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Cumulative Risk of Breast Cancer to Age 70 Years According to Risk Factor Status: Data from the Nurses' Health Study

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Because of the temporal relations between reproductive risk factors and incidence of breast cancer, the authors developed a nonlinear Poisson regression that accounts for time and summarizes risk to age 70 years. Reproductive risk factors, benign breast disease, use of postmenopausal hormones, weight, and alcohol intake were evaluated as risk factors. Among 58,520 women aged 30–55 years in 1980, followed through June 1, 1994, 1,761 incident invasive breast cancer cases were identified. All risks are multivariate adjusted. History of benign breast disease is associated with a 57% increase (95% confidence interval (CI): 43%, 73%) in cumulative risk of breast cancer by age 70 years. Use of unopposed postmenopausal estrogen from ages 50–60 years increases risk of breast cancer to age 70 by 23% (95% CI: 6%, 42%) compared with a woman who never uses hormones. Ten years of use of estrogen plus progestin increases risk to age 70 years by 67% (95% CI: 18%, 136%). Compared with never drinking alcohol, one drink per day from age 18 years increases risk to age 70 by 7% (95% CI: 0%, 13%). Use of unopposed postmenopausal hormones for 10 years significantly increases the risk of breast cancer, and the addition of progestin further increases the risk. *Am J Epidemiol* 2000;152:950–64.

breast neoplasms; hormones; incidence; reproduction; risk

Biomathematic models relate epidemiologic risk factors to disease incidence and provide a structure within which we might interpret the process of carcinogenesis (1). We developed a multiple-births Poisson regression model (2) that extends an analytic approach to breast cancer incidence proposed by Pike et al. (3) in 1983. The Pike model and similar work by Moolgavkar et al. (4) relate the timing of reproductive events that are established risk factors for breast cancer to the incidence of disease. Early applications of nonlinear models produced parameters that were difficult to interpret (5). Subsequently, we modified our analytic approach to allow ready estimation of relative risks, thus making the results more accessible to epidemiologists and clinicians familiar with the relative risk as a measure of the relation between an exposure and disease.

Based on the Nurses' Health Study data, our previous reports included age at menarche, age at first birth, age at subsequent births, and age at menopause in the regression model predicting breast cancer incidence (2). The underlying biologic concept is that these reproductive factors modify the rate of breast cell proliferation and the accumulation of DNA damage (3). Age at menopause has been shown to be positively related to risk of breast cancer; for each year increase in age at menopause, the risk of breast cancer increases by approximately 3 percent (6, 7). In addition, the type of menopause is an important determinant of breast cancer risk. Bilateral oophorectomy substantially reduces the risk of breast cancer (8). Thus, if age at menopause or type of menopause either is not included or is inaccurately specified (e.g., by categorization into two or three broad age at menopause groups) in a traditional statistical analysis, then the estimated effects of other postmenopausal breast cancer risk factors may be biased (9).

Duration of postmenopausal hormone (PMH) use is positively related to the risk of breast cancer across many epidemiologic studies, although the magnitude of the increase in risk with increasing duration of use varies among studies (10). The combined reanalysis of data from 50 studies, including more than 50,000 cases of breast cancer, indicates that the risk of breast cancer increases significantly by 2.3 percent with each year of use (11). That is, the relative risk (RR) per year of use was 1.023 (95 percent confidence interval (CI): 1.011, 1.036, $p = 0.0002$). The risk for 5 or more years of use was 1.35 (95 percent CI: 1.21, 1.49). Because typical analytic methods used in epidemiologic studies control for age, age at menopause, and duration of use of hormones using somewhat broad categories, such as 5-year age or age at menopause groups, there is potential for considerable residual confounding that may lead to misspecification of the risk associated with use of PMH. Long-term users at any given age are likely to have had an earlier menopause than other women of the same age. For example, in the

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Abbreviations: BMI, body mass index; BBD, benign breast disease; CI, confidence interval; ERT, estrogen replacement therapy; PMH, postmenopausal hormones; RR, relative risk.

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Nurses' Health Study, we presented results controlling for age at menopause in three categories: 47 or less, 48–52, and 53 or more years (12). Among women aged 45–49 years who had menopause before age 47, there are substantial differences in duration of menopause across categories of use of PMH. For never users of hormones, the mean duration of menopause is 6.9 years; for current users of less than 5 years duration, the mean duration of menopause is 5.3 years; and for current users with 5 or more years of use, it is 10.2 years. Clearly, this stratification did not control for age at menopause with sufficient rigor to remove bias in estimates of the effects of PMH due to the differing durations of menopause. As Pike et al. noted, age at menopause is invariably negatively associated with duration of use of PMHs. Thus, this standard approach to statistical modeling with incomplete control for age at menopause does not give an unbiased estimate of the effect of PMHs but rather underestimates the relation between use of hormones and the risk of breast cancer (9). As indicated in more detail in Materials and Methods, because duration of menopause is crucial, we excluded women with hysterectomy since the age at which periods ceased is unknown.

Comparison of the long-term impact of risk factors for breast cancer is often difficult because risk factors frequently change in magnitude and even direction over different periods of life. Cumulative incidence to age 70 years provides one measure that avoids these limitations of age-specific relative risks. In this paper, we address the contributions of benign breast disease (BBD), PMH, reproductive factors, adiposity (BMI), height, alcohol use, and family history to the incidence of breast cancer and the probability of diagnosis prior to age 70. These analyses are conducted within the Nurses' Health Study.

MATERIALS AND METHODS

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire that included terms about known or suspected risk factors for cancer and cardiovascular diseases. Baseline information included details of known or suspected breast cancer risk factors. In 1976, women reported their age at first full-term pregnancy and the number of pregnancies lasting 6 months or more. In 1978, this information on the number of children was updated, and the ages of living children were recorded by the participants. Every 2 years, follow-up questionnaires have been mailed to the women to bring the information on risk factors up to date and to ascertain whether major medical events have occurred. Data on parity were updated through 1985. On each questionnaire, we inquired about whether breast cancer had been diagnosed and, if so, requested the date of diagnosis. All women who reported breast cancer (or the next-of-kin for deceased participants) were contacted for permission to review the relevant hospital records and confirm the self-reported diagnosis. Pathology reports were obtained for 93 percent of the cases, and information on histologic tumor type, tumor size, and node involvement was extracted by physicians. Although permission to review pathology reports and hospital records could not be obtained for 7 percent of cases, we based our analysis on all incident breast cancers because the rate of accuracy of self-reporting was extremely high (99.6 percent). We excluded from analysis the small number of carcinomas in situ. To extend the model of breast cancer incidence, we added terms to the Poisson regression model previously described (2). We now address the impact of six additional breast cancer risk factors: benign breast disease, type of menopause, use of PMH, weight, height, and alcohol intake.

The data on benign breast disease are drawn from responses to the Nurses' Health Study questionnaire (13). The baseline questionnaire in 1976 asked women whether they had had a physician diagnosis of fibrocystic breast disease or other benign breast disease. On subsequent follow-up questionnaires mailed every 2 years, these questions were repeated. An affirmative response to either of these questions classified a woman as having benign breast disease from that time on.

For menopause, women indicated whether their periods had ceased and if so how—naturally, due to hysterectomy with bilateral oophorectomy, due to hysterectomy with one ovary removed, or due to hysterectomy without removal of ovaries. In this cohort, report of surgical menopause is highly accurate (14). We therefore classified type of menopause as natural, bilateral oophorectomy, or hysterectomy with either one or no ovaries removed. Data on the type of menopause were updated every 2 years so that newly postmenopausal women were classified as such and were added to the population of postmenopausal women. We did not change the age or type of menopause reported by a woman on subsequent reports after her first indication that her menstrual periods had ceased.

We defined type of PMH used on the basis of the response on the 1978 questionnaire and subsequent questionnaires. From 1978 onward, women indicated whether they used conjugated estrogens or progestin and, if so, the dose of estrogen and progestin used. In addition, from 1980 onward, women indicated whether they used hormones continuously or if they stopped estrogen for 7 days per month or used progestin for only 10–14 days per month or continuously.

