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THE USE OF ESTROGENS AND PROGESTINS AND THE RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN

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Abstract *Background.* The effect of adding progestins to estrogen therapy on the risk of breast cancer in postmenopausal women is controversial.

Methods. To quantify the relation between the use of hormones and the risk of breast cancer in postmenopausal women, we extended our follow-up of the participants in the Nurses' Health Study to 1992. The women were asked to complete questionnaires every two years to update information on their menopausal status, use of estrogen and progestin preparations, and any diagnosis of breast cancer. During 725,550 person-years of follow-up, we documented 1935 cases of newly diagnosed invasive breast cancer.

Results. The risk of breast cancer was significantly increased among women who were currently using estrogen alone (relative risk, 1.32; 95 percent confidence interval, 1.14 to 1.54) or estrogen plus progestin (relative risk, 1.41; 95 percent confidence interval, 1.15 to 1.74), as compared with postmenopausal women who had never used hormones. Women currently taking hormones who had used such therapy for 5 to 9 years had an adjusted relative risk of breast cancer of 1.46 (95 percent confidence interval, 1.22 to 1.74), as did those currently using hormones who had done so for a total of 10 or more years (relative risk, 1.46; 95 percent confidence interval, 1.20 to 1.76). The increased risk of breast cancer associated with five or more years of postmenopausal hormone therapy was greater among older women (relative risk for women 60 to 64 years old, 1.71; 95 percent confidence interval, 1.34 to 2.18). The relative risk of death due to breast cancer was 1.45 (95 percent confidence interval, 1.01 to 2.09) among women who had taken estrogen for five or more years.

Conclusions. The addition of progestins to estrogen therapy does not reduce the risk of breast cancer among postmenopausal women. The substantial increase in the risk of breast cancer among older women who take hormones suggests that the trade-offs between risks and benefits should be carefully assessed. (N Engl J Med 1995;332:1589-93.)

ENDOGENOUS gonadal hormones have an important role in causing breast cancer. Early age at menarche and late menopause increase the risk of breast cancer.[1,2] The number and timing of deliveries also affect this risk.[3] Furthermore, among postmenopausal women, obesity is positively associated with serum concentrations of endogenous estrogen[4] and with moderate elevations in both the incidence of breast cancer and mortality from the disease.[5,6]

Hormone therapy also increases the risk of breast cancer in postmenopausal women. Meta-analyses and reviews[7] have assessed the relation between the duration of postmenopausal hormone therapy and the risk of breast cancer, but questions remain. Unresolved issues include the risks associated with estrogen plus progestins,[8] the risks with progestins alone, and the variation in risk according to age.[9] To address these issues, we extended the analysis of the participants in the Nurses' Health Study through 1992, adding 50 percent more prospective data to those in our previous report.[10]

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METHODS

The Nurses' Health Study was established in 1976, when 121,700 female registered nurses 30 to 55 years of age completed a mailed questionnaire that included items about known or suspected risk factors for cancer and cardiovascular diseases. Base-line information included details of risk factors for breast cancer,[11,12] the use of oral contraceptives, and the postmenopausal use of hormones. Every two years, we mail follow-up questionnaires to the women and ask them to update the information on risk factors, including whether they currently take hormones, the duration of hormone use, and the type of hormone preparation used (starting in 1978). We used the information on each questionnaire to define the women's status with respect to hormone therapy for the subsequent two-year period.

Identification of Cases of Breast Cancer

On each questionnaire, we asked whether breast cancer had been diagnosed and, if so, the date of diagnosis. We routinely searched the National Death Index for deaths among women who did not respond to the questionnaires. We asked all women who reported breast can-

cer (or the next of kin, for those who had died) for permission to review the relevant hospital records and confirm the diagnosis. Pathology reports, obtained for 93 percent of the cases, confirmed breast cancer in all but 10 women who reported it. Although hospital records could not be obtained for 7 percent of the cases, we based our analysis on all cases of newly diagnosed breast cancer, because the degree of accuracy of the participants' reports was extremely high among those for whom records were obtained. We omitted the small number of cases of carcinoma in situ (n = 157) from the primary analysis.

