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Risk factors for uncommon histologic subtypes of breast cancer using centralized pathology review in the Breast Cancer Family Registry

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Abstract

Epidemiologic studies of histologic types of breast cancer including mucinous, medullary, and tubular carcinomas have primarily relied on International Classification of Diseases-Oncology (ICD-O) codes assigned by local pathologists to define histology. Using data from the Breast Cancer Family Registry (BCFR), we compared histologic agreement between centralized BCFR pathology review and ICD-O codes available from local tumor registries among 3,260 breast cancer cases. Agreement was low to moderate for less common histologies; for example, only 55 and 26 % of cases classified as mucinous and medullary, respectively, by centralized review were similarly classified using ICD-O coding. We then evaluated risk factors for each histologic subtype by comparing each histologic case group defined by centralized review with a common set of 2,997 population-based controls using polytomous logistic regression. Parity [odds ratio (OR) = 0.4, 95 % confidence interval (95 % CI): 0.2–0.9, for parous vs. nulliparous], age at menarche (OR = 0.5, 95 % CI: 0.3–0.9, for age 13 vs. 11), and use of oral contraceptives (OCs)

(OR = 0.5, 95 % CI: 0.2–0.8, OC use >5 years vs. never) were associated with mucinous carcinoma ($N = 92$ cases). Body mass index (BMI) (OR = 1.05, 95 % CI: 1.0–1.1, per unit of BMI) and high parity (OR = 2.6, 95 % CI: 1.1–6.0 for ≥ 3 live births vs. nulliparous) were associated with medullary carcinoma ($N = 90$ cases). We did not find any associations between breast cancer risk factors and tubular carcinoma ($N = 86$ cases). Relative risk estimates from analyses using ICD-O classifications of histology, rather than centralized review, resulted in attenuated, and/or more imprecise, associations. These findings suggest risk factor heterogeneity across breast cancer tumor histologies, and demonstrate the value of centralized pathology review for classifying rarer tumor types.

Keywords

Epidemiology; Mucinous breast cancer; Medullary breast cancer; Centralized pathology; Parity; Oral contraceptives

Introduction

Breast cancer is a heterogeneous disease defined by multiple tumor characteristics, including histology. Epidemiologic studies classifying breast cancer by histology have identified important differences in etiologic factors according to histologic subtype [1–15]. However, these studies are often limited by sample size and generally examine the most common histologies, such as ductal and lobular carcinoma [2, 4, 12–14]. Few studies exist on the less common histologies of mucinous, medullary, and tubular carcinoma.

Mucinous carcinoma, representing 1–3 % of breast cancers, has an average age at diagnosis of 70 [16], and is commonly estrogen receptor (ER)-positive and of low tumor grade [17]; survival is generally better than for ductal carcinoma [18–20]. *Medullary carcinoma*, representing 1–2 % of breast cancers, is more common among *BRCA1* and *BRCA2* mutation carriers, has an early age at onset, and is associated with hormone receptor negativity and high grade, but with similar or better survival compared with ductal carcinoma [16, 17, 19–23]. *Tubular carcinoma*, representing 1–2 % of breast cancers, is similar in age at diagnosis distribution to ductal carcinoma, but associated with small tumor size and better survival [16, 18–20, 23, 24].

Despite differing clinical characteristics and outcomes, little is known about how risk factors differ for these histologic types. Studies examining uncommon histologies often have limited information on some known or suspected etiologic factors [1, 8, 9]. Most studies rely on data from local cancer registries, such as International Classification of Diseases-Oncology (ICD-O) codes, for histologic classification, rather than utilizing a centralized pathology review process. Evidence for several cancers suggests that relying on ICD-O coding for rarer tumor types could introduce or increase inter-observer diagnostic variability, resulting in heterogeneity within pathological groupings [12, 25, 26].

Using existing data from the Breast Cancer Family Registry (BCFR), we studied histologic agreement for 3,260 breast cancer cases by comparing centralized BCFR pathology review according to the study protocol with ICD-O codes available from local pathology reports.

We then evaluated risk factors for each histologic subtype defined by centralized pathology review by comparing each histologic case group to a common set of 2,997 population-based controls. We compared estimates based on centralized pathology review with those based solely on ICD-O codes available from local pathology reports.

