

Use of Postmenopausal Hormones, Alcohol, and Risk for Invasive Breast Cancer

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Background: Physiologic evidence suggests that use of alcohol increases the risk for breast cancer through a hormonal mechanism, but the relationship among breast cancer, alcohol, and postmenopausal hormones (PMH) remains unclear.

Objective: To examine the relation between concurrent use of alcohol and PMH and invasive breast cancer.

Design: Prospective cohort study

Setting: Nurses' Health Study.

Participants: 44 187 postmenopausal women.

Measurements: Self-reported data on PMH use and breast cancer obtained from biennial questionnaires completed from 1980 to 1994 and average alcohol consumption in 1980, 1984, 1986, and 1990.

Results: 1722 women developed invasive breast cancer. Risk for

breast cancer was elevated in women who currently used PMH for 5 or more years and did not drink alcohol (relative risk, 1.32 [95% CI, 1.05 to 1.66]) and those who never used PMH but drank 20 or more g (1.5 to 2 drinks) of alcohol daily (relative risk, 1.28 [CI, 0.97 to 1.69]). Current users of PMH for 5 or more years who consumed 20 or more g of alcohol daily had a relative risk for breast cancer nearly twice (1.99 [CI, 1.42 to 2.79]) that of non-drinking nonusers of PMH. A hypothetical postmenopausal woman whose lifetime risk for breast cancer is 4% could increase her risk to 8% with 5 or more years of current PMH use and consumption of more than one alcoholic drink daily.

Conclusions: Both alcohol consumption and PMH use were associated with an increased incidence of breast cancer. Women who are currently taking PMH may want to consider the added risks of regular alcohol consumption.

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Since the first epidemiologic study linking risk for breast cancer and alcohol consumption (1), many mechanisms have been postulated to explain how alcohol intake increases the risk for breast cancer. These proposed mechanisms include disruption of cell membrane integrity, direct cytotoxic effect, interference with DNA repair, and impairment of hepatic metabolism of carcinogens. Physiologic evidence strongly suggests that alcohol increases risk for breast cancer, at least in part, by altering circulating steroid hormone levels. In premenopausal women, alcohol consumption increased both plasma and urinary levels of estradiol and estrone by 15% to 30%, depending on the phase of the menstrual cycle (2). In postmenopausal women taking postmenopausal hormones (PMH), acute ingestion of alcohol caused an average increase of 300% in estradiol levels compared with placebo. This effect of alcohol was not demonstrated in women not taking PMH (3). Although both PMH use and alcohol consumption are important modifiable risk factors in the development of invasive breast cancer in postmenopausal women, the interaction between the two has not been well quantified.

The magnitude of the risk for breast cancer associated with PMH use has been clarified as follow-up has accumulated in large prospective cohort studies. In a reanalysis of worldwide data, a relative risk for breast cancer of 1.35 (95% CI, 1.21 to 1.49) was reported among current users of PMH for 5 or more years compared with never-users (4).

Alcohol intake has also been consistently associated with an increased risk for breast cancer. In a pooled analysis of six large prospective cohort studies, multivariable relative risks were 1.16 (CI, 0.98 to 1.38) for women who

consumed 15.0 to 30.0 g of alcohol daily (about 1.5 to 2.5 drinks) and 1.41 (CI, 1.18 to 1.69) for those who consumed 30.0 to 60.0 g/d (about 2.5 to 4 drinks) compared with women who did not drink alcohol (5). A meta-analysis that used data from both cohort and case-control studies had similar findings (6).

Previous epidemiologic studies have been inconclusive in characterizing the interaction between alcohol and PMH use. With shorter follow-up in the Nurses' Health Study, exploratory analyses revealed that risk for breast cancer was elevated in users of PMH who drank more than 15 g of alcohol daily (age-adjusted relative risk, 1.56 [CI, 1.2 to 2.0]) but not in PMH users who did not drink alcohol (age-adjusted relative risk, 0.99 [CI, 0.62 to 1.60]). At that time, the confidence intervals were wide and there was insufficient power to further characterize the interaction (7). The Iowa Women's Health Study, a prospective cohort study of 41 837 postmenopausal women, reported similar results after 3 years of follow-up. When alcohol abstainers and never-users of PMH were used as the reference group, PMH users who did not drink alcohol had a multivariable relative risk for breast cancer of 0.88 (CI, 0.67 to 1.15) compared with 1.83 (CI, 1.18 to 2.85) for PMH users who consumed more than 15 g of alcohol daily (8). Several case-control studies, however, found no difference in the alcohol effect between PMH users and nonusers (9-13). The recent pooled analysis did not find an interaction between PMH and alcohol consumption, but the failure to update information on alcohol and PMH use may have led to misclassification of concurrent use (5).