Population for Analysis

We excluded from the analysis all women who had reported breast cancer or other cancer (except nonmelanoma skin cancer) on the 1976 questionnaire and all premenopausal women. We classified a woman as postmenopausal from the time she returned a questionnaire on which she reported natural menopause or hysterectomy with bilateral oophorectomy. We classified women who reported hysterectomy without bilateral oophorectomy as postmenopausal when they reached the age at which natural menopause had occurred in 90 percent of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers).

As reported on the 1976 questionnaire, 23,965 women were postmenopausal; these women entered follow-up in the period from 1976 to 1978. The women's reported menopausal status was updated every two years, and the study population was expanded to include women in whom menopause occurred. By 1990, the beginning of the final two-year follow-up period for this analysis, 69,586 women were classified as postmenopausal. Follow-up of the cohort for the identification of nonfatal breast cancer by means of questionnaires and telephone interviews was 95 percent complete. For fatal breast cancer, follow-up was more than 98 percent complete.[13]

Statistical Analysis

For each participant, follow-up time was allocated according to the 1976 exposure variables, which were updated at the beginning of each two-year period on the basis of the information provided by the women on follow-up questionnaires. Follow-up terminated with the date of diagnosis of breast cancer, the date of death, or June 1, 1992. Women who reported a diagnosis of cancer other than nonmelanoma skin cancer on any questionnaire were excluded from subsequent follow-up. If no questionnaire was returned for a follow-up cycle and the woman had previously reported current postmenopausal hormone use, her hormone-use status was classified as missing in the updated analysis.

As a measure of association, we used the relative risk, defined as the incidence of breast cancer among women who had taken hormones after menopause divided by the incidence among women who had never used such therapy. We conducted stratified analyses to control for risk factors and to assess the possible influence of other risk factors for breast cancer on the effect of postmenopausal hormone use. We used proportional-hazards models to adjust for multiple risk factors simultaneously.[14]

To assess the relation between postmenopausal hormone therapy and mortality due to breast cancer, we identified all deaths due to breast cancer from 1976 through June 1, 1992, among women who were postmenopausal at the time of the diagnosis (n = 359). For each woman who died of breast cancer, we matched 10 women selected at random from among the women who were free from breast cancer, according to the year of birth and the age at menopause. We defined hormone use for these case patients and their controls as that reported on the questionnaire completed immediately before the diagnosis of breast cancer. To estimate the relative risk of breast cancer according to current and past postmenopausal hormone therapy, we used the odds ratio from a logistic regression in which we controlled for the year of birth and the age at menopause. This approach accounted for changes in estrogen use over time and avoided bias due to the discontinuation of hormone use by women who had received a diagnosis of breast cancer.

Results

During 725,550 person-years of follow-up, we identified 1935 cases of invasive breast cancer among postmenopausal women. Even though progestin use increased in this cohort, it did not add to the risk of breast cancer associated with the use of estrogen alone. Before 1986, few women took progestin. In 1986, 18 percent of postmenopausal women taking hormones used progestin; this proportion rose to 30 percent in 1990. Most women (73 percent) used conjugated estrogens; 77 percent of those who used estrogen omitted taking the drug for one week each month in 1986, and 66 percent did so in 1988. Almost all women receiving progestin took it for 14 or fewer days per month; the most common dose of medroxyprogesterone was 10 mg per day (used by 58 percent of the women who took this drug).