Weight was reported on every follow-up questionnaire, and in 1980, women were asked to report their weight at age 18 years. The validity of self-reported current weight and weight at age 18 is high (15, 16). We then estimated weight at single years of age by using linear interpolation methods. With this weight, we calculated BMI (weight/height^2) at each year of age by using height reported in 1976. Alcohol intake was reported in 1980. We assumed that this applied to adult intake and then updated alcohol intake with each subsequent follow-up questionnaire on which this was reported. If a questionnaire was missing or alcohol was not assessed, the intake was assumed to be unchanged. Family history of breast cancer diagnosed in a mother or a sister was recorded in 1976 and updated in 1982 and 1988. We do not include age at diagnosis among the first-degree relatives when fitting family history in this model.

Population for analysis

There were a total of 121,700 women in the Nurses Health Study cohort in 1976, of whom 119,421 did not report a history of any cancer (excluding nonmelanoma skin cancer) on the 1976 questionnaire; of these women, 105,423 returned the 1978 questionnaire that sought details on the age of each child. We further excluded 4,205 women for whom the number of pregnancies reported in 1976 was different by two or more children from the estimated number of pregnancies in 1976 on the basis of reported ages of children in 1978. We excluded another 6,993 women for whom the number of living children derived from the 1978 response differed from their parity (reported in two separate questions) in 1978. We also excluded 2,758 women for whom the number of living children in 1978 was less than their reported number of children in 1976. In addition, we excluded 412 women whose age at first birth estimated from the reported ages of children in 1978 was greater than (three + age at first birth reported in 1976). In addition, we excluded 768 women whose age at menarche either was unknown or was reported to be less than or equal to 8 or greater than or equal to 22 years. Further exclusions included unknown parity ($n = 199$), age at any birth greater than age at menopause ($n = 677$), women reported to be nulliparous in 1976 whose age of the oldest child was greater than 2 years in 1978 ($n = 202$), and women whose menopausal status and/or age at menopause was unknown ($n = 49$). We also excluded 10 women whose age of death was unknown. This left 89,150 women. For the current analyses, we excluded 10,752 women with missing height (in 1976) or weight at age 18 years and 1,266 for whom we were missing details of PMH use. To allow accurate control for age at menopause, we excluded 3,012 women with hysterectomy and one ovary removed, 9,066 women with a hysterectomy and no ovaries removed, and 6,534 women with "other" types of menopause (including missing type). For these women, we did not have an age at menopause and could not control for the duration of menopause. As we have shown (17), inclusion of these women and allocation of a presumed age at menopause leads to a biased estimate of the relations between duration of hormone use and risk of breast cancer.

The number of cases from 1980 through 1994 is 1,761 confirmed among 58,520 women during 766,817 person-years of follow-up. Subjects were followed until June 1, 1994, the date of return of the last questionnaire, the development of any cancer, or death, whichever occurred first. Person-years of follow-up varied by age, ranging from 4,235 for women aged 70–74 years to more than 135,000 among each of the age groups 45–49, 50–54, and 55–59 years.

Description of model

Model fitting. The approach to model fitting is to assume that incidence at time $t(I_t)$ is proportional to the number of breast cell divisions C_t accumulated throughout life up to age t, that is

$$I_t = kC_t \tag{1}$$

The cumulative number of breast cell divisions is factored as follows:

$$C_t = C_0 X \prod_{i=0}^{t-1} (C_{i+1}/C_i) = C_0 X \prod_{i=0}^{t-1} \lambda_i. \tag{2}$$

Thus, $\lambda_i = C_{i+I}/C_i$ represents the rate of increase of breast cell divisions from age i to age $i + 1$. Log (λ_i) is assumed to be a linear function of risk factors that are relevant at age i. The relevant risk factors vary according to the stage of reproductive life. The details of the representation of the C_i are given in appendix 1. We have:

$$\begin{aligned}
\log I_t = {} & \alpha + \beta_0(t^* - t_0) \\
& + \beta_1 b + \beta_2(t_1 - t_0) b_{1,t-1} \\
& + \gamma_1(t - t_m) m_A + \gamma_2(t - t_m) m_B \\
& + \delta_1 dur_PMH_A + \delta_2 dur_PMH_B + \delta_3 dur_PMH_C \\
& + \delta_4 PMH_{cur,t} + (\delta_4 + \delta_5) PMH_{past,t} \\
& + \beta_3 BMI_1 + \beta_3^* BMI_2 + \beta_4 h_1 + \beta_4^* h_2 \\
& + \beta_5 ALC_1 + \beta_5^* ALC_2 + \beta_5^{**} ALC_3 \\
& + \alpha_1 BBD + \alpha_2 BBD\, t_0 + \alpha_3 BBD\, (t^* - t_0) \\
& + \alpha_4 BBD\, (t - t_m) m_t + \theta\, FHX
\end{aligned} \tag{3}$$

where t = age;
t_0 = age at menarche;
t_m = age at menopause;
t^* = min(age, age at menopause);
$m_i = 1$ if postmenopausal at age i, $= 0$ otherwise;
s = parity;
t_i = age at ith birth, $i = 1,..,s$;
b = birth index $= \sum_{i=1}^{s} (t^* - t_i) b_{it}$
$b_{it} = 1$ if parity $\geq i$ at age t, $= 0$ otherwise;
$m_A = 1$ natural menopause, $= 0$ otherwise;
$m_B = 1$ if bilateral oophorectomy, $= 0$ otherwise;
$BBD = 1$ if benign breast disease = yes, $= 0$ otherwise;
$FHX = 1$ if family history of breast cancer = yes, $= 0$ otherwise;
dur_PMH_A = number of years on oral estrogen;
dur_PMH_B = number of years on oral estrogen and progestin;
dur_PMH_C = number of years on other types of postmenopausal hormones;
$PMH_{cur,t} = 1$ if current user of postmenopausal hormones at age t, $= 0$ otherwise;
$PMH_{past,t} = 1$ if past user of postmenopausal hormones at age t, $= 0$ otherwise;

BMI_j = body mass index at age j (kg/m^2);
ALC_j = alcohol consumption (grams) at age j;
h = height (inches).

$$BMI_1 = \sum_{j=t_o}^{t^*-1}(BMI_j - 21.8) + \sum_{j=t_m}^{t-1}(BMI_j - 24.4)PMH_{cur,j}\,m_j$$

$$BMI_2 = \sum_{j=t_m}^{t-1}(BMI_j - 24.4)(1 - PMH_{cur,j})m_j$$

$$h_1 = (h - 64.5)(t^* - t_o) + (h - 64.4)\sum_{j=t_m}^{t-1}PMH_{cur,j}m_j$$

$$h_2 = (h - 64.4)\sum_{j=t_m}^{t-1}(1 - PMH_{cur,j})m_j$$

$$ALC_1 = \sum_{j=18}^{t^*-1}ALC_j$$

$$ALC_2 = \sum_{j=1}^{t-1}ALC_jPMH_{cur,j}m_j$$

$$ALC_3 = \sum_{j=t_m}^{t-1}ALC_j(1 - PMH_{cur,j})m_j.$$

β_0 represents the rate of increase in incidence prior to menopause among women without BBD. β_1 and β_2 represent modification to this rate of increase for parous women according to the number and precise spacing of births. The regression coefficient for the birth index can be interpreted as the decrease in the age-specific log incidence for each year after an additional child is born. β_2 represents the immediate increase in log incidence after first birth per year increase in $t_1 - t_0$. δ_1, δ_2, and δ_3 represent modifications to the rate of increase after menopause among women currently using PMH according to the type of PMH used. The terms δ_4 and δ_5 represent the immediate effect of starting and stopping PMH use on rates of increase after menopause. θ represents the effect of family history of breast cancer on the number of breast cell divisions at birth (i.e., C_0).

