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## Original Contribution

# Risk Factors for Specific Histopathological Types of Postmenopausal Breast Cancer in the NIH-AARP Diet and Health Study

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Risk factor associations for rare breast cancer variants are often imprecise, obscuring differences between tumor types. To clarify differences, we examined risk factors for 5 histological types of breast cancer in the National Institutes of Health-AARP Diet and Health Study. Risk factor information was self-reported. We followed 192,076 postmenopausal women aged 50–71 years from 1995–1996 through 2006. During that time period, 5,334 ductal, 836 lobular, 639 mixed ductal-lobular, 216 mucinous, and 132 tubular breast cancers were diagnosed. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards regression. Heterogeneity was evaluated using case-only logistic regression. The strongest differences were for menopausal hormone therapy ($P_{heterogeneity} < 0.01$) and age at first birth ($P_{heterogeneity} < 0.01$). Risk of tubular cancer in relation to current menopausal hormone therapy (for current use vs. never use, hazard ratio (HR) = 4.39, 95% confidence interval (CI): 2.77, 6.96) was several times stronger than risk of other histological types (range of HRs, 1.39–1.75). Older age at first birth was unassociated with risk of mucinous (for ≥30 years vs. 20–24 years, HR = 0.62, 95% CI: 0.27, 1.42) or tubular (HR = 1.08, 95% CI: 0.51, 2.29) tumors, in contrast to clear positive associations with lobular (HR = 1.82, 95% CI: 1.39, 2.37) and mixed ductal-lobular (HR = 1.87, 95% CI: 1.39, 2.51) tumors. Differing associations for hormonal factors and mucinous and tubular cancers suggest etiologies distinct from those of common breast cancers.

breast neoplasms; cohort studies; histology; risk factors

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; ICDO-3, *International Classification of Diseases for Oncology, Third Edition*; MHT, menopausal hormone therapy; NIH, National Institutes of Health; NST, no special type.

Breast cancer is a heterogeneous disease with multiple histological types. In the United States, the most common histological types are ductal (70%–75% of tumors), lobular (8%), and mixed ductal-lobular (7%–11%) (1, 2). Other tumors include special variants of ductal breast cancer, defined by specific growth patterns, and other histological types. The mucinous special variant (2% of tumors) is characterized by a large amount of epithelial mucin within and surrounding tumor cells (1–3). The tubular variant (1%) is characterized by a glandular growth pattern in more than 75% of the tumor (1–3).

Little is known about the etiologies of mucinous and tubular breast cancers, but differences in tumor characteristics, age-incidence rates, and survival suggest that they are distinct from ductal tumors of no special type (NST). Both mucinous and tubular tumors are generally small in size and hormone-receptor-positive (2–7). Furthermore, mucinous tumors tend to occur in older women, and rates increase steadily with age rather than slowing at very old ages, as is the established pattern for other tumor types, including ductal NST and tubular (8). Finally, women with mucinous and tubular tumors have better survival than women with ductal NST tumors (5, 9–14).

Risk factors for mucinous and tubular cancers have not been well-established, and most investigations have focused

on hormonal and reproductive factors. Regarding mucinous tumors, data suggest that earlier menopause is positively associated with risk and that late age at menarche, parity, and oral contraceptive use are inversely associated with risk (15–17). For tubular cancers, late age at first birth and menopausal hormone therapy (MHT) have been positively associated with risk (15, 16, 18–22), whereas parity, later menarche, and earlier menopause have been inversely associated (16, 19, 21). Fewer studies have addressed nonreproductive factors. In one, height and alcohol use were positively associated with risk of mucinous tumors (21). Height, alcohol use, and family history of breast cancer have been associated with increased risk of tubular tumors (19–21). To further clarify risk factor patterns for specific breast cancer histological types, we compared risk factor associations for mucinous and tubular tumors with associations for ductal, lobular, and mixed ductal-lobular tumors among postmenopausal women in the National Institutes of Health (NIH)-AARP Diet and Health Study, a large prospective study.

## MATERIALS AND METHODS

### Study population

The NIH-AARP Diet and Health Study has been described previously (23). Briefly, the cohort was established in 1995–1996 when a self-administered questionnaire regarding health and nutrition was sent to members of AARP (formerly the American Association of Retired Persons) aged 50–71 years who were living in the states of California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania, and the metropolitan areas of Atlanta, Georgia, and Detroit, Michigan. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. Questionnaire completion was considered to imply informed consent.

Of 617,119 questionnaires returned, 567,169 were completed satisfactorily (23). For this analysis, we excluded duplicate questionnaires ($n = 179$), proxy responses ($n = 15{,}760$), men ($n = 325{,}172$), respondents who had prevalent cancer ($n = 23{,}961$), respondents who moved out of the study area ($n = 322$) or died ($n = 270$) on or before the date of study entry or withdrew ($n = 9$), and women who were premenopausal or of unknown menopausal status ($n = 9{,}420$); this resulted in 192,076 eligible subjects. A second questionnaire, mailed to enrolled participants in 1996–1997, collected additional information, including data on use of mammography and MHT formulations. Of the 192,076 women who completed the first questionnaire, 122,093 (64%) completed the second questionnaire. Characteristics of women who completed the second questionnaire were similar to those of the full population.

### Cohort follow-up

Cohort members were followed annually for changes of address using data from the US Postal Service, other address update services, and participant updates. Vital status was determined through annual linkage to the Social Security Administration Death Master File, responses to study mailings, National Death Index searches, and cancer registry linkages. Follow-up time was calculated from the date on which the study questionnaire was returned through the earliest of the following: breast cancer diagnosis, movement out of the registry ascertainment area, death, or December 31, 2006. Follow-up for analyses involving the second questionnaire began on the date on which that questionnaire was returned. A total of 13,168 (7%) women moved from the registry ascertainment area prior to the end of follow-up; these women were younger and more frequently current MHT users but were otherwise similar to the rest of the cohort.

