Published in final edited form as:

Breast Dis. 2010 ; 32(0): 5–24. doi:10.3233/BD-2010-0319.

EPIDEMIOLOGY OF TRIPLE NEGATIVE BREAST CANCERS

Gierach L. Gretchen, PhD, MPH,

Hormonal and Reproductive Epidemiology Branch, DHHS/NIH/NCI/Division of Cancer Epidemiology and Genetics (DCEG), EPS, Room 5016, 6120 Executive Blvd, Bethesda, MD 20892-7244, Phone: 301 594 5635, Fax: 301 402 4916

Aileen Burke, MPH, and

Hormonal and Reproductive Epidemiology Branch, DHHS/NIH/NCI/Division of Cancer Epidemiology and Genetics (DCEG), EPS, Room 5007, 6120 Executive Blvd, Bethesda, MD 20892-7244, Phone: 301 594 3262, Fax: 301 402 4916

William F. Anderson, MD, MPH

Biostatistics Branch (BB), DHHS/NIH/NCI/Division of Cancer Epidemiology and Genetics (DCEG), EPS, Room 8036, 6120 Executive Blvd, Bethesda, MD 20892-7244, Phone: 301 594 9125, Fax: 301 402 0081

Gierach L. Gretchen: gierachg@mail.nih.gov; Aileen Burke: burkeai@mail.nih.gov; William F. Anderson: wanderso@mail.nih.gov

Keywords

breast cancer; triple negative breast cancers; breast cancer molecular subtypes; estrogen receptor (ER); progesterone receptor (PR); human epidermal growth factor receptor-2 (HER2); breast cancer risk factors; breast cancer epidemiology

INTRODUCTION

Triple negative (TN) breast cancers fail to express the three most common breast cancer receptors; i.e., estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). Accumulating data demonstrate that epidemiological risk factor profiles also vary between TN (ER–PR–HER2–) and other breast cancers, especially the so-called Luminal A breast cancers (ER+PR+HER2–) [1]. A more comprehensive understanding of the epidemiology of TN breast cancers has important public health implications for risk assessment [2], prevention and treatment.

The epidemiology of TN breast cancers can be first understood in the age-related reproductive risk factor patterns for ER, PR, and HER2. For example, there is a clear and strong association between older age at diagnosis (and therefore postmenopausal status) and the development of ER positive, PR positive, and HER2 negative breast cancers. On the other hand, younger age at diagnosis (and premenopausal status) is related to the

Correspondence to: William F. Anderson, wanderso@mail.nih.gov.

Disclaimer: None of the co-authors has a financial conflict of interest that would have affected this research. This research was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

development of ER negative, PR negative, and HER2 positive breast cancers. This gives rise to the somewhat counterintuitive suggestion that menopause has a greater relative impact upon hormone receptor negative than positive breast cancers [3–4].

Throughout this review, we will primarily contrast ER–PR–HER2– (TN) with ER+PR±HER– (Luminal A) breast cancers. We will first summarize the population-based age-specific incidence rate patterns and clinical outcomes, and then will review the available analytical studies. Information sources for this review included the National Cancer Institute’s Surveillance, Epidemiology, and End Results 13 Registries Public-Use Database [5], CANCERLIT, Index Medicus, and PubMed.

CASE DEFINITIONS AND THE RELATIONSHIPS OF TRIPLE NEGATIVE (TN) TO BRCA1 AND BASAL-LIKE BREAST CANCERS

It is widely recognized that breast cancers are heterogeneous with respect to histopathological appearance, molecular alterations, presentation, and clinical outcome. Unsupervised or “semi-supervised” [6] hierarchical clustering of gene expression profiles demonstrates four “intrinsic” breast cancer types within two main groups according to ER expression and/or epithelial cell of origin (i.e., luminal and basal) [1, 7–8], so-called intrinsic because the gene set was chosen for inherent breast cancer characteristics irrespective of clinical outcome.

There are two ER positive (luminal A and B) and two ER negative intrinsic breast cancers (HER2+ and basal-like) [9]. The intrinsic breast cancer molecular signatures have been identified over different cDNA microarray platforms [10–13], for invasive and pre-invasive breast cancers [14–16], among different racial/ethnic groups [17–19], and can be roughly approximated with protein expression patterns using standard immunohistochemical stains for ER, PR, and HER2 (Table 1) [20–23].

Finally, even though not selected for clinical outcome, the intrinsic molecular subtypes are associated with different breast cancer survival patterns. Overall and relapse-free survival are most favorable for luminal A and least favorable for basal-like breast cancers [1, 8, 24–25].

