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THE RISK OF BREAST CANCER AFTER ESTROGEN AND ESTROGEN–PROGESTIN REPLACEMENT

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Abstract To examine the risk of breast cancer after noncontraceptive treatment with estrogen, we conducted a prospective study of 23,244 women 35 years of age or older who had had estrogen prescriptions filled in the Uppsala region of Sweden. During the follow-up period (mean, 5.7 years) breast cancer developed in 253 women.

Compared with other women in the same region, the women in the estrogen cohort had an overall relative risk of breast cancer of 1.1 (95 percent confidence interval, 1.0 to 1.3). The relative risk increased with the duration of estrogen treatment ($P = 0.002$), reaching 1.7 after nine years (95 percent confidence interval, 1.1 to 2.7). Estradiol (used in 56 percent of the treatment periods in the cohort) was associated with a 1.8-fold increase in risk after more than six years of treatment (95 percent confidence interval, 0.7 to 4.6). No increase in risk was found after the use of conjugated estrogens (used in 22 percent of the treatment periods) or other types, mainly estriols (used in 22 percent of the treatment periods).

Although the numbers of women were smaller, the risk of breast cancer was highest among the women who took estrogen and progestin in combination for extended periods. The relative risk was 4.4 (95 percent confidence interval, 0.9 to 22.4) in women who used only this combination for more than six years. Among women who had previously used estrogens alone, the relative risk after three years or more of use of the combination regimen was 2.3 (95 percent confidence interval, 0.7 to 7.8).

We conclude that in this cohort, long-term perimenopausal treatment with estrogens (or at least estradiol compounds) seems to be associated with a slightly increased risk of breast cancer, which is not prevented and may even be increased by the addition of progestins. (N Engl J Med 1989; 321:293-7.)

THERE is substantial evidence that endogenous hormones are involved in the causation of breast cancer,[1] and that breast cancer can be induced in laboratory animals by exogenous estrogens.[2] Epidemiologic studies of the risk of breast cancer after treatment with estrogen for the symptoms of menopause have given conflicting results.[3-15] Some studies have failed to show an overall excess risk,[3-6] whereas others have indicated an increased risk after long-term use.[7-15]

In particular, the effects on the breast of the addition of cyclic progestins to the estrogen treatment have been difficult to assess.[15] Such combination therapy has become more widely used in recent years, and there are reports indicating that the increased risk of endometrial cancer found after estrogen therapy might be prevented by the addition of progestins.[16] Similar enthusiasm has been expressed for the possibility that such combination therapy might also reduce any excess risk of breast cancer associated with long-term estrogen treatment.[17] Conversely, a recent review of research on endogenous and exogenous hormonal factors in the causation of breast cancer has led to the hypothesis that the combination therapy may in fact increase this risk substantially above that associated with estrogen alone.[18]

The aim of the present study was to analyze the risk of breast cancer after perimenopausal treatment with estrogens and combinations of estrogen and progestin in a large, population-based cohort recruited through an examination of prescription records.

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METHODS

The Cohort

All women for whom replacement estrogens had been prescribed for conditions related to menopause were identified through a study of prescription forms for estrogen from all the pharmacies in the health care region around Uppsala, Sweden, which contains about 1.3 million inhabitants. Recruitment began in April 1977 and ended in March 1980. Each woman's national registration number — permitting the identification of any person living in Sweden — and data on the brand, dosage, and package size of estrogen were entered on the computer from the prescription forms. The final cohort was based on the examination of 77,147 prescription forms, which were estimated to represent at least 92 percent of all estrogen-replacement prescriptions issued in the region during the period of investigation.[19] The prescription forms corresponded to 23,244 women 35 years of age or older who lived in the region and had filled at least one prescription.

