Relationship between Established Breast Cancer Risk Factors and Risk of Seven Different Histologic Types of Invasive Breast Cancer


Background: Important differences in the contributions of certain exposures to the risks of ductal versus lobular breast carcinomas have been observed, but few studies have evaluated the relationships between established breast cancer risk factors and other histologic types.

Methods: Information on family history of cancer and reproductive, hormonal, anthropometric, and lifestyle characteristics were collected in a multicenter population-based case-control study consisting of 3,463 ductal, 274 lobular, 261 ductal-lobular, 91 medullary, 77 tubular, 70 comedo, and 61 mucinous invasive breast carcinoma cases (ages 35–64 years, newly diagnosed 1994-1998) and 4,682 controls. Associations between each of these histologic types and various exposures were evaluated using polytomous regression.

Results: Heterogeneity in the risks of different histologic types of breast cancer was observed for three exposures: menopausal hormone use, body mass index (BMI), and alcohol consumption. Specifically, current use of unopposed estrogen was associated with a reduced risk of ductal carcinoma and increased risk of comedocarcinoma, and current use of estrogen and progestin was associated with elevated risks of ductal-lobular and tubular carcinomas. Among postmenopausal women, BMI was only inversely related to risk of ductal-lobular carcinoma, and alcohol use was only positively related to risk of lobular carcinoma.

Conclusions: Variations in the associations between known breast cancer risk factors and risk of different breast cancer histologies were observed. Although these findings require confirmation, and the analyses of some histologic groups were limited by small sample sizes, they provide some insight into the different etiologies of various histologic subtypes of breast cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(5):946–54)

Introduction

Numerous risk factors for breast cancer have been identified, including a family history of the disease and reproductive, hormonal, anthropometric, and lifestyle characteristics (1). However, most of these factors are associated with but a modest increase in breast cancer risk. This may partly be because breast cancer is a heterogeneous disease. Histology is one means of categorizing breast cancers that seem to have etiologic importance; given the results of several recent studies evaluating differences between ductal and lobular breast carcinomas. Specifically, whereas it is now well established that use of combined estrogen and progestin hormone therapy among postmenopausal women increases breast cancer risk (2, 3), six (4-9) of seven (10) studies that have specifically reported on associations between different types of hormone therapy and risk of lobular (pure lobular and/or mixed ductal-lobular tumors) versus ductal carcinomas indicate that this association varies by histologic type (4-9). The six studies reporting a difference by histology find that whereas use of combined hormone therapy is associated with 2.0- to 3.9-fold increases in risk of lobular carcinoma, it has less of an effect on ductal carcinoma risk. Five (4-8) of these six studies, in fact, found that combined hormone therapy is not associated with an elevated risk of ductal carcinoma. Oral contraceptives (11, 12) and alcohol use (13) also seem to be more strongly associated with an increased risk of lobular carcinoma than with ductal carcinoma. However, earlier reproductive events, such as parity, age at first full-term pregnancy, and breast-feeding, seem to be similarly related to risk of ductal, lobular, and mixed ductal-lobular tumors (14). In addition to differences in their risk factor profiles and pathologic features, numerous clinical (15) and molecular (16-19) differences between lobular and ductal carcinomas have been well described. These investigations have provided insight into differences in the etiologies of lobular compared with ductal tumors, and they suggest that lobular carcinomas are more hormonally responsive than ductal carcinomas. Few studies have evaluated the relationship between established breast cancer risk factors and other histologic types. Such
investigations are important because the etiologies of rarer histologic types of breast cancer, which account for ~7% of all cases in the United States (20), are largely unknown.

We evaluated the relationships between major known risk factors for breast cancer and seven different histologic types of breast cancer in a large multicenter U.S. case-control study.

Materials and Methods

Details of the methods used in the Women's Contraceptive and Reproductive Experiences Study have been described previously (21). Briefly, a population-based case-control study was conducted at five metropolitan sites in the United States (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle). White and Black women ages 35 to 64 years without a history of in situ or invasive breast cancer who were diagnosed with invasive breast cancer from July 1994 to April 1998 were eligible as cases. These women were ascertained by Surveillance, Epidemiology, and End Results registry staff at four sites (Atlanta, Detroit, Los Angeles, and Seattle) and by field center staff at one site (Philadelphia). Controls were women without a history of breast cancer who were identified using random digit dialing. Controls were frequency matched to cases within strata of site, race, and 5-year age group; 76.5% of eligible cases and 78.6% of eligible controls participated in this study, for a total of 4,575 cases and 4,682 controls (21).

The study protocol was approved by each of the local institutional review boards at each of the sites where this study was conducted. Written informed consent was obtained from all study subjects. All interviews were conducted in person, typically in subjects’ homes, using standardized procedures. The main purpose of this study was to assess the relationship between oral contraceptives and breast cancer risk, but self-reported information on other possible risk factors for breast cancer were also obtained. The data collected included a detailed family history of cancer, reproductive history, anthropometric characteristics, use of menopausal hormone therapy, lifetime smoking history, and lifetime alcohol use. The methods used to assess alcohol use (22) in this study are described in detail elsewhere. Our questioning was limited to exposures that occurred before each subject’s reference date. The reference date used for each woman with breast cancer was her diagnosis date. The reference date assigned to each control was the date of our first random digit dialing contact with her household.

The histology of each breast cancer case was ascertained from the data collected by each of the Surveillance, Epidemiology, and End Results cancer registries through routine medical record abstractions (except in Philadelphia where these data were collected by field center staff). Cases were grouped into the seven following histologic categories based on the International Classification of Diseases-Oncology codes assigned to their tumors, similar to how they have been categorized previously (20). The categories included ductal (International Classification of Diseases-Oncology code 8500, n = 3,463), lobular (code 8520, n = 274), ductal-lobular (code 8522, n = 261), medullary (codes 8510 and 8512, n = 91), tubular (codes 8211 and 8201, n = 77), comedo (code 8501, n = 70), and mucinous (code 8480, n = 61). The 278 women with other International Classification of Diseases-Oncology codes, representing 6.1% of all cases, were excluded from all of our analyses, leaving a total of 4,297 cases.

