Original Contribution

Hormone-related Risk Factors and Postmenopausal Breast Cancer Among Nulliparous Versus Parous Women: An Aggregated Study

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Nulliparity is an established breast cancer risk factor, particularly when compared with parity at young ages. The authors aggregated data from 4 US prospective studies (1979–2006) including 32,641 nulliparous (1,612 breast cancers) and 204,270 parous (8,180 breast cancers) women to examine the hypothesis that nulliparity may increase susceptibility to established postmenopausal breast cancer risk factors. The aggregated hazard ratio for nulliparous versus all parous women = 1.27 (95% confidence interval: 1.21, 1.34), and that for nulliparous versus women <25 years of age at first birth = 1.38 (95% confidence interval: 1.30, 1.46). Among nulliparous women, the hazard ratios for current menopausal hormone therapy use (vs. never use), body mass index >30 kg/m² (vs. <25 kg/m²), and weekly consumption of ≥7 alcoholic drinks (vs. none) ranged from 1.3 to 1.6. The hazard ratios did not differ by parity. In a model including all women, the joint association for each of these factors and nulliparity combined compared with first birth before age 25 years was an approximately 2-fold increased breast cancer risk. Although the baseline risk is higher for nulliparous women compared with parous women, these results suggest that the associations between hormone-related factors and breast cancer do not differ by parity.

alcohol drinking; body mass index; breast neoplasms; hormone replacement therapy; parity; prospective studies; risk factors

Abbreviations: BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USRT, US Radiologic Technologists Study.
risk factors such as obesity, alcohol consumption, menopausal hormonal therapy (MHT), and benign breast disease. Epidemiologic studies, however, have not found evidence that risk factor associations differ by parity status. These studies include relatively small case-control studies focused on nulliparous women (15–17) and larger pooled case-control and cohort studies that conducted subgroup analyses stratified by parity for individual breast cancer risk factors including MHT use, body mass index, alcohol consumption, and family history of breast cancer (18–21). We undertook a large, aggregated analysis of 4 prospective studies to examine, in detail, the associations with established risk factors among nulliparous versus parous women. We then estimated the joint associations of nulliparity with other, common breast cancer risk factors.

MATERIALS AND METHODS

Selected studies

We aggregated and analyzed primary data from 4 National Cancer Institute prospective studies that included female subjects and ascertained basic hormone-related and reproductive exposures: the Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP) (22, 23), the National Institutes of Health-AARP Diet and Health Study (NIH-AARP) (24), the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (25, 26), and the US Radiologic Technologists Study (USRT) (27, 28). Baseline hormone-related and reproductive factors, demographic characteristics, and potential confounders were ascertained by each study from self-administered questionnaires or telephone-based interviews (Table 1). The studies are approved annually by the Special Studies Institutional Review Board of the National Cancer Institute.

Inclusion criteria

From each study, we selected postmenopausal Caucasian women (because of limited numbers of non-Caucasians) with known parity status. Women were considered postmenopausal if they reported that their periods stopped completely because of natural menopause, surgery (hysterectomy and/or bilateral oophorectomy), or other/unknown noncancer reasons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons. Women who reported at least 1 livebirth or provided an age at first birth were classified as parous. Women were considered nulliparous if they reported no births to both the sons.

Case definition

We defined cases as a first primary invasive or in situ breast cancer. The 4 individual studies used different methods to ascertain cancers, including linkage with state cancer registries and the National Death Index as well as self-report with or without verification by medical or pathology record review. In NIH-AARP, cancer ascertainment was made by linkage to state cancer registries (24). BCDDP cancer cases were ascertained by self-report (the majority of which were subsequently confirmed by medical reports) with additional ascertainment made from cancer registry linkage and the National Death Index (22). Cancer cases were ascertained in PLCO from annual study update forms completed by participants and next-of-kin (subsequently confirmed from medical records), death certificates, and data from cancer registries (25). USRT cancer cases were ascertained by self-report, death certificates, limited linkage with state cancer registries, and the National Death Index Plus service (27). A previous validation effort of self-reported breast cancers in USRT demonstrated ≥95% agreement (27).