Complete follow-up with regard to the development of cases of breast cancer in the cohort was made possible by linking the national registration numbers of these women with those of the women with new cases of breast cancer reported to the national Cancer Registry in Sweden. In Sweden, both clinicians and pathologists are required to report all newly diagnosed cases of cancer to the Cancer Registry. Thus, reports are collected from two independent sources, and the data in the Cancer Registry have been shown to have a very high degree of accuracy, with a rate of underreporting of breast cancer of less than 2 percent.[20]

The Subgroup

From the total cohort of 23,244 women a subgroup was selected, in order to characterize the women more fully with respect to exposure to estrogens and progestins and risk factors for breast cancer. Thus, a random sample of 1 in 30 women was chosen, and 735 women were sent a questionnaire in 1980, which was answered satisfactorily by 653 (89 percent). The questionnaire requested detailed information on the presence of risk factors for breast cancer; exposure to estrogens before, during, and after the period in which the prescriptions were studied; compliance with drug treatment;

and the concomitant cyclic use of progestins. To facilitate the recall of information on exposures, the women were given a list of 13 estrogen and 3 progestin preparations used in Sweden. They were asked to indicate when and for how long they had used the drugs on the list. These hormonal preparations are prescribed almost exclusively in Sweden for menopausal symptoms. This was confirmed by the reports of the women themselves, who listed a wide variety of such symptoms as the indications for drug use. No use was reported for contraception.

Of the women who responded to the questionnaire, 9 percent reported no intake of the drugs, and 50 percent reported starting treatment before 1977. Estradiol compounds were used in 56 percent of all treatment periods, conjugated estrogens in 22 percent, and other types of estrogens (mainly estriol compounds) in 22 percent. In 31 percent of the treatment periods, progestins were added for 7 to 10 days in each treatment cycle.[21] The reliability of the drug information supplied in the questionnaires by the women was assessed by comparison with the drug data from the prescription forms for the three years in which the prescriptions were recorded. A concordance of over 85 percent was found with regard to the type of drug, the beginning and duration of exposure, and the dosage.[22]

In 1982 and 1984, additional questionnaires were sent to the women who had answered the initial one, to ascertain their exposure to estrogens after 1980. Data through 1983 were obtained from 638 of the women originally sampled.

Patients with Breast Cancer

Through December 1983, all 253 women in whom invasive breast cancer developed after their inclusion in the cohort received shortly after diagnosis a questionnaire that was identical to the one sent to the women in the subcohort. Fifty-one of the patients with breast cancer did not respond to the questionnaire (37 declined to answer, and 14 could not be contacted). In addition, six patients gave incomplete answers. Thus, complete data were available for 196 women with breast cancer (77 percent). To assess the reliability of the data, the information provided by these respondents was compared with the data from the prescription forms, as had been done with the women in the subcohort.[22] Except that the proportion of women who reported no estrogen use was higher, equally close agreement between the questionnaire data and the prescription data was found for the patients with breast cancer (unpublished data).

Classification of Exposure

Estrogen exposure was considered in several ways. First, estrogen use was examined without regard to type or concomitant use of progestin. Second, estrogens were considered according to concomitant use of progestins, with the women separated into five groups: those who had never used progestins, those who had always used progestins in conjunction with estrogens, those whose use of the two in combination had been preceded by five or fewer years of estrogen use alone, those whose use of the combination had been preceded by more than five years of estrogen use alone, and those whose patterns of use did not fit into any of these categories. Finally we investigated the risks associated with the use of particular types of estrogens — estradiols, conjugated estrogens, and other estrogens (mainly estriols) — with and without the concomitant use of progestin. Because the women tended to use several types of estrogens, analyses of the use of a single type were generally based on small samples. Therefore, we also considered the risk associated with the use of each type of estrogen without regard to the concomitant use of other types.