β_3 represents the effect of BMI either before menopause or while currently on PMH and after menopause. β^*_3 represents the effect of BMI after menopause, while not on PMH. β_4 and β^*_4 are similarly defined effects for height. β_5, β^*_5, and β^{**}_5 are effects of 1 ounce of alcohol consumption before menopause, after menopause while on hormones, and after menopause while not on hormones, respectively. The rationale for the separate terms is the finding in exploratory analyses and previous literature that effects of BMI and possibly height and alcohol are different before and after menopause and that the effect of BMI after menopause differed according to whether a women was or was not currently on PMH (18).

α_1, α_2, α_3, and α_4 represent modification to 1) the number of breast cell divisions at birth, 2) the rates of increase in the number of cell divisions after birth and before menarche, 3) the rates of increase in the number of cell divisions after menarche and before menopause, and 4) the rates of increase in the number of cell divisions after menopause, respectively, among women with BBD. The rationale for the extra terms involving BBD (α_1,…,α_4) is the observation made in exploratory analyses that the relative risk for BBD (yes vs. no) varied according to age; it was strongest among younger women and diminished over time.

We calculated cumulative incidence to age 70 years and report relative risks for the cumulative risks. Confidence intervals are calculated for these relative risks (see appendix 2 for the derivation of the formulas of the confidence intervals).

RESULTS

We examined models separately for women without family history and for those with family history. Because relationships were similar in each stratum, we combined data and controlled for family history to derive the breast cancer incidence model. Results for the total population are presented in table 1.

Consistent with previously reported results (5), reproductive factors showed the known relations with risk of breast cancer (table 1). There were important differences between BBD-positive and BBD-negative women, particularly regarding the effects of age at menarche. For nulliparous BBD-negative women, there was a strong effect of age at menarche (RR = $e^{-(0.085)4} = 0.71$ comparing women with an age at menarche of 15 years with women with an age at menarche of 11, $p < 0.001$). However, for BBD-positive women, there was virtually no effect of age at menarche (RR = $e^{-4[(0.085-0.014-0.067]} = 0.98$, p = nonsignificant). In addition, there was a nonsignificant increase in risk at birth for BBD-positive versus BBD-negative women when all other factors were held constant ($e^{0.190} = 1.21$), possibly implying a differential genetic profile at birth. The incidence profile of BBD-positive and BBD-negative women is depicted in figure 1. This figure represents the multivariate-adjusted incidence for a woman with two births (at ages 20 and 23 years), no family history of breast cancer, natural menopause at age 50 years, menarche at age 13, and no use of PMH, who is of average height and average BMI and a lifetime nondrinker of alcohol. Subsequent figures pertain to BBD-negative women and vary one risk factor while holding other risk factors of the above levels. Other aspects of the reproductive risk profile were similar for BBD-positive and BBD-negative women (data not shown).

Regarding pregnancy history, women with multiple births with a first birth at an early age had a reduced risk relative to nulliparous women at or after menopause ($p < 0.001$). For example, woman A, with four births at ages 20, 23, 26, and 29

TABLE 1. Fitted breast cancer incidence model, Nurses' Health Study, 1976–1994

	Beta	SE*
Fitted model		
Constant	–9.396	0.251
Duration of premenopause (years)†	0.085	0.007
Menopause		
Duration of menopause (years)		
Natural	0.025	0.006
Bilateral oophorectomy	0.009	0.009
Pregnancy history		
Age at 1st birth – age at menarche (years)	0.010	0.005
Birth index	–0.0042	0.0008
BBD*		
BBD (yes vs. no)	0.190	0.525
BBD × age at menarche	0.067	0.026
BBD × (duration of premenopause)	–0.014	0.010
BBD × (duration of menopause)	–0.015	0.007
Postmenopausal hormones		
Duration of oral estrogen use	0.049	0.011
Duration of oral estrogen and progesterone	0.097	0.026
Duration of use of other types of postmenopausal hormones	0.038	0.017
Current postmenopausal hormone use	–0.129	0.088
Past postmenopausal hormone use	–0.195	0.081
BMI*		
(Average BMI during premenopause – 21.8) × (duration of premenopause)‡	–0.0013	0.00027
(Average BMI after menopause – 24.4) × (duration of menopause)§	0.0049	0.0008
Height		
(Height – 64.5) × duration of pre-menopause‡	0.00096	0.00033
(Height – 64.4) × duration of menopause§	–0.0018	0.0018
Alcohol		
Cumulative ounces before menopause	0.00017	0.00008
Cumulative ounces after menopause		
With use of hormones	0.00031	0.0002
Without use of hormones	0.00022	0.0004
Family history (yes vs. no)	0.40	0.07

* SE, standard error; BBD, benign breast disease; BMI, body mass index.
† MIN (age, age at menopause), age at menarche.
‡ Including time postmenopause when on postmenopausal hormones.
§ Time postmenopause when not on postmenopausal hormones.

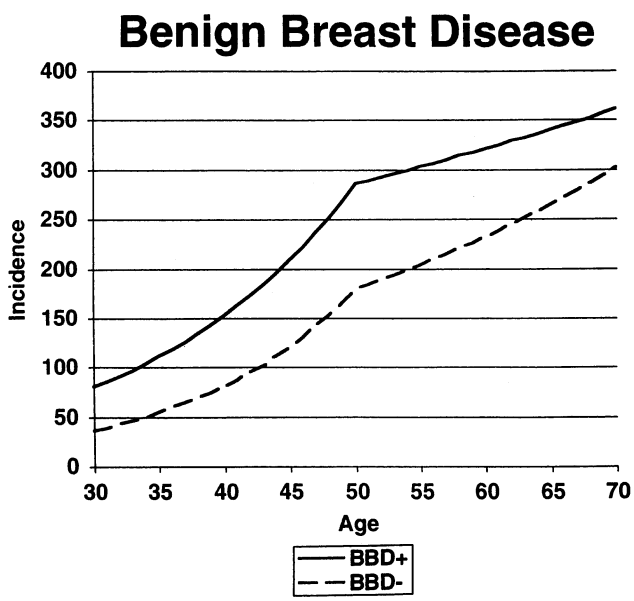

FIGURE 1. Age-specific incidence per 100,000 person-years of breast cancer for women with benign breast disease, assuming age at menarche = 13 years, age at natural menopause = 50 years, two births at ages 20 and 23 years, no family history, no use of PMH, average height, average BMI, and lifetime nondrinkers.

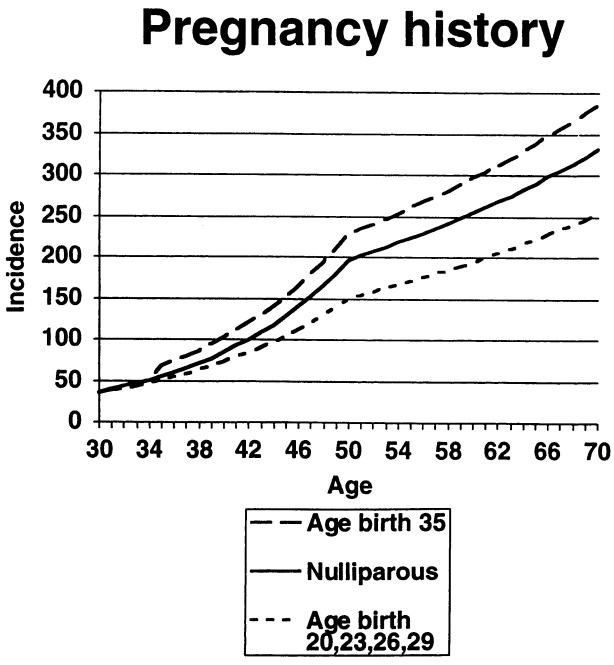

FIGURE 2. Age-specific incidence of breast cancer for a nulliparous woman, a parous woman with births at ages 20, 23, 26, and 29 years, and a parous woman with a single birth at age 35 years.

years, age at menopause = 50 years, and age at menarche = 13, had a birth index of 102 and relative risk at or after menopause of $e^{[-0.0042(102)+0.010(7)]} = e^{-0.358} = 0.70$ compared with a nulliparous woman with the same age at menarche and at menopause. Conversely, a woman with a single birth at a late age (e.g., age 35 years) with the same age at menarche and at menopause (woman B) had a birth index of 15 and a relative risk at or after menopause of $e^{[-0.0042(15)+0.010\ (22)]} = e^{0.157} = 1.17$ compared with a nulliparous woman. In addition, there was a differential effect of pregnancy history according to age, with parity affording more protection as a premenopausal woman progresses to menopause. For example, at age 35 years, the birth index for woman A = 42, and the comparative relative risk versus a nulliparous woman would be $e^{[-0.0042(42)\ +\ 0.010(7)]} = 0.90$. For woman B, the birth index = 0, and the comparable relative risk versus a nulliparous woman would be $e^{0.010(22)} = 1.25$. A comparison of incidence rates from ages 30 to 70 years according to pregnancy history is given in figure 2.