Materials and methods

The BCFR is a consortium of six sites established in 1995 (for details see [27–29]). Three BCFR sites sampled cases and controls using population-based sampling in California, Ontario, Canada, and Melbourne, Australia. In brief, cases included women 18–69 years starting in 1995. Of the eligible cases, questionnaires were completed by 2,287 from California, 1,687 from Ontario, and 1,133 from Australia (76, 72, and 75 %, respectively, of the eligible cases). Controls were randomly sampled from the population living in the same catchment area of the cases and frequency matched to cases on 5-year age groupings. We included a total of 2,997 controls including 623 from California, 1,706 from Ontario, and 668 from Australia (67, 64, and 74 %, respectively, of the eligible controls). Cases and population-based controls completed structured questionnaires assessing breast cancer risk factors and family history of cancer.

Pathology data

All cases had histology data available through ICD-O codes obtained from local cancer registries; of these, 1,522 (67 %), 1,210 (72 %), and 571 (50 %) of cases from California, Ontario, and Australia, respectively, had either pathology samples ($N = 2,176$) or pathology reports/medical records ($N = 1,127$) available for centralized review. The distribution of reproductive and other risk factors was no different between cases who did and did not have pathology data available (data not shown).

BCFR pathologists examined sections from histologic slides and/or paraffin tumor blocks and determined primary and secondary (if available) histologic pattern(s) using standardized pathology review forms. Where tissue samples were unavailable, pathologists reviewed pathology reports and recorded primary and secondary histology types using standard pathology review forms, allowing for a centralized process of review and classification of histology. Pathologists used two definitions of histology to classify the cases. In the first (primary) definition, they classified cases as a specific histologic subtype if the tumor's primary histology was of that subtype. The five histological categories included ductal, lobular, mucinous, tubular, and medullary types. In the second definition, they classified cases by subtype if their primary OR secondary histology was of that subtype, with the exception of ductal histology, for which the primary AND secondary histology was required to be ductal. Breast cancers not meeting the classification for any of these types (including cribriform, micropapillary, secretory, and all other types, $n = 43$) were excluded from analysis, resulting in a sample of 3,260 cases.

Statistical analyses

We first compared the overall agreement between histology determined by centralized review and histology defined using ICD-O codes obtained from local cancer registries, using percent agreement and kappa statistic.

We then used multivariable unordered polytomous logistic regression to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for each subtype compared to a common referent group of controls. Case/case comparisons were made by comparing the ratio of the OR for any two histologic subtypes. We examined the following risk factors: education (<high school education, high school education), OC use (>5 years, 5 years, never), hormone replacement therapy (current, former, or never user); age at menarche (11, 12, 13 years); parity (nulliparous, 1–2 live births, 3 live births); age at first birth (continuous, per 1-year increase); breastfeeding duration (never, 3 months, 3–11 months, 12 months); smoking (current, former, or never), body mass index (BMI-continuous, per 1-unit increase), and menopausal status (pre- or post-menopausal). We adjusted all regression analyses for age (continuous), race (non-Hispanic White or Other), study site, and history of breast cancer in a first-degree relative.

We fitted all final models using classification via both primary and secondary histologic type, and compared estimates to those obtained from fitting models using only the primary type to evaluate whether including secondary histologic types influenced inferences. We also compared the estimates from models using centralized pathology review to define histology with estimates from models using the ICD-O code to define histology, to determine if method of classification influenced measures of association between risk factors and histologic type. All statistical analyses used SAS Version 9.2 (SAS Institute, Cary, NC).

Results

Agreement of BCFR central pathology review to ICD-O codes from local tumor registries

When comparing histology defined by centralized pathology review versus that defined by ICD-O codes, agreement was excellent for ductal pathology (96 %), but lower for the remaining histologies: lobular (58 %), mucinous (55 %), tubular (39 %), and medullary (26 %), with an overall kappa of 0.57 (Table 1). When comparing agreement with centralized review using only the primary pattern, we found that agreement improved for less-common types (Table 2); the overall kappa was 0.69. We also examined if agreement between centralized review and ICD-O classification differed when we stratified our centralized review sample by whether the cases had histology determined via tissue sample ($N = 2,176$) or pathology report ($N = 1,127$). Agreement between centralized review and ICD-O code was lower for cases whose source of pathology review was a tissue sample (overall kappa = 0.49), particularly for the rarer histologies (mucinous: 45 % agreement, tubular: 26 % agreement, and medullary: 22 % agreement).

Table 3 summarizes demographic, tumor, and risk factor characteristics using centralized pathology review. The prevalence of the uncommon histologies (mucinous, tubular, and

medullary) was 2–3 % when defined using both primary and secondary histologic pattern. Medullary tumors were most unlike the other types in that they were more likely to be ER– (77 vs. 9–27 %), PR– (74 vs. 14–32 %), grade 3 (92 vs. 5–44 %), and have occurred in *BRCA1* mutation carriers (21 vs. 0–4 %).