Statistical Analysis

The total number of person-years for the women in the cohort was calculated from the date of the first prescription recorded through the end of follow-up (December 31, 1983) or the date of death, emigration, or diagnosis of breast cancer. The estimate of the total number of cases expected in the health care region was calculated from the number of person-years and the incidence rates of breast cancer according to age group in the region in which the cohort was recruited, after the exclusion of the patients with breast cancer and the number of person-years accounted for by the study cohort. Thus, the entire female population of the Uppsala health care region, except for the women in the cohort, composed the comparison, or reference, population. The cases were identified by the Cancer Registry, and the size of the population at risk was supplied by the Swedish Population Register. This resulted in a comparison group that had not received menopausal hormonal therapy, for the most part. In fact, on the basis of a questionnaire sent to a sample of the general population who were not in the cohort, 12 percent had a history of menopausal hormonal use, predominantly before the study period. The total number of cases of breast cancer in the reference population was 4213, in 2,064,29 person-years of observation. The overall relative risk was then calculated as the ratio of the number of cases observed to the number expected, with the 95 percent confidence interval based on the Poisson distribution of the number of cases observed.

The design of most of the analyses in the present study has recently been described as following a case–cohort approach.[23] From the questionnaires, detailed data on estrogen exposure were known for the women with breast cancer in the cohort and for all women in the subcohort. The OCMAP computer program[24] was used to determine the number of person-years according to age and exposure strata in the subcohort, and the results were extrapolated to the total cohort. In accordance with a method of conducting case–cohort studies with external comparisons,[23] these estimates were based on data from the respondents in the subcohort, and therefore patients with breast cancer (case patients) for whom exposure data were incomplete or absent were assigned according to age to exposure categories in proportion to the distribution of responding case patients for whom complete information on exposure was available. The relative risk was calculated as the ratio of the number of cases observed to the number expected. The variance of the relative risk was calculated as a combination of the variances for the observed and expected numbers of cases, thus including the sampling error due to the allocation of the person-years on the basis of those of the subcohort. The significance of the trends in relative risk was also assessed, with the test described by Breslow et al.,[25] assuming a multiplicative effect of exposure on calendar year–specific incidence rates at a given age. This test does not allow for the variance in the expected values caused by the allocation of person-years on the basis of those of the subcohort. However, because of the size of the subcohort and the allocation of person-years according to only one variable (duration), any resulting underestimation of the P value should be small.

To take into account possible confounding factors, a matched case–control analysis within the cohort was also performed. Although it did not permit a comparison of the use with the nonuse of hormones, this method allowed an efficient evaluation of dose-response relations in the women exposed to estrogen, after we controlled for a variety of potentially confounding variables.[26] All 196 respondents with breast cancer and 11 patients with carcinoma in situ were evaluated, and one to five controls were selected from among the respondents in the subcohort, matched for year of birth and year of inclusion in the cohort — i.e., the control had to have received her first prescription before the case patient received her diagnosis, and the control also had to be alive and free of breast cancer by the time the respondent became a case patient. Each control was assigned a date identical to the date of diagnosis of the case patient to whom she was matched, and all events after that date were ignored, as they were for the case patient. The PECAN computer program[27] was used in the matched case–control analysis. This program fits a multiplicative relative-risk regression model that uses an exact conditional likelihood.

Results

Cohort Analysis

The median age of the women in the cohort at inclusion in the study was 53.7 years. On the basis of information from the random sample, 6 percent of the cohort was premenopausal; among the menopausal women, 80 percent had had a natural menopause and

20 percent a surgical menopause, and the median age at menopause was 50 years. Thirty-three percent of the women had had eight or more years of schooling, 14.2 percent were nulliparous, their median age at menarche was 13 years, their average height was 163.7 cm, and their average weight was 66.5 kg.

The total number of person-years for the cohort at the end of the follow-up in 1983 was 133,375, and the average individual follow-up period was 5.7 years. By the end of 1983, breast cancer had developed in 253 of the women in the cohort. The expected number was 222.5, giving an overall relative risk of 1.1 (95 percent confidence interval, 1.0 to 1.3).