We compared cases of each histologic type to controls using multivariate polytomous logistic regression (23). All analyses were conducted using Stata SE version 8.2 (Stata Corp., College Station, TX). Odds ratios (ORs) and associated 95% confidence intervals (95% CI) were calculated as estimates of the relative risk. All analyses were adjusted for age, race, and study site because controls were frequency

### Table 1. Distribution of demographic characteristics among controls and cases with different histologic types of breast cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Controls (n = 4,682)</th>
<th>Ductal (n = 3,463)</th>
<th>Lobular (n = 274)</th>
<th>Ductal-lobular (n = 261)</th>
<th>Medullary (n = 91)</th>
<th>Tubular (n = 77)</th>
<th>Comedo (n = 70)</th>
<th>Mucinous (n = 61)</th>
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</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
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<tr>
<td>White</td>
<td>3,021 (64.5)</td>
<td>2,220 (64.1)</td>
<td>193 (70.4)</td>
<td>195 (74.7)</td>
<td>27 (29.7)</td>
<td>62 (80.5)</td>
<td>39 (55.7)</td>
<td>47 (77.0)</td>
</tr>
<tr>
<td>Black</td>
<td>1,661 (35.5)</td>
<td>1,243 (35.9)</td>
<td>81 (29.6)</td>
<td>66 (25.3)</td>
<td>64 (70.3)</td>
<td>15 (19.5)</td>
<td>31 (44.3)</td>
<td>14 (23.0)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
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<tr>
<td>Atlanta</td>
<td>895</td>
<td>722 (84.4)</td>
<td>47 (5.5)</td>
<td>43 (5.0)</td>
<td>10 (1.2)</td>
<td>5 (0.6)</td>
<td>21 (2.5)</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Detroit</td>
<td>779</td>
<td>541 (88.5)</td>
<td>33 (5.4)</td>
<td>14 (2.3)</td>
<td>6 (1.0)</td>
<td>9 (1.5)</td>
<td>2 (0.3)</td>
<td>6 (1.0)</td>
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<td>879 (75.1)</td>
<td>65 (5.6)</td>
<td>112 (9.6)</td>
<td>45 (3.8)</td>
<td>27 (2.3)</td>
<td>26 (2.2)</td>
<td>16 (1.4)</td>
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<tr>
<td>Philadelphia</td>
<td>736</td>
<td>527 (80.2)</td>
<td>47 (7.2)</td>
<td>27 (4.1)</td>
<td>22 (3.3)</td>
<td>11 (1.7)</td>
<td>13 (2.0)</td>
<td>10 (1.5)</td>
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<tr>
<td>Seattle</td>
<td>1,017</td>
<td>794 (79.1)</td>
<td>82 (8.2)</td>
<td>65 (6.5)</td>
<td>8 (0.8)</td>
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<td>8 (0.8)</td>
<td>2 (0.2)</td>
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<td><strong>Education</strong></td>
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<tr>
<td>&lt;High school</td>
<td>444 (9.5)</td>
<td>308 (8.9)</td>
<td>27 (9.9)</td>
<td>19 (7.3)</td>
<td>7 (7.7)</td>
<td>5 (6.5)</td>
<td>8 (11.4)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>High school</td>
<td>1,250 (28.8)</td>
<td>998 (82.8)</td>
<td>70 (25.5)</td>
<td>75 (28.7)</td>
<td>31 (34.1)</td>
<td>23 (29.9)</td>
<td>24 (34.3)</td>
<td>18 (29.5)</td>
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<tr>
<td>Tech school</td>
<td>1,495 (31.9)</td>
<td>1,134 (32.8)</td>
<td>78 (28.5)</td>
<td>76 (29.1)</td>
<td>41 (45.1)</td>
<td>27 (35.1)</td>
<td>20 (28.6)</td>
<td>18 (29.5)</td>
</tr>
<tr>
<td>College</td>
<td>1,393 (29.8)</td>
<td>1,022 (29.5)</td>
<td>99 (36.1)</td>
<td>91 (34.9)</td>
<td>12 (13.2)</td>
<td>22 (28.6)</td>
<td>18 (25.7)</td>
<td>19 (31.1)</td>
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<td><strong>Income, US$</strong></td>
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<tr>
<td>&lt;10,000</td>
<td>397 (8.7)</td>
<td>332 (9.9)</td>
<td>21 (8.0)</td>
<td>18 (7.1)</td>
<td>9 (10.5)</td>
<td>2 (2.7)</td>
<td>12 (17.6)</td>
<td>3 (5.1)</td>
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<tr>
<td>10,000-19,999</td>
<td>472 (10.3)</td>
<td>322 (9.6)</td>
<td>22 (8.4)</td>
<td>22 (8.7)</td>
<td>14 (16.3)</td>
<td>10 (13.3)</td>
<td>7 (10.3)</td>
<td>5 (8.5)</td>
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<tr>
<td>20,000-34,999</td>
<td>925 (20.3)</td>
<td>691 (20.7)</td>
<td>52 (19.8)</td>
<td>43 (17.1)</td>
<td>16 (18.6)</td>
<td>13 (17.3)</td>
<td>12 (17.6)</td>
<td>9 (13.5)</td>
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<tr>
<td>35,000-49,999</td>
<td>789 (17.3)</td>
<td>599 (17.9)</td>
<td>50 (19.0)</td>
<td>49 (19.4)</td>
<td>22 (25.6)</td>
<td>16 (21.3)</td>
<td>12 (17.6)</td>
<td>8 (13.6)</td>
</tr>
<tr>
<td>&gt;50,000</td>
<td>1,978 (43.4)</td>
<td>1,400 (41.9)</td>
<td>118 (44.9)</td>
<td>120 (47.6)</td>
<td>25 (29.1)</td>
<td>34 (45.3)</td>
<td>25 (36.8)</td>
<td>34 (57.6)</td>
</tr>
</tbody>
</table>