Table 4 presents the multivariable ORs for each histologic type obtained by comparing subtypes of cases with the control group, for each exposure of interest, using centralized review for classifying histologies.

Uncommon histologies (mucinous, tubular, and medullary)

Mucinous—Use of OCs was inversely associated with mucinous carcinoma (OR = 0.50, 95 % CI: 0.28–0.91, for OC use ≤ 5 years; OR = 0.45, 95 % CI: 0.24–0.84, for OC use >5 years), as was late age at menarche (OR = 0.52, 95 % CI: 0.29–0.93 13 years vs. 11 years), and parity (OR = 0.39, 95 % CI: 0.18–0.88, for 1–2 live births vs. nulliparous, OR = 0.40, 95 % CI: 0.15–1.02, for ≥ 3 live births vs. nulliparous). Late age at first birth was positively associated with mucinous carcinoma (OR = 1.08, 95 % CI: 1.02–1.15, per 1-year increase). When we considered case/case comparisons with ductal carcinoma as the reference group, OC use ≤ 5 years was inversely associated with mucinous carcinoma, with an OR of 0.49, (95 % CI 0.27–0.90), while OC use >5 years was inversely associated with mucinous carcinoma with an OR of 0.52 (95 % CI, 0.28–0.96). Parity remained inversely related to mucinous carcinoma (OR = 0.44, 95 % CI: 0.20–0.97, for 1–2 live births vs. nulliparous, OR = 0.43, 95 % CI: 0.17–1.10, for ≥ 3 live births vs. nulliparous) relative to ductal subtype.

Tubular—While associations with tubular carcinoma were not statistically significant, the magnitude of the OR was similar to that of mucinous carcinoma for higher age at menarche compared to lower age (OR = 0.58, 95 % CI, 0.32–1.03).

Medullary—Former smoking was inversely related to medullary carcinoma (OR = 0.30, 95 % CI: 0.15–0.62, vs. never smoking). BMI was positively associated with medullary carcinoma (OR = 1.05, 95 % CI: 1.01–1.08, for each 1-unit increase in BMI), and the effect estimate did not differ by menopausal status (Table 4), as was high parity (OR = 2.61, 95 % CI: 1.13–6.00, for ≥ 3 live births vs. nulliparous). When using ductal carcinoma as the reference group, the OR for ≥ 3 live births vs. nulliparous was 2.65 (95 % CI 1.15–6.10) for medullary carcinoma.

Common histologies (ductal and lobular)

Breast-feeding ≥ 12 months was inversely associated with many histologies with the exception of tubular, and statistically significant for ductal carcinoma (OR = 0.66, 95 % CI: 0.54–0.81). Former and current smoking were positively associated with lobular carcinoma (OR = 1.33, 95 % CI: 1.03–1.73, former vs. never; OR = 1.42, 95 % CI: 1.04–1.95, current vs. never), and postmenopausal status was inversely associated with lobular carcinoma (OR = 0.61, 95 % CI: 0.41–0.88). Other factors (parity, age at first birth, age at menarche, OC use, and HRT use) were not significantly associated with ductal or lobular carcinoma.

compared with controls. When we included only women with an intact uterus in our analysis of HRT, the overall findings with HRT did not materially differ (data not shown).

Comparison with primary histology patterns only

We repeated all models using only the tumor's primary histologic type to classify the tumor, with controls as the referent group (See Fig. 1, classification B). The OR for mucinous carcinoma associated with OC use ≤ 5 years was not significant when using primary histology only (OR = 0.78, 95 % CI: 0.38–1.61); however, the estimate for the association with >5 years use did not change (OR = 0.38, 95 % CI: 0.16–0.92). Former smoking was associated with increased risk of the tubular subtype in analyses using primary histology only (OR = 2.01, 95 % CI: 1.02–3.94) but not with analyses where secondary histology was used (Table 4). Other findings did not differ appreciably by whether we used primary histology only or both primary and secondary histology to define the case subgroups. We also repeated all models excluding cases whose histology had been defined without a tumor sample, and found overall few material differences from the main analyses with the exception that later age at menarche was more strongly associated with tubular carcinoma (OR = 0.36, 95 % CI: 0.15–0.91, 12 vs. 11, and OR = 0.43, 95% CI: 0.21–0.86, 13 vs. 11).