Therefore, we sought to clarify the risks of alcohol and PMH use, both separately and concurrently.

METHODS

The Nurses' Health Study cohort was established in 1976, when 121 700 female registered nurses 30 to 55 years of age completed a baseline questionnaire that included items on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been mailed to update information.

Dietary Data

Dietary information was first collected in 1980, when participants completed a semi-quantitative food-frequency questionnaire and reported their average frequency of consumption of specific food and beverage items during the previous 12 months. Consumption of beer, wine, and spirits was ascertained in separate items. Alcohol consumption, in grams per day, was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g of alcohol per 12-oz serving of beer, 11.0 g per 4-oz serving of wine, and 14.0 g per standard serving of spirits) (14). The dietary data were updated in 1984, 1986, and 1990. Alcohol intake as measured by the food-frequency questionnaire was highly correlated with intake as calculated from detailed food diaries completed by a sample of study participants (Spearman rank-correlation coefficient = 0.90) (15).

Sample for Analysis

In 1980, 98 462 nurses returned the dietary questionnaires. Women who left 10 or more food items blank (4%), those with implausibly high or low scores for total food intake (2.7%), and those who reported any diagnosis of cancer (except nonmelanoma skin cancer) before 1980 were excluded from analysis. Women who developed any type of cancer (except nonmelanoma skin cancer) were censored at the time of their report of the diagnosis.

Our analysis is limited to postmenopausal women. A woman was classified as postmenopausal from the time she returned a questionnaire reporting natural menopause or hysterectomy with bilateral oophorectomy. Self-report of natural menopause and extent of ovarian surgery has been shown to be highly accurate and reproducible (16). Women who reported that their menses ended after hysterectomy without bilateral oophorectomy were considered hormonally premenopausal and were thus excluded from the analysis until the age at which natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers), at which time they were considered postmenopausal. Menopausal status was updated every 2 years, and the sample was expanded to include women who became postmenopausal after 1980. Women for whom information on a covariate or exposure, such as use of PMH or alcohol, was missing on a specific questionnaire were excluded from the analysis for that

Context

Evidence links alcohol and breast cancer and suggests a hormonal mechanism. However, the relationships between alcohol, postmenopausal hormone use, and breast cancer are unclear.

Contribution

Using self-reported data from a cohort of nurses, this study showed that ≥ 1.5 drinks/d and ≥ 5 years of postmenopausal hormone replacement therapy are associated with increased risk for breast cancer. The relative risk for breast cancer was 1.32 for postmenopausal hormones alone, 1.28 for alcohol alone, and 1.99 for both.

Implications

Women should consider increased risk for breast cancer when deciding about drinking alcohol, taking postmenopausal hormones, and, especially, both together.

—The Editors

2-year period but reentered the analysis when the information was complete. The **Appendix Table** (available at www.annals.org) shows the distribution of missing data.

For this analysis, 27 262 women met the aforementioned criteria and entered the initial follow-up period (1980 to 1982). By 1994, the beginning of the final 2-year follow-up period, 44 186 women were postmenopausal and eligible for analysis.

Identification of Cases of Breast Cancer

The primary end point was diagnosis of invasive 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 cancer (or next of kin for those who had died) for permission to review the pertinent medical records for confirmation. Pathology reports, obtained in 96% of cases, showed a 99.4% confirmation rate. Because of the accuracy of participants' self-reports, analyses were based on all cases of incident invasive breast cancer. Carcinomas in situ were excluded. Follow-up of the cohort for identification of nonfatal breast cancer was 95% complete.

Statistical Analysis

Follow-up began in 1980 and terminated with the diagnosis of any type of cancer, death, or 1 June 1996, whichever came first. Use of PMH (current, past, or never) at the time of the questionnaire was used to define the subsequent 2-year period. Alcohol intake for the first follow-up period was defined by the response to the 1980 dietary questionnaire and was updated with responses from the 1984, 1986, and 1990 questionnaires. For the 2-year periods in which dietary questionnaires were not readministered, alcohol intake from the previous period was used.