1. Row percentages for cases only are shown (all other percentages shown are column percentages).
2. Data on education level were missing for one control, and data on household income were missing for 121 controls and 119 ductal, 11 lobular, 9 ductal-lobular, 5 medullary, 2 tubular, 2 comedo, and 2 mucinous cases.
interaction terms for menopausal status and reproductive factors and menopausal status and height, but these interaction models did not differ from the main-effects models ($P_{interaction} > 0.05$).

### Results

Controls and ductal carcinoma cases, which comprised 80.6% of all cases, had similar age and racial distributions (Table 1). Cases with lobular, ductal-lobular, tubular, or mucinous cancers tended to be 50 years of age and older and more commonly White compared with control participants, whereas those with medullary or comedo carcinomas tended to be younger and more commonly Black than controls. Controls and ductal cases also were similarly distributed across study sites, but the distribution of other histologic groups differed somewhat by study site. In particular, greater proportions of women in Seattle and Los Angeles had ductal-lobular carcinoma, and greater proportions of women in Los Angeles and Philadelphia had medullary carcinoma compared with breast cancer cases enrolled at the other study sites. For the most part, education level was similar across the control and case groups, although lobular and ductal-lobular cases were somewhat more likely, and medullary carcinoma cases were somewhat less likely to have had some college education. With respect to income, control subjects and ductal carcinoma cases were similar, although patients with ductal-lobular or
mucinous tumors tended to have higher incomes, whereas those with medullary or comedo carcinoma tended to have lower incomes.

A first-degree family history of breast cancer was associated with a 1.7- to 2.1-fold increase in risk of each histologic type of breast cancer except for mucinous carcinoma (OR, 1.0; 95% CI, 0.5-2.3; Table 2). In general, the magnitude of these associations was stronger when the analysis was restricted to premenopausal women; although menopausal status was not a statistically significant effect modifier of this relationship (P = 0.15). Among premenopausal women, those with a first-degree family history of breast cancer had 2.1- to 3.5-fold increases in risk of all histologic types of breast cancer (although the risks associated with tubular and comedo carcinomas were within the limits of chance). Among postmenopausal women with a first-degree family history of breast cancer, 1.6- to 2.1-fold increases in risks of ductal, lobular, ductal-lobular, tubular, and comedo carcinomas (but not of medullary or mucinous carcinomas) were observed, although the risks associated with tubular and comedo carcinomas were within the limits of chance.

Although some differences in the risks associated with various reproductive factors were observed by histologic type (described below), it is noteworthy that statistically significant heterogeneity in these risks across histologies was not observed for any of these factors (Table 3). Compared with women whose age at menarche was 11 years or younger, those whose age at menarche occurred at 14 years of age or older had a reduced risk of lobular carcinoma (OR, 0.5; 95% CI, 0.4-0.8) that was statistically different from the risk estimate for ductal carcinoma (P = 0.02). Later age at menarche was not related to risk of any other histologic type of breast cancer. The ORs for parous women compared with nulliparous women ranged from 0.6- to 0.9-fold for ductal, lobular, ductal-lobular, tubular, and comedo carcinomas, although the associations with tubular and comedo carcinomas were within the limits of chance. Furthermore, compared with nulliparous women, women who had three or more live births had reduced risks of ductal, lobular, ductal-lobular, tubular, comedo, and mucinous carcinomas, although the associations with tubular, comedo, and mucinous carcinomas were within the limits of chance. Compared with women who were 19 years of age or younger at first-term pregnancy, those whose first-term pregnancy was at age 25 years or older had elevated risks of lobular carcinoma. A statistically different difference in the risk estimates associated with age at first full-term pregnancy for lobular versus ductal carcinomas was observed (P = 0.004). Compared with women who never breast fed or breast fed for ≤1 month, the ORs for those who breast fed for ≥12 months ranged from 0.4 to 0.7 for ductal, medullary, tubular, and