Comparison of results with alternative case definitions

We repeated the models using the same set of individuals reported in Table 4 with histologic classification according to ICD-O code rather than via centralized review. Measures of association were generally more attenuated when utilizing ICD-O classifications (See Fig. 1, Classification C). For example, for cases defined as mucinous using both primary and secondary histology, parity was associated with an OR of 0.39 (95 % CI: 0.18–0.85, for parous vs. nulliparous), compared with an OR of 0.59 (95 % CI: 0.30–1.27) using ICD-O coding. Similarly, OC ever use versus never use was associated with an OR of 0.48 (95 % CI: 0.29–0.80) with mucinous defined by primary and secondary histology using centralized review, compared with an OR of 0.62 (95 % CI: 0.32–1.21) using ICD-O coding (Fig. 1). There were greater differences in estimates for histologic types with poor agreement between classification systems such as medullary carcinoma (Fig. 2). For example, for medullary cases, high parity (≥ 3 live births vs. nulliparous) was associated with an OR of 2.60 (95 % CI: 1.13–5.98) when defined using primary and secondary histology by centralized review, compared with an OR of 9.62 (95 % CI: 1.73–53.38) using ICD-O coding. Figures 1 and 2 also illustrate that associations with some risk factors (e.g. age at menarche and BMI) did not differ greatly according to histology classification.

Discussion

Agreement of histologic classification

We used centralized pathology review and primary and secondary histology to classify tumors into different subtypes. This process identified a greater number of cases with uncommon tumor types (Tables 1, 2). Our finding that, for less common subtypes, agreement between histology obtained by centralized review and that obtained using ICD-O codes is low, even when using the primary histology only, indicates that studies relying on

local cancer registry data to provide tumor histology will be prone to undercounting of rarer subtypes.

Two previous studies that used centralized pathology review to examine risk factors for ductal, lobular, and ducto-lobular cancer found excellent agreement (94 %, kappa = 0.91) for these subtypes between study pathologists, but these studies did not also examine ICD-O histologic classifications from local cancer registries nor did they examine uncommon histologies [12, 14]. A study examining agreement between centralized pathology review and SEER registry data for classifying tumors by joint ER/PR status found that agreement was good and did not influence risk factor association estimates for the common breast cancer subtypes, ER+/PR+ and ER-/PR-, but was poor for ER+/PR- and ER-/PR+ types (kappa 0.3 and 0.05, respectively), leading to the conclusion that SEER registry data might not be reliable for estimating risk factor associations for less common cancer subtypes [26].

While centralized pathology review for classification may be considered a “gold standard”, classification of some rare subtypes is still imperfect. A recent validation study by BCFR pathologists indicated that classification agreement on mucinous and tubular histology in the present population was high (kappa = 1.0 and 0.8, respectively), but only moderate for medullary histology (kappa = 0.4), indicating outcome misclassification may be present in medullary carcinoma [30]. If present, misclassification would be non-differential by exposure, since pathologists were unaware of the exposure status of cases.

Uncommon histology (mucinous, medullary, and tubular) findings

Our parity findings with mucinous histology mirror those from a Danish cohort study, which found that nulliparity was associated with a nearly threefold increased risk of mucinous carcinoma [1]. A recent prospective study of 1.2 million women, including 23,000 with breast cancer and 330 cases with mucinous histology, also found nulliparity positively associated with mucinous carcinoma; and also found that having 3 live births was positively associated with medullary carcinoma [15]. However, a population-based case-control study using pathology data obtained from the SEER program did not find an association between either nulliparity and the mucinous type or high parity and the medullary type [8]. Our finding regarding age at menarche and mucinous carcinoma contradicts the findings of Reeves et al. [15] who found no association, but is consistent with those of Li [8], who found an inverse association for menarche occurring at >13 vs. 11 years. Our finding of late age at first birth and a positive association with the mucinous type contradicts the Reeves and Li studies.

Our finding that late age at menarche is inversely associated, and nulliparity and late age at first birth are positively associated with the mucinous subtype, suggests that women who have many menstrual cycles uninterrupted by pregnancy could be more susceptible to the mucinous histology.

We found that a having a greater number of children was associated with a higher risk of the medullary subtype. This could be explained by the correlation between medullary subtype and ER, PR, and HER2 negativity (triple-negative breast cancer), which has been associated with having a large number of children in some [31–33], but not all [34, 35], previous

studies. The mechanism for this association is unclear, however, studies have demonstrated that triple-negative as well as medullary tumors are more likely to occur relatively soon after pregnancy (0–5 years) [36, 39]. Triple-negative breast cancer has also been associated with higher BMI and metabolic syndrome [37], (although not in all studies, see [34, 38]), one component of which is obesity; this may explain why we observed that medullary cancer was associated with higher BMI.