TABLE 2. Annual increase in risk of breast cancer according to menopausal status, type of hormone replacement therapies, reproductive history, and BBD* status†, Nurses' Health Study, 1976–1994

Menopausal status	Parity	Type of menopause	BBD-negative women			BBD-positive women		
			Type of hormone replacement therapy (%)			Type of hormone replacement therapy (%)		
			None	ERT*	HRT*	None	ERT	HRT
Postmenopausal	Any	Bilateral oophorectomy	1.0	6.0	11.2	0.0	4.4	9.5
Postmenopausal	Any	Natural	2.6	7.7	13.0	1.1	6.0	11.3
Premenopausal	0		8.9			7.4		
Premenopausal	2		8.0			6.5		
Premenopausal	4		7.1			5.6		

* BBD, benign breast disease; ERT, oral estrogen replacement therapy; HRT, oral estrogen and progesterone replacement therapy.
† Controlling for menopause, pregnancy history, BBD, postmenopausal hormone use, body mass index, height, alcohol use, and family history of breast cancer.

The rate of increase in incidence of breast cancer after menopause is generally slower than that during premenopause. However, the actual rate of increase depends on the type of menopause, whether PMH are used, and which specific type of hormone is used. In addition, the rate of increase is different for BBD-positive and BBD-negative women. The results are summarized in table 2. For BBD-negative women who do not use hormone replacement therapy, the rate of increase is 2.6 percent per year (95 percent CI: 1.4 percent, 4.0 percent) for women who have had a natural menopause and 1.0 percent per year (95 percent CI: –1.0, 2.8 percent) for women who have had a bilateral oophorectomy.

Women who used estrogen replacement therapy (ERT) with natural menopause had an annual increase in risk that was 7.7 percent (95 percent CI: 5.0 percent, 10.5 percent) per year of use, and women who used estrogen plus progestin had an annual increase that was 13.0 percent per year of use (95 percent CI: 7.2 percent, 19.1 percent). The rate of increase with estrogen plus progestin was borderline statistically significant greater than the rate among women using ERT ($p = 0.06$). The effects of age at menopause, type of menopause, and type of PMH therapy for BBD-negative women are illustrated in figures 3–5.

We next examined dose of estrogen and observed no increase in risk with higher dose. We also examined patterns

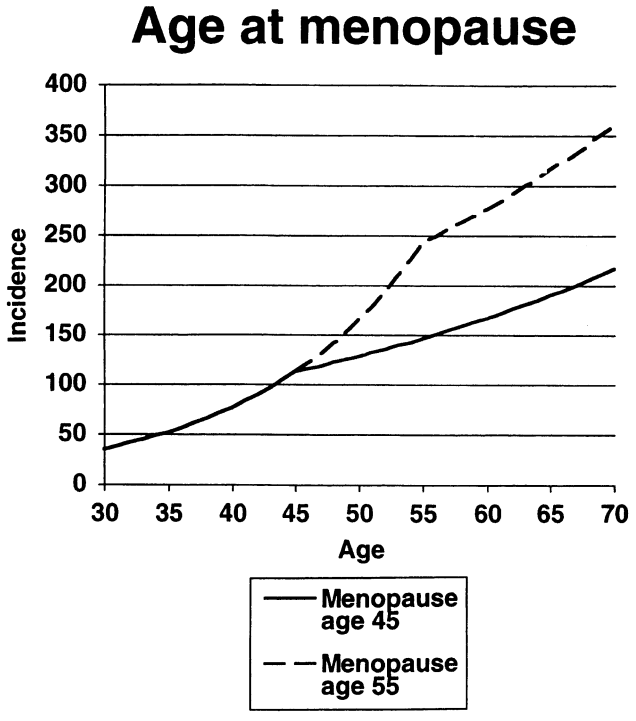

FIGURE 3. Age-specific incidence of breast cancer for a woman with menopause at age 45 years and another with menopause at age 55 years.

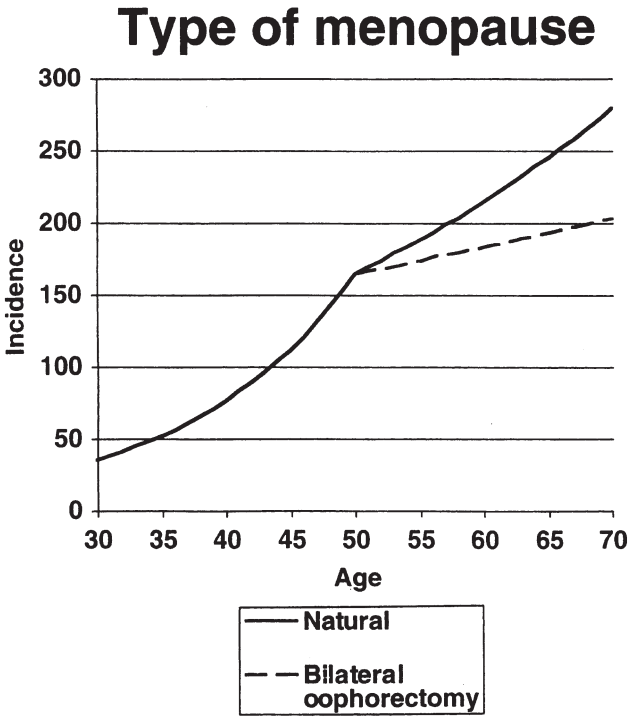

FIGURE 4. Age-specific incidence of breast cancer for a woman with natural menopause at age 50 years, and a woman with bilateral oophorectomy at age 50 years.

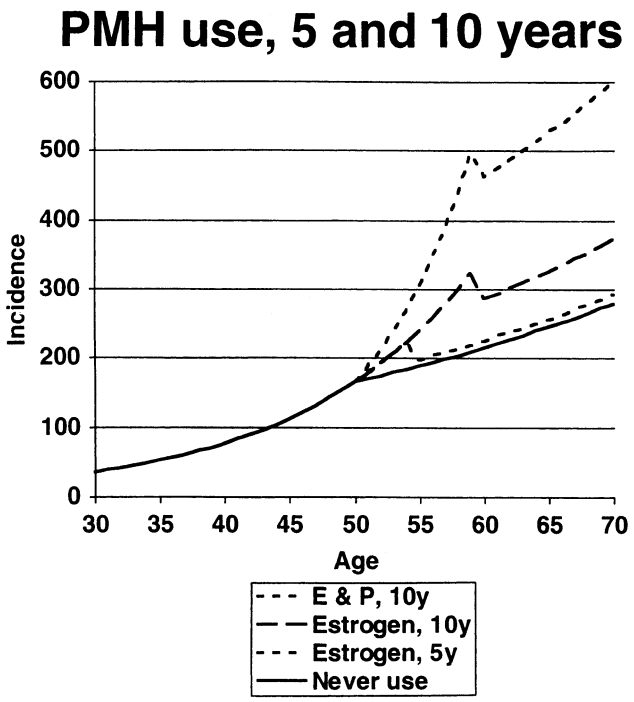

FIGURE 5. Age-specific incidence of breast cancer for a woman who never used PMH, a woman who used estrogen alone from ages 50–60 and 50–55 years and a woman who used estrogen plus progestin from ages 50–60.

of use and observed that cyclic use did not confer greater risk than continuous use of hormones. The number of women using progesterone continuously was small, however, so this analysis had low power to detect differences.