These molecular observations demonstrate the importance of genomic variations as determinants of breast cancer incidence and clinical outcome, and provide the basis for revised conceptual themes that emphasize breast cancer biology over cancer stage [26]. However, the relationship between breast cancer genomic expression and traditional epidemiological (etiologic) risk factor patterns remains somewhat uncertain, and it is still not known just how many different breast cancers actually exist [27–28]. At the very least, there appears to be a two-class [12, 24, 29] difference between the breast cancers that express ER and luminal genes (luminal A) and those that do not (basal-like). Luminal A (ER+PR±HER2–) and basal-like breast cancers are inversely correlated at the clinical, genomic, transcriptomic, proteomic, and prognosis/prediction levels. Though generally TN (ER–PR–HER2–), the basal-like molecular signature has been found in different breast cancer types [9, 30], ranging from indolent adenoid cystic, aggressive metaplastic, medullary

histopathological subtype, and *BRCA1*-associated breast cancers. The majority of *BRCA1*-associated breast cancers are also TN. TN breast cancers, therefore, are an important though not obligate subset of basal-like and *BRCA1*-related breast cancers; the relation between *BRCA* mutations and TN breast cancers is reviewed further by Isaacs and Peshkin in this issue.

DESCRIPTIVE EPIDEMIOLOGY FOR TN (ER–PR–HER2–) AND LUMINAL A (ER+PR ±HER2–) BREAST CANCERS

Population-based age-specific incidence rates in the SEER database by hormone receptor expression

The age-specific incidence rate patterns for TN breast cancers cannot be fully understood until population-based resources such as the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [5] record and report HER2 expression data. SEER has recorded ER and PR status since 1990 but HER2 expression is not yet available from its large-scale Public-Use Database [31]. Therefore, at present, SEER rates for ER–PR–HER2– age-specific incidence must be inferred and/or approximated from ER–PR– expression patterns.

Age-specific rates for ER–PR– breast cancers rise rapidly until ages 40–50 years then flatten or fall (Figure 1A). In contrast, ER+PR+ breast cancers rise rapidly then continue to increase at a slower pace. The inflection near age 50 years has been referred to as Clemmesen's hook [32]. The Clemmesen's phenomenon is observed worldwide for female breast cancer, is associated with menopause, and is absent in male breast cancer [33]. Prior to Clemmesen's menopausal hook, age-specific risks are greater for ER–PR– than ER+PR+ breast cancers, after which rates are higher for ER+PR+ breast cancers. The ER–PR– to ER+PR+ crossover is a qualitative (or reversing) age interaction [34].

Collectively, qualitative age interactions and Clemmesen's hook suggest age-related breast cancer heterogeneity, where hormone receptor negative and positive breast cancers reflect different mixtures and/or relative risks for early- or late-onset cancer pathways [34–36]. In this conceptual framework, carcinogenic transformation proceeds along dual age-dependent cancer pathways: 1) early-onset and basal (or myoepithelial) differentiation versus 2) late-onset and luminal (glandular) differentiation. Hormone receptor negative breast cancers are enriched with early-onset cancers, whereas hormone receptor positive cancers are enriched with late-onset disease. The premenopausal reversal of incidence rate ratios for ER–PR– to ER+PR+ breast cancers suggests that menopause has greater relative impact upon the development of ER–PR– than ER+PR+ breast cancers [3–4, 37].

Population-based age-specific incidence rates in the SEER Residual Tissue Repository (RTR) by hormone receptor and HER2 expression

In 2001, the SEER program established residual tissue repositories in the Hawaii, Iowa, and Los Angeles Tumor Registries to collect discarded tissue blocks from pathological laboratories within their catchment areas. The Hawaii Tumor Registry (HTR) generated a tissue microarray (TMA) that included 354 breast cancer cases that were diagnosed in 1995,

representing 51% of all breast cancer cases in the HTR overall for that year [23]. The overall HTR cases and TMA cases were similar with respect to patient demographics and clinical characteristics. The intrinsic molecular breast cancer subtypes were recapitulated with immunohistochemical stains for ER, PR, and HER2 as described in Table 1.

Population denominators for the calculation of age-specific incidence rates were estimated according to the fraction of 1995 HTR cases that were captured in the TMA and the population data in the HTR for that year. Imputed age-specific incidence rates for ER+PR+HER2- and ER-PR-HER2- breast cancers were qualitatively similar (Figure 1B) to the ER+PR+ and ER-PR- patterns in the entire SEER database (Figure 1A). Emerging data from the California Cancer Registry appear to corroborate the HTR results, i.e., the addition of HER2- status does not substantially alter the basic age-specific incidence rate pattern for ER+PR+ and ER-PR- breast cancers [38–39].