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Controls (n = 4,682)</th>
<th>Ductal (n = 3,463)</th>
<th>Lobular (n = 274)</th>
<th>Ductal-lobular (n = 261)</th>
<th>Medullary (n = 91)</th>
<th>Tubular (n = 77)</th>
<th>Comedo (n = 70)</th>
<th>Mucinous (n = 61)</th>
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<td>Age at menarche (y)</td>
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<tr>
<td>≤11</td>
<td>1,260</td>
<td>878 (1.0 (ref))</td>
<td>88 1.0 (ref)</td>
<td>65 1.0 (ref)</td>
<td>25 1.0 (ref)</td>
<td>16 1.0 (ref)</td>
<td>14 1.0 (ref)</td>
<td>16 1.0 (ref)</td>
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<tr>
<td>12-13</td>
<td>2,459</td>
<td>1,916 1.1 (1.0-1.2)*</td>
<td>148 0.8 (0.6-1.1)</td>
<td>149 1.2 (0.9-1.6)</td>
<td>49 1.1 (0.7-1.8)</td>
<td>44 1.4 (0.8-2.5)</td>
<td>39 1.4 (0.8-2.6)</td>
<td>38 1.2 (0.6-2.1)</td>
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<tr>
<td>≥14</td>
<td>949</td>
<td>648 1.0 (0.9-1.1)</td>
<td>37 0.5 (0.4-0.8)*</td>
<td>47 1.0 (0.7-1.4)</td>
<td>17 0.9 (0.5-1.7)</td>
<td>17 1.4 (0.7-2.9)</td>
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<td>7 0.6 (0.2-1.4)</td>
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<td>Parity</td>
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<tr>
<td>Nulliparous</td>
<td>805</td>
<td>664 1.0 (ref)</td>
<td>51 1.0 (ref)</td>
<td>61 1.0 (ref)</td>
<td>12 1.0 (ref)</td>
<td>20 1.0 (ref)</td>
<td>17 1.0 (ref)</td>
<td>11 1.0 (ref)</td>
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<tr>
<td>Parous</td>
<td>3,868</td>
<td>2,798 0.9 (0.8-1.0)*</td>
<td>223 0.8 (0.6-1.1)</td>
<td>200 0.7 (0.5-1.0)*</td>
<td>79 1.3 (0.7-2.4)</td>
<td>57 0.6 (0.3-1.0)*</td>
<td>53 0.7 (0.4-1.2)</td>
<td>50 0.9 (0.5-1.8)</td>
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<td>≤19</td>
<td>1,096</td>
<td>766 1.0 (ref)</td>
<td>38 1.0 (ref)</td>
<td>49 1.0 (ref)</td>
<td>25 1.0 (ref)</td>
<td>20 1.0 (ref)</td>
<td>17 1.0 (ref)</td>
<td>11 1.0 (ref)</td>
</tr>
<tr>
<td>20-24</td>
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<td>969 1.0 (0.9-1.2)</td>
<td>94 1.9 (1.3-2.9)*</td>
<td>67 1.0 (0.7-1.5)</td>
<td>24 1.1 (0.6-2.0)</td>
<td>27 1.9 (0.9-3.9)</td>
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<tr>
<td>25-29</td>
<td>682</td>
<td>546 1.2 (1.0-1.4)</td>
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<td>47 1.4 (0.9-2.2)</td>
<td>13 1.4 (0.7-2.9)</td>
<td>13 2.0 (0.8-4.7)</td>
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<td>10 1.2 (0.5-2.9)</td>
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<tr>
<td>≥30</td>
<td>483</td>
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<td>15 1.5 (0.7-3.2)</td>
<td>3 0.7 (0.2-2.5)</td>
<td>7 0.9 (0.4-2.3)</td>
<td>6 1.1 (0.4-3.2)</td>
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<td>Never</td>
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<td>1/2</td>
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<td>122 1.0 (ref)</td>
<td>109 1.0 (ref)</td>
<td>55 1.0 (ref)</td>
<td>31 1.0 (ref)</td>
<td>27 1.0 (ref)</td>
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<tr>
<td>1-11</td>
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<td>733 0.8 (0.7-0.9)*</td>
<td>55 0.9 (0.6-1.2)</td>
<td>53 0.8 (0.6-1.2)</td>
<td>16 0.6 (0.4-1.1)</td>
<td>18 1.1 (0.6-2.0)</td>
<td>9 0.5 (0.3-1.6)</td>
<td>11 1.6 (0.6-2.0)</td>
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<tr>
<td>≥12</td>
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<td>464 0.7 (0.6-0.8)*</td>
<td>46 1.0 (0.7-1.5)</td>
<td>38 0.8 (0.6-1.2)</td>
<td>8 0.4 (0.2-0.9)*</td>
<td>8 0.7 (0.3-1.5)</td>
<td>13 1.1 (0.6-2.2)</td>
<td>7 0.6 (0.3-1.5)</td>
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<td>Type of menopause</td>
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<td>117 1.0 (ref)</td>
<td>85 1.0 (ref)</td>
<td>20 1.0 (ref)</td>
<td>29 1.0 (ref)</td>
<td>16 1.0 (ref)</td>
<td>22 1.0 (ref)</td>
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<tr>
<td>Induced</td>
<td>562</td>
<td>502 0.7 (0.6-0.9)*</td>
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<td>28 0.9 (0.5-1.3)</td>
<td>4 0.5 (0.2-1.6)</td>
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<td>301</td>
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<td>14 1.0 (ref)</td>
<td>10 1.0 (ref)</td>
<td>1 1.0 (ref)</td>
<td>2 1.0 (ref)</td>
<td>4 1.0 (ref)</td>
<td>3 1.0 (ref)</td>
</tr>
<tr>
<td>48-50</td>
<td>224</td>
<td>182 1.1 (0.8-1.4)</td>
<td>24 1.8 (0.9-3.6)</td>
<td>16 1.9 (0.8-4.4)</td>
<td>5 5.9 (0.7-51.7)</td>
<td>5 2.5 (0.5-13.1)</td>
<td>4 1.4 (0.3-6.3)</td>
<td>3 1.1 (0.2-5.5)</td>
</tr>
<tr>
<td>≥51</td>
<td>266</td>
<td>220 1.1 (0.8-1.4)</td>
<td>27 1.5 (0.8-2.9)</td>
<td>13 1.3 (0.5-3.2)</td>
<td>8 7.8 (0.9-64.5)</td>
<td>7 2.9 (0.6-14.5)</td>
<td>3 1.0 (0.2-5.0)</td>
<td>4 1.0 (0.2-4.7)</td>
</tr>
</tbody>
</table>
mucinous carcinomas. The results for tubular and mucinous carcinomas may have been due to chance. Women who had an induced or surgical menopause (bilateral oophorectomy) were at lower risk of all histologic types, with ORs ranging from 0.4 to 0.9, but the results for ductal carcinoma were within the limits of chance. Women with later ages at menopause (ages ≥51 years) had 1.5- to 7.8-fold increased risks of ductal-lobular, medullary, and tubular carcinomas, but these increases could also be chance findings.