Table 1. Alcohol Consumption, Postmenopausal Hormone Use, and Risk Factors for Breast Cancer among Postmenopausal Women in the Nurses' Health Study in 1982 and 1994*

Characteristic	Year	
	1982	1994
Participants, <i>n</i>	29 867	44 186
Median age, <i>y</i>	55.8	62.7
Alcohol intake		
Mean, <i>g/d</i>	6.8	5.3
Median, <i>g/d</i>	1.8	1.1
Average daily intake, <i>n</i> (%)		
None	9842 (33.0)	17 439 (39.5)
0.1–4.9 g	9419 (31.5)	14 333 (32.4)
5.0–9.9 g	3102 (10.4)	4389 (9.9)
10.0–19.9 g	4708 (15.8)	5111 (11.6)
≥20.0 g	2796 (9.4)	2914 (6.6)
Type of menopause, <i>n</i> (%)		
Natural	19 583 (65.6)	27 202 (61.6)
Surgical†	7203 (24.1)	7812 (17.7)
Other	3081 (10.3)	9172 (20.8)
Postmenopausal hormone use, <i>n</i> (%)		
Never	16 150 (54.1)	14 189 (32.1)
Past	7567 (25.3)	9889 (22.4)
Current, <5 years' duration	2649 (8.9)	6119 (13.8)
Current, ≥5 years' duration	3501 (11.7)	13 989 (31.7)
Type of PMH use		
Estrogen alone	5791 (94.2)	11 164 (55.5)
Estrogen and progesterone	194 (3.2)	8222 (40.9)
Other	165 (2.7)	722 (3.6)

* Not all percentages may total 100% because of rounding errors. PMH = postmenopausal hormones.

† Defined as both hysterectomy and bilateral oophorectomy.

Despite the high correlation between alcohol consumption in 1980 and 1990 (Spearman rank-correlation coefficient = 0.71; $P < 0.001$), updated alcohol intake was chosen because analyses that used 1980 alcohol consumption without updating failed to show as consistent a dose–response relationship.

Postmenopausal women were categorized into 1 of 20 groups according to average daily alcohol intake (no alcohol, <2 drinks/wk [0.1 to 4.9 g/d], 3 to 6 drinks/wk [5.0 to 9.9 g/d], about 1 drink/d [10.0 to 19.9 g/d], or ≥2 drinks/d [≥20.0 g/d]) and PMH use (never, past, current with <5 years' use, or current with ≥5 years' use). The alcohol use categories divided the cohort into 5 groups of roughly equivalent size. Current PMH users were classified into those who used PMH for less than 5 years or 5 or more years because the effect of PMH on risk for breast cancer is significantly greater with longer duration of use (4).

Relative risks were calculated as a measure of association. Pooled logistic regression, which approximates the results of time-dependent proportional hazards models when intervals between outcome events are short and the probability of an event in each interval is small (17), was used to compute age-adjusted and multivariable-adjusted relative risks and 95% CIs. Covariates in the model included age (continuous), age at menopause (continuous), type of menopause (natural, surgical with bilateral oophorectomy, other), age at menarche (continuous), parity (nul-

liparous, 1 to 2 births, >2 births), age at first birth (nulliparous, <22 years, 23 to 25 years, >25 years), weight gain of more than 10 kg since 18 years of age (yes or no), family history of breast cancer in a first-degree relative (yes or no), and self-report of benign breast disease (yes or no). An interaction between alcohol and PMH use was evaluated by using a likelihood ratio test with a cross-product interaction term representing the duration of PMH use and alcohol intake and a Wald test comparing the parameter estimates for alcohol effect among different categories of PMH use. For all covariates, complete case analysis was performed. All analyses were performed by using SAS software, version 6.0 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The research was completely funded by the National Institutes of Health. The funding source had no part in collecting, analyzing, or interpreting the data.

RESULTS

During 557 984 person-years of follow-up, 1722 cases of invasive breast cancer were identified among postmenopausal women with complete data on alcohol and PMH use. Table 1 shows the distribution and changes over time in alcohol and PMH use. Questions about specific types of PMH were first asked in 1982. Consistent with national trends (18, 19), alcohol use has decreased and PMH use has increased. In 1982, 11.7% of the postmenopausal cohort were current PMH users, which more than doubled to 31.7% in 1994. Among PMH users, estrogen alone remained the most popular therapy, but combination estrogen and progesterone gained popularity, increasing from 3.2% to 40.9% of current PMH users in 1994.