Population-based age-specific incidence rates in the SEER database by hormone receptor expression and race

Hormone receptor positive and negative breast cancers are stratified by Black and White race in Figure 2. ER+PR+ breast cancers show a qualitative age interaction by race (Figure 2A); black women have greater risk prior to Clemmesen's menopausal phenomenon after which rates are higher for white women. In contrast, black women have equal or greater risk for ER-PR- breast cancers at all ages (Figure 2B), i.e., there is no qualitative age interaction or crossover pattern. Recent data from the California Cancer Registry confirm higher population-based incidence rates of TN breast cancers among young Black women [38–40]. However, these data do not imply that breast cancers are biologically different in Blacks than Whites, but they do show that Blacks have less of the more favorable hormone receptor positive breast cancers (Figure 2A) and more of the worse hormone receptor negative breast cancers (Figure 2B) [41–42].

Population-based breast cancer outcome in the SEER database overall and in SEER's RTR in Hawaii has been demonstrated with cumulative and conditional breast cancer-specific survival (Figure 3), using Kaplan-Meier (KM) estimates (KM figures 3A and 3C) [43] and spline functions (Figure 3B and 3D) [44–48], respectively (see Appendix for additional detail). In brief, KM estimates assess the cumulative or percent breast cancer survival from the time of initial diagnosis. The annual hazard rate for breast cancer-specific death describes the instantaneous rate of cancer death in a specified time interval (percentage dying per year) following diagnosis, conditioned upon women who are alive at the beginning of the time interval.

In general, 5-year percent survival is around 75% for ER-PR- (Figure 3A) and ER-PR-HER2- breast cancers (Figure 3C). On the other hand, 5-year percent survival is approximately 90% for both ER+PR+ and ER+PR+HER2- breast cancers. Hazard rates for breast cancer death peak near 7.5% per year 2 years following diagnosis for ER-PR- (Figure 3B) and ER-PR-HER2- (Figure 3D) then decline rapidly [45–46]. In contrast, ER+PR+ and ER+PR+HER2- hazard rates lack a sharp peak but are relatively constant at 1–2% per year. Falling ER-PR-/ER-PR-HER2- hazard rates and constant ER+PR+/ER+PR+HER2- rates cross approximately 7 years following breast cancer diagnosis after which

prognosis is paradoxically better for hormone receptor negative than hormone receptor positive breast cancers. The ER–PR–/ER–PR–HER2– to ER+PR+/ER+PR+HER2– hazard rate crossover is another type of qualitative (or reversing) interaction that further suggests biological heterogeneity between hormone receptor positive (e.g., luminal A) and negative (e.g., TN) breast cancers.

ANALYTIC DATA

As described above, multiple lines of evidence including population-based incidence and mortality rates as well as the histopathological and biologic features of breast cancers support the concept of TN breast cancer (ER–PR–HER2–) as a distinct disease, especially in contrast to hormone positive or luminal A (ER+PR+HER2–). It is only within the past few years that epidemiologic studies using case-control, case-case, and prospective study designs have begun to use the “triple designation” to characterize etiologic heterogeneity in risk factor association studies.

We identified seven case-control studies that evaluated triple negative breast and luminal A breast cancers compared with cancer-free controls [49–56]; the design features of these analytical studies are reviewed in Table 2. Two studies additionally included epidermal growth factor receptor (HER1/EGFR) and cytokeratin 5 (ck5) antibodies in their marker panel to better approximate the characterization of basal-like breast cancers (i.e., ER–PR–HER2–EGFR+CK5+) [51, 55]; the remainder evaluated only ER, PR and HER2 status. All studies used immunohistochemistry (IHC) to evaluate molecular markers; some studies [52–53] used fluorescence in situ hybridization (FISH) to verify HER2 expression when HER2 status by IHC was questionable. All of the case-control studies were population-based with the exception of Xing et al. [56], which identified cases from a single hospital in China and controls from the local population. Five of the studies were carried out in the United States, one in China and one in Poland. Most included pre- as well as postmenopausal women; however, the study reported by Phipps et al. [52–53] was restricted to postmenopausal women aged 55–74 years, and two studies focused on younger pre- and postmenopausal women ranging in age from 21–45 and 20–54 years [49, 54]. Two of the studies examined a racially homogenous population [55–56]; the remainder included racially diverse populations but had a majority of non-Hispanic white cases. Only Millikan et al. [51] included non-invasive breast cancers in their analysis. Most studies frequency-matched cases to controls on age; Ma et al. [50] and Millikan et al. [51] also matched on race, and Yang et al. [55] additionally matched on study site. The studies that did not match cases to controls adjusted for age in their analyses [49, 54], and Trivers et al. [54] additionally adjusted for race.