From 1978 to 1992, we observed a significant elevation in the risk of breast cancer among women using conjugated estrogens alone (adjusted relative risk, 1.32; 95 percent confidence interval, 1.14 to 1.54), estrogen plus progestin (adjusted relative risk, 1.41; 95 percent confidence interval, 1.15 to 1.74), and progestins alone (adjusted relative risk, 2.24; 95 percent confidence interval, 1.26 to 3.98) (Table 1). These relative risks did not differ significantly from each other. For each age at menopause, the relative risk of breast cancer was at least as high for women taking estrogen plus progestin as for those taking conjugated estrogens alone. The small number of cases among women taking estrogen plus progestin precluded detailed analysis of the risk according to duration of use and age. However, the similar relative risks for estrogen alone and for estro-

Table 1. Type of Hormone Currently Used by Postmenopausal Women and Relative Risk of Breast Cancer in the Nurses' Health Study, 1978 to 1992.

Hormone	Cases of Breast Cancer*	Person-Years of Follow-up	Relative Risk Adjusted for Age at Menopause and Type of Menopause	Multivariate Adjusted Relative Risk (95% CI)†
None	923	344,942	1.0	1.0
Conjugated estrogens alone	270	89,427	1.36	1.32 (1.14–1.54)
Other estrogens	53	16,202	1.37	1.28 (0.97–1.71)
Estrogen plus progestin	111	28,946	1.50	1.41 (1.15–1.74)
Progestins alone	12	1,983	2.40	2.24 (1.26–3.98)
Estrogen plus testosterone	4	810	1.78	1.64 (0.53–5.09)

*Cases do not total 1935, since only cases diagnosed from 1988 to 1992 in women who never used or currently used hormones are included.

†Adjusted for age in five-year intervals, type of menopause, age at menopause, parity, age at first delivery, age at menarche, family history of breast cancer, and history of benign breast disease. CI denotes confidence interval.

gen plus progestin suggest that these types of hormone use could be combined in analyses of the duration of therapy.

Among women currently taking hormones, the relative risk of breast cancer was highest among the oldest women (relative risk, 1.69 for women 65 to 69 years old, 1.42 for women 60 to 64 years old, 1.41 for those 55 to 59 years old, 1.46 for those 50 to 54 years old, and close to 1.0 for women younger than 50). The risk of breast cancer increased significantly only among women currently using hormone therapy who had used such therapy for five or more years. The dose of estrogen among these women did not differ from that received by women who had taken estrogen for less than five years. In contrast, women who had formerly used hormone therapy had no significant increase in risk as compared with women who had never used hormone therapy; this was true even for women who had taken hormones for five or more years in the past (Table 2).

Table 2. Duration of Current and Past Postmenopausal Hormone Therapy and Relative Risk of Breast Cancer in the Nurses' Health Study, 1976 to 1992.

Hormone Use	Cases of Breast Cancer	Person-Years of Follow-up	Adjusted Relative Risk (95% CI)*
None	972	374,197	1.0
Current			
1–23 Mo	82	31,966	1.14 (0.91–1.45)
24–59 Mo	140	49,672	1.20 (0.99–1.44)
60–119 Mo	150	44,112	1.46 (1.22–1.74)
⩾120 Mo	141	37,454	1.46 (1.20–1.76)
Past			
1–23 Mo	193	81,047	0.90 (0.77–1.05)
24–59 Mo	120	54,046	0.86 (0.71–1.05)
60–119 Mo	89	34,952	1.00 (0.80–1.26)
⩾120 Mo	48	18,104	1.03 (0.76–1.41)

*Adjusted for age, type of menopause, age at menopause, parity, age at first delivery, age at menarche, family history of breast cancer, history of benign breast disease, and time period. CI denotes confidence interval.

As compared with postmenopausal women who had never taken hormones, and after controlling for the age at menopause, the type of menopause, and family history, the relative risk of breast cancer among postmenopausal women who used hormones was 1.54 (95 percent confidence interval, 1.19 to 2.00) for those 55 to 59 years of age who had taken hormones for five or more years. For women 60 to 64 years of age, the relative risk was 1.71 (95 percent confidence interval, 1.34 to 2.18). A shorter duration of use was not consistently related to the risk of breast cancer (Fig. 1).

