the medication on an other-than-daily basis. Data were few, but an analysis based on usual strength and frequency was consistent with that shown in Table 5.

Results were confirmed by a discriminant-function analysis. The two risk indicators with the greatest ability to discriminate cases of breast cancer from non-cases, parity and presence or absence of benign breast disease after estrogen was started, were entered into a linear discriminant function. (The latent period effect was controlled by limitation of the analysis to women followed for more than nine years.) To this function, information on frequency of use and strength of medication was added. In the presence of one another and the risk indicators, both factors relating to use provided independent, statistically significant contributions to the ability of the function to discriminate the breast-cancer cases from the non-cases. This analysis was done only to assess the relative independence of the contribution of these measures. "Statistical significance" should be interpreted

**Table 4. Observed and Expected Cases of Breast Cancer According to Follow-up Duration and Strength and Frequency of Estrogen Used.\***

| FOLLOW-UP DURATION (Yr) | STRENGTH      |                 |                 | FREQUENCY    |             |
|-------------------------|---------------|-----------------|-----------------|--------------|-------------|
|                         | 0.3 MG (873)† | 0.625 MG (1262) | >0.625 MG (246) | DAILY (1830) | OTHER (278) |
| <10:                    |               |                 |                 |              |             |
| Observed                | 13.0          | 17.0            | 4.0             | 25.0         | 5.0         |
| Expected                | 13.8          | 16.5            | 3.2             | 25.4         | 4.1         |
| Relative risk           | 0.9           | 1.0             | 1.3             | 1.0          | 1.2         |
| 95% confidence interval | 0.5 - 1.5     | 0.6 - 1.6       | 0.4 - 3.3       | 0.7 - 1.5    | 0.4 - 2.8   |
| 10+:                    |               |                 |                 |              |             |
| Observed                | 14.0          | 11.0            | 8.0             | 20.0         | 9.0         |
| Expected                | 8.5           | 9.8             | 3.0             | 14.8         | 3.9         |
| Relative risk           | 1.6           | 1.1             | 2.7             | 1.4          | 2.3         |
| 95% confidence interval | 0.9 - 2.7     | 0.5 - 2.0       | 1.2 - 5.3       | 0.9 - 2.2    | 1.1 - 4.4   |

\*Tabulated according to whether ever used a particular type of therapy. No. of women >total in study since in this classification a woman could be in >1 category.

†Figures in parentheses denote no. of women.

Table 5. Observed and Expected Cases of Breast Cancer Cross-tabulated According to Follow-up Duration, Whether >0.625 Mg of Medication Ever Used and Whether It Was Ever Taken Daily.

| USE OF ESTROGEN                      | WOMEN WHO EVER USED ≤ 0.625 MG |           | WOMEN WHO EVER USED > 0.625 MG |           |
|--------------------------------------|--------------------------------|-----------|--------------------------------|-----------|
|                                      | FOLLOW-UP DURATION (YR)        |           |                                |           |
|                                      | <10                            | 10+       | <10                            | 10+       |
| Ever used daily:                     |                                |           |                                |           |
| Observed                             | 24.0                           | 20.0      | 4.0                            | 6.0       |
| Expected                             | 24.8                           | 14.1      | 2.8                            | 2.8       |
| Relative risk                        | 1.0                            | 1.4       | 1.4                            | 2.1       |
| 95% confidence interval              | 0.6 - 1.5                      | 0.9 - 2.2 | 0.4 - 3.6                      | 0.8 - 4.6 |
| Ever used on other than daily basis: |                                |           |                                |           |
| Observed                             | 5.0                            | 7.0       | 2.0                            | 7.0       |
| Expected                             | 3.5                            | 3.5       | 1.5                            | 1.5       |
| Relative risk                        | 1.4                            | 2.0       | 1.3                            | 4.7       |
| 95% confidence interval              | 0.5 - 3.3                      | 0.8 - 4.1 | 0.2 - 4.7                      | 1.9 - 9.7 |

cautiously since these measures were chosen for this analysis from the many variables possible, on the basis of their association with excess risk in our other analyses.

In the period between the follow-up date originally intended and that finally used (December, 1969, to December, 1972), 15 cases of breast cancer were observed versus 8.7 expected (Southern rates) (relative risk = 1.7). If the data are restricted to those accrued through the end of 1969, the relative risks by follow-up duration are 0.7 for zero to four years, 0.9 for five to nine years, 1.6 for 10 to 14 years, and 2.2 for 15+ years. In addition, the associations with parity, oophorectomy, benign breast disease, strength of tablet and frequency of use are virtually identical to those presented here.

The 186 women lost to follow-up study were followed for an average of six years before being lost, half the average follow-up duration of the entire group. They entered the study primarily in the earlier years; their average year of beginning observation was 1953, five years before that for the total cohort. In most other respects they were similar to the entire study group. Their average age when they started therapy was 48 years. Fifty-four per cent had had a bilateral oophorectomy, 11 per cent had benign breast disease, 13 per cent had taken the 1.25-mg or 2.50-mg tablet, and 15 per cent had used the hormone on an other-than-daily basis. All these percentages are within 2 percentage points of the values for the entire group. They were slightly less parous (33 per cent nulliparous) than the total group.