Statistical methods

Hazard ratios and 95% confidence intervals for associations of risk factors and breast cancer incidence were estimated by using multivariable Cox regression methods (Proc PHREG, SAS version 9.1; SAS Institute, Inc., Cary, North Carolina) with age as the underlying time metric. Follow-up for the present analysis began at the age of the second questionnaire for all women in NIH-AARP, the baseline questionnaire for all women in PLCO, and the first questionnaire on which a woman reported that her periods stopped completely for BCDDP and USRT. Women were considered at risk until they experienced a diagnosis of first primary invasive or in situ breast cancer or were censored because of death, diagnosis of noncancer other than nonmelanoma skin cancer, loss to follow-up, age 85 years, or study end date (administrative censor), whichever occurred first. Following the July 2002 Women’s Health Initiative report, MHT use dropped significantly in the United States (29). Analyses in which MHT use was the primary exposure were censored at June 30, 2002, because we could not account for the likely dramatic changes in MHT use that occurred after this time point. Recency of exposure is known to be a key determinant of breast cancer risk from MHT (18).

For most analyses, separate models were fit to nulliparous and parous women. Two-sided P < 0.05 was considered statistically significant. We visually examined the hazard plots to check assumptions of proportional hazards for all covariates in the model. All variables were modeled categorically. Fully adjusted models included age at menarche, age at natural menopause, body mass index (calculated from weight [kg]/height [m]^2), MHT use at the time of baseline, history of breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline, breast cancer in a first-degree relative, personal history of benign breast disease, typical alcohol consumption at the time of baseline.
nulliparous and parous women separately. Heterogeneity between studies for the risk factors listed in Table 2 was assessed by using a Wald test. Because of the large number of tests, we used a Bonferroni correction and considered \( P < 0.007 = (0.05/7) \) statistically significant for purposes of identifying heterogeneity between studies.

In BCDDP and PLCO, alcohol consumption was first ascertained after baseline. The study-specific hazard ratios were similar if we classified alcohol use at the start of follow-up using the alcohol data subsequently reported during follow-up (method 1) or started follow-up at the time of the alcohol ascertainment (method 2). Therefore, we report method 1 results on the basis of the large number of women available for analysis. Benign breast disease was also retrospectively classified for some women in USRT.

**Aggregated analysis.** Following the study-specific analyses, data from each study were aggregated into a single data set. For variables demonstrating significant differences among studies, study-exposure interaction terms were included in the Cox model. Among parous women, heterogeneity was detected between BCDDP and the other studies for benign breast disease; the aggregated estimates are presented for the other 3 studies only. Because the protection from parity is confined primarily to young age at first birth (2), we stratified parous women by age at first birth (<25 years of age/≥25 years of age) in all aggregated analyses. We stratified analyses of body mass index by MHT use as it has been previously reported that the association between body mass index and breast cancer is modified by MHT and mainly confined to women who do not use MHT (19, 31).

As previous studies have suggested a stronger association

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**Table 1.** Select Study Characteristics and Hazard Ratios and 95% Confidence Intervals for the Association Between Nulliparity and Breast Cancer Risk Among Postmenopausal Caucasian Women in the 4 US Prospective Studies Included in the Aggregated Analysis, 1979–2006

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age at entry, years (range)</th>
<th>Years of questionnaires</th>
<th>Years of follow-up (median time)</th>
<th>No. of Women</th>
<th>No. of Casesb</th>
<th>HR 95% CI</th>
<th>HR 95% CI</th>
<th>HR 95% CI</th>
<th>HR 95% CI</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH-AARP</td>
<td>63.0 (51–72)</td>
<td>1995–1996</td>
<td>1996–2003 (7.1)</td>
<td>15,965</td>
<td>681</td>
<td>1.35</td>
<td>1.24, 1.47</td>
<td>1.38</td>
<td>1.21, 1.56</td>
<td>1.38</td>
</tr>
<tr>
<td>BCDDP</td>
<td>57.0 (35–85)</td>
<td>1979–1986</td>
<td>1979–1998 (11.5)</td>
<td>6,094</td>
<td>373</td>
<td>1.43</td>
<td>1.27, 1.62</td>
<td>1.38</td>
<td>1.21, 1.56</td>
<td>1.38</td>
</tr>
<tr>
<td>PLCO</td>
<td>63.0 (50–78)</td>
<td>1993–2001</td>
<td>1993–2006 (8.2)</td>
<td>5,567</td>
<td>286</td>
<td>1.10</td>
<td>1.00, 1.21</td>
<td>1.14</td>
<td>0.99, 1.30</td>
<td>1.19</td>
</tr>
<tr>
<td>USRT</td>
<td>51.7 (23–85)</td>
<td>1983–1989</td>
<td>1983–2006 (9.9)</td>
<td>5,015</td>
<td>272</td>
<td>1.27</td>
<td>1.17, 1.38</td>
<td>1.29</td>
<td>1.14, 1.46</td>
<td>1.30</td>
</tr>
<tr>
<td>Aggregated</td>
<td>60.8 (23–85)</td>
<td>1995–1998</td>
<td>1979–2006 (7.1)</td>
<td>32,641</td>
<td>1,612</td>
<td>1.27</td>
<td>1.21, 1.34</td>
<td>1.27</td>
<td>1.21, 1.34</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Abbreviations: BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USRT, US Radiologic Technologists Study.