We evaluated the possible interaction between past use and duration of use of estrogen therapy. This interaction was not significant. We also evaluated the possible interaction between type of menopause and age. Again, the interaction was not significant.

Body mass index

As shown in table 1, we observed that risk accumulated less rapidly with higher BMI before menopause. After menopause, higher BMI was positively associated with accumulation of risk among women who were not using PMH. Among women using PMH, those with higher BMI had a less rapid accumulation, similar to the pattern seen for premenopausal women. Because weight had a different relation to breast cancer risk before and after menopause, to summarize risk of breast cancer from ages 30–70 years, we created profiles of women according to their weight percentiles at different ages (18, 50, 60, and 70 years) for women of average height (approximately 64.5 inches (1.64 m)). The average woman gained 19 pounds (8.63 kg) from ages 18 to 50 years. This woman was compared with a "stable weight woman" who did not gain weight and with a woman with an above-average weight gain, who gained approximately 60 pounds (27.2 kg) over this period. These

TABLE 3. Age-specific and cumulative incidence of breast cancer by weight profile, Nurses' Health Study, 1976–1994

Descriptor for 18–70 years*	Weight percentile										Age-specific incidence ($\times 10^{-5}$)			Cumulative incidence for ages 30–70 years ($\times 10^{-5}$)	RR†
	18 years			50 years			60 years			70 years					
	%	Pounds‡	kg/m^2	%	Pounds‡	kg/m^2	%	Pounds‡	kg/m^2	%	Pounds‡	kg/m^2	50 years	60 years	70 years		
Average women	50	123	20.8	50	142	24.1	50	146	24.8	50	145	24.6	167	245	280	6,083	1.0
Stable weight	50	123	20.8	10	118	20.0	10	120	20.4	10	118	20.0	182	189	197	5,564	Reference
Above average weight gain	50	123	20.8	90	185	31.4	90	190	32.2	90	185	31.4	143	264	487	7,023	0.92
Consistently lean	10	105	17.8	10	118	20.0	10	120	20.4	10	118	20.0	197	206	215	6,027	1.19
Consistently obese	90	150	25.4	90	185	31.4	90	190	32.2	90	185	31.4	126	233	429	6,387	1.00
																	1.06

* Age at menarche = 13 years; parity = 2; ages at births = 20 and 23 years; age at menopause = 50 years; type of menopause = natural; no postmenopausal hormone therapy; women with no benign breast disease, no family history, average height (i.e., height before menopause = 64.5 inches (163.8 cm); height after menopause = 64.4 inches (163.6 cm), lifetime nondrinkers.
† RR, relative risk.
‡ 1 pound = 0.454 kg.

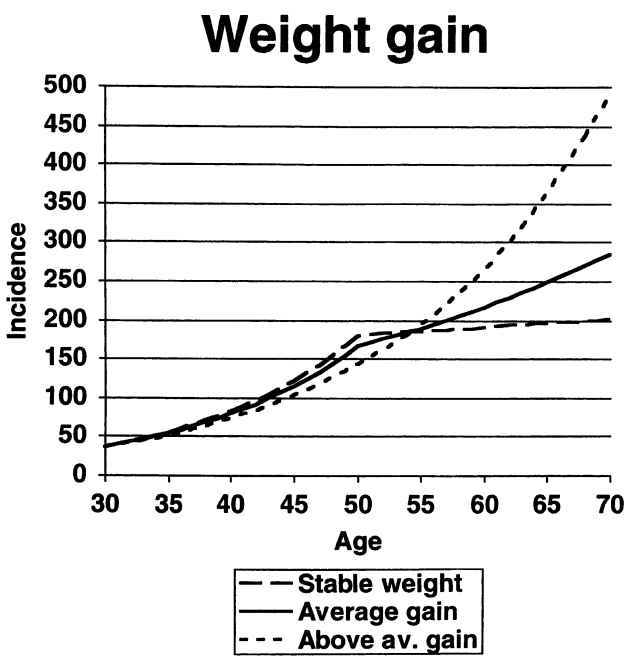

FIGURE 6. Age-specific incidence of breast cancer for a woman of average weight through ages 18–70 years, for a woman with stable weight, and for a woman with above-average weight gain who never used PMH.

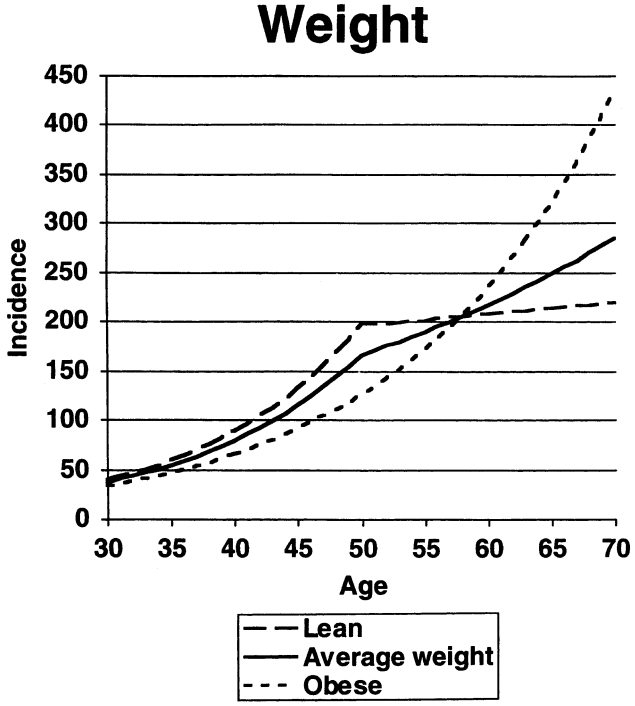

FIGURE 7. Age-specific incidence of breast cancer for a woman who is consistently lean (at the 10th percentile for weight), for a woman of average weight and for a woman who is consistently obese (90th percentile of weight).

comparisons were made among women who were never users of PMH. Although considerable differences in age-specific incidence were noted for these hypothetical women (table 3 and figure 6), because of the differential effects of weight before and after menopause, there was essentially no difference in cumulative incidence from ages 30–70 years between the women with stable weight and those with average weight. The women with above-average weight gain had a 19 percent higher cumulative risk of breast cancer than did the average women.

In addition, we compared an average woman with a woman who was consistently lean and one who was consistently obese throughout ages 18–70 years (table 3 and figure 7). Again, there was little difference in cumulative incidence, with the consistently obese woman having a 6 percent higher cumulative incidence than the average woman, while the consistently lean woman had the same risk as the average woman.

Height

As seen in table 1, there was an increase in risk accumulation prior to menopause with greater height ($p < 0.001$), with no additional risk accumulation after menopause. Therefore, this would translate to higher incidence for tall versus short women both before and after menopause. To illustrate these relations, we compared the age-specific and cumulative incidences for an average woman (64 inches (1.63 m)) with those of a short woman (61 inches (1.55 m)) and a tall woman (67 inches (1.70 m)) (table 4 and figure 8). We see that there was approximately a 12 percent difference in cumulative incidence from ages 30 to 70 years between the short and tall women (figure 8).

Alcohol

We measured alcohol separately for intake before and after menopause. The increase in risk of breast cancer was most clearly observed among premenopausal women. The adjusted relative risk for one 12-g drink per day for 35 years of premenopause is $e^{0.00017 \times 35 \times 12} = 1.07$ (95 percent CI: 1.01, 1.15). Overall, drinking one alcoholic beverage per day increases risk of breast cancer up to age 70 years by 7 percent (95 percent CI: 0 percent, 13 percent). (figure 9).