### Case ascertainment

Information on cancer diagnosis was obtained from state cancer registries in the 8 study areas plus the adjacent states of Texas, Arizona, and Nevada. First and last name, address (updated annually), sex, birth date, and Social Security number were used to match participants with registry records using probabilistic linkage methods, described in detail previously (24). In a validation study comparing registry findings with self-reports and medical records, Michaud et al. (24) estimated that linkage identified 90% of incident cancers among participants. Cases were defined as incident primary invasive carcinomas of the breast that were diagnosed after study enrollment. Histological type was obtained from cancer registry records and defined using the *International Classification of Diseases for Oncology, Third Edition* (ICDO-3) (25). A total of 7,698 cases were diagnosed after a mean 9.6 years of follow-up (standard deviation, 2.5 years) and were comprised predominantly of 5 histological types: ductal (ICDO-3 code 8500/3 or 8523/3; $n = 5{,}334$), lobular (ICDO-3 code 8520/3 or 8524/3; $n = 836$), mixed ductal-lobular (ICDO-3 code 8522/3; $n = 639$), mucinous (ICDO-3 code 8480/3; $n = 216$), and tubular (ICDO-3 code 8211/3; $n = 132$) (Table 1). The remaining 541 cases were a mixture of histological types. Data on estrogen receptor (ER) expression were not reported systematically by Florida, Pennsylvania, or Texas; 2,741 cases were ascertained by means of these registries. Information on overexpression of human epidermal growth factor receptor 2, also called receptor tyrosine-protein kinase ErbB-2, was not routinely collected and was unavailable for analysis.

### Risk factors

Risk factor information was self-reported at enrollment, with the exception of information on use of mammography and specific estrogen and/or progesterone MHT preparations, which was collected on the second questionnaire. Type of menopause was determined from the reported reason menstrual periods had stopped, whether women had undergone surgery to remove their ovaries, and age at the last menstrual period. Height (in meters) and weight (in kilograms) were categorized into quartiles based on their distributions in the cohort. Body mass index (BMI) was calculated as weight divided by squared height and was categorized using World Health Organization cutpoints (26). Frequency of vigorous physical activity was defined by how often women participated in exercise, sports, or carrying of heavy loads that increased sweating, breathing, or heart rate and lasted for ≥20 minutes.

**Table 1.** Clinical Characteristics of 7,698 Invasive Breast Cancer Cases Diagnosed Between 1995 and 2006 in the NIH-AARP Diet and Health Study Cohort[a]

| | Histological Type | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ductal | | Mucinous | | Tubular | | Lobular | | Mixed Ductal-Lobular | | Other | |
| | No. | %[b] | No. | %[b] | No. | %[b] | No. | %[b] | No. | %[b] | No. | %[b] |
| Distribution of cases | 5,334 | 69[c] | 216 | 3[c] | 132 | 2[c] | 836 | 11[c] | 639 | 8[c] | 541 | 7[c] |
| Tumor stage at initial diagnosis or treatment | | | | | | | | | | | | |
| Local | 2,649 | 73 | 132 | 92 | 86 | 95 | 363 | 62 | 256 | 63 | 212 | 63 |
| Regional | 886 | 24 | 8 | 6 | 5 | 5 | 194 | 33 | 140 | 34 | 86 | 25 |
| Distant | 88 | 2 | 3 | 2 | 0 | 0 | 26 | 4 | 11 | 3 | 41 | 12 |
| Missing data | 1,711 | | 73 | | 41 | | 253 | | 232 | | 202 | |
| Tumor grade | | | | | | | | | | | | |
| 1 | 1,142 | 23 | 85 | 63 | 87 | 87 | 124 | 26 | 123 | 22 | 59 | 17 |
| 2 | 2,209 | 44 | 39 | 29 | 12 | 12 | 248 | 53 | 308 | 55 | 110 | 32 |
| 3 | 1,527 | 31 | 8 | 6 | 1 | 1 | 88 | 19 | 117 | 21 | 163 | 47 |
| 4 | 87 | 2 | 2 | 1 | 0 | 0 | 12 | 3 | 9 | 2 | 17 | 5 |
| Missing data | 369 | | 82 | | 32 | | 364 | | 82 | | 192 | |
| ER status[d] | | | | | | | | | | | | |
| ER+ | 2,218 | 81 | 101 | 93 | 63 | 94 | 424 | 96 | 354 | 93 | 134 | 64 |
| ER– | 519 | 19 | 8 | 7 | 4 | 6 | 19 | 4 | 26 | 7 | 75 | 36 |
| Borderline | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Missing data | 672 | | 29 | | 20 | | 101 | | 67 | | 118 | |
| PR Status[d] | | | | | | | | | | | | |
| PR+ | 1,835 | 69 | 84 | 81 | 51 | 77 | 326 | 76 | 277 | 78 | 107 | 52 |
| PR– | 827 | 31 | 20 | 19 | 15 | 23 | 102 | 24 | 78 | 22 | 98 | 47 |
| Borderline | 12 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 2 | 1 | 2 | 1 |
| Missing data | 739 | | 34 | | 21 | | 113 | | 90 | | 121 | |
| ER and PR status[d] | | | | | | | | | | | | |
| ER+/PR+ | 1,779 | 67 | 83 | 81 | 50 | 76 | 321 | 75 | 273 | 76 | 100 | 48 |
| ER+/PR– | 357 | 13 | 12 | 12 | 12 | 18 | 85 | 20 | 57 | 16 | 31 | 15 |
| ER–/PR+ | 47 | 2 | 0 | 0 | 1 | 2 | 2 | 0 | 4 | 1 | 7 | 3 |
| ER–/PR– | 469 | 18 | 8 | 8 | 3 | 5 | 17 | 4 | 21 | 6 | 66 | 32 |
| ER or PR borderline | 16 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 2 | 1 | 3 | 1 |
| Missing data | 745 | | 35 | | 21 | | 116 | | 90 | | 121 | |

Abbreviations: ER, estrogen receptor; IQR, interquartile range; NIH, National Institutes of Health; PR, progesterone receptor.

[a] The median ages at diagnosis for women with ductal, mucinous, tubular, lobular, mixed ductal-lobular, and other types of tumors were 68 (IQR, 64–72), 69 (IQR, 66–73), 69 (IQR, 63–72), 69 (IQR, 64–72), 68 (IQR, 64–72), and 68 (IQR, 64–72) years, respectively.

[b] Percentages may not add up to 100 because of rounding.

[c] Row percentage.

[d] Calculated only among cases reported by registries that collected hormone receptor information (California; Louisiana; New Jersey; North Carolina; Nevada; Arizona; Atlanta, Georgia; and Detroit, Michigan).