Compared with never users of postmenopausal hormone therapy, former users of any type of hormone therapy and current users of unopposed estrogen had elevated risks of comedo carcinoma (OR, 4.4; 95% CI, 1.1-17.9 and OR, 4.1; 95% CI, 1.2-14.5, respectively) and reduced risks of ductal carcinoma (OR, 0.7; 95% CI, 0.5-0.9 and OR, 0.7; 95% CI, 0.6-0.9, respectively) but did not have altered risks of any other histologic type of breast cancer (Table 4). Current users of an estrogen plus progestin (combined) regimen had 1.5-fold (95% CI, 1.0-2.4), 2.9-fold (95% CI, 1.7-4.9), 3.2-fold (95% CI, 1.3-7.5), and 3.0-fold (95% CI, 0.6-14.7) elevated risks of lobular, ductal-lobular, tubular, and comedo carcinoma, respectively (although the associations with lobular and comedo carcinoma were within the limits of chance). The test for homogeneity of risk across histologic types associated with use of hormone therapy indicated a significant difference in the ORs (P = 0.0004). Also noteworthy was that a statistically significant difference was observed when the risk estimates for ductal-lobular tumors were compared with those of ductal tumors (P = 0.003). However, no differences were observed when the risk estimates for ductal-lobular tumors were compared with lobular tumors or when lobular tumors were compared with ductal tumors.

Height was positively associated with risk of ductal-lobular and mucinous carcinomas (for the comparisons of women ≥170 cm versus those ≤160 cm, the risks were OR, 1.5; 95% CI, 1.0-2.1 and OR, 2.5; 95% CI, 1.2-5.1, respectively; Table 5). However, heterogeneity across histologic types was not observed (P = 0.52), and the risk estimates for ductal-lobular and mucinous carcinomas were not statistically different from those for ductal carcinoma (P = 0.1957 and P = 0.07, respectively). Among premenopausal women, BMI was not associated with risk of any histologic type of breast cancer, except that women in the highest BMI group had a reduced risk of tubular breast cancer. This result, however, was based on very few women. Among postmenopausal women, those in the upper tertile of BMI compared with women in the lowest tertile had a reduced risk of ductal-lobular carcinoma (OR, 0.6; 95% CI, 0.4-1.0). Furthermore, women in the upper two tertiles seemed to have reduced risks of lobular, tubular, and mucinous carcinomas, but these reductions were within the limits of chance. A statistically significant heterogeneity in the risks of different histologic types of postmenopausal breast cancer associated with BMI was observed (P = 0.008), and the risk estimates for ductal-lobular carcinoma were statistically different from those for ductal carcinoma (P = 0.003).

Women who consumed seven or more alcoholic beverages per week had elevated risks of ductal, lobular, and medullary carcinomas when compared with women who never drank alcohol (OR, 1.2; 95% CI, 1.0-1.4; OR, 1.5; 95% CI, 1.0-2.1; and OR, 1.9; 95% CI, 1.0-3.4, respectively; Table 6). However, alcohol use among premenopausal women was not associated with risk of any histologic type of breast cancer. In contrast, elevations in risks of ductal, lobular, ductal-lobular, medullary, and mucinous carcinomas were observed among postmenopausal women who consumed seven or more alcoholic beverages per week relative to nondrinkers (although only the risk estimate for lobular carcinoma was statistically significant). These OR estimates varied significantly across histologic types (P = 0.0422), and in particular, the risk estimates for lobular tumors differed from those for ductal tumors (P = 0.0471).

Discussion

Certain limitations of our study should be considered when interpreting the results. First, this study was limited by relatively small numbers of medullary, tubular, comedo, and mucinous carcinomas. In our analyses of these tumors, there were five or fewer cases in some of our exposure categories, resulting in estimates with wide confidence limits. However, previous studies have not comprehensively assessed the relationships between various risk factors for breast cancer and risks of these histologic types. Compared with other studies of breast cancer, this study was relatively large as it included 4,575 cases. Nevertheless, this study should be viewed as hypothesis generating, and its results should be interpreted with caution particularly because we conducted multiple comparisons with numerous exposures and outcomes. Another limitation of this study is that we did not perform independent or centralized pathology reviews of the tumors, but instead relied on the diagnoses made by local pathologists across each of the study sites as recorded by the local Surveillance, Epidemiology, and End Results registry (Atlanta, Detroit, Los Angeles, and Seattle) or ascertained by our field staff (Philadelphia). Misclassification of tumor histology may have resulted in some cases. For instance, it is unclear whether or not the differences in the proportions of these tumors diagnosed across the different study sites is due differences in the demographic and risk factor profiles of these populations (e.g., differences in racial distributions or patterns of hormone therapy use) or to differences in pathologic practices across these sites. However, all analyses are adjusted

**Table 4. Relationship between use of postmenopausal hormone therapy and risk of different histologic types of breast cancer**

<table>
<thead>
<tr>
<th>HT use</th>
<th>Controls (n = 2,029)</th>
<th>Ductal (n = 1,424)</th>
<th>Lobular (n = 146)</th>
<th>Ductal-lobular (n = 109)</th>
<th>Medullary (n = 26)</th>
<th>Tubular (n = 36)</th>
<th>Comedo (n = 22)</th>
<th>Mucinous (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Never</td>
<td>731</td>
<td>553.1 (1.0 ref)</td>
<td>55</td>
<td>1.0 (ref)</td>
<td>28</td>
<td>1.0 (ref)</td>
<td>15</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Former</td>
<td>208</td>
<td>114.7 (0.5-0.9)*</td>
<td>14</td>
<td>1.0 (0.5-1.8)</td>
<td>6</td>
<td>0.7 (0.3-1.8)</td>
<td>2</td>
<td>0.6 (1-2.6)</td>
</tr>
<tr>
<td>Current E</td>
<td>543</td>
<td>315.1 (0.6-0.9)*</td>
<td>35</td>
<td>1.0 (0.6-1.5)</td>
<td>28</td>
<td>1.3 (0.7-2.3)</td>
<td>4</td>
<td>0.5 (0.2-1.6)</td>
</tr>
<tr>
<td>Current E + P</td>
<td>365</td>
<td>347.1 (1.0-1.5)</td>
<td>42</td>
<td>1.5 (1.0-2.4)</td>
<td>47</td>
<td>2.9 (1.7-4.9)*</td>
<td>3</td>
<td>0.8 (0.3-3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: E, unopposed estrogen hormone therapy; E + P, combined estrogen and progestin hormone therapy.