a Estimated from individual Cox proportional hazards models (SAS PHREG; SAS Institute, Inc., Cary, North Carolina) that used attained age as the time scale. Study-specific estimates were adjusted for birth year (all) and entry year (all studies except NIH-AARP) by using study-specific quantiles. Aggregated model estimates were adjusted for birth year (before 1927, 1927–1932, 1933–1938, 1939 or later), calendar year of entry (before 1987, 1987–1995, 1996 or later), and study.

b First primary invasive and in situ breast cancers.
### Table 2. Hazard Ratios and 95% Confidence Intervals for the Associations Between Baseline Hormonal Factors and Breast Cancer Risk Among Postmenopausal Caucasian Women in the Aggregated Sample From 4 US Prospective Studies, 1979–2006

| Hormonal Factor | Nulliparous Women (32,641 Women) | | | Parous Women Aged <25 Years at First Birth (139,255 Women) | | | Parous Women Aged ≥25 Years at First Birth (65,015 Women) | |
|-----------------|---------------------------------|--------|----------------|-------------------|--------|----------------|-------------------|
|                 | No. of Cases | HR \(^{b} \) | 95% CI | No. of Cases | HR \(^{b,c} \) | 95% CI | \(P_{\text{heterogeneity}}^{d} \) | No. of Cases | HR \(^{b,c} \) | 95% CI | \(P_{\text{heterogeneity}}^{e} \) |
| **Age at menarche\(^{f} \)** | | | | | | | | | | | |
| Early | 642 | 1.00 Referent | | 1,993 | 1.00 Referent | | 1,099 | 1.00 Referent | | |
| Middle | 739 | 0.93 0.83, 1.04 | | 2,345 | 0.92 0.86, 0.98 | | 1,477 | 0.96 0.88, 1.04 | | |
| Late | 215 | 0.95 0.80, 1.11 | | 726 | 0.89 0.82, 0.98 | | 483 | 0.94 0.84, 1.05 | | 0.91 |
| **Age at a natural menopause, years** | | | | | | | | | | | |
| <45 | 128 | 0.81 0.67, 0.99 | | 223 | 0.78 0.68, 0.90 | | 161 | 0.81 0.68, 0.95 | | |
| 45–49 | 325 | 0.91 0.79, 1.05 | | 751 | 0.96 0.88, 1.05 | | 519 | 0.91 0.82, 1.01 | | |
| 50–54 | 499 | 1.00 Referent | | 1,395 | 1.00 Referent | | 1,045 | 1.00 Referent | | |
| ≥55 | 106 | 0.95 0.80, 1.11 | | 726 | 0.89 0.82, 0.98 | | 483 | 0.94 0.84, 1.05 | | 0.91 |
| Surgery/other/unknown\(^{g} \) | 548 | 0.77 0.67, 0.87 | | 2,313 | 0.80 0.74, 0.86 | | 1,082 | 0.88 0.80, 0.96 | | |
| **Body mass index, kg/m\(^{2} \)** | | | | | | | | | | | |
| <25 | 858 | 1.00 Referent | | 2,316 | 1.00 Referent | | 1,653 | 1.00 Referent | | |
| 25–<30 | 450 | 1.09 0.97, 1.22 | | 1,635 | 1.11 1.04, 1.18 | | 928 | 1.12 1.03, 1.21 | | |
| ≥30 | 254 | 1.10 0.95, 1.27 | | 1,031 | 1.12 1.03, 1.21 | | 437 | 1.11 1.00, 1.24 | | 0.94 |
| **Menopausal hormone therapy use\(^{h} \)** | | | | | | | | | | | |
| Never | 554 | 1.00 Referent | | 1,423 | 1.00 Referent | | 1,010 | 1.00 Referent | | |
| Former | 187 | 0.99 0.84, 1.18 | | 562 | 0.99 0.99, 1.21 | | 395 | 0.95 0.86, 1.05 | | |