Case–Cohort Analysis

Forty-five women with breast cancer reported never having taken estrogens, as compared with the expected number of 28.8 (relative risk, 1.6; 95 percent confidence interval, 1.1 to 2.1), leaving 208 women with breast cancer who had taken estrogens. The distribution of observed and expected cases is shown in Table 1, along with the relative risks and 95 percent confidence intervals according to the length of exposure to estrogens in any form, with or without concomitant progestin exposure. There was a trend toward increasing relative risk with increasing duration of use; the relative risk rose to 1.7 (95 percent confidence interval, 1.1 to 2.7) among women treated for more than nine years. Reviews of the medical records of the women with breast cancer who reported no use of hormones indicated that most of them were likely to have been short-term users. If the observed and expected values in this group were included in the category with six months or less of exposure, the relative risk for this group was 1.1.

Among the women who used only estrogen with no progestins added, the same pattern emerged (Table 2). The relative risk rose from 0.8 in short-term users to 1.8 (95 percent confidence interval, 1.0 to 3.1) with more than nine years of estrogen use on the basis of 23 cases. In women who received only combined treatment, an even higher relative risk was found among long-term users — 4.4 (95 percent confidence interval, 0.9 to 22.4) with more than six years of use — on the basis of data on 10 patients. Also, high relative risks were found among women who received treatment with estrogen and progestin in combination after a period of use of estrogen alone. The relative risk among all women who switched from estrogen alone to the combination therapy was 2.3 (95 percent confidence interval, 0.7 to 7.8) after three years of use of the combination treatment, on the basis of 11 such women with breast cancer. It should be pointed out, however, that the total period of estrogen exposure in these women was longer than in those who used the combination all the time and the estimates were based on small numbers. The 95 percent confidence intervals for the risk estimates in Table 2 were wide, and they all included 1.0.

Estradiol was the drug used most commonly by the women in the cohort, accounting for 56 percent of all treatment episodes. One hundred twenty-five of the women with breast cancer had been treated with estradiol compounds as compared with 104 expected, yielding a relative risk of 1.2 (95 percent confidence interval, 1.0 to 1.4). The risk estimates increased significantly with longer treatment (Table 3). In the case of conjugated estrogens and other types of estrogens, no trend was found with duration. In the analyses of women who used only one type of drug, the outcomes were similar to those in women with exposures to several types of drugs.

Table 1. Observed and Expected Numbers of Cases of Breast Cancer, with Relative Risks and 95 Percent Confidence Intervals, According to the Duration of Estrogen Treatment.

Months of Treatment	Number of Cases		Relative Risk* (Confidence Interval)
	Observed	Expected†	
≤6	23	34.5	0.7 (0.4–1.0)
7–36	72	65.3	1.1 (0.9–1.4)
37–72	53	52.2	1.0 (0.8–1.4)
73–108	31	24.6	1.3 (0.9–1.9)
≥109	29	17.1	1.7 (1.1–2.7)
Any treatment	208	193.7	1.1 (1.0–1.3)

*P for trend = 0.002.

†On the basis of rates derived from age and calendar time for the female population with no estrogen exposure of the Uppsala health care region.

Case–Control Analysis

The matched case–control study within the cohort was used to adjust for the possible effects of confounding factors on the risk estimates. It also afforded the opportunity to include 11 cases of breast cancer in situ that were identified in the cohort but not included in the case–cohort analysis, since the Cancer Registry routinely publishes rates only for invasive disease. Since the entire cohort was exposed to estrogens, the reference category for the analyses was that of short-term use (six months or less). The case patients and controls who reported themselves to have been noncompliant were included in this category. Ten poten-

Table 2. Relative Risk of Breast Cancer Associated with the Use of Different Treatment Regimens and 95 Percent Confidence Interval, According to the Duration of Use.*

Regimen†	Months of Estrogen Treatment				
	≤6	7–36	37–72	73–108	≥109
	relative risk (95 percent confidence interval)				
Estrogen only	0.8 (0.5–1.4)	1.1 (0.8–1.5)	0.9 (0.6–1.3)	0.9 (0.5–1.6)	1.8 (1.0–3.1)
Combination only	0.5 (0.2–1.8)	0.7 (0.3–1.3)	0.9 (0.3–2.6)	4.4 (0.9–22.4)	—
After ≤5 yr of estrogen	1.2 (0.5–2.6)		1.5 (0.3–6.7)		
After >5 yr of estrogen	0.8 (0.0–26.9)		7.2 (—)‡		

*Risks shown are relative to a risk of 1.0 for the rate among the female population with no estrogen exposure of the Uppsala health care region with adjustment for age and calendar time.