Alcohol use (in grams per day) was estimated from the frequency and amount of beer, wine, and liquor consumed, as described previously (27). Family history of breast cancer was determined on the basis of history in a first-degree female relative. Recent mammography was defined as a mammogram in the previous 3 years. MHT use at enrollment was determined from questions about how long women used "replacement hormones" and whether they were currently using hormones. The second questionnaire collected detailed information, including types of hormones and dates of use. Women were classified as using combination (estrogen plus progestin) MHT if they used estrogen and progestin pills during the same period or within 90 days of each other. Other variables included parity, age at menarche, number of previous breast biopsies, and the potential confounders education, marital status, and race/ethnicity. Data were missing for fewer than 5% of participants for

**Table 2.** Associations[a] Between Reproductive Factors and Postmenopausal Breast Cancer Risk by Histological Type in the NIH-AARP Diet and Health Study Cohort, 1995–2006

| | Person-Years | Histological Type | | | | | | | | | | | | | | | *P* for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Age at menarche, years | | | | | | | | | | | | | | | | | |
| ≤12 | 896,035 | 2,660 | 1 | Reference | 123 | 1 | Reference | 72 | 1 | Reference | 387 | 1 | Reference | 326 | 1 | Reference | 0.08 |
| 13–14 | 766,087 | 2,191 | 0.98 | 0.92, 1.04 | 77 | 0.63 | 0.46, 0.87 | 49 | 0.74 | 0.50, 1.07 | 374 | 1.09 | 0.94, 1.28 | 257 | 0.87 | 0.73, 1.04 | |
| ≥15 | 174,041 | 469 | 0.92 | 0.83, 1.03 | 16 | 0.70 | 0.40, 1.22 | 11 | 0.73 | 0.38, 1.43 | 72 | 0.96 | 0.73, 1.26 | 54 | 0.89 | 0.65, 1.20 | |
| *P*-trend | | | | 0.15 | | | 0.01 | | | 0.13 | | | 0.68 | | | 0.16 | |
| Parity[c] | | | | | | | | | | | | | | | | | |
| Nulliparous | 256,371 | 881 | 1 | Reference | 35 | 1 | Reference | 29 | 1 | Reference | 118 | 1 | Reference | 110 | 1 | Reference | 0.10 |
| Parous | 1,561,723 | 4,364 | 0.78 | 0.72, 0.84 | 179 | 0.89 | 0.59, 1.34 | 103 | 0.55 | 0.35, 0.87 | 702 | 1.02 | 0.81, 1.27 | 520 | 0.84 | 0.66, 1.05 | |
| No. of children (among parous women)[c] | | | | | | | | | | | | | | | | | |
| ≥3 | 898,983 | 2,465 | 1 | Reference | 103 | 1 | Reference | 57 | 1 | Reference | 376 | 1 | Reference | 274 | 1 | Reference | 0.48 |
| 2 | 474,043 | 1,346 | 1.03 | 0.96, 1.11 | 52 | 0.97 | 0.67, 1.40 | 37 | 1.25 | 0.81, 1.92 | 218 | 1.13 | 0.94, 1.35 | 177 | 1.20 | 0.98, 1.47 | |
| 1 | 188,697 | 553 | 1.12 | 1.02, 1.24 | 24 | 1.11 | 0.68, 1.81 | 9 | 0.90 | 0.44, 1.85 | 108 | 1.45 | 1.15, 1.83 | 69 | 1.18 | 0.89, 1.58 | |
| *P*-trend | | | | 0.03 | | | 0.80 | | | 0.79 | | | <0.01 | | | 0.10 | |
| Age at first birth (among parous women), years | | | | | | | | | | | | | | | | | |
| ≤19 | 325,305 | 799 | 0.91 | 0.83, 0.99 | 38 | 1.18 | 0.78, 1.78 | 13 | 0.59 | 0.30, 1.13 | 92 | 0.79 | 0.61, 1.02 | 68 | 0.64 | 0.47, 0.87 | <0.01 |
| 20–24 | 803,597 | 2,239 | 1 | Reference | 93 | 1 | Reference | 58 | 1 | Reference | 318 | 1 | Reference | 249 | 1 | Reference | |
| 25–29 | 323,109 | 961 | 1.03 | 0.95, 1.12 | 40 | 1.17 | 0.78, 1.75 | 24 | 0.95 | 0.58, 1.58 | 207 | 1.58 | 1.31, 1.91 | 140 | 1.28 | 1.02, 1.60 | |
| ≥30 | 104,584 | 350 | 1.15 | 1.01, 1.30 | 8 | 0.62 | 0.27, 1.42 | 8 | 1.08 | 0.51, 2.29 | 82 | 1.82 | 1.39, 2.37 | 62 | 1.87 | 1.39, 2.51 | |
| *P*-trend | | | | <0.01 | | | 0.34 | | | 0.28 | | | <0.01 | | | <0.01 | |
| Type of menopause and age at menopause, years | | | | | | | | | | | | | | | | | |
| Natural, <45 | 127,949 | 329 | 0.84 | 0.74, 0.96 | 12 | 1.19 | 0.62, 2.29 | 7 | 0.68 | 0.31, 1.51 | 58 | 0.94 | 0.69, 1.28 | 41 | 0.82 | 0.56, 1.19 | 0.01 |
| Natural, 45–49 | 298,055 | 877 | 0.93 | 0.85, 1.02 | 30 | 1.21 | 0.74, 1.98 | 27 | 0.96 | 0.59, 1.56 | 133 | 0.91 | 0.73, 1.13 | 92 | 0.78 | 0.60, 1.01 | |
| Natural, 50–54 | 516,047 | 1,630 | 1 | Reference | 48 | 1 | Reference | 52 | 1 | Reference | 270 | 1 | Reference | 208 | 1 | Reference | |
| Natural, ≥55 | 114,664 | 465 | 1.27 | 1.13, 1.41 | 13 | 1.29 | 0.67, 2.47 | 15 | 1.36 | 0.76, 2.45 | 73 | 1.06 | 0.79, 1.40 | 60 | 1.32 | 0.97, 1.78 | |
| Bilateral oophorectomy | 375,409 | 910 | 0.69 | 0.63, 0.75 | 64 | 1.53 | 0.98, 2.38 | 12 | 0.21 | 0.11, 0.42 | 140 | 0.63 | 0.50, 0.80 | 95 | 0.55 | 0.42, 0.73 | |

Table continues

**Table 2.** Continued

| | Person-Years | Histological Type | | | | | | | | | | | | | | | | P for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Other surgical menopause | 362,901 | 976 | 0.82 | 0.75, 0.90 | 43 | 1.28 | 0.81, 2.03 | 14 | 0.31 | 0.17, 0.58 | 144 | 0.74 | 0.59, 0.93 | 114 | 0.73 | 0.56, 0.94 | |
| Medically induced menopause or unknown age at natural menopause | 48,209 | 147 | 0.92 | 0.76, 1.11 | 6 | 1.66 | 0.65, 4.27 | 5 | 0.78 | 0.31, 1.98 | 18 | 0.55 | 0.31, 0.99 | 29 | 1.32 | 0.86, 2.04 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Estimates were adjusted for age at baseline, education, race, marital status, menopausal hormone use, oral contraceptive use, alcohol use, body mass index, frequency of vigorous physical activity, number of previous breast biopsies, family history of breast cancer (first-degree relative), and all other variables in the table, except where noted.