## DISCUSSION

Since the advent of estrogen replacement therapy, there has been widespread speculation about the effect of this practice on risk of breast cancer. This speculation has ranged from fears of a widespread estrogen-caused epidemic to hopes for prophylaxis against the disease. Our data indicate that neither is likely. Overall, the observed number of breast cancers is 30 per cent greater than that expected, and this figure is

of borderline statistical significance. In addition, little or no excess is seen during the 10 to 12 years after initiation of therapy.

Although this observation is somewhat comforting, several findings raise concern about the role of estrogens in the cause of breast cancer. Of special concern is the trend in risk with increasing interval from first exposure, particularly after 10 years follow-up observation. In addition, after 10 years, two factors usually related to low risk of breast cancer, nulliparity and oophorectomy, no longer are. All these considerations could be highly relevant since endocrine phenomena associated with changes in risk of breast cancer (oophorectomy and early age at natural menopause) take about 10 years before their first effect on risk appears.<sup>29</sup>

The relation between estrogen use, benign breast disease and breast cancer may also be cause for concern. The expected increased risk of cancer among women with a history of histologically confirmed benign disease is present in this data. However, the magnitude of the risk is determined by the temporal sequence between the diagnosis of the benign condition and the use of estrogens. The risk of breast cancer for women with benign disease diagnosed before estrogen use is about twice that of the general population. The risk among women with disease diagnosed after they started taking estrogen is seven times greater than that of the general population. It may be that benign disease and breast cancer are part of one response to an estrogenic stimulus — at least among some women.

The increased risks associated with the stronger medication and the non-daily regimens are based on small numbers but are statistically significant. Since the predominant mode of therapy in this practice was small daily doses, it is possible that the women not placed on this regimen were unusual in some way related to breast-cancer risk. However, the analysis indicates that such peculiarities would not be related to parity or history of benign breast disease. There is practical importance in a full evaluation of these associations, in that the usual doses given in most areas of this country are relatively higher (1.25 mg) than those given in this practice.<sup>30</sup>

We attempted to negate the effect of any potential biases involved in use of the general population for a control group by doing analyses taking into account most of the known characteristics relevant to breast cancer — e.g., age, time, parity, ovarian status and presence of benign disease. In addition, there is evidence that, at the initiation of therapy, the study women were similar to the population used to generate the expected values for these characteristics, except for their high prevalence of surgical menopause. Specifically, if the parity experience of the study group in 1960 is age-standardized, with use of the age distribution of the entire United States, white, urban, female population over the age of 15 years in 1960,<sup>31</sup> the per cent nulliparous is 28.1. This figure is to be compared with the 32.1 per cent nulliparity prevalence in the standard population. In addition, if the incidence

rates of benign breast disease from a recent Boston survey (unpublished data) are applied to all the person-years accumulated by the study women up to the time they became eligible for the study, the expected prevalence of a history of benign disease is 147.7. One hundred and sixty-six women gave such a history (relative risk of 1.1,  $P = 0.13$ ). In summary, there is no evidence that the women in this study are unusual for the presence of these breast-cancer risk indicators.

The women in this study were generally of upper-middle or upper-socioeconomic class. Rates of breast cancer have a direct social-class gradient. However, this effect has not been marked. The conclusion drawn in one, large, multi-area study in this country<sup>32</sup> was that if there was a direct association between income level and breast-cancer incidence in this country, it was not a very strong one. In addition, many of the socioeconomic differences noted in the literature may be attributable to differences in parity, a factor accommodated in this analysis. Finally, any social-class effect would not be expected to produce an increasing trend in risk with follow-up duration.

Contrary to our findings, those previously reported have generally been negative. However, these studies have been seriously hampered by small numbers of women studied, and incomplete and, in many of them, only short-term follow-up observation. These liabilities do not apply to the most recently reported study of 735 women from Nashville, Tennessee, followed for an average of 15 years after they started estrogens.<sup>19</sup> Overall, 21 cases of breast cancer were observed versus 18 expected. Despite this apparent negative result, the findings of this study may be considered similar to ours. Half of the Nashville group had undergone bilateral oophorectomy, but the anticipated protection against breast cancer was not noted for this group. In addition, although the study was limited to those receiving estrogens for five or more years, the first five years were erroneously included in the calculation of the expected value, and in the face of this discrepancy, the authors noted "protection" among the young and excess risk among the old.<sup>33</sup> If we limit our study to women followed for five years or more but include the expected value accrued in the first five years and fail to adjust for follow-up duration, we achieve similar results. It would be useful to compare our data to a tabulation from the Nashville study that eliminated the first five years of follow-up observation and was arranged by follow-up duration thereafter.

Our findings clearly indicate that menopausal estrogen use does not protect against breast cancer. Although the data do not by themselves indict exogenous estrogens as a cause of breast cancer, they raise this risk as a definite possibility, and indicate that a thorough evaluation is necessary. They further indicate that a full evaluation of these agents will be difficult, and will necessitate the incorporation of several factors lacking in studies done before ours. These factors include latent period, risk indicators for breast cancer, type of therapeutic regimen and total accumulated dosage.

We are indebted to Mrs. Nancy Guerin for assistance, to Ms. Karen Beckwith for assistance in the analysis, to Drs. Joseph Fraumeni and Robert Miller for advice and support and to Mrs. Phyllis Ray, who abstracted the information, conducted the follow-up study and otherwise made this study possible.

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