Family history

Family history of breast cancer diagnosed in a mother or sister significantly increases the risk of breast cancer (table 1). The relative risk compared with women without a family history is 1.49 (95 percent CI: 1.30, 1.71). Limited numbers of cases precluded detailed analysis accounting for mothers' age at diagnosis. Any family history in a first-

TABLE 4. Age-specific and cumulative incidence of breast cancer by height among women without family history, Nurses' Health Study, 1976–1994

Descriptor for 18–70 years*	Height percentile (%)	Age specific incidence (10^{-5})			Cumulative incidence ($\times 10^{-5}$)	RR†
		50	60	70		
Average height (64 inches‡)	50	163	211	274	5,913	1.06
Short woman (61 inches)	10	146	200	273	5,593	1.0 Reference
Tall woman (67 inches)	90	181	223	274	6,258	1.12

* Age at menarche = 13; parity = 2; ages at births = 20 and 23; age at menopause = 50; type of menopause = natural; no postmenopausal hormone therapy; women with no benign breast disease and no family history, average weight throughout life (weight at age 18 years = 123 pounds (55.8 kg), at age 50 years = 142 pounds (64.5 kg), at age 60 years, 146 pounds (66.3 kg), and age 70 years = 145 pounds (65.8 kg).
† RR, relative risk.
‡ 1 inch = 2.54 cm.

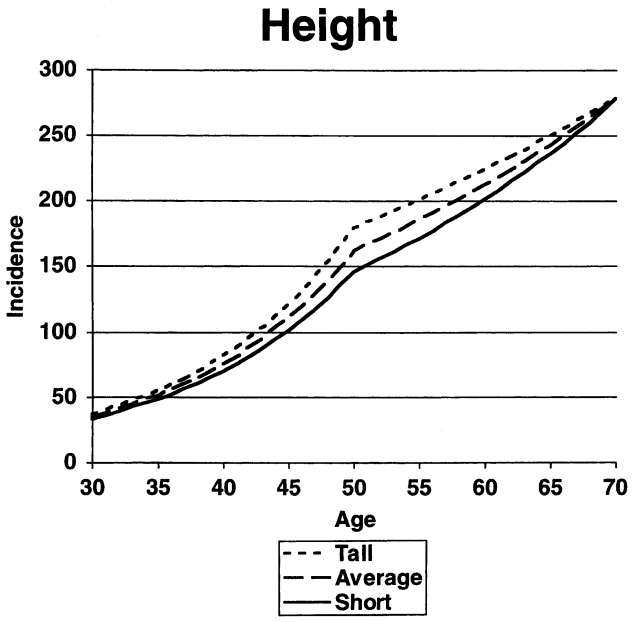

FIGURE 8. Age-specific incidence of breast cancer for an average woman (64 inches (1.63 m)), a short woman (61 inches (1.55 m)), and a tall woman (67 inches (1.70 m)).

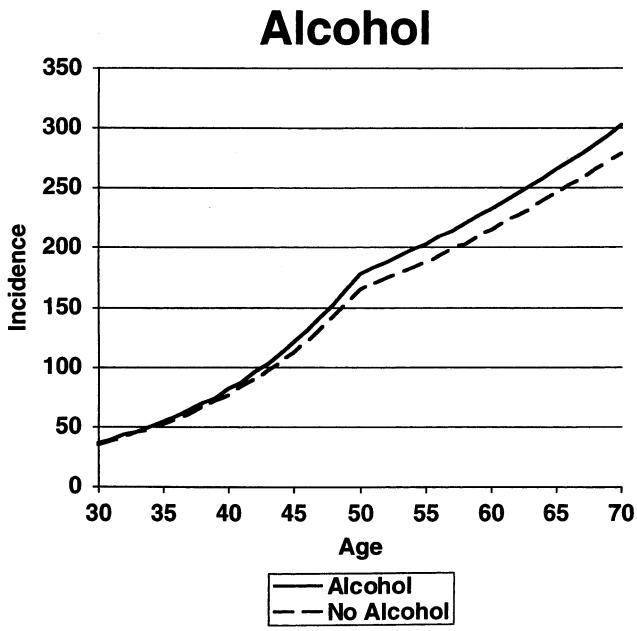

FIGURE 9. Age-specific incidence of breast cancer for a woman consuming one drink per day and a woman who never drinks alcohol.

degree relative increased the cumulative risk of breast cancer before age 70 years by 46 percent. (figure 10).

Cumulative incidence

Comparison of the long-term impact of specific risk factors based on age-specific incidence is difficult because risk factors often change in magnitude and direction over different periods of life. Therefore, in table 5, we provide cumulative incidence (that is, the probability of diagnosis with invasive breast cancer prior to age 70 years) for hypothetical women with varying levels of specific risk factors, while holding levels of all other risk factors constant.

The risk factors with the greatest impact on cumulative incidence were PMH use and history of benign breast disease. The underlying Nurses' Health Study data included 235 cases of breast cancer diagnosed among women taking estrogen and progestin; 38 percent of these were in women who had used estrogen and progestin for 5–10 years. Some 1.1 percent of postmenopausal women had used estrogen and progestin for 5–10 years. We therefore limited the cumulative incidence analysis to 10 years of use to avoid extrapolation beyond the underlying observed incidence data. Women using ERT for 10 years (ages 50–60 years) had a 23 percent increase in cumulative incidence to age 70, while women using estrogen plus progestin for the same period had a 67 percent increase in cumulative incidence compared with never users. BBD-positive women had a 57 percent increase in cumulative incidence compared with BBD-negative women.

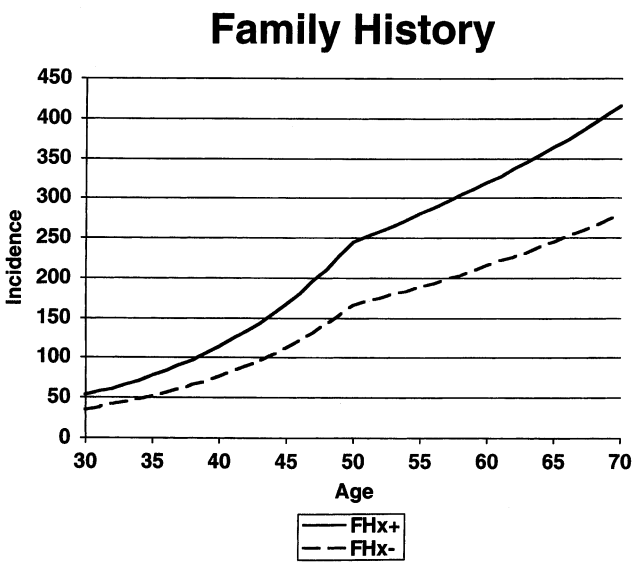

FIGURE 10. Age-specific incidence of breast cancer for women with a first-degree family history of breast cancer and those without.

We see that women with an age at menarche of 15 years have a 31 percent lower cumulative incidence than do women with age at menarche of 11. Women with four births spaced 3 years apart and with a first birth at age 20 years have a 27 percent lower cumulative incidence than do nulliparous women. Women with age at menopause of 55 years have a 44 percent higher cumulative incidence than do women with age at menopause of 45. Small effects are noted for type of menopause; women with an bilateral oophorectomy have a 11 percent lower risk than do women with a natural menopause. Similarly, as noted above, small effects were seen for different weight profiles on cumulative incidence. Finally, tall (67 inches (1.70 m)) women had approximately a 12 percent increase in risk compared with short (61 inches (1.55 m)) women.

DISCUSSION

Relations between reproductive events and risk of breast cancer in this cohort are consistent with a broad range of epidemiologic studies. Early age at menarche increases risk of breast cancer, early menopause decreases risk, and parity is associated with a decreased risk of breast cancer that varies according to age at first birth. With additional follow-up and accumulation of cases of breast cancer, the previously observed interaction between family history and reproductive factors (2) no longer persisted in the analysis.