†Combination therapy included estrogen and cyclic progestin.

‡The confidence interval was unreliable because of the small expected value (number of cases observed, 5; number expected, 0.7).

Table 3. Observed and Expected Numbers of Cases of Breast Cancer, with Relative Risk and 95 Percent Confidence Interval, According to the Duration of Treatment with Estradiol Compounds, Conjugated Estrogens, and Other Estrogens (Mainly Estriols).

Months of Treatment	Number of Cases		Relative Risk* (Confidence Interval)
	Observed	Expected†	
Estradiol compounds			
≤6	18	18.5	1.0 (0.6–1.7)
7–36	44	49.1	0.9 (0.6–1.2)
37–72	36	23.5	1.5 (1.0–2.3)
73–108	17	7.5	2.3 (1.2–4.3)
≥109	10	5.4	1.8 (0.7–4.6)
Total	125	104.0	1.2 (1.0–1.4)
Conjugated estrogens			
≤6	12	8.2	1.5 (0.6–3.6)
7–36	23	20.5	1.1 (0.7–1.9)
37–72	15	16.5	0.9 (0.5–1.7)
≥73	13	9.8	1.3 (0.6–2.9)
Total	63	55.1	1.1 (0.9–1.5)
Other estrogens			
≤6	23	25.0	0.9 (0.5–1.6)
7–36	36	35.0	1.0 (0.7–1.5)
37–72	23	15.8	1.5 (0.8–2.6)
≥73	10	12.6	0.8 (0.4–1.8)
Total	92	88.3	1.0 (0.8–1.3)

*P for trend = 0.001 for estradiol, 0.7 for conjugated estrogens, and 0.7 for other estrogens.

†On the basis of rates derived from age and calendar time for the female population with no estrogen exposure of the Uppsala health care region.

tial confounding variables were evaluated, including the recognized risk factors for breast cancer (age at birth of first child, family history of breast cancer, previous breast biopsy, menopausal status, age at menopause, age at menarche, parity, height, weight, and years of schooling). Adjustment for three variables (education, previous breast biopsy for benign disease, and type of menopause) resulted in alterations in the estimates of relative risk. The adjusted odds ratios tended to be generally somewhat higher than the crude ones (Table 4), as was also true in all the analyses according to different types of exposure (data not shown). The case–control analyses generally confirmed the findings in the cohort analyses. The magnitudes of the risk estimates were not directly comparable, however, since the case–control analyses were based on internal and the case–cohort on external comparisons. There was a statistically significant trend toward a higher risk of breast cancer with longer duration of estrogen treatment ($P = 0.02$ by conditional regression analysis).

Table 4. Odds Ratios in the Case–Control Analyses for Breast Cancer, According to Duration of Estrogen Treatment.*

Months of Treatment	Odds Ratio	
	Crude	Adjusted (95% Confidence Interval)†
≤6	1.0	1.0
7–36	1.0	1.0 (0.6–1.6)
37–72	1.2	1.2 (0.7–2.0)
73–108	1.3	1.5 (0.8–2.9)
≥109	2.1	2.3 (1.1–4.8)

*Odds ratios shown are relative to an odds ratio of 1.00 for women in the cohort who used estrogens for six months or less, including noncompliant subjects.

†Adjustment was made for education, previous breast biopsy for benign breast disease, and type of menopause (natural vs. surgical due to oophorectomy or hysterectomy) with conditional logistic regression analyses. $P = 0.02$ for trend with increasing duration.