[b] Two-sided *P* value from the Wald test, simultaneously comparing associations for ductal, mucinous, tubular, lobular, and mixed ductal-lobular types.

[c] Not adjusted for age at first birth.

all variables, except assessment of MHT on the second questionnaire, on which data were missing for 5.6% of women.

### Statistical analysis

Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards regression with age as the time metric, and tests of linear trend were conducted. Time-dependent interactions were tested for each risk factor to establish that hazards were proportional over time (all $P$'s > 0.05). Tests of statistical heterogeneity were performed using case-only polytomous logistic regression. Models included adjustment for age at enrollment, risk factors, and the a priori set of confounders described above; however, related variables, such as BMI, height, and weight, were not included in the same models. A combination variable of nulliparity and age at first birth was used in the models, except where noted. Subjects with missing data were not included in the models. Analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina). Statistical tests were 2-sided, and $P$ values less than 0.05 were considered statistically significant.

Previous studies have shown interactions between MHT use and BMI (28–31); therefore, we evaluated BMI associations among MHT never users and MHT associations among nonobese women (BMI <30). We also evaluated MHT only among women with a recent mammogram to minimize potential detection bias related to MHT use.

We additionally estimated histology-specific associations for ER-positive cancers; there were too few ER-negative cases for analysis. Women living in states that did not collect hormone receptor data had lower levels of education and lower frequencies of MHT and oral contraceptive use than other women. Therefore, analysis of ER-positive cancers was restricted to participants in states where registries collected receptor data. We estimated risk associations, regardless of receptor status, using data from these states and compared estimates with those for ER-positive cancers.

## RESULTS

Associations for age at first birth ($P_{\text{heterogeneity}} < 0.01$) and type of menopause ($P_{\text{heterogeneity}} = 0.01$) differed by histological type (Table 2). Late age at first birth was associated with increased risks of ductal (for ≥30 years vs. 20–24 years, hazard ratio (HR) = 1.15, 95% confidence interval (CI): 1.01, 1.30), lobular (HR = 1.82, 95% CI: 1.39, 2.37), and mixed-ductal lobular (HR = 1.87, 95% CI: 1.39, 2.51) tumors but not mucinous (HR = 0.62, 95% CI: 0.27, 1.42) or tubular (HR = 1.08, 95% CI: 0.51, 2.29) tumors. Compared with natural menopause at age 50–54 years, surgical menopause was associated with lower risks of ductal, tubular, lobular, and mixed ductal-lobular tumors (range of HRs, 0.21–0.82; Table 2) but not mucinous tumors (for bilateral oophorectomy, HR = 1.53, 95% CI: 0.98, 2.38; for other surgery, HR = 1.28, 95% CI: 0.81, 2.03). Associations were consistent with lower breast cancer risk for women with early natural menopause for all histological types except mucinous and lobular. Differences for other reproductive characteristics were less pronounced. Parity appeared to be

associated with lower risk of all histological types except lobular; however, associations were not statistically different ($P_{heterogeneity} = 0.10$). There were no clear differences for age at menarche or number of children.

Associations for MHT use also differed by histology ($P_{heterogeneity} < 0.01$; Table 3). Current use of any MHT was associated with an increased risk of tubular tumors that was more than twice as strong as risk for other types (for tubular tumors, HR = 4.39, 95% CI: 2.77, 6.96; for other types, HRs = 1.39–1.75). Patterns were similar for duration of MHT use ($P_{heterogeneity} = 0.02$) and when analysis was restricted to the nonobese or women with a recent mammogram (data not shown). Associations with tubular tumor risk were driven by combination MHT (for current use, HR = 4.97, 95% CI: 2.74, 9.01); current use of estrogen-only MHT increased tubular risk to a lesser degree (HR = 2.50, 95% CI: 1.04, 6.02). Oral contraceptive use was associated with a lower risk of mucinous tumors, and the magnitude intensified with increasing duration of use ($P_{trend} < 0.01$; Table 3). Associations between oral contraceptive use and other histological types were suggestive of slightly increased risk, but differences by histology did not reach significance ($P_{heterogeneity} = 0.10$).

There were few other differences by histological type. Height was positively associated with all tumor types, and BMI and weight were associated with increased risks of all types when only never users of MHT were considered (Table 4). Associations between the number of times per week women participated in vigorous physical activity and risk were weak and did not differ statistically by histology, although there was a slightly decreased risk of ductal tumors ($P_{trend} = 0.03$) and an increased risk of mucinous tumors with more frequent vigorous physical activity, in comparison with never or rarely performing vigorous activity. Alcohol use was positively associated with all histological types except mucinous, whereas previous breast biopsy and family history of breast cancer were positively associated with all types (Table 5).

To examine relationships with ER-positive disease, we first repeated our analysis among women in states that reported hormone receptor data. Risk factor associations in this restricted cohort were similar to those in the full cohort, with the exception of strengthened associations of MHT and oral contraceptive use with tubular risk and a null association of family history with tubular risk (data not shown). Associations for risk of ER-positive tumors were similar to what was seen overall in the restricted cohort; heterogeneity by histological type was unchanged (data not shown).

## DISCUSSION

We examined associations between breast cancer risk factors and 5 histological types of postmenopausal breast cancer. We were interested specifically in associations for mucinous and tubular tumors, since their epidemiology has not been well-defined. The largest prior study of these tumors examined reproductive risk factors and MHT use among women aged 50–71 years at study enrollment (16) and included 1,062 tubular tumors and 330 mucinous tumors. Other studies have evaluated from <100 to 200 tubular tumors (15, 17, 19–21, 32) and from <100 to 150 mucinous tumors (15, 17, 29, 32). These smaller studies have included a wide age range of women and, apart from BMI and MHT analyses, have not routinely stratified the data by menopausal status. In this analysis, we examined a range of risk factors in postmenopausal women in order to help establish associations where power has been limited. Associations differed significantly by histological type for age at first birth, type of menopause, and MHT use, indicating that these factors may not be related to all histological types in the same manner.