| Current, <5 years\(^{i} \) | 163 | 1.38 1.15, 1.66 | | 527 | 1.33 1.19, 1.47 | | 362 | 1.38 1.19, 1.57 | | |
| Current, ≥5 years\(^{j} \) | 408 | 1.59 1.37, 1.83 | | 1,391 | 1.60 1.47, 1.74 | | 711 | 1.53 1.37, 1.70 | | 0.46 |
| **First-degree family history of breast cancer** | | | | | | | | | | | |
| No | 1,286 | 1.00 Referent | | 4,010 | 1.00 Referent | | 2,459 | 1.00 Referent | | |
| Yes | 278 | 1.37 1.20, 1.56 | | 965 | 1.56 1.45, 1.67 | | 554 | 1.42 1.29, 1.56 | | 0.65 |
| **Personal history of benign breast disease** | | | | | | | | | | | |
| No | 870 | 1.00 Referent | | 2,923 | 1.00 Referent | | 1,783 | 1.00 Referent | | |
| Yes | 681 | 1.31 1.18, 1.45 | | 1,638\(^{k} \) 1.41\(^{k} \) 1.33, 1.51 | | 869\(^{k} \) 1.42\(^{k} \) 1.30, 1.55 | | 0.25 |
| **Weekly consumption of alcohol** | | | | | | | | | | | |
| None | 432 | 1.00 Referent | | 1,547 | 1.00 Referent | | 835 | 1.00 Referent | | |
| <7 drinks | 801 | 0.93 0.83, 1.04 | | 2,563 | 0.98 0.88, 1.04 | | 1,553 | 0.93 0.83, 1.04 | | |
| ≥7 drinks | 268 | 1.30 1.11, 1.52 | | 609 | 1.22 1.11, 1.35 | | 450 | 1.33 1.19, 1.50 | | 0.75 |

Abbreviations: BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USRT, US Radiologic Technologists Study.

\(^{a} \) First primary invasive and in situ breast cancers.

\(^{b} \) Estimated from Cox proportional hazards models (SAS PHREG; SAS Institute, Inc., Cary, North Carolina) that used attained age as the time scale. Separate models were fit to nulliparous women, parous women aged <25 years at first birth, and parous women aged ≥25 years at first birth. Models include all variables presented in the table as well as birth year (before 1927, 1927–1932, 1933–1938, 1939 or later), calendar year of entry (before 1987, 1987–1995, 1996 or later), oral contraceptive use (ever, never, missing), and study. Models include missing category for each variable (data not shown).

\(^{c} \) Further adjusted for number of livebirths (<3, ≥3, missing).

\(^{d} \) \(P_{\text{heterogeneity}} \) between nulliparous women and parous women aged <25 years at first birth based on a Wald test.

\(^{e} \) \(P_{\text{heterogeneity}} \) between nulliparous women and parous women aged ≥25 years at first birth based on a Wald test.

\(^{f} \) Age at menarche groups: NIH-AARP and BCDDP—early, ≤12 years; middle, 13–14 years; late, ≥15 years; PLCO and USRT—early, ≤11 years; middle, 12–13 years; late, ≥14 years.

\(^{g} \) Includes hysterectomy without bilateral oophorectomy. This category not included in heterogeneity tests.

\(^{h} \) Follow-up censored at June 30, 2002.

\(^{i} \) Includes <6 years for PLCO.

\(^{j} \) Includes ≥6 years for PLCO.

\(^{k} \) Estimates and case numbers presented for NIH-AARP, PLCO, and USRT.