Table 2 shows the main effect of alcohol and PMH use. Risk for breast cancer increased with both increasing alcohol intake and PMH use. Current PMH use was more strongly associated with risk for breast cancer than was past use, and current use for 5 or more years was associated with greater risk than was less than 5 years of use. Consumption of 10.0 to 19.9 g of alcohol daily was associated with a multivariable relative risk of 1.22 (CI, 1.06 to 1.42), and consumption of 20.0 or more g of alcohol daily was associated with a multivariable relative risk of 1.33 (CI, 1.12 to 1.58), consistent with a linear relationship. At consumption of less than 10.0 g of alcohol daily, risk for breast cancer was not significantly increased (relative risk, 1.07 [CI, 0.95 to 1.20]) for 0.1 to 4.9 g/d and 0.99 [CI, 0.83 to 1.18] for 5.0 to 9.9 g/d). The test for trend for alcohol (analyzed as a continuous variable) was significant ($P < 0.001$).

To investigate the effect of concurrent alcohol and PMH use, postmenopausal women were classified into 1 of 20 categories according to alcohol and PMH use (Table 3). Compared with nondrinkers who never used PMH, current PMH users for 5 or more years who consumed 20 or more g of alcohol daily had an adjusted relative risk for

Table 2. Relative Risk for Invasive Breast Cancer in Postmenopausal Women, by Alcohol Intake and Postmenopausal Hormone Use, 1980–1996

Substance	Cases of Breast Cancer, <i>n</i>	Person-Years	Age-Adjusted Relative Risk	Multivariable Relative Risk*
Alcohol intake†				
None	594	205 686	1.00 (referent)	1.00 (referent)
0.1–4.9 g/d	538	177 176	1.08 (0.96–1.22)	1.07 (0.95–1.20)
5.0–9.9 g/d	166	57 346	1.01 (0.85–1.20)	0.99 (0.83–1.18)
10–19.9 g/d	257	73 194	1.24 (1.07–1.44)	1.22 (1.06–1.42)
≥20.0 g/d	167	44 582	1.34 (1.13–1.58)	1.33 (1.12–1.58)
Postmenopausal hormone use				
Never	680	243 286	1.00 (referent)	1.00 (referent)
Past	378	130 554	0.96 (0.84–1.09)	1.05 (0.92–1.20)
Current, <5 years	262	75 874	1.39 (1.20–1.60)	1.37 (1.18–1.59)
Current, ≥5 years	402	108 270	1.27 (1.12–1.44)	1.49 (1.29–1.74)

* Adjusted for age at menarche, age at menopause, age, age at first birth, parity, type of menopause, family history of breast cancer, benign breast disease, postmenopausal hormone use, and weight gain ≥10 kg since 18 years of age.

† Alcohol consumption was updated in 1980, 1984, 1986, and 1990. Alcohol content per drink was 12.8 g of alcohol per serving of beer, 11.0 g of alcohol per serving of wine, and 14.0 g of alcohol per serving of liquor.

breast cancer of 1.99 (CI, 1.41 to 2.79). In contrast, the adjusted relative risk was 1.32 (CI, 1.05 to 1.66) in women taking PMH for 5 or more years who consumed no alcohol and 1.28 (CI, 0.97 to 1.69) in never-users of PMH who consumed 20 or more g of alcohol daily.

As seen with the main effect of alcohol, average alcohol intake of less than 10 g/d did not significantly increase the risk for breast cancer in women who did not take PMH, compared with those who did not take PMH and consumed no alcohol. Similarly, for current PMH users who drank less than 10 g of alcohol daily, the risk was not increased above that for current PMH users who did not

drink alcohol. Therefore, intake of less than 10 g of alcohol daily does not modify the relation between PMH and breast cancer risk, since the strength of the association with PMH was consistent in alcohol abstainers and light drinkers. The converse was true as well: The lack of a strong association for light drinkers was consistent in both PMH users and nonusers.