Our findings suggest that some factors related to reproductive events contribute less to mucinous breast cancer risk than to risk of other histological types. For example, surgical menopause was associated with lower risks of all histological types except mucinous, and early natural menopause was associated with lower risks of all types except mucinous and lobular. This was consistent with 2 previous studies (16, 21) that did not observe lower risk of mucinous cancers with early menopause; in one of these studies, women who underwent menopause at less than 45 years of age had a 2-fold increased risk of mucinous cancer in comparison with women who underwent menopause at ages 50–54 years (16). The magnitudes of association we observed for age at menopause and ductal, lobular, mixed-ductal lobular, and tubular tumors were weaker than those of Reeves et al. (16), which may reflect our separate analysis of surgical menopause and age at natural menopause.

We also found that later age at first birth was not associated with risk of mucinous or tubular tumors, which is consistent with some previous studies of mucinous (16, 17) and tubular (19) tumors but not others (15, 16, 20, 21). Some studies have suggested that late age at first birth may be related specifically to ER-positive breast cancer risk (33, 34); however, associations between age at first birth and risk of ER-positive cancers by histology were similar to those seen among all cases. Therefore, it is unlikely that differences were due to differences in the prevalence of ER-positive tumors by histology.

Current and long-term use of MHT was related more strongly to risk of tubular breast cancer than to other types of tumors. These results were similar to those of a recent meta-analysis (18) and a subsequent study (22) with respect to histological differences and the magnitude of association for tubular risk. Differences persisted even after data were restricted to women who had had a recent mammogram, women who were nonobese, or women who were diagnosed with ER-positive tumors, suggesting that differences were not due to these factors. Study participants lost to follow-up were more likely to be MHT users, but it is unlikely that loss of these women induced the association between MHT use and tubular risk. Preferential loss of MHT users from the cohort would lead to loss of women most likely to be diagnosed with tubular tumors, biasing the tubular association downwards. If this occurred, the true association with tubular risk would be stronger than that observed, thus not changing our conclusion that MHT was associated more strongly with tubular types than with other histological types.

Associations were generally similar by histological type for nonreproductive risk factors, though some associations differed for specific histological types without reaching statistical significance. Oral contraceptive use was associated

**Table 3.** Association[a] Between Exogenous Hormone Use and Postmenopausal Breast Cancer Risk by Histological Type in the NIH-AARP Diet and Health Study Cohort, 1995–2006

| | Person-Years | Histological Type | | | | | | | | | | | | | | | *P* for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Any MHT | | | | | | | | | | | | | | | | | |
| Never use | 846,195 | 2,213 | 1 | Reference | 91 | 1 | Reference | 30 | 1 | Reference | 350 | 1 | Reference | 243 | 1 | Reference | <0.01 |
| Former use | 171,131 | 445 | 1.08 | 0.97, 1.21 | 20 | 1.05 | 0.62, 1.80 | 7 | 1.31 | 0.54, 3.19 | 59 | 0.91 | 0.68, 1.23 | 35 | 0.82 | 0.56, 1.20 | |
| Current use | 821,582 | 2,667 | 1.39 | 1.30, 1.49 | 105 | 1.40 | 0.99, 1.97 | 95 | 4.39 | 2.77, 6.96 | 426 | 1.45 | 1.22, 1.72 | 357 | 1.75 | 1.44, 2.13 | |
| Years of MHT use | | | | | | | | | | | | | | | | | |
| Never use | 846,195 | 2,139 | 1 | Reference | 91 | 1 | Reference | 30 | 1 | Reference | 344 | 1 | Reference | 231 | 1 | Reference | 0.02 |
| <5 | 353,116 | 1,007 | 1.19 | 1.10, 1.30 | 36 | 1.14 | 0.74, 1.77 | 28 | 2.52 | 1.44, 4.40 | 150 | 1.17 | 0.94, 1.44 | 120 | 1.29 | 1.01, 1.64 | |
| 5–9 | 250,532 | 848 | 1.38 | 1.26, 1.52 | 25 | 1.16 | 0.70, 1.93 | 36 | 4.48 | 2.62, 7.66 | 135 | 1.47 | 1.18, 1.84 | 113 | 1.69 | 1.32, 2.18 | |
| ≥10 | 391,198 | 1,260 | 1.46 | 1.34, 1.59 | 64 | 1.58 | 1.07, 2.35 | 38 | 4.84 | 2.82, 8.30 | 200 | 1.43 | 1.15, 1.77 | 161 | 1.83 | 1.44, 2.33 | |
| *P*-trend | | | | <0.01 | | | 0.03 | | | <0.01 | | | <0.01 | | | <0.01 | |
| Estrogen-only MHT[c] | | | | | | | | | | | | | | | | | |
| Never use | 429,280 | 1,156 | 1 | Reference | 48 | 1 | Reference | 19 | 1 | Reference | 181 | 1 | Reference | 117 | 1 | Reference | 0.27 |
| Former use | 87,972 | 210 | 0.97 | 0.82, 1.13 | 12 | 0.98 | 0.48, 2.00 | 1 | | | 36 | 1.14 | 0.78, 1.68 | 19 | 0.98 | 0.59, 1.63 | |
| Current use | 228,010 | 597 | 1.15 | 1.01, 1.29 | 34 | 1.30 | 0.76, 2.21 | 11 | 2.50 | 1.04, 6.02 | 114 | 1.51 | 1.12, 2.03 | 77 | 1.60 | 1.13, 2.28 | |
| Combination (estrogen plus progestin) MHT[c] | | | | | | | | | | | | | | | | | |
| Never use | 429,280 | 1,156 | 1 | Reference | 48 | 1 | Reference | 19 | 1 | Reference | 181 | 1 | Reference | 117 | 1 | Reference | 0.02 |
| Former use | 119,810 | 377 | 1.23 | 1.08, 1.40 | 22 | 1.84 | 1.06, 3.21 | 8 | 1.10 | 0.40, 3.04 | 57 | 1.24 | 0.90, 1.70 | 43 | 1.39 | 0.96, 2.02 | |
| Current use | 187,165 | 844 | 1.74 | 1.58, 1.93 | 18 | 1.21 | 0.66, 2.21 | 48 | 4.97 | 2.74, 9.01 | 130 | 1.66 | 1.29, 2.14 | 129 | 2.50 | 1.89, 3.30 | |
| Oral contraceptives | | | | | | | | | | | | | | | | | |
| Never use | 1,117,014 | 3,216 | 1 | Reference | 163 | 1 | Reference | 71 | 1 | Reference | 505 | 1 | Reference | 379 | 1 | Reference | 0.10 |
| Ever use | 710,050 | 2,071 | 1.06 | 0.99, 1.13 | 52 | 0.67 | 0.47, 0.95 | 61 | 1.33 | 0.91, 1.94 | 325 | 1.10 | 0.94, 1.30 | 254 | 1.09 | 0.91, 1.31 | |
| Years of oral contraceptive use | | | | | | | | | | | | | | | | | |
| Never use | 1,117,014 | 3,216 | 1 | Reference | 163 | 1 | Reference | 71 | 1 | Reference | 505 | 1 | Reference | 379 | 1 | Reference | 0.09 |
| 1–4 | 315,458 | 904 | 1.04 | 0.96, 1.13 | 31 | 0.91 | 0.59, 1.38 | 26 | 1.38 | 0.85, 2.24 | 130 | 1.00 | 0.81, 1.24 | 119 | 1.18 | 0.94, 1.49 | |
| 5–9 | 222,214 | 650 | 1.08 | 0.98, 1.18 | 15 | 0.64 | 0.36, 1.12 | 15 | 1.07 | 0.60, 1.92 | 100 | 1.05 | 0.82, 1.34 | 77 | 1.05 | 0.81, 1.38 | |
| ≥10 | 172,378 | 517 | 1.07 | 0.97, 1.18 | 6 | 0.28 | 0.11, 0.70 | 20 | 1.53 | 0.90, 2.60 | 95 | 1.35 | 1.06, 1.71 | 58 | 0.98 | 0.73, 1.32 | |
| *P*-trend | | | | 0.08 | | | <0.01 | | | 0.17 | | | 0.04 | | | 0.86 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH, National Institutes of Health.