The multivariate adjusted relative risk for five or more years of past use was 0.92 (95 percent confidence interval, 0.63 to 1.35) among women 55 to 59 years old and 1.13 (95 percent confidence interval, 0.83 to 1.55) among those 60 to 64 years old when these women were compared with those who never took hormones. Women who stopped taking hormones after five or more years of use were at increased risk of breast cancer for a short period after stopping. For those who had stopped taking hormones less than two years earlier, the multivariate adjusted relative risk was 1.44 (95 percent confidence interval, 0.99 to 2.08); for those who had stopped two to four years earlier, the relative risk was 0.80 (95 percent confidence interval, 0.55 to 1.16); and for those with five or more years since their most recent use of hormones, the relative risk was 0.95 (95 percent confidence interval, 0.74 to 1.25).

On the basis of the 359 deaths due to breast cancer among women who were postmenopausal at the time of diagnosis, the overall relative risk of death, adjusted for family history and history of benign breast disease, was 1.14 (95 percent confidence interval, 0.85 to 1.51) for women currently taking hormones and 0.80 (95 percent confidence interval, 0.60 to 1.07) for those who used hormones in the past. The relative risk for women currently taking hormones with less than five years of use at the time of diagnosis was 0.99 (95 percent confidence interval, 0.66 to 1.48), and for women with five or more years of use, the relative risk of death from breast cancer was 1.45 (95 percent confidence interval, 1.01 to 2.09).

Discussion

In this prospective cohort study, we observed an elevated risk of invasive breast cancer among postmenopausal women who were currently taking estrogen alone or both estrogen and progestin. The increase in risk was most pronounced among women over the age of 55 and was largely limited to the women who had used hormone therapy for five or more years. These

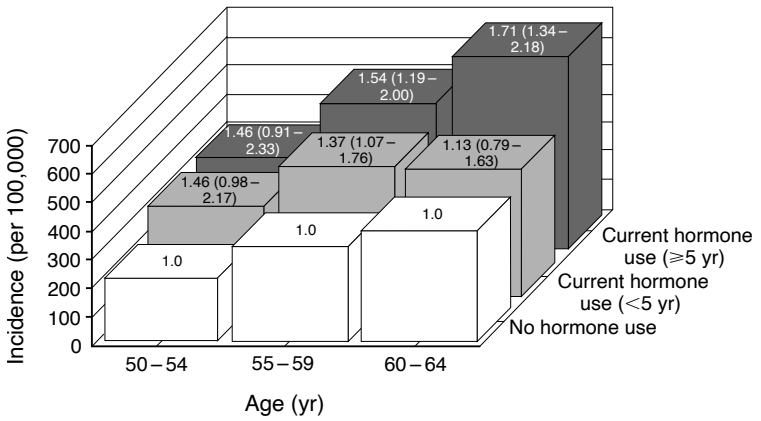

Figure 1. Incidence and Relative Risk of Breast Cancer According to Age and the Duration of Current Postmenopausal Hormone Therapy.

Relative risks and 95 percent confidence intervals are shown on the top of the bars; relative risks are expressed in comparison with the risk among women in each age group who never received hormone therapy. Data have been adjusted for age at menopause, type of menopause, and family history of breast cancer in a proportional-hazards analysis.

data on women in the United States thus confirm findings from Europe, where combination therapy with estrogen plus progestins has been associated with an increased risk of breast cancer.[15-17] Because widespread use of progestins is a recent phenomenon, we were unable to examine associations with risk according to the dose or duration of progestin use. Furthermore, we have no data to explain why women in this cohort take hormones after menopause or why they stop.