*P < 0.05.

Heterogeneity in the ORs across the six different histologic types of breast cancer.
for study site. Additionally, we were able to interview only 76.5% of eligible cases and 78.6% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to the various exposures we collected. Finally, similar to all studies of this type, we cannot rule out the possibility of recall bias because we relied on participants’ recall of their exposures.

In this comprehensive assessment of associations between established breast cancer risk factors and risk of seven different histologic types of breast cancer, we observed some variations by histology. A first-degree family history of breast cancer was associated with elevations in risk of similar magnitudes for all histologic types of breast cancer except for mucinous carcinoma, and the magnitudes of these risks were generally higher among premenopausal women compared with postmenopausal women. However, menopausal status was not a statistically significant effect modifier of these associations, and heterogeneity in the risk estimates was not observed across the different histologic types we evaluated. Only one previous study has evaluated the relationship between family history of breast cancer and risk of different histologic types of breast cancer (25). This was an international multicenter hospital-based case-control study conducted by the WHI. It consisted of 1,924 ductal, 303 lobular, 72 medullary, 18 tubular, and 52 mucinous carcinomas. Similar to our study, it found that women with a family history of breast cancer had 2.2- to 3.0-fold increases in risk of ductal, lobular, and medullary carcinomas. However, it also observed that a family history of breast cancer was associated with an elevated risk of mucinous but not tubular carcinomas, although the number of tubular cases included was quite small. An important limitation of the WHO study is that details of the analytic approach used to estimate these risks (and whether or not analyses considered potential confounding factors) and their 95% CIs were not reported. Given that both the WHO study and our study had limited numbers of cases with rare histologic types of breast cancer, further studies are needed to evaluate how a family history of breast cancer alters risks of different histologic types of breast cancer.

With respect to reproductive factors, parity and an induced menopause were each associated with reduced risks of all histologic types. However, our results suggest that lobular carcinomas may be more strongly influenced by certain reproductive characteristics, as both an early age at menarche and a late age at first live birth were associated with elevated risks of lobular but not of ductal carcinoma. Both of these ages are related to important periods of breast proliferation and differentiation (26-28). Age at menarche marks the period of rapid breast growth and development that occurs with puberty. At first live birth marks the time when breasts become further differentiated in response to the hormonal stimuli of pregnancy. This primarily involves the further differentiation of lobular structures in the breast, which results in a long-term reduced risk of breast cancer. Thus, there may be a biological basis for the statistical associations we found between these two factors with lobular carcinoma, although our findings should be interpreted with caution as they require replication in additional studies.

Not surprisingly, our results are consistent with the recent report by Ursin et al. (14) who used these same data in a detailed evaluation of the relationships between certain reproductive characteristics and risks of ductal, lobular, and ductal-lobular carcinomas only. Similar to our analyses of these data, they found no significant heterogeneity in the risks

### Table 5. Relationship between anthropometric factors and risk of different histologic types of breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 4,681)</th>
<th>Ductal (n = 3,457)</th>
<th>Lobular (n = 274)</th>
<th>Ductal-lobular (n = 261)</th>
<th>Medullary (n = 91)</th>
<th>Tubular (n = 77)</th>
<th>Comedo (n = 70)</th>
<th>Mucinous (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>BMI at reference date, tertiles (kg/m²): premenopausal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤21.59</td>
<td>1,493</td>
<td>1.027 1.0 (ref)</td>
<td>65</td>
<td>1.0 (ref)</td>
<td>29</td>
<td>1.0 (ref)</td>
<td>24</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>21.60-25.70</td>
<td>1,955</td>
<td>1.1 (1.0-1.2)*</td>
<td>116</td>
<td>1.3 (1.0-1.8)</td>
<td>33</td>
<td>0.9 (0.6-1.5)</td>
<td>33</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>≥25.70</td>
<td>1,233</td>
<td>1.1 (0.8-1.6)</td>
<td>80</td>
<td>1.5 (1.0-2.1)*</td>
<td>29</td>
<td>1.3 (0.8-2.2)</td>
<td>20</td>
<td>1.0 (0.5-1.8)</td>
</tr>
<tr>
<td>**P_homogeneity</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI at reference date, tertiles (kg/m²): postmenopausal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤23.40</td>
<td>671</td>
<td>1.0 (0.9-1.2)</td>
<td>32</td>
<td>1.0 (ref)</td>
<td>38</td>
<td>1.0 (ref)</td>
<td>15</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>23.41-27.81</td>
<td>677</td>
<td>1.1 (0.7-1.8)</td>
<td>42</td>
<td>1.1 (0.7-1.8)</td>
<td>13</td>
<td>0.7 (0.3-1.5)</td>
<td>12</td>
<td>0.7 (0.3-1.4)</td>
</tr>
<tr>
<td>≥27.82</td>
<td>693</td>
<td>1.1 (0.7-1.7)</td>
<td>43</td>
<td>1.1 (0.7-1.7)</td>
<td>22</td>
<td>1.0 (0.5-2.0)</td>
<td>3</td>
<td>0.1 (0.0-0.5)*</td>
</tr>
<tr>
<td>**P_homogeneity</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NOTE: All ORs are adjusted for age, race, and study site.