[a] Estimates were adjusted for age at baseline, education, race, marital status, age at menarche, parity/age at first birth, type of and age at menopause, alcohol use, body mass index, frequency of vigorous physical activity, number of previous breast biopsies, family history of breast cancer (first-degree relative), and all other variables in the table, except where noted. Associations are not shown for comparisons involving fewer than 5 cases.

[b] Two-sided *P* value from the Wald test, simultaneously comparing associations for ductal, mucinous, tubular, lobular, and mixed ductal-lobular types.

[c] Assessed only among women who completed the second study questionnaire.

**Table 4.** Associations[a] Between Anthropometric Factors, Physical Activity, and Postmenopausal Breast Cancer Risk by Histological Type in the NIH-AARP Diet and Health Study Cohort, 1995–2006

| | Person-Years | Histological Type | | | | | | | | | | | | | | | *P* for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Height, m[c] | | | | | | | | | | | | | | | | | |
| ≤1.57 | 472,453 | 1,271 | 1 | Reference | 41 | 1 | Reference | 32 | 1 | Reference | 179 | 1 | Reference | 141 | 1 | Reference | 0.19 |
| >1.57–1.63 | 525,942 | 1,460 | 1.01 | 0.93, 1.09 | 70 | 1.58 | 1.06, 2.36 | 38 | 0.99 | 0.60, 1.62 | 229 | 1.14 | 0.93, 1.41 | 176 | 1.13 | 0.89, 1.43 | |
| >1.63–1.68 | 255,471 | 757 | 1.08 | 0.98, 1.19 | 30 | 1.25 | 0.76, 2.08 | 13 | 0.70 | 0.36, 1.37 | 143 | 1.48 | 1.18, 1.87 | 83 | 1.05 | 0.78, 1.41 | |
| >1.68 | 561,973 | 1,759 | 1.12 | 1.03, 1.21 | 71 | 1.42 | 0.94, 2.15 | 49 | 1.28 | 0.81, 2.04 | 271 | 1.19 | 0.97, 1.46 | 233 | 1.33 | 1.06, 1.67 | |
| *P*-trend | | | | <0.01 | | | 0.26 | | | 0.32 | | | 0.05 | | | 0.02 | |
| Weight, kg[d] | | | | | | | | | | | | | | | | | |
| ≤60.8 | 445,164 | 1,167 | 1 | Reference | 34 | 1 | Reference | 42 | 1 | Reference | 180 | 1 | Reference | 137 | 1 | Reference | 0.20 |
| >60.8–68.1 | 373,457 | 1,045 | 1.11 | 1.01, 1.21 | 46 | 1.65 | 1.04, 2.62 | 30 | 0.94 | 0.58, 1.52 | 163 | 1.04 | 0.83, 1.30 | 139 | 1.31 | 1.02, 1.69 | |
| >68.1–79.5 | 542,944 | 1,568 | 1.14 | 1.05, 1.24 | 59 | 1.44 | 0.92, 2.24 | 37 | 0.86 | 0.54, 1.36 | 260 | 1.20 | 0.98, 1.48 | 195 | 1.43 | 1.13, 1.80 | |
| >79.5 | 416,573 | 1,373 | 1.41 | 1.29, 1.53 | 66 | 2.16 | 1.38, 3.39 | 21 | 0.73 | 0.41, 1.28 | 207 | 1.53 | 1.23, 1.90 | 142 | 1.39 | 1.07, 1.80 | |
| *P*-trend | | | | <0.01 | | | <0.01 | | | 0.26 | | | <0.01 | | | 0.01 | |
| Weight among MHT never users, kg[d] | | | | | | | | | | | | | | | | | |
| ≤60.8 | 180,343 | 382 | 1 | Reference | 9 | 1 | Reference | 7 | 1 | Reference | 52 | 1 | Reference | 35 | 1 | Reference | 0.44 |
| >60.8–68.1 | 158,257 | 374 | 1.11 | 0.95, 1.29 | 15 | 1.95 | 0.82, 4.65 | 5 | 0.95 | 0.29, 3.10 | 64 | 1.10 | 0.74, 1.63 | 43 | 1.57 | 0.97, 2.57 | |
| >68.1–79.5 | 247,739 | 659 | 1.24 | 1.08, 1.41 | 22 | 1.82 | 0.80, 4.13 | 7 | 0.91 | 0.30, 2.73 | 111 | 1.38 | 0.98, 1.94 | 84 | 2.08 | 1.35, 3.22 | |
| >79.5 | 223,013 | 709 | 1.52 | 1.32, 1.74 | 37 | 3.18 | 1.44, 7.01 | 11 | 1.49 | 0.51, 4.33 | 114 | 1.83 | 1.30, 2.58 | 70 | 1.82 | 1.15, 2.88 | |
| *P*-trend | | | | <0.01 | | | <0.01 | | | 0.49 | | | <0.01 | | | 0.01 | |
| BMI[e] | | | | | | | | | | | | | | | | | |
| <18.5 | 23,325 | 50 | 0.71 | 0.52, 0.97 | 0 | | | 3 | | | 3 | | | 6 | 0.56 | 0.21, 1.50 | 0.36 |
| 18.5–<25 | 761,112 | 2,112 | 1 | Reference | 74 | 1 | Reference | 66 | 1 | Reference | 347 | 1 | Reference | 263 | 1 | Reference | |
| 25–<30 | 584,455 | 1,700 | 1.10 | 1.03, 1.18 | 67 | 1.12 | 0.78, 1.59 | 42 | 0.97 | 0.65, 1.45 | 275 | 1.12 | 0.94, 1.32 | 214 | 1.27 | 1.05, 1.54 | |
| ≥30 | 404,976 | 1,275 | 1.29 | 1.19, 1.39 | 63 | 1.74 | 1.20, 2.52 | 19 | 0.72 | 0.41, 1.26 | 180 | 1.23 | 1.01, 1.51 | 134 | 1.18 | 0.94, 1.50 | |
| *P*-trend | | | | <0.01 | | | <0.01 | | | 0.29 | | | 0.01 | | | 0.03 | |
| BMI among MHT never users | | | | | | | | | | | | | | | | | |
| <18.5 | 10,720 | 20 | 0.77 | 0.47, 1.27 | 0 | | | 1 | | | 1 | | | 3 | | | 0.63 |
| 18.5–<25 | 304,906 | 670 | 1 | Reference | 20 | 1 | Reference | 10 | 1 | Reference | 112 | 1 | Reference | 75 | 1 | Reference | |
| 25–<30 | 269,877 | 738 | 1.25 | 1.12, 1.40 | 25 | 1.32 | 0.71, 2.48 | 10 | 1.37 | 0.55, 3.39 | 120 | 1.24 | 0.94, 1.64 | 88 | 1.47 | 1.05, 2.04 | |
| ≥30 | 221,071 | 685 | 1.46 | 1.30, 1.65 | 38 | 2.60 | 1.44, 4.71 | 9 | 1.35 | 0.48, 3.80 | 107 | 1.49 | 1.11, 2.01 | 68 | 1.28 | 0.88, 1.86 | |
| *P*-trend | | | | <0.01 | | | <0.01 | | | 0.74 | | | <0.01 | | | 0.13 | |