Am J Epidemiol 2011;173:509–517
between MHT use and breast cancer among lean women than among obese women (18), we also examined the association between MHT use and breast cancer according to body mass index.

With the final aggregated models, the heterogeneity of hazard ratios from separate models for nulliparous women compared with parous women <25 years of age at first birth and parous women ≥25 years of age at first birth was evaluated by using a Wald test. We estimated the joint associations between nulliparity and other hormone-related factors in a model fit to all women combined that included interaction terms of the parity groups and other risk factor levels.

RESULTS

A summary of study characteristics from the 4 cohorts is presented in Table 1. There were a total of 1,612 first primary breast cancers reported among 32,641 nulliparous women, 5,098 breast cancers among 139,255 parous women <25 years of age at first birth, and 3,082 breast cancers among 65,015 parous women with age at first birth ≥25 years. The mean age at start of follow-up ranged from 51.7 years in USRT to 63 years in NIH-AARP and PLCO. The median years of follow-up ranged from 7.1 years in NIH-AARP to 11.5 years in BCDDP. NIH-AARP was the largest cohort contributing approximately 50% of women and 40% of cases to the analyses. Overall 90% of women who first gave birth before age 25 years and approximately 80% of women who first gave birth at age 25 or older reported having 2 or more births. Women in the younger age at first birth category were more likely to report having had 3 or more births (66%) compared with women who first gave birth after age 25 years (40%).

The overall aggregated hazard ratio for the risk of breast cancer for nulliparous women compared with parous women was 1.27 (95% confidence interval (CI): 1.21, 1.34) (Table 1). Nulliparous women had a 1.38-fold increased risk of breast cancer compared with parous women who first gave birth before 25 years of age (95% CI: 1.30, 1.46), while the risk among nulliparous women was only slightly elevated compared with that of parous women with older ages at first birth (hazard ratio (HR) = 1.11, 95% CI: 1.05, 1.18). These results were consistent across the 4 studies.

Among nulliparous women, breast cancer risk was significantly lower among women who reported a natural menopause before age 45 years (HR = 0.81, 95% CI: 0.67, 0.99) compared with women who reported a natural menopause at ages 50–54 years (Table 2). A reduction in breast cancer risk was also observed among nulliparous women who reported a natural menopause at ages 45–49 years (HR = 0.91, 95% CI: 0.79, 1.05), but this was not statistically significant. Overall, body mass index was not significantly associated with breast cancer risk among nulliparous women. However, among nulliparous women who reported never use of MHT at baseline, body mass index ≥30 kg/m² was associated with a significant increase in breast cancer risk (HR = 1.30, 95% CI: 1.05, 1.61) (Table 3). Among nulliparous women who reported current use of MHT at baseline, the hazard ratios for short- and long-term use compared with never use were 1.38 (95% CI: 1.15, 1.66) and 1.59 (95% CI: 1.37, 1.83), respectively (Table 2). The associations between current MHT use at baseline and breast cancer were attenuated with increasing body mass index and no longer statistically significant among women with body mass index ≥30 kg/m² (data not shown). History of breast cancer in a first-degree relative (HR = 1.37, 95% CI: 1.20, 1.56), personal history of benign breast disease (HR = 1.31, 95% CI: 1.18, 1.45), and consumption of 7 or more alcoholic drinks per week (HR = 1.30, 95% CI: 1.11, 1.52) were also associated with increased breast cancer risk.

There was no evidence of heterogeneity of the magnitude of associations between nulliparous and parous women for any of the factors examined (Tables 2 and 3).

The results did not change in a series of sensitivity analyses including the use of calendar-time instead of age as the underlying time metric, restriction to women who had complete covariate data, exclusion of the small percentage of women in BCDDP for whom we could not confirm baseline cancer history, restriction of outcome classification to invasive breast tumors only (in situ breast tumor diagnosis was a censoring event), and censoring at age 80 years for all women. When we restricted the analysis to women who reported a natural menopause, the hazard ratios for MHT use were stronger than in the main models, but there was no evidence of heterogeneity by parity status.