*p < 0.05.

**P_homogeneity in the ORs across the six different histologic types of breast cancer.
of these three histologic types for parity, number of full-term pregnancies, or breast-feeding. Three other studies have also evaluated the relationship between reproductive factors and the risk of different histologic types of breast cancer. Again, it is difficult to compare the results of the WHO study to our results because of the way in which the analyses conducted were presented. However, in a case-only analysis in which they compared patients with lobular or tubular carcinomas to those with other carcinomas, they observed that women with lobular/tubular carcinomas were more likely than women with other histologic types of breast cancer to have had a later age at first live birth. Otherwise, they observed no differences in the reproductive characteristics of lobular/tubular cases to cases with other histologic types. The second study is a population-based Danish cohort study that included 8,669 ductal, 963 lobular, 294 medullary, 187 tubular, and 143 mucinous carcinomas (29). The findings of this study are partially consistent with ours in the following respects: parity was associated with a reduced risk of ductal carcinoma; women who had three or more live births had a reduced risk of ductal carcinoma but not of any other histologic types of breast cancer; and a later age at first live birth was only associated with elevated risks of ductal and lobular carcinomas, and the magnitude of this association was stronger for lobular than for ductal carcinomas. Unlike our study, parity was also associated with a reduced risk of mucinous but not lobular carcinoma. Finally, the third study was a population-based case-control study of women ages 65 to 79 years conducted in the Seattle area that only compared ductal (n = 656) and lobular/ductal-lobular (n = 196) histologies (12). The results of the present study compared with this study are similar with respect to breast-feeding but not with respect to age at menarche, parity, number of full-term births, type of menopause, or age at menopause. However, because the age group evaluated in our population did not overlap with the age group included in that Seattle study, and this study grouped lobular and ductal-lobular cases together, the two are not directly comparable. Thus, additional studies are needed to further clarify the relationships between reproductive characteristics and risk of different histologic types of breast cancer.

The differences in risks associated with hormone therapy between ductal and lobular cases has been reported previously using data from this study (7), and these differences are consistent with several other reports in finding that use of combined estrogen plus progestin therapy is more strongly associated with an increased risk of lobular and/or ductal/lobular carcinomas than with risk of ductal carcinoma (4-9). Here, we extend these analyses to additional histologic types, and we observed that current use of combined estrogen plus progestin therapy is associated with elevations in risk of both tubular and comedo carcinomas. We also observed that current use of unopposed estrogen was associated with an increased risk of comedo carcinoma but not other histologic types of breast cancer. These findings suggest that tubular and comedo carcinomas may be two other histologic types of breast cancer (in addition to lobular and ductal-lobular carcinoma) that are stimulated by the use of exogenous hormones among

Table 6. Relationship between alcohol use and risk of different histologic types of breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 4,676)</th>
<th>Ductal (n = 3,454)</th>
<th>Lobular (n = 273)</th>
<th>Ductal-lobular (n = 260)</th>
<th>Medullary (n = 91)</th>
<th>Tubular (n = 76)</th>
<th>Comedo (n = 70)</th>
<th>Mucinous (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use (drinks/wk): all women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2,682</td>
<td>1,919 (1.0)</td>
<td>140 (1.0)</td>
<td>141 (1.0)</td>
<td>55 (1.0)</td>
<td>35 (1.0)</td>
<td>43 (1.0)</td>
<td>29 (1.0)</td>
</tr>
<tr>
<td>&lt;7</td>
<td>1,222</td>
<td>1,130 (0.9-1.1)</td>
<td>405 (1.0-1.4)*</td>
<td>38 (1.5) (1.0-2.1)*</td>
<td>22 (1.0) (0.6-1.6)</td>
<td>14 (1.9) (1.0-3.4)*</td>
<td>6 (0.9) (0.4-2.1)</td>
<td>7 (0.9) (0.4-2.1)</td>
</tr>
<tr>
<td>≥7</td>
<td>472</td>
<td>625 (1.0)</td>
<td>70 (1.0)</td>
<td>40 (1.0)</td>
<td>17 (1.0)</td>
<td>5 (0.8)</td>
<td>6 (1.0)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>P_homogeneity</td>
<td>= 0.22</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 1,826)</th>
<th>Ductal (n = 1,426)</th>
<th>Lobular (n = 93)</th>
<th>Ductal-lobular (n = 123)</th>
<th>Medullary (n = 47)</th>
<th>Tubular (n = 25)</th>
<th>Comedo (n = 35)</th>
<th>Mucinous (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use (drinks/wk): premenopausal women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,065</td>
<td>823 (1.0)</td>
<td>46 (1.0)</td>
<td>69 (1.0)</td>
<td>31 (1.0)</td>
<td>14 (1.0)</td>
<td>25 (1.0)</td>
<td>12 (1.0)</td>
</tr>
<tr>
<td>&lt;7</td>
<td>770</td>
<td>625 (1.0)</td>
<td>36 (1.0)</td>
<td>41 (0.8) (0.6-1.3)</td>
<td>12 (0.7) (0.4-1.4)</td>
<td>15 (1.4) (0.7-3.1)</td>
<td>9 (0.5) (0.2-1.1)</td>
<td>9 (0.9) (0.4-2.2)</td>
</tr>
<tr>
<td>≥7</td>
<td>223</td>
<td>188 (1.0)</td>
<td>10 (1.0)</td>
<td>13 (0.9) (0.5-2.0)</td>
<td>7 (1.3) (0.6-3.0)</td>
<td>3 (1.0) (0.3-3.6)</td>
<td>3 (0.6) (0.2-1.9)</td>
<td>2 (0.7) (0.1-3.0)</td>
</tr>
<tr>
<td>P_homogeneity</td>
<td>= 0.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 1,806)</th>
<th>Ductal (n = 1,302)</th>
<th>Lobular (n = 152)</th>
<th>Ductal-lobular (n = 119)</th>
<th>Medullary (n = 25)</th>
<th>Tubular (n = 35)</th>
<th>Comedo (n = 19)</th>
<th>Mucinous (n = 28)</th>
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<tbody>
<tr>
<td>Alcohol use (drinks/wk): postmenopausal women</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,281</td>
<td>873 (1.0)</td>
<td>78 (1.0)</td>
<td>62 (1.0)</td>
<td>17 (1.0)</td>
<td>18 (1.0)</td>
<td>13 (1.0)</td>
<td>11 (1.0)</td>
</tr>
<tr>
<td>&lt;7</td>
<td>557</td>
<td>379 (1.0)</td>
<td>50 (1.4)</td>
<td>38 (1.3) (0.8-1.9)</td>
<td>6 (1.4) (0.5-3.6)</td>
<td>14 (1.6) (0.8-3.3)</td>
<td>5 (1.2) (0.4-3.4)</td>
<td>16 (3.2) (1.4-7.1)*</td>
</tr>
<tr>
<td>≥7</td>
<td>189</td>
<td>166 (1.2)</td>
<td>24 (1.9)</td>
<td>18 (1.7) (1.0-3.1)</td>
<td>3 (2.1) (0.6-7.3)</td>
<td>3 (0.9) (0.3-3.3)</td>
<td>4 (2.6) (0.8-8.4)</td>
<td>3 (1.7) (0.5-6.2)</td>
</tr>
<tr>
<td>P_homogeneity</td>
<td>= 0.04</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P_interaction</td>
<td>= 0.47</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