Table continues

**Table 4.** Continued

| | Person-Years | Histological Type | | | | | | | | | | | | | | | *P* for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Frequency of vigorous physical activity | | | | | | | | | | | | | | | | | |
| Never/rarely | 407,016 | 1,219 | 1 | Reference | 39 | 1 | Reference | 31 | 1 | Reference | 177 | 1 | Reference | 145 | 1 | Reference | 0.14 |
| 1–3 times/month | 261,760 | 760 | 0.94 | 0.85, 1.04 | 20 | 1.03 | 0.58, 1.82 | 19 | 0.92 | 0.50, 1.68 | 133 | 1.16 | 0.91, 1.48 | 84 | 0.85 | 0.63, 1.13 | |
| 1–2 times/week | 385,734 | 1,117 | 0.95 | 0.87, 1.03 | 66 | 1.96 | 1.26, 3.05 | 28 | 0.93 | 0.54, 1.59 | 175 | 1.03 | 0.82, 1.29 | 129 | 0.87 | 0.68, 1.13 | |
| 3–4 times/week | 462,780 | 1,329 | 0.93 | 0.85, 1.01 | 62 | 1.72 | 1.10, 2.68 | 38 | 0.88 | 0.52, 1.48 | 213 | 1.03 | 0.83, 1.29 | 170 | 0.90 | 0.71, 1.15 | |
| ≥5 times/week | 302,101 | 842 | 0.90 | 0.82, 0.99 | 28 | 1.11 | 0.64, 1.91 | 15 | 0.58 | 0.30, 1.11 | 126 | 0.90 | 0.70, 1.16 | 106 | 0.89 | 0.68, 1.18 | |
| *P*-trend | | | | 0.03 | | | 0.12 | | | 0.15 | | | 0.37 | | | 0.53 | |

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; NIH, National Institutes of Health.

[a] Estimates were adjusted for age at baseline, education, race, marital status, age at menarche, parity/age at first birth, type of and age at menopause, menopausal hormone use, oral contraceptive use, alcohol use, family history of breast cancer (first-degree relative), number of previous breast biopsies, and all other variables in the table, except where noted. Associations are not shown for comparisons involving fewer than 5 cases.

[b] Two-sided *P* value from the Wald test, simultaneously comparing associations for ductal, mucinous, tubular, lobular, and mixed ductal-lobular types.

[c] Not adjusted for weight or BMI.

[d] Not adjusted for height or BMI.

[e] Weight (kg)/height $(m)^2$.

**Table 5.** Associations[a] of Alcohol Use, Previous Breast Biopsy, and Family History of Breast Cancer With Postmenopausal Breast Cancer Risk by Histological Type in the NIH-AARP Diet and Health Study Cohort, 1995–2006

| | Person-Years | Histological Type | | | | | | | | | | | | | | | *P* for Heterogeneity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ductal | | | Mucinous | | | Tubular | | | Lobular | | | Mixed Ductal-Lobular | | | |
| | | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | |
| Alcohol use, g/day | | | | | | | | | | | | | | | | | |
| 0 | 548,469 | 1,516 | 1 | Reference | 75 | 1 | Reference | 23 | 1 | Reference | 206 | 1 | Reference | 158 | 1 | Reference | 0.91 |
| >0–5 | 865,007 | 2,451 | 1.02 | 0.95, 1.09 | 89 | 0.77 | 0.55, 1.08 | 66 | 1.55 | 0.93, 2.58 | 394 | 1.08 | 0.90, 1.29 | 304 | 1.13 | 0.91, 1.39 | |
| >5–10 | 132,872 | 393 | 1.06 | 0.94, 1.20 | 12 | 0.78 | 0.41, 1.49 | 14 | 1.94 | 0.96, 3.94 | 68 | 1.12 | 0.83, 1.52 | 49 | 1.15 | 0.81, 1.63 | |
| >10–20 | 165,811 | 508 | 1.10 | 0.99, 1.23 | 17 | 0.96 | 0.55, 1.66 | 17 | 1.78 | 0.91, 3.49 | 90 | 1.10 | 0.83, 1.45 | 73 | 1.32 | 0.97, 1.79 | |
| >20 | 131,074 | 466 | 1.26 | 1.12, 1.41 | 23 | 1.10 | 0.62, 1.95 | 12 | 1.78 | 0.86, 3.68 | 78 | 1.42 | 1.07, 1.89 | 55 | 1.26 | 0.90, 1.77 | |
| *P*-trend | | | | <0.01 | | | 0.84 | | | 0.08 | | | 0.03 | | | 0.07 | |
| No. of previous breast biopsies | | | | | | | | | | | | | | | | | |
| 0 | 1,393,687 | 3,667 | 1 | Reference | 142 | 1 | Reference | 88 | 1 | Reference | 560 | 1 | Reference | 421 | 1 | Reference | 0.43 |
| 1 | 285,731 | 1,041 | 1.34 | 1.25, 1.45 | 48 | 1.45 | 1.01, 2.08 | 26 | 1.41 | 0.90, 2.22 | 159 | 1.37 | 1.13, 1.65 | 128 | 1.40 | 1.13, 1.73 | |
| ≥2 | 152,601 | 599 | 1.50 | 1.37, 1.65 | 25 | 1.43 | 0.90, 2.28 | 18 | 2.08 | 1.24, 3.48 | 114 | 1.87 | 1.50, 2.33 | 87 | 1.98 | 1.55, 2.53 | |
| *P*-trend | | | | <0.01 | | | 0.03 | | | <0.01 | | | <0.01 | | | <0.01 | |
| Family history of breast cancer (first-degree relative) | | | | | | | | | | | | | | | | | |
| No | 1,533,801 | 4,153 | 1 | Reference | 156 | 1 | Reference | 110 | 1 | Reference | 674 | 1 | Reference | 489 | 1 | Reference | 0.44 |
| Yes | 225,792 | 931 | 1.48 | 1.37, 1.60 | 47 | 1.87 | 1.32, 2.65 | 21 | 1.33 | 0.83, 2.16 | 132 | 1.32 | 1.08, 1.60 | 122 | 1.60 | 1.30, 1.98 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Estimates were adjusted for age at baseline, education, race, marital status, age at menarche, parity/age at first birth, type of and age at menopause, menopausal hormone use, oral contraceptive use, body mass index, frequency of vigorous physical activity, and all other variables in the table.