The addition of progestin to estrogen therapy has been growing more common in the United States, but epidemiologic data on the effects of combination therapy are limited.[18] The initial report by Gambrell et al.[19] (based on 11 cases of breast cancer among women receiving estrogen plus progestin) suggested that combination therapy has a protective effect against breast cancer, but that study did not control for age or other confounding factors. Subsequent studies have found an elevated risk of breast cancer among Danish women who took sequential estrogen plus progestin (62 cases; relative risk, 1.4) and among Swedish women with a history of long-term use of combined hormone therapy (10 cases; relative risk, 4.4). In a British study, the risk of breast cancer was similar among women taking estrogen alone and among those taking estrogen plus progestin. Among three U.S. case–control studies[20-22] (a total of 48 cases in women who took hormones), two found an increased risk in association with combined therapy (as compared with no use of hormones),[20,22] and one found no association.[21] The multivariate adjusted relative risk of breast cancer that we observed (1.41) is compatible with the confidence intervals in all previous studies (except that of Gambrell et al.) and is based on 111 cases in women taking estrogen plus progestin. These data clearly indicate that the addition of progestin does not reduce the risk of breast cancer that is associated with estrogen use in postmenopausal women. Ductal cells of the breast therefore respond differently from the endometrium, where the addition of a progestin counters the adverse effect of estrogen. Hence, these data do not support the use of progestin by women who have undergone hysterectomy.

Estrogens increase serum hormone concentrations to approximate those in premenopausal women,[23-26] and 1.25 mg of conjugated estrogens has a greater effect than 0.625 mg.[26] There is evidence that progestins, when added to estrogen, may enhance the proliferation of epithelial cells in the breast.[27]

One potential source of bias in our study is the differences in the rates of participation in mammographic screening. We addressed this problem in several ways. First, because mammography detects a larger proportion of in situ breast cancers than other methods, we excluded such cases from this analysis. As expected, current use of hormones was somewhat more strongly associated with in situ disease (age-adjusted relative risk, 1.95), a finding that is consistent with the slightly higher frequency of screening mammography among postmenopausal women taking hormones. However, the age-standardized rate of screening mammography was only about 14 percent higher among women currently using hormones and 8 percent higher among past users of hormones than among postmenopausal women who never used hormones. Furthermore, from 1988 to 1992, only 9 percent of women who never used hormones, 6 percent of past users, and 3 percent of those currently using hormones did not undergo at least one mammogram. This difference is proportionately much smaller than the increase in risk for current users of hormones, and the large majority of women had been screened previously. Thus, it is unlikely that differences in the frequency of mammographic studies can explain the elevation in the risk of breast cancer among current postmenopausal recipients of hormone therapy. Moreover, postmenopausal women who received hormone therapy in the past and those who had been taking such hormones for less than five years were not at increased risk for breast cancer despite a higher rate of screening mammography. Finally, the higher risk of death due to breast cancer among women who had taken hormone therapy for five or more years at the time of diagnosis adds further weight to the causal association, because analyses based on mortality overcome problems of lead time and selective detection of tumors.[28]

In this analysis, we confirmed our earlier finding of a greater increase in the risk of breast cancer among older women taking hormones after menopause. This finding is consistent with data from several case–control studies that suggested an increased risk among older women, independent of the duration of hormone use.[21,29,30] This effect was stronger among women with five or more years of current use of hormones. The lack of association between current estrogen therapy and breast cancer among younger women may be due at least in part to the short time since menopause. Our data and those from several case–control studies suggest that the use of hormones at older ages after menopause may have a particularly deleterious effect on the risk of breast cancer.

These findings suggest that women over 55 years of age should carefully consider the risks and benefits of estrogen therapy, especially if they have used estrogen for five or more years. It is not clear that benefits outweigh risks for all women, particularly women with few risk factors for heart disease. Furthermore, short-term estrogen therapy — for up to seven years — in the decade after menopause cannot be expected to protect against osteoporotic fractures many years later.[31,32] Our data indicate that the addition of progestins to postmenopausal estrogen therapy does not reduce the risk of breast cancer. Estrogen alone, estrogen plus progestin, and progestins alone all appear to raise the risk of breast cancer. The significant increase in the risks of breast cancer and of death due to breast cancer among postmenopausal women over 55 who are currently taking hormones and who have used this therapy for five or more years suggests that the risks and benefits of hormone therapy among older women should be carefully assessed.

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