None of the established breast cancer factors was significantly associated with tubular breast cancer, although we observed an inverse relation with late age at menarche. These findings are supported by Reeves et al. [7, 15], who found that late age at menarche was inversely related to tubular carcinoma, but contradicts Reeves' other findings that parity was inversely, and late age at first birth and HRT use positively associated with tubular carcinoma. Li et al. found no association between late age at first birth and tubular carcinoma [8], but did find that HRT use was positively associated with tubular carcinoma. Both the Reeves et al. and Li et al. [7, 8] studies relied on registry-provided data for histology classification. Both authors also noted the effect was much stronger for combined HRT users versus estrogen-only users. In our study, we did not have information regarding whether HRT users utilized estrogen-only or combined estrogen–progestin products; however, an analysis in which we only included women with intact uteri, who would presumably be exposed to combined HRT, did not yield any differences in findings (data not shown).

Methodologic considerations

For our primary analyses, we used population-based controls as the common referent group. We did not observe many established associations between hormonal and reproductive factors and breast cancers of the ductal or lobular subtypes. For example, while 12 months of breastfeeding was inversely associated with ductal carcinoma in our study, as reported elsewhere [5], we did not observe significant associations with HRT use that have been reported by several studies [4, 5, 7, 8, 12, 14]. We did not find associations between other hormonal and reproductive factors and the ductal subtype, inconsistent with other published studies [1, 5, 8, 14, 15]. We have previously reported differences in education and reproductive factors between population-based controls and unaffected sisters within our BCFR families, which likely were driven by different response rates and contributed to not observing established risk factors within the ductal subgroup [29]. However, the control group would not affect case/case inferences as we used an unordered polytomous regression model with the same referent group, so case/case comparisons can be made by simply taking the ratio of the OR. Thus, our inferences about rarer histologies compared to more common ductal and lobular histologies would not be affected by lower response rates in the control group.

Case selection—Our sample of cases is not representative of all women with breast cancer; they are younger, more often ethnic and racial minorities, and more often have a family history of breast cancer. Our distribution of the different histologic subtypes might not be representative of these subtypes in a sample of cases unselected for these characteristics. For example, mucinous carcinoma has a median diagnosis age of 70 years,

whereas in our study cases with mucinous carcinoma had an average age at diagnosis of 46 years. Mucinous carcinoma could have different risk factors for younger women than for older women. However, we did observe agreement between histologic types and tumor characteristics that have been reported previously in the literature: ER/PR negativity, high grade, and *BRCA1* mutation positivity were more common for medullary cases, while ER/PR positivity was common for lobular, mucinous, and tubular cases [16–18, 23].

Selection bias—A subset of cases in our study did not have material or pathology reports reviewed by BCFR pathologists. If these women were not representative of all eligible cases, one or more findings could be biased, with the direction of the bias differing depending on the differences between those who participated and had pathology for review and those who did not. Distributions of parity and other risk factors for our sample and the entire case sample were similar (data not shown), and an analysis of all cases demonstrated minimal differences in measures of association for risk factor associations, improving the likelihood that cases with pathology data available are representative of histology distribution for the entire case sample.

Information bias—The possibility of recall bias exists because we relied on participants' recalls of their exposures. However, the purpose of this analysis was to determine whether risk factor associations differed by histologic type, using controls as a common reference. Because it is unlikely that cases report exposures differently based on histologic type, it is unlikely estimates would be affected by recall bias of exposures that are differential by subtype.

Multiple comparisons—We conducted multiple comparisons with different exposures and five outcomes, making it likely that one or more findings are due to chance. However, we did restrict our comparison to selected breast cancer risk factors and specifically examined whether key findings were robust to outcome classification.

Summary

Overall, we found that several etiologic factors were more associated with uncommon breast cancer histologic types than they were for common histologies. Specifically, reproductive characteristics and OC use could be of importance in the etiology of mucinous histology. Having 3 live births and high BMI could be important risk factors for development of medullary carcinoma. We also found that histology classification using centralized pathology review resulted in different findings than classification relying on ICD-O codes from local reporting, particularly for rarer histologies that are undercounted in registry-provided sources. Our findings add to increasing evidence that risk factors differ across histologic breast cancer subtypes, provide evidence on the role of some factors in the etiology of uncommon histologic types, and underscore the importance of consistent pathology review processes in studies involving histological classification of tumors.