The joint associations for nulliparity and 3 modifiable hormone-related factors, baseline MHT use, body mass index, and alcohol consumption, are presented in Table 4. The referent group in each of the 3 analyses is parous women <25 years of age at first birth in the lowest category of risk (i.e., no history of MHT use, body mass index <25 kg/m², and no alcohol consumption). For body mass index, we restricted the analysis to women who reported no history of MHT use at baseline. The joint hazard ratio for current MHT use at baseline and nulliparity was 1.96 (95% CI: 1.67, 2.31) for short (<5 years) duration of use and 2.23 (95% CI: 2.00, 2.50) for long (≥5 years) duration of use. The joint hazard ratio of nulliparity and obesity was 1.94 (95% CI: 1.60, 2.35). The joint hazard ratio for consumption of at least 7 drinks per week and nulliparity was 1.79 (95% CI: 1.57, 2.04).

DISCUSSION

This large and detailed prospective investigation allowed us to investigate the associations between well-known breast cancer risk factors among postmenopausal nulliparous women. Compared with parous women who first gave birth before age 25 years, nulliparous women had a 38% increased risk of breast cancer. The relative increase in breast cancer risk among nulliparous women was only 11% compared with parous women who first gave birth after age 25 years. The relative risks for all established hormone-related breast cancer risk factors were generally consistent between nulliparous and parous women, irrespective of age at first birth. Younger age at natural menopause was associated with a reduced risk of breast cancer, whereas obesity, current MHT use at baseline, family history of breast cancer in

Am J Epidemiol 2011;173:509–517
nulliparous women and parous women aged <25 years at first birth, and parous women aged ≥25 years at first birth. Our observation that the associations between established hormone-related risk factors and postmenopausal breast cancer risk did not vary by parity status. The associations between a first-degree relative, personal history of benign breast disease, and consumption of 7 or more alcoholic drinks per week were associated with increased breast cancer risk (HRs = 1.3–1.6). The combination of nulliparity and current use of MHT at baseline, obesity, or consumption of 7 or more alcoholic drinks per week was associated with a 1.8-fold increased risk of breast cancer relative to unexposed parous women who first gave birth before 25 years of age.

Our observation that the associations between established hormone-related risk factors and postmenopausal breast cancer are not significantly modified by parity is consistent with observations from previous case-control studies of nulliparous women (15–17). The numbers of breast cancer cases in these studies, however, were substantially smaller than those in our study, and only 1 study (17) directly assessed heterogeneity between nulliparous and parous women. Other large, pooled analyses that conducted subgroup analyses stratified by parity for body mass index (19), MHT use (18), family history of breast cancer (20), and alcohol consumption (21) similarly concluded that the effects associations between these factors and breast cancer risk did not vary by parity status. The associations between age at natural menopause and benign breast disease have not been previously reported in a large sample of postmenopausal nulliparous women. Few, if any, large studies quantified the joint associations of nulliparity and common modifiable breast cancer risk factors.

On the basis of previously reported structural and molecular differences observed in nulliparous and parous breast tissue (13, 14), we hypothesized that hormone-related exposures would have differential effects on postmenopausal breast cancer risk in these 2 groups. During pregnancy, the terminal ductal lobule units undergo differentiation, and it is hypothesized that these differentiated cells are less susceptible to hormonal stimulation, DNA damage, and therefore carcinogenesis (8). Pregnancy may also induce long-term protective molecular changes, and a number of molecular differences such as expression of genes related to DNA repair and apoptosis have been observed between nulliparous and parous breast tissue (10, 11, 14). In humans, these molecular differences have been reported in postmenopausal women (14), although structural differences between the groups seem to attenuate with time (13). The biologic relevance of these molecular differences, however, is not well understood.

Table 3. Hazard Ratios and 95% Confidence Intervals for the Association Between Body Mass Index and Breast Cancer Risk Stratified by Baseline Menopausal Hormone Therapy Use Among Postmenopausal Caucasian Women in the Aggregated Sample From 4 US Prospective Studies, 1979–2006