Alcohol consumption of 10 or more g/d was significantly associated with increased risk for breast cancer in both PMH users and nonusers. With use of the relative risk estimates, the interaction between alcohol and PMH appears to be slightly greater than a multiplicative model:

Table 3. Relative Risk for Invasive Breast Cancer in Postmenopausal Women, by Concurrent Postmenopausal Hormone and Alcohol Use, 1980–1996

Alcohol Intake, g/d	Postmenopausal Hormone Use	Cases of Breast Cancer, <i>n</i>	Person-Years	Multivariable Relative Risk (<i>n</i> = 1722)*
None	Never	250	46 377	1.00 (referent)
	Past	134	24 613	1.04 (0.84–1.29)
	Current, <5 years	88	12 500	1.45 (1.13–1.86)
	Current, ≥5 years	122	19 353	1.31 (1.05–1.66)
0.1–4.9	Never	201	37 946	1.00 (0.83–1.20)
	Past	84	12 873	1.18 (0.95–1.48)
	Current, <5 years	131	17 569	1.38 (1.07–1.78)
	Current, ≥5 years	131	17 569	1.59 (1.27–1.98)
5.0–9.9	Never	62	11 986	1.00 (0.75–1.32)
	Past	33	6496	0.99 (0.69–1.43)
	Current, <5 years	27	4427	1.27 (0.85–1.89)
	Current, ≥5 years	44	5766	1.61 (1.16–2.24)
10.0–19.9	Never	102	15 500	1.27 (1.01–1.60)
	Past	56	8666	1.26 (0.94–1.69)
	Current, <5 years	34	5204	1.35 (0.94–1.94)
	Current, ≥5 years	65	7227	1.90 (1.44–2.52)
≥20.0	Never	65	9834	1.28 (0.97–1.69)
	Past	33	5304	1.22 (0.85–1.77)
	Current, <5 years	29	2933	2.08 (1.41–3.08)
	Current, ≥5 years	40	4220	1.99 (1.41–2.79)

* Adjusted for age at menarche, age at menopause, age, age at first birth, parity, type of menopause, family history of breast cancer, benign breast disease, and weight gain ≥10 kg since 18 years of age.

1.28 (nondrinking PMH users) \times 1.32 (never-PMH users who drank ≥ 20 g/d) = 1.69, which is less than the observed relative risk of 1.99 (PMH users who drank ≥ 20 g/d). However, no significant statistical interaction or effect modification was observed between PMH use and alcohol intake of more than 20 g/d. In other words, there was no greater risk associated with using both PMH and alcohol together than would be expected from using either one alone.

We also analyzed the alcohol and PMH categories stratified by the presence or absence of a weight change of more than 10 kg since 18 years of age. To increase power to detect differences, alcohol consumption was divided into three categories corresponding to 10-g/d differences in intake. The effect of alcohol and PMH tended to be stronger in women who had gained less than 10 kg since 18 years of age (data not shown), but an interaction term was not significant. Stratified analyses by folate intake and alcohol and PMH categories resulted in small case numbers and less stable risk estimates.

To avoid misclassification of menopausal status, only person-time for women who were known to be postmenopausal or had surpassed the age when more than 90% of the cohort was menopausal was included. The PMH effect may differ in premenopausal or perimenopausal women, who have higher endogenous estrogen levels than do postmenopausal women. The relative risks did not change substantially when analyses were restricted to women who had bilateral oophorectomy or natural menopause (20, 21). Cigarette smoking was considered as a potential confounder, but the associations did not change significantly with the addition or exclusion of smoking in the model. Analyses excluding and including carcinomas in situ yielded similar results (**Appendix Table**, available at www.annals.org). Since not all invasive breast cancers evolve from carcinomas in situ, nor do all carcinomas in situ progress to invasive breast cancer, only analyses limited to invasive breast cancer were reported.

Despite the recent increase in estrogen and progesterone use, combination therapy represents less than 10% of the total person-time of current PMH users. Alcohol categories had to be collapsed for this analysis. Among women who consumed less than 10 g of alcohol per day, a trend was observed toward increased risk in current users of combination PMH therapy for less than 5 years (relative risk, 1.23 [CI, 1.03 to 1.46] for estrogen alone and 1.63 [CI, 1.31 to 2.03] for combination therapy) and 5 or more years (relative risk, 1.63 [CI, 1.31 to 2.03] for estrogen alone and 1.69 [CI, 1.34 to 2.13] for combination therapy). For women who consumed 10 or more g of alcohol daily, no significant difference was observed between current users for less than 5 years (relative risk, 1.60 [CI, 1.12 to 2.29] for estrogen alone and 1.37 [CI, 0.92 to 2.06] for combination therapy) and current users for 5 or more years (relative risk, 1.76 [CI, 1.37 to 2.27] for estrogen alone and 1.34 [CI, 0.87 to 2.07] for combination therapy).