The observation regarding risk in women with benign breast disease was unexpected. These women have a higher intercept compared with women without BBD, indicating that they may have an inherited risk. Furthermore, we observed no effect of age at menarche on breast cancer risk among women with BBD. However, further work is needed to confirm these findings and to identify genetic and environmental factors that may account for this. It would be interesting to divide risk according to the time before and time after BBD in a manner similar to time before and after menopause.

The relation between duration of hormone use among postmenopausal women and risk of breast cancer is consistent with predictions by Key and Pike (19). They estimate, on the basis of estrogen levels, that risk should increase 2.1 percent per year of use of unopposed estrogen. We observed a slightly higher increase per year of use. Further, the magnitude of risk differed significantly depending on type of hormone used. Women with natural menopause not on PMH showed an annual increase of 2.6 percent per year compared with women using estrogen alone, who showed an annual increase of 7.7 percent per year of use, and women using estrogen plus progestin, who had an annual increase of 13.0 percent per year of use. This significant increase in risk with duration of use is consistent with data from previous case-control and cohort studies (10). In the combined reanalysis, age at menopause was controlled in four categories. We controlled for exact age at menopause and so may have reduced potential bias for our estimate. Further, the higher risk among women using estrogen plus progestin is supported by evidence that progestin is the dominant mitogen for human breast cells (11, 20). The addition of progestin to postmenopausal estrogen potentially increases the rate of cell proliferation and, as demonstrated in these data, the risk of breast cancer. Our inability to observe significant variations in risk with different doses of conjugated estrogen may reflect, in part, the minimal increase in free estradiol with higher levels of supplementation among postmenopausal women and our limited power. While cyclic use of hormones may be predicted to have a more adverse effect than does continuous use, we failed to observe such an association. However, the small number of women who reported continuous use of progestin gave us limited power to evaluate this relation. The model we fitted included a term for current use (yes/no) and for duration. The terms were such that cessation of use after 5 years returns the woman to the risk of a never user (figure 5). However, with longer use, the risk upon cessation does not return to that of the never user, but rather reflects an accumulation in risk that presumably reflects additional accumulation of DNA damage with longer use of hormones.

In a study of women with natural menopause experiencing menopausal symptoms, as indicated by hot flashes, lower estrogen levels were observed, and a significant inverse association was seen between hot flashes and serum estrone and estradiol (21). Similar results have been observed in other studies (22), and severity of hot flashes was related to lower levels of estrone, estradiol, and free estradiol (23). Thus, this and other observational studies may be biased toward underestimating the adverse effect of postmenopausal estrogens, as women at a hormonally lower risk of breast cancer may, on average, be more likely to take hormones.

Additional evidence in support of the role of estrogens in the etiology of postmenopausal breast cancer comes from studies of blood levels and of bone density. Prospective studies show higher levels of estradiol are associated with increased risk of breast cancer (24–26), but women with low bone density have a substantially lower risk of breast cancer

TABLE 5. Comparative effect of different breast cancer risk factors on cumulative incidence from ages 30–70 years among women,* Nurses' Health Study, 1976–1994

Risk factor and classification	Cumulative incidence ($\times 10^{-5}$)	RR†	95% CI†
Age at menarche (years)			
11	7,186	1.0	
15	4,966	0.69	0.65, 0.74
Ages at births (years)			
Nulliparous	6,920	1.0	
35	8,033	1.16	0.96, 1.41
20, 23, 26, 29	5,073	0.73	0.63, 0.86
Age at menopause (years)			
45	4,931	1.0	
55	7,087	1.44	1.26, 1.64
Type of menopause			
Natural	5,977	1.0	
Bilateral oophorectomy	5,312	0.89	0.80, 0.98
Postmenopausal hormone use‡			
None	5,977	1.0	
ERT†	7,322	1.23	1.06, 1.42
HRT†	9,988	1.67	1.18, 2.36
Weight§			
Average woman	6,053	1.0	
Stable weight	5,564	0.92	0.88, 0.96
Above-average weight gain	7,203	1.19	1.08, 1.31
Consistently lean	6,027	1.00	0.94, 1.05
Consistently obese	6,387	1.06	0.95, 1.17
Height (inches)			
61 (short)	5,593	1.0	
64 (average)	5,913	1.06	0.99, 1.13
67 (tall)	6,258	1.12	0.97, 1.28
Benign breast disease			
No	5,977	1.0	
Yes	9,400	1.57	1.43, 1.73
Family history			
No	5,977	1.0	
Yes	8,746	1.46	1.29, 1.67
Alcohol			
Never drink	5,977	1.0	
1 drink/day	6,374	1.07	1.00, 1.13

* Unless otherwise specified, all women are assumed to have age at menarche of 13 years, age at births of 20 and 23 years, age at menopause of 50 years, natural type of menopause, no postmenopausal hormone use, no benign breast disease, no alcohol use, average height and average weight, and no family history of breast cancer.

† RR, relative risk; CI, confidence interval; ERT, oral estrogen replacement therapy; HRT, oral estrogen and progesterone replacement therapy.

‡ Used continuously from ages 50–60 years.

§ See table 3 for definitions of weight categories.

compared with high bone density (a marker of estrogen) exposure (27–29).

The model developed and reported here is the most extensive attempt to relate breast cancer risk factors to incidence of breast cancer, allowing for temporal relations through model fitting. Other, more limited models provide the conceptual framework for this work (30). Application of cumulative risk of cancer provides a more appropriate metric for

communication of cancer risk (31). Confidence intervals on the cumulative risk ratio are also novel.

In summary, history of benign breast disease, family history of breast cancer, and use of PMH were the major predictors in our analysis of risk of breast cancer up to age 70 years. Age at menopause, age at menarche, height, and parity also affect the cumulative risk substantially. Reproductive risk factors influence risk accumulated by the time of menopause. Hormones thus appear to drive the risk of breast cancer. Obesity among postmenopausal women and use of PMH elevate circulating hormone levels and increase the risk of breast cancer. The addition of progestins appears to exacerbate the adverse effect of estrogen therapy.

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APPENDIX 1.

Details on factors influencing λ_l at different stages of reproductive life

We assume that risk at birth is potentially different between BBD-positive and BBD-negative women as well as between family history-positive and family-history negative women. Hence, we have

$$\log C_0 = \alpha + \alpha_1 BBD + \theta\, FHX. \qquad (A1)$$

We also assume that among BBD-positive women there is potentially cell proliferation between birth and menarche, Hence,

$$\log \lambda_i = \alpha_2 \, BBD, \, i = 0, \ldots, t_0 - 1. \qquad (A2)$$

For the period from menarche to menopause (i.e., the premenopause period), we assume that the log of the rate of cell proliferation is a linear function of parity, BMI, height, and alcohol consumption. We also assume that there is a one-time increase in cell proliferation at the time of first birth that is proportional to (age at first birth – age at menarche). Finally, we also assume that the rate of cell proliferation from menarche to menopause is different for BBD-positive versus BBD-negative women. Hence, we have

$$\log(\lambda_i) = \beta_0 + \beta_{1i} x_{1i} + \beta_2 x_{2i}(b_{1i} - b_{1,i-1}) + \beta_3(BMI_i - 21.8) + \beta_4(h - 64.5) + \beta_5 \, ALC_i + \alpha_3 BBD, i = t_o, \ldots, t_{m^{-1}} \qquad (A3)$$

where

x_{1i} = parity at age i;
x_{2i} = age at first birth -age at menarche if parous at age i, = 0 otherwise;
BMI_i = BMI at age i (kg/m^2);
ALC_i = alcohol intake at age i (ounces);
h = height (inches);
b_{1i} = 1 if parous at age i, = 0 if nulliparous at age i.