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Abbreviations

BCFR	Breast Cancer Family Registry
BMI	Body mass index
CI	Confidence interval
ER	Estrogen receptor
HRT	Hormone replacement therapy
ICD-O	International Classification of Diseases-Oncology codes
OC	Oral contraceptives
OR	Odds ratio
PR	Progesterone receptor
SEER	Surveillance, Epidemiology and End Results

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OC Use: Ever vs. Never

A. Primary and/or Secondary (N=90)

B. Primary Histology Only (N=46)

C. ICD-O Code (N=37)

Parity: Parous vs. Nulliparous

A. Primary and/or Secondary (N=90)

B. Primary Histology Only (N=46)

C. ICD-O Code (N=37)

Age at Menarche: ≥ 13 vs. ≤ 11

A. Primary and/or Secondary (N=90)

B. Primary Histology Only (N=46)

C. ICD-O Code (N=37)

Fig. 1.

Comparison of ORs for mucinous carcinoma by OC use, parity and age at menarche, by classification type, BCFR (All ORs adjusted for age, race, study site, education, family history, and all factors in Table 3). BCFR Breast Cancer Family Registry; *ICD-O* International Classification of Diseases-Oncology; *OC* oral contraceptives

Fig. 2. Comparison of ORs for *medullary* carcinoma by parity and continuous BMI, by Classification Type, BCFR (All ORs adjusted for age, race, study site, education, family history, and all factors in Table 4). *BCFR* Breast Cancer Family Registry; *ICD-O* International Classification of Diseases-Oncology

Table 1

Level of agreement for 3,260 cases between pathologist classification using centralized pathology review (primary and secondary histology) and classification by International Classification of Diseases-Oncology (ICD-O) codes, BCFR^a

ICD-O codes: Centralized review	8000–8140 Malignant neoplasm, histology NOS ^b	8500, 8523 Ductal	8522 Ducto-lobular	8520, 8524 Lobular	8480 Mucinous	8211 Tubular	8510–8513 Medullary	All other	Total	% Agreement
Ductal (N)	132	2,275^c	61	18	2	12	8	57	2,565	96.0
Lobular (N)	28	161	79	154	0	1	2	2	427	58.3
Mucinous (N)	5	37	0	0	47	0	0	1	90	55.3
Tubular (N)	2	48	1	2	0	32	0	1	86	38.6
Medullary (N)	4	64	1	0	0	0	23	0	92	26.1
Total	171	2,585	142	174	49	45	33	61	3,260	

BCFR Breast Cancer Family Registry; NOS not otherwise specified

^aOverall kappa (j) = 0.57

^bTumors classified by ICD-O as malignant neoplasm, histology NOS were not included in the calculations of agreement

^cValues with bold represent cells with agreement between classification method

Table 2

Level of agreement of 3,260 cases by pathologist classification using centralized pathology review (primary histology only) and classification by International Classification of Diseases-Oncology (ICD-O) codes (Classification C), BCFR^a

ICD-O codes: Centralized review	8000–8140 Malignant neoplasm, histology NOS ^b	8500, 8523 Ductal	8522 Ducto-lobular	8520, 8524 Lobular	8480 Mucinous	8211 Tubular	8510–8513 Medullary	All other	Total	% Agreement
Ductal (N)	148	2,520^c	114	32	12	17	15	60	2,918	95.1
Lobular (N)	16	20	28	140	0	1	2	1	208	87.5
Mucinous (N)	2	7	0	0	37	0	0	0	46	84.1
Tubular (N)	1	18	0	2	0	27	0	0	48	57.4
Medullary (N)	4	20	0	0	0	0	16	0	40	44.0
Total	171	2,585	142	174	49	45	33	61	3,260	

BCFR Breast Cancer Family Registry; NOS not otherwise specified

^aOverall kappa (j) = 0.69

^bTumors classified by ICD-O as malignant neoplasm, histology NOS were not included in the calculations of agreement

^cValues with bold represent cells with agreement between classification methods

Distribution of demographic and tumor variables in controls and cases by histologic type using centralized pathology review, BCFR, 1995–2004