NOTE: All ORs are adjusted for age, race, and study site.

*p < 0.05.

1P_homogeneity in the ORs across the six different histologic types of breast cancer.

2P_interaction between menopausal status and alcohol use in relation to risk of different histologic types of breast cancer based on likelihood ratio testing.
postmenopausal women. In addition, we observed that use of unopposed estrogen was inversely associated with ductal carcinoma risk. This is consistent with the Women’s Health Initiative randomized trial of unopposed estrogen, which found a nearly statistically significant reduction in risk of breast cancer overall, of nearly the same magnitude, among unopposed estrogen users (30). In addition, as previously reported by Daling et al. (7), this reduction in risk was somewhat more pronounced among users of unopposed estrogen for ≥5 years. However, these findings should be interpreted with caution because we had limited statistical power to assess these associations by recurrence or duration of use, and these results require confirmation in additional studies.

Our assessment of anthropometric factors suggests that taller women have elevated risks of ductal-lobular and mucinous carcinomas, and that obese postmenopausal women had a reduced risk of ductal-lobular carcinoma. The Seattle study of women ages 65 to 79 years described above also evaluated these associations among ductal and lobular cases (12). It observed that taller women had increased risks of both ductal and lobular/ductal-lobular carcinomas, and that obese women had an increased risk of ductal but not of lobular/ductal-lobular carcinomas. Our results are, therefore, inconsistent with the Seattle study, but we are also curious because we did not observe the well-reported associations with BMI and breast cancer risk; that is, that obese premenopausal women have a reduced risk of breast cancer, whereas obese postmenopausal women have an increased risk (1, 31). The reasons why these associations were not observed are unclear, although they could be the result of recall bias as data on all anthropometric factors were based on self-report only and queried weight 5 years before the established reference date for each woman. We did conduct additional analyses of BMI among our larger histology groups (ductal and lobular) and found that the directions of the risks associated with BMI did not change for these subtypes when we used either finer categories (quartiles) or clinically relevant categories (≥25 kg/m² for overweight, ≥30 kg/m² for obese). In addition, no interaction between BMI and postmenopausal hormone use, which has been reported in other studies (32), was observed.

With respect to alcohol use, we observed that women who consumed seven or more alcoholic beverages per week over their lifetime had increased risks of ductal, lobular, ductal-lobular, and medullary carcinomas. This relationship seemed to vary by menopausal status, as alcohol use was not associated with risk of any histologic type of breast cancer among premenopausal women but was associated with increased risks among postmenopausal women, particularly for lobular carcinoma. A stronger association between alcohol use and risk of lobular compared with ductal carcinoma among postmenopausal women has been observed previously (13). In addition, whereas differences between risks of lobular and ductal carcinomas associated with alcohol use have already been reported using data from this study (22), this analysis did not evaluate risk among the other histologic types separately. Although alcohol use has been consistently shown to confer a modest increase in risk of breast cancer (33), the magnitude of this association does seem to vary by histologic type. Multiple hypotheses have been proposed to explain the relationship between alcohol use and breast cancer risk. One of the main hypotheses relates to the effects that alcohol has on increasing hormone levels in postmenopausal women (34). Given that lobular carcinomas seem to be more hormonally responsive compared with other histologic types of breast cancer, including ductal carcinoma, because these tumors are more commonly estrogen and progesterone receptor positive (35, 36), a stronger association between alcohol and lobular carcinoma is not surprising and has now been observed in more than one study.

Because this is one of the first reports to document many of these associations, and because we were limited by relatively small numbers of cases of certain histologic types, these results need to be interpreted with caution. The analyses presented here should be viewed as hypothesis generating because the findings were based on multiple comparisons. However, where prior data exist, our results are generally consistent with the associations reported. Thus, taken as a whole, our study and previous studies indicate that risk factor profiles may vary to some extent by histologic type. These variations may point to differences in the etiologies of different histologic types of breast cancer. A greater understanding of pathways leading to different breast cancer histologies may be an important means of advancing our knowledge of this heterogeneous disease.

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References


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