Since the confidence intervals overlap and there were relatively few regular alcohol consumers who used combination therapy, no conclusions can be drawn as to whether a true difference exists. Average duration of unopposed estrogen use was longer than that of combination therapy.

DISCUSSION

In this analysis of long-term follow-up in the Nurses' Health Study, alcohol and PMH use were independent risk factors for development of invasive breast cancer. Current users of PMH for 5 or more years who also consumed 20 or more g of alcohol (1.5 to 2 drinks) daily had almost twice the risk for breast cancer (multivariable relative risk, 1.99 [CI, 1.41 to 2.79]) as those who did not drink alcohol and never used PMH. Our results imply that a hypothetical postmenopausal woman with a lifetime risk for breast cancer of 4% in the absence of alcohol or PMH use would increase her risk to 6% (relative risk, 1.49) with current PMH use for at least 5 years and to 8% (relative risk, 1.99) with the concurrent consumption of more than 1 drink/d. We could not detect a large difference between women who drink alcohol less regularly (< 10 g or 1 drink/d) and those who do not drink alcohol.

Our current study provides greater power to examine an interaction effect, with longer follow-up and more than three times as many cases as the Iowa Women's Health study. We separately analyzed past and current PMH users. The effects of PMH can appear weaker when past and current users are combined, since risk for breast cancer is most closely tied to current use and returns to baseline with past use (4, 22). For alcohol, the same seems to hold true. In the meta-analysis of alcohol and breast cancer, the studies with the longest duration since assessment of alcohol intake were those that showed the weakest effect, suggesting that recent exposure is more important than past exposure (6). Similarly, our analyses using baseline 1980 alcohol consumption without updating information failed to show as consistent a dose-response relationship. In addition, the synergy of alcohol and PMH with blood estrogen levels appears to reflect an acute effect (3). Because the pooled analysis of cohort studies of alcohol and breast cancer did not update PMH and alcohol use, the interaction between concurrent PMH therapy and alcohol use was not examined in as much detail as in the current study (5). Previous studies that did not find an effect of PMH on development of breast cancer may not have adequately controlled for alcohol use, which may be less prevalent among "healthy" PMH users; this effect would lead to an apparently lower risk for breast cancer compared with non-PMH users who may consume more alcohol.

The effect of average consumption of more than three alcoholic drinks daily could not be adequately evaluated within our cohort, since only a small proportion of participants consumed that much alcohol. However, the drinking habits of our sample were fairly representative of U.S.

women of the same age group (18, 19, 23). Because regularity of drinking was not assessed, we cannot determine whether binge drinking and daily moderate drinking that provides the same average alcohol intake would have similar effects.

Because this was an observational study and PMH and alcohol use was not randomly assigned, other unobserved factors may explain differences in risk for breast cancer. However, the consistency of the results by duration of hormone use and amount of alcohol and the stability of the results, regardless of whether other risk factors for breast cancer were considered, make a true relationship more likely. For an unobserved confounder with a prevalence of 10% to explain a relative risk of 2.0, the association between that unobserved variable and breast cancer would need to be greater than 4.0 (allowing the association between the confounder and alcohol and PMH use to vary from 1.5 to 10.0) (24). Misclassification of women with simple hysterectomy would tend toward underestimation of the risk of PMH use (20, 21).

Sensitivity analyses were performed to evaluate the effect of missing data. In all scenarios, relative risks changed by less than 10%. Although complete case analysis provides the most valid estimates when data are missing completely at random (a very stringent assumption), the prevalence of missing data in our cohort was generally low and therefore unlikely to introduce substantial bias, regardless of the mechanism of the missing data. Observational studies also depend on self-reported data. Since alcohol use was measured accurately in our cohort, correction for measurement error results in relative risks that are only minimally weakened (25, 26). Observational data may remain our main source of information, since a long-term randomized trial of alcohol and PMH use will probably never be performed.