Table 3

	Controls N = 2,997 N (%)	Ductal N = 2,565 N (%)	Lobular N = 427 N (%)	Mucinous N = 90 N (%)	Tubular N = 86 N (%)	Medullary N = 92 N (%)
Age (I ± s.d.)	48.1 ± 10.3	46.9 ± 9.7	48.6 ± 9.2	45.5 ± 10.5	50.9 ± 8.7	42.3 ± 10.3
Site						
Ontario	1,706 (57)	856 (33)	220 (52)	38 (42)	37 (43)	40 (43)
Australia	668 (22)	440 (17)	92 (22)	7 (8)	10 (12)	16 (17)
California	623 (21)	1,269 (49)	115 (27)	45 (50)	39 (45)	36 (39)
Race/ethnicity						
White	2,487 (86)	1,617 (63)	347 (81)	49 (54)	57 (66)	66 (72)
Black	96 (3)	261 (10)	24 (6)	10 (11)	9 (10)	7 (8)
Hispanic	72 (2)	204 (8)	31 (7)	10 (11)	6 (7)	11 (12)
Asian	165 (6)	424 (17)	22 (5)	17 (19)	13 (15)	7 (8)
Other	82 (3)	46 (2)	3 (1)	4 (4)	1 (1)	1 (1)
1° Family history						
No	2,732 (91)	1,775 (69)	295 (69)	68 (76)	59 (69)	70 (76)
Yes	263 (9)	784 (31)	131 (31)	21 (24)	27 (31)	22 (24)
Menopausal status						
Pre	1,566 (55)	1,481 (61)	238 (59)	60 (70)	38 (48)	61 (69)
Post	1,262 (45)	965 (39)	166 (41)	26 (30)	42 (53)	28 (31)
ER status						
Positive		1,658 (65)	337 (79)	76 (84)	71 (83)	10 (11)
Negative		705 (27)	51 (12)	8 (9)	8 (9)	71 (77)
Borderline/unknown		202 (8)	39 (9)	6 (7)	7 (8)	7 (12)
PR status						
Positive		1,525 (59)	328 (77)	67 (74)	64 (75)	17 (18)
Negative		809 (32)	61 (14)	15 (17)	15 (17)	68 (74)
Borderline/unknown		231 (9)	38 (9)	8 (9)	7 (8)	7 (8)
Grade						
1, 2		1,348 (53)	330 (77)	74 (82)	78 (91)	5 (6)
3		1,134 (44)	72 (17)	11 (12)	4 (5)	85 (92)

	Controls N = 2,997 N (%)	Ductal N = 2,565 N (%)	Lobular N = 427 N (%)	Mucinous N = 90 N (%)	Tubular N = 86 N (%)	Medullary N = 92 N (%)
Unknown		83 (3)	25 (6)	5 (6)	4 (4)	2 (2)
BRCA1 status						
BRCA1 positive		74 (4)	5 (2)	0 (0)	0 (0)	16 (21)
BRCA1 negative		1,707 (96)	298 (98)	62 (100)	62 (100)	62 (79)
Education						
<High school	908 (30)	754 (30)	132 (31)	28 (31)	24 (28)	26 (29)
High school	2,082 (70)	1,756 (70)	294 (69)	62 (69)	61 (72)	65 (71)
OC use						
Never	646 (22)	646 (26)	94 (22)	36 (40)	28 (33)	17 (19)
5 years	1,117 (37)	970 (39)	167 (40)	27 (30)	31 (36)	34 (37)
>5 years	1,216 (41)	883 (35)	159 (38)	26 (30)	26 (31)	40 (44)
HRT use						
Never	2,081 (70)	1,862 (77)	308 (76)	69 (78)	52 (63)	68 (78)
Former	168 (6)	94 (4)	11 (3)	5 (6)	6 (7)	5 (6)
Current	737 (24)	477 (20)	86 (21)	15 (18)	24 (29)	14 (16)
Age at menarche						
11	406 (14)	363 (15)	65 (16)	19 (22)	19 (24)	13 (15)
12	711 (25)	594 (25)	100 (25)	23 (27)	22 (28)	20 (23)
13	1,760 (61)	1,391 (60)	231 (58)	43 (51)	37 (47)	53 (62)
Parity						
Nulliparous	531 (18)	610 (24)	70 (16)	27 (30)	16 (19)	19 (21)
1–2 live births	1,334 (45)	1,104 (43)	191 (45)	41 (46)	35 (41)	36 (39)
3 live births	1,132 (37)	851 (33)	166 (39)	22 (24)	35 (41)	37 (40)
Age at first birth (mean)	24.8	24.8	25.3	26.7	24.3	24.5
Breastfeeding duration						
Never	1,203 (40)	1,232 (49)	173 (41)	43 (48)	40 (47)	42 (46)
3 months	409 (14)	331 (13)	73 (17)	19 (21)	11 (13)	15 (16)
>3, <12 months	582 (19)	447 (17)	72 (17)	12 (13)	11 (13)	14 (15)
12 months	803 (27)	522 (20)	108 (25)	16 (18)	24 (28)	21 (23)
Smoking status						
Never smoker	1,542 (52)	1,484 (58)	204 (48)	65 (73)	47 (55)	64 (70)