<table>
<thead>
<tr>
<th>Body mass index among</th>
<th>Nulliparous Women</th>
<th>Parous Women Aged &lt;25 Years at First Birth</th>
<th>Parous Women Aged ≥25 Years at First Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index among never users of menopausal hormone therapy, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>312</td>
<td>1.00 Referent</td>
<td>685</td>
</tr>
<tr>
<td>25–&lt;30</td>
<td>184</td>
<td>1.18 0.98, 1.41</td>
<td>558</td>
</tr>
<tr>
<td>≥30</td>
<td>128</td>
<td>1.30 1.05, 1.61</td>
<td>463</td>
</tr>
<tr>
<td>Body mass index among former users of menopausal hormone therapy, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>123</td>
<td>1.00 Referent</td>
<td>315</td>
</tr>
<tr>
<td>25–&lt;30</td>
<td>65</td>
<td>1.04 0.77, 1.42</td>
<td>247</td>
</tr>
<tr>
<td>≥30</td>
<td>26</td>
<td>0.81 0.52, 1.25</td>
<td>163</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 3 continued...

References...

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Age-related changes to breast tissue may have contributed to our observation that the associations between hormone-related risk factors and postmenopausal breast cancer are not significantly modified by parity. In a small study of breast tissue obtained from women undergoing mammoplasty, well-differentiated lobules ("type 3") constituted 70%–80% of breast structures among parous women until age 40 years (13). Among parous women older than age 40 years and nulliparous women of all ages, they mainly observed the least-differentiated lobule type ("type 1"). A larger study of women with benign breast disease examined the prevalence of involution according to age and several breast cancer risk factors (32). The overall prevalence of complete terminal ductal lobule unit involution was somewhat higher among nulliparous women (27.1%) than among parous women (21.2%), but age seemed to be a much stronger determinant of involution. Irrespective of parity, breast cancer risk appeared to decrease as the degree of terminal ductal lobule unit involution increased. Potentially, age-related involution displaces pregnancy-induced differences, rendering nulliparous and parous breast cells similarly susceptible to the proliferative and/or genotoxic effects of hormone-related exposures.

Parity might also act through a mechanism independent of the hormone-related exposures evaluated in our study. Consistent with this, although not definitive, is the observation by several studies that circulating levels of endogenous estrogen levels in postmenopausal women appear to be similar among nulliparous and parous women (33, 34).

We did not examine breast cancer risk according to baseline MHT formulation (i.e., estrogen only or estrogen plus progestin), because the information was not available for all of the cohorts. Although the magnitude of risk of breast cancer differs by formulation (35–38), it is unlikely that availability of this information would have changed our inference that parity does not modify the association between baseline MHT and breast cancer. In a recent analysis conducted in the NIH-AARP cohort, there was no evidence of heterogeneity by parity for either estrogen alone or combined estrogen + progestin MHT (38). All analyses were based on information reported by the women at baseline. As recency of MHT exposure is known to be an important determinant of breast cancer risk (18), it is possible that we underestimated the association with recent MHT use if women stopped using MHT during follow-up. Additionally, women reporting “never use” at baseline may have used MHT during follow-up, which would also attenuate the relative risk comparing “current” or “former” with “never” users. We also lacked information about the estrogen- and progesterone-receptor status of breast cancers. Previous studies suggest that breast cancer risk factors, including nulliparity, may differ by hormone receptor status (39). Differences in risk factor profiles (5) and hormone receptor status patterns of breast cancers (40) across racial and ethnic
groups may limit the generalizability of the magnitude of our results to non-Caucasian women.

A key strength of our aggregated study was the large sample size of more than 32,000 nulliparous women, which allowed us to assess multiple hormone-related breast cancer risk factors with adequate power. In addition, we were able to compare our results with 2 groups of parous women, defined by age at first birth. This is important given that animal (8) and epidemiologic (2) studies have clearly established age at first birth as a strong determinant of breast cancer risk. The large sample size also enabled us to estimate the combined associations of parity status and several modifiable breast cancer risk factors with adequate power. Another major strength was the use of prospective data, which ensured that all nulliparous and parous women enrolled were included whether or not they developed cancer.

In summary, the observed risk associated with older age at menopause, obesity, current use of MHT at baseline, first-degree family history of breast cancer, benign breast disease, and regular alcohol consumption was similar among nulliparous and parous women. Although we acknowledge the importance of reducing the prevalence of modifiable breast cancer risk factors in all women, quantification of the joint associations of nulliparity and certain exposures provides risk estimates that are specific to nulliparous women who have a higher baseline risk than parous women.

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REFERENCES