[b] Two-sided *P* value from the Wald test, simultaneously comparing associations for ductal, mucinous, tubular, lobular, and mixed ductal-lobular types.

with a lower risk of mucinous breast cancer, consistent with results from 2 other studies (17, 32). This decreased risk was in the opposite direction from the association we observed for other histological types, as well as the positive association with breast cancer overall in the literature (35, 36). Most studies of oral contraceptive use and breast cancer risk have not included results specific to mucinous breast cancer. Thus, it is difficult to evaluate this result in the context of the larger literature. The positive association we observed between BMI and all histological types was similar to previously reported associations in MHT nonusers (28–31). We did not observe dose-response relationships between height or alcohol use and risk of mucinous or tubular cancers; previous studies have found both positive associations and no association (20, 21). The association between breast cancer family history and risk of tubular cancer was similar to the positive, nonsignificant associations reported in studies from the United States and Poland (19, 21) but not the strong positive association observed in a Swedish study (20). Generalizations are difficult because of the imprecision inherent in estimating associations for these rare tumors and the small number of studies available for comparison. Additional studies are needed to accurately characterize these associations.

Biological reasons for the risk factor differences we observed are unclear. Other than ductal NST tumors, the histological types that we examined were ER-positive in more than 90% of cases, and histology-specific associations for ER-positive tumors were similar to what was observed overall. This analysis was limited by the fact that some cancer registries did not collect hormone receptor data. These results should be confirmed in a population with more complete ER data, but our data indicate that ER status did not influence the associations we observed.

Previous research has identified heterogeneous breast cancer groups, or intrinsic molecular subtypes, that possess distinct genetic, epigenetic, and prognostic profiles (37–41), but it is unlikely that molecular subtype could explain the differences seen in this study. The few studies that have evaluated intrinsic molecular subtype for mucinous and tubular tumors have suggested that the majority are luminal A (39, 42), consistent with the high frequency of ER-positivity. Gene expression studies indicate that mucinous and tubular tumors exhibit differences from other breast tumors, even when controlling for grade and intrinsic molecular subtype (43–45). Tubular tumors have shown up-regulation of estrogen signaling pathway genes when compared with other ER-positive tumors (45). It could be hypothesized that higher activity in this pathway could account for the strong relationship between MHT use and tubular risk.

The biology underlying risk of mucinous tumors is less clear, especially since mucinous tumors also express estrogen-related genes at higher levels than grade- and molecular-subtype-matched ductal NST tumors (44), yet they tended to lack associations with hormonal risk factors in our study. This issue may be complicated by the fact that mucinous tumors can be subclassified into at least 2 types (paucicellular and hypercellular) with divergent molecular features (44, 46). Data on mucinous subtypes are not reported to cancer registries and were not available in this study. Better understanding of mucinous subtypes may be needed to fully define the etiology of this tumor. The unique characteristics associated with mucinous and tubular tumors, even when matched by ER expression or molecular subtype, suggest that there is potential to further stratify luminal A tumors into distinct etiological subgroups.

Our study was limited in that we were unable to perform centralized pathology review. A comparison between local pathology reports and centralized review by Work et al. (17) showed good agreement for ductal (95%), lobular (88%), and mucinous (84%) types of tumors but lower agreement for tubular tumors (57%) (17). It is possible that a subset of tumors in this study were misclassified, which would have biased assessments of heterogeneity towards the null. Other limitations include the fact that risk factor data were self-reported and may have been subject to misclassification error. Data were gathered prospectively, however, and any misclassification should have been nondifferential between cases and noncases and by histology, biasing the relative risks towards the null in the same manner for all case types and not affecting case-case comparisons. Additionally, some information was assessed only on the second questionnaire, which limited statistical power in analyses of type of MHT use. Despite this, we still detected a strong association between MHT use and risk of tubular cancer, and differences by histology were consistent regardless of whether we examined any MHT or combination MHT.

We estimated associations for a large number of risk factors in this study, and there is potential that some findings may have been due to chance. However, the consistency of our main results with those of other studies suggests that these are not spurious associations. Finally, while the large number of cases allowed for the precise estimation of ductal, lobular, and mixed-ductal cancer associations, the lower numbers of mucinous and tubular cases resulted in imprecise estimates for some comparisons. Pooled analyses that produce more precise results will help clarify associations for these histological types. This approach has been undertaken by some researchers with respect to hormone use (18) but could be expanded.

In summary, associations between some reproductive factors and risk of mucinous breast cancer and between MHT use and risk of tubular breast cancer differed from associations for the other histological types. Our findings suggest that these variants of ductal breast cancer have unique etiologies. Increased knowledge of risk factor profiles associated with these tumors may help determine what factors, in addition to intrinsic molecular subtype, are involved in the etiology of these good-prognosis breast tumors.

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