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	Controls N = 2,997 N (%)	Ductal N = 2,565 N (%)	Lobular N = 427 N (%)	Mucinous N = 90 N (%)	Tubular N = 86 N (%)	Medullary N = 92 N (%)
Former smoker	919 (31)	619 (24)	142 (33)	14 (16)	29 (34)	12 (13)
Current smoker	533 (18)	443 (17)	80 (19)	10 (11)	10 (12)	16 (17)
BMI (mean)	25.9	26.1	25.9	25.9	26.2	26.9

BCFR Breast Cancer Family Registry; *ER* estrogen receptor; *PR* progesterone receptor

BMI body mass index; *HRT* hormone replacement therapy; *OC* oral contraceptives

N listed for categorical covariates and mean (*μ*) listed for continuous covariates

Table 4
Relation between etiologic factors and five different histologic types of breast cancer, BCFR

	Ductal		Lobular		Mucinous		Tubular		Medullary	
	N = 2,565		N = 427		N = 90		N = 86		N = 92	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
OC use										
Never	1.00 ^a	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
5 years	1.02	0.86, 1.21	1.07	0.79, 1.46	0.50	0.28, 0.91 *	0.75	0.41, 1.35	1.14	0.59, 2.18
>5 years	0.88	0.74, 1.05	0.97	0.70, 1.33	0.45	0.24, 0.84 *	0.67	0.36, 1.26	1.28	0.67, 2.45
HRT use										
Never	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Former	0.66	0.48, 0.93 *	0.52	0.27, 1.01	1.30	0.35, 4.90	1.27	0.48, 3.38	2.39	0.80, 7.16
Current	0.85	0.70, 1.04	0.94	0.66, 1.32	1.71	0.75, 3.87	1.19	0.61, 2.31	1.20	0.51, 2.82
Age at menarche										
11	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
12	1.02	0.84, 1.24	0.93	0.66, 1.30	0.79	0.41, 1.51	0.79	0.41, 1.52	1.01	0.51, 2.02
13	1.01	0.86, 1.20	0.89	0.66, 1.19	0.52	0.29, 0.93 *	0.58	0.32, 1.03	1.26	0.70, 2.27
Parity										
Nulliparous	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
1–2 live births	0.88	0.72, 1.09	1.13	0.77, 1.67	0.39	0.18, 0.88 *	0.99	0.45, 2.14	1.31	0.62, 2.75
3 live births	0.98	0.78, 1.24	1.28	0.83, 1.96	0.40	0.15, 1.02	1.28	0.54, 3.03	2.61	1.13, 6.00 *
Age at first birth (per year)	1.01	0.99, 1.03	1.03	1.00, 1.06	1.08	1.02, 1.15 *	0.99	0.93, 1.05	1.02	0.96, 1.08
Breastfeeding duration										
Never	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
3 months	0.89	0.71, 1.10	1.19	0.83, 1.72	1.71	0.75, 3.87	0.63	0.26, 1.52	0.88	0.42, 1.82
>3, <12 months	0.87	0.71, 1.06	0.80	0.56, 1.15	0.95	0.39, 2.31	0.65	0.29, 1.46	0.55	0.26, 1.16
12 months	0.66	0.54, 0.81 *	0.76	0.53, 1.08	0.75	0.30, 1.83	1.08	0.56, 2.09	0.58	0.29, 1.19
Smoking status										
Never smoker	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Former smoker	0.91	0.78, 1.06	1.33	1.03, 1.73 *	0.52	0.25, 1.05	1.36	0.80, 2.33	0.30	0.15, 0.62 *

	Ductal		Lobular		Mucinous		Tubular		Medullary	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
	N = 2,565		N = 427		N = 90		N = 86		N = 92	
Current smoker	1.11	0.93, 1.32	1.42	1.04, 1.95*	0.65	0.30, 1.42	0.81	0.37, 1.80	0.71	0.39, 1.31
Menopausal status										
Premenopausal	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Post menopausal	0.84	0.68, 1.04	0.61	0.41, 0.88*	0.44	0.19, 1.03	0.58	0.26, 1.27	1.43	0.63, 3.25
BMI (pre only)	1.00	0.98, 1.01	0.99	0.96, 1.02	1.01	0.96, 1.06	0.98	0.91, 1.05	1.04	1.00, 1.09
BMI (post only)	1.01	0.99, 1.03	1.00	0.97, 1.03	1.00	0.93, 1.08	1.00	0.95, 1.06	1.05	0.99, 1.12

BCFR Breast Cancer Family Registry; BMI body mass index; CI confidence intervals; HRT hormone replacement therapy; OC oral contraceptives; OR odds ratio

* P < 0.05, statistically significant results are in bolded

^a All ORs adjusted for age, race, study site, education, family history of breast cancer, and all factors in the table