In summary, women who are currently taking or contemplating starting PMH therapy should consider the effects of concurrent alcohol consumption on their risk for breast cancer. We could not show evidence for a statistical interaction between alcohol and PMH. However, the lack of a significant statistical interaction does not support or refute the hypothesis that alcohol mediates risk for breast cancer through hormone levels. Instead, the lack of a statistical interaction implies that the absolute excess risks associated with alcohol exist across all levels of PMH use. Our study suggests that women taking PMH who consume an average of more than one alcoholic drink daily have a significantly increased risk for breast cancer, independent of the risk associated with PMH alone. Longer follow-up is required to evaluate whether combination estrogen and progesterone therapy interacts differently with alcohol than does unopposed estrogen. In addition, the deleterious effects of alcohol on the development of breast cancer need to be weighed against the beneficial effects of light to moderate alcohol drinking on cardiovascular disease and overall mortality (27, 28).

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He is dead, and I feel an odd triumph about it. He is dead, the thing (when I was small) I used to dread more than any other, but I'm still here, my mother's still here, I can hear her breathing, the world has ended but we've survived, we're OK.

He is dead—no rage against the dying of the light, no terror and delirium, only a nightlight smothered in its own wax. Sitting here, the body silent between us as we peer into it for a sign of some kind, I'm on a shock-induced high. If I listen hard enough, I know I'll hear his own count-your-blessings verdict: "Well, that wasn't so bad, was it? When I think how it could have been—drawn-out, or abrupt and messy, or in hospital rather than here—it makes me feel lucky. A good death and a good life too: who could beat it?"

Blake Morrison
And When Did You Last See Your Father?
New York: Picador; 1996:149

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.—*The Editor*

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Appendix Table. Relative Risk for Invasive Breast Cancer, by Use of Postmenopausal Hormones and Alcohol, in Postmenopausal Women with and without Carcinomas in Situ*

Alcohol Intake, g/d	Postmenopausal Hormone Use	Multivariable Relative Risk (95% CI)	
		Invasive Carcinoma Only	Invasive and in Situ Carcinoma
None	Never	1.0 (referent)	1.0 (referent)
	Past	1.04 (0.84–1.29)	1.02 (0.83–1.25)
	Current, <5 years	1.45 (1.13–1.86)	1.44 (1.14–1.83)
	Current, ≥5 years	1.31 (1.05–1.66)	1.32 (1.07–1.64)
0.1–4.9	Never	1.00 (0.83–1.20)	1.06 (0.89–1.27)
	Past	1.18 (0.95–1.48)	1.21 (0.98–1.49)
	Current, <5 years	1.38 (1.07–1.78)	1.40 (1.10–1.78)
	Current, ≥5 years	1.59 (1.27–1.98)	1.61 (1.31–1.99)
5.0–9.9	Never	1.00 (0.75–1.32)	1.04 (0.80–1.35)
	Past	0.99 (0.69–1.43)	1.04 (0.74–1.46)
	Current, <5 years	1.27 (0.85–1.89)	1.34 (0.92–1.94)
	Current, ≥5 years	1.61 (1.16–2.24)	1.64 (1.21–2.23)
10–19.9	Never	1.27 (1.01–1.60)	1.29 (1.03–1.61)
	Past	1.26 (0.94–1.69)	1.29 (0.98–1.70)
	Current, <5 years	1.35 (0.94–1.94)	1.39 (0.99–1.95)
	Current, ≥5 years	1.90 (1.44–2.52)	1.86 (1.42–2.43)
≥20.0	Never	1.28 (0.97–1.69)	1.22 (0.93–1.59)
	Past	1.22 (0.85–1.77)	1.15 (0.80–1.65)
	Current, <5 years	2.08 (1.41–3.08)	2.27 (1.59–3.24)
	Current, ≥5 years	1.99 (1.41–2.79)	1.90 (1.36–2.63)

* Only person-time for postmenopausal women was included in the analysis. Person-time was excluded for missing data on unclear menopausal status due to hysterectomy without oophorectomy or type of surgery unknown (14.8%), current weight or weight at 18 years of age (9.3%), current alcohol consumption (6.1%), current status or duration of postmenopausal hormone use (3.8%), age at menopause or menarche (2.0%), and parity or age at first birth (1.2%).