Analyses of the relative risk of breast cancer according to the length of time since the first use of hormones (latency) were conducted in both the case–cohort and the case–control evaluations. In both analyses, the relative risks rose with increasing latency (e.g., to 1.4 for 10 years or more after the first use in the case–cohort analysis). Because of the high correlation between latency and duration of use, the independence of the effects of these two measures could not be assessed adequately.

Discussion

Overall, we noted a 10 percent increase in the relative risk of breast cancer in 23,244 women for whom estrogens were prescribed for symptoms of menopause. There was a tendency for this risk to increase with increasing duration of treatment, to an excess risk of 70 percent in women with more than nine years of use. This is consistent with the findings in two other cohort studies[7,15] and several case–control studies.[8-11] The present results thus provided added evidence of an increased risk of breast cancer after long-term perimenopausal exposure to estrogens.

In addition, we were able to evaluate the risk of breast cancer according to the type of estrogen used and the presence of progestin. Estradiol, the drug used most commonly in the cohort, is a potent estrogen. The separate analyses of estradiol use showed somewhat higher estimates of risk than the analyses of total estrogens, and approximately a doubling in the relative risk after more than six years of treatment. We found no association between weaker estrogens (mainly estriols) and the development of breast cancer. Nor was there any clear evidence of an increased risk of breast cancer after the use of conjugated estrogens, which are also potent estrogens and those most commonly used in the United States, where most of the previous studies have been done. The discrepancy between our negative findings and the American results with conjugated estrogens could be due to a lack of power in our data, since conjugated estrogens were involved in only approximately 20 percent of the treatment periods, and few of these periods exceeded five years. There was also a difference in the doses used. In the U.S. studies, a conjugated-estrogen dose of 1.25 mg or more was the most common,[9,10] whereas in our cohort most women used only 0.625 mg.[21]

Our study found that the addition of progestin offered no protection against the development of breast cancer. This observation raises concern about the long-term treatment with a combination of estrogens and progestins that has been proposed for widespread use as prophylaxis against osteoporosis in menopausal

women.[28] It also suggests different endocrine pathways in carcinogenesis in the breast and endometrium. Although progestins may have antiestrogenic properties in the breast as well as the endometrium,[29] high rates of division of the epithelial cells of the breast in the luteal as compared with the follicular phase of the menstrual cycle have been interpreted to suggest that estrogen in combination with progesterone may actually increase the risk of breast cancer over that associated with exposure to estrogen alone.[18]

In the interpretation of our findings, methodologic issues deserve some attention. Whereas the cohort was identified from prescription records initially, detailed characterization of the exposure with respect to the specific estrogen, the duration of use, and the use of progestins came from the questionnaires completed by the study subjects. The concerns raised by this procedure include the possibility of inaccurate recordings of exposure and the standard problem in case–control studies — the possibility of biased ascertainment of exposure — since the women with breast cancer completed the questionnaires after diagnosis. Neither possibility seems to give major reason for concern in this study, since a comparison of the prescription records with the reports of the study subjects for the same three-year period revealed a high level of correlation, similar for the patients with breast cancer and the cohort sample. Indeed, if anything, there seemed to be a tendency for patients with well-documented short-term use of estrogens to report that no such use had occurred — perhaps contributing to an underestimation of the relative risk associated with short-term use.

Concerns over potential confounding by other risk factors for breast cancer that might be associated with measures of hormonal drug use also seem to be groundless. When such potential confounding factors were taken into account in the case–control study within the cohort, the adjusted estimates of relative risk were very close to the unadjusted values. Finally, whereas a number of the relative risks and associated trends in this investigation were statistically significant, the number of observations on which they are based was relatively small. Some findings could be due to chance and need to be considered in the context of the results in other studies. In particular, the higher relative risks associated with the use of the combination regimen were not statistically different from the risks of estrogen use alone. Although this result is somewhat worrisome, we currently interpret it as indicating a lack of evidence that the concomitant use of progestin reduces the excess risk of breast cancer associated with long-term estrogen use. However, further research must also investigate the possibility that the addition of progestins to estrogen therapy may increase the risk of breast cancer.

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