For the time after menopause (i.e., $i \geq t_m$), we assume that the log of the rate of cell proliferation is a function of the type of menopause (m_A, m_b) and whether and which type of PMH was used (PMH$_A$, PMH$_B$, or PMH$_C$). Furthermore, we assume that the log of the rate of cell proliferation is a linear function of height, BMI, and alcohol, but that the effects of height, BMI, and alcohol vary according to whether PMH are or are not used. For height and BMI, while on PMH, the regression coefficients are assumed to be the same as in the premenopausal period (β_3 and β_4), while not on PMH, they are potentially different (β^*_3 and β^*_4). Furthermore, we assume that the rate of cell proliferation is potentially increased upon first starting to use PMH (u_{4i}) and is potentially decreased upon stopping use of PMH (u_{5i}). Finally, we assume that the rate of cell proliferation after menopause is potentially different for BBD-positive and BBD-negative women. Hence,

$$\log \lambda_i = \gamma_{1i} m_A + \gamma_2 m_B + \delta_1 PMH_{A,i} + \delta_2 PMH_{B,i} + \delta_3 PMH_{c,i} + \delta_4 u_{4i} + \delta u_{5_{5i}} + \beta_3(BMI_i - 24.4) PMH_{cur,i} + \beta^*_3(BMI_i - 24.4) \times$$

$$(1 - PMH_{cur,i})\beta_4 h PMH_{cur,i} + \beta^*_4 h(1 - PMH_{cur,i}) + \beta^{**}_5 ALC_i \, PMH_{cur,i} + \beta^{**}_5 ALC_i(1 - PMH_{cur,i})$$

$$+ \alpha_4 BBD, \, i = t_m, \ldots, t - 1. \qquad (A4)$$

where
m$_A$ = 1 if natural menopause = 0 otherwise;
m$_B$ = 1 if bilateral oophorectomy = 0 otherwise;
$PMH_{A,i}$ = 1 if user of oral estrogen at age i, = 0 otherwise;
$PMH_{B,i}$ = 1 if user of oral estrogen and progesterone at age i, = 0 otherwise;
$PMH_{C,i}$ = 1 if user of other type of PMH at age i, = 0 otherwise;
$PMH_{cur,i}$ = 1 if current user of PMH at age i, = 0 otherwise
u_{4i} = 1 if currently using PMH at age i and never user of PMH at age i – 1, = 0 otherwise;
u_{5i} = 1 if past user of PMH at age i and current user at age i – 1, = –1 if current user at age i and past user at age i – 1, = 0, otherwise;
u_{6i} = 1 if currently using PMH at age i, = 0 otherwise.
Upon combining equations A1–A4 and collecting terms, we obtain the log incidence model given in equation 3.

APPENDIX 2

Confidence intervals for relative risk based on cumulative incidence

Suppose we are interested in cumulative incidence from age $t_0 + 1$ to age $t_0 + T$. Let X be a $k \times T$ matrix of possibly time-dependent risk factors, where X_{ij} refers to the ith risk factor ascertained at age $t_0 + j$. Let $I(t,x_t)$ be the incidence at age $t_0 + t$ for a subject with covariates x_t at age $t_0 + t$. From the log incidence model, we have

$$\log[I(t, x_t)] = \sum_{q=1}^{k} \beta_q x_{qt}. \tag{A5}$$

It follows that the cumulative incidence is given by

$$\mathrm{CI}(x) = 1 - \prod_{t=1}^{T}\left[1 - \exp\left(\sum_{q=1}^{k}\beta_q x_{qt}\right)\right].$$

We compare cumulative incidence for two subjects with covariate matrices X and X^* as expressed by the following relative risk functions:

$$RR = \frac{\mathrm{CI}(x)}{\mathrm{CI}(x^*)} = \frac{1 - \prod_{t=1}^{T}\left[1 - \exp\left(\sum_{q=1}^{k}\beta_q x_{qt}\right)\right]}{1 - \prod_{t=1}^{T}\left[1 - \exp\left(\sum_{q=1}^{k}\beta_q x^*_{qt}\right)\right]}.$$

We wish to obtain confidence limits for RR. For this purpose, we have

$$\mathrm{var}[\log \widehat{\mathrm{RR}}] = \mathrm{var}[\log \mathrm{CI}(x)] + \mathrm{var}[\log \mathrm{CI}(x^*)] - 2\mathrm{Cov}[\log \mathrm{CI}(x), \log \mathrm{CI}(x^*)]. \tag{A6}$$

To obtain var[log CI(x)], we use the delta method to express var[log CI(x)] in terms of var[log(1 – CI(x))] whereby

$$\mathrm{var}\,[\log \mathrm{CI}(x)] = \mathrm{var}\,[\log\,(1 - \mathrm{CI}(x))][1 - \mathrm{CI}(x)]^2/\mathrm{CI}^2(x). \tag{A7}$$

Furthermore, because

$$\log[1 - \mathrm{CI}(x)] = \sum_{t=t_0+1}^{t_0+T} \log[1 - I(t, x_t)] \tag{A8}$$

we have

$$\mathrm{var}[\log(1 - \mathrm{CI}(x))] = \sum_{t=t_0+1}^{t_0+T} \mathrm{var}[\log(1 - I(t, x_t))] + \sum_{t_1 \neq t_2 = t_0+1}^{t_0+T} \mathrm{Cov}[\log(1 - I(t_1, x_{t_1})), \log(1 - I(t_2, x_{t_2}))] = A + B. \tag{A9}$$

Upon use of the delta method

$$A = \sum_{t=t_0+1}^{t_0+T} x_t' \sum\nolimits_{\beta} x_t I^2(t, x_t)/[1 - I(t, x_t)]^2 \tag{A10}$$

where Σ_β is the variance-covariance matrix from the log incidence model in equation A5, and x_t is a $k \times 1$ vector of covariates at time t. Similarly, upon use of the delta method it can be shown that

$$B = \sum_{t_1 \neq t_2 = t_0+1}^{t_0+T} x_{t_1}' \sum\nolimits_{\beta} x_{t_2} I(t_1, x_{t_1}) I(t_2, x_{t_2})/\{[1 - I(t_1, x_{t_1})][1 - I(t_2, x_{t_2})]\}. \tag{A11}$$

Upon combining equations A7 and A9–A11, we obtain

$$\mathrm{var}[\log \mathrm{CI}\,(x)] = \{[1 - \mathrm{CI}\,(x)]^2/\mathrm{CI}^2(x)\}\left\{\sum_{t=t_0+1}^{t_0+T} x_t' \sum\nolimits_{\beta} x_t I^2(t, x_t)/[1 - I(t, x_t)]^2 \right. \tag{A12}$$

$$\left. + \sum_{t_1 \neq t_2 = t_0+1}^{t_0+T} x_{t_1}' \sum\nolimits_{\beta} x_{t_2} I(t_1, x_{t_1}) I(t_2, x_{t_2})/\{[1 - I(t_1, x_{t_1})][1 - I(t_2, x_{t_2})]\}\right\}$$

with a similar expression for var[log CI (x^*)].
Using a similar approach based on the delta method, we obtain

$$\mathrm{Cov}[\log \mathrm{CI}(x), \log \mathrm{CI}(x^*)] = [1 - \mathrm{CI}(x)][1 - \mathrm{CI}(x^*)]/[\mathrm{CI}(x)\mathrm{CI}(x^*)] \tag{A13}$$

$$\times \sum_{t_1,\, t_2 = t_0 + 1}^{t_0 + T} I(t_1, x_{t_1}) I(t_2, x^*_{t_2}) / \{[1 - I(t_1, x_{t_1})][1 - I(t_2, x^*_{t_2})]\} x_{t_1}{}' \sum \beta x^*_{t_2}.$$

We now combine equations A6, A12, and A13 to obtain a closed form expression for var[log $\widehat{\mathrm{RR}}$]. An approximate 95 percent confidence interval for the relative risk is then given by [exp(c_1), exp(c_2)] where (c_1, c_2) = log $\widehat{\mathrm{RR}}$ ± 1.96 SE [log $\widehat{\mathrm{RR}}$] and SE (log $\widehat{\mathrm{RR}}$) = $\sqrt{\mathrm{var}(\log \widehat{\mathrm{RR}})}$.