Within the case-control studies, Millikan et al. [51] and Trivers et al. [54] also carried out case-case analyses, in which risk factor distributions for triple negative breast cancers were compared with luminal A breast cancers. The case-case design offers an alternative and efficient analytic approach to begin to expose etiologic heterogeneity between breast cancer subtypes [57–58]. We identified six additional case-case studies (five reports) [59–65] that compared triple negative cases to either luminal A cases or all other subtypes (Table 2). IHC and FISH were used in each of these studies for case identification and HER2 expression

confirmation, in a manner identical to that described above for the case-control studies. With the exception of a pooled analysis of 34 studies participating in an international consortium [65], all studies were carried out in the U.S. and were of a variety of study designs. Only Millikan et al. [51] and Trivers et al. [54] were population-based studies with specific upper and lower age limits. The study by Parise et al. [60] was the largest, identifying cases from a state cancer registry. Shinde et al. [64] and Stead et al. [63] recruited cases from a hospital, and Stark et al. [61–62] recruited cases from a health maintenance organization (HMO). Kwan et al. [59] carried out a pooled analysis of cases participating in two cohort studies of breast cancer survivors, both of which had a lower age limit of 18 years. All studies included multiple races, and, with the exception of the large pooled analysis from an international consortium (of which 92% of participants were of European ancestry [65]), all studies adjusted for race/ethnicity in multivariate models. As mentioned above, only the Millikan et al. study [51] included *in situ* cases.

Most recently, we identified five reports from two U.S.-based prospective multi-center studies which evaluated risk factor associations with triple negative breast cancer [66–70] (Table 2). Reports from the Women's Health Initiative include postmenopausal participants who were ages 50–79 years at the time of enrollment [66, 68–69]. Analyses from the Breast Cancer Surveillance Consortium (BCSC), a collaborative network of mammography registries, were restricted to women with no history of personal breast cancer and who were ages 40–84 years at the time of mammography screening [67, 70]. Analyses in these prospective studies did not distinguish between luminal A and luminal B breast cancers but rather focused on risk factor associations for ER+ as compared to those for triple negative breast cancer. All multivariate models adjusted for race/ethnicity.

In Tables 3–5, we present findings from the epidemiologic studies we identified as having evaluated risk factors for triple negative breast cancer. The risk estimates presented are from multivariate models wherever possible.

Non-modifiable risk factors

Age at breast cancer diagnosis—Given the various age ranges and methods of matching and/or age adjustment, it is difficult to compare the analytical and population-based results for age at initial breast cancer diagnosis. Only two of the case-control studies examined age at diagnosis as a risk factor for triple negative or luminal A breast cancer (Table 3). Trivers et al. [54] compared women diagnosed at ages 20–39 and 40–49 with women diagnosed at 50 years or greater and observed an increased risk of triple negative breast cancer associated with a young age at diagnosis (odds ratio (OR) for 20–39 years: 1.77, 95% confidence interval (CI) 1.18–2.64). No association was found between age at diagnosis and risk of luminal A breast cancers. The study by Dolle et al. [49] found the opposite effect when comparing women aged 40–45 with those aged less than 30, but the estimate was not statistically significant (OR 2.2, 95% CI 0.7–7.4) and was based on small numbers and a restricted age range.

Case-case analyses comparing triple negative to luminal A cancers have provided more data to evaluate age-specific breast cancer risks (Table 4). The studies that examined multiple age groups observed a trend of increasing risk with younger age at diagnosis, and both the

Carolina Breast Study [51] and a hospital-based study from Texas [64] observed statistically significant increasing risk estimates for each age group when compared with women diagnosed at age 60 or older. Similar to their case-control analysis, Trivers et al. [54] found an increased risk for the youngest age group only (OR 2.13, 95% CI 1.34–3.39). This was also seen by Kwan et al. [59], where the association was significant for women younger than 50 compared with women older than 65 (OR 2.78, 95% CI 1.99–3.90), but not for women aged 50–64 at diagnosis (OR 1.99, 95% CI 0.85–1.62). Stark et al. [62] estimated the decrease in risk to be 16% per decade (OR 0.84, 95% CI 0.74–0.95).

Other studies that compared triple negative cases to all other types of breast cancer produced similar but less striking estimates related to age at diagnosis. Parise et al. [60] and Stead et al. [63] both compared women younger than 50 at diagnosis to those older than 50, although only the former found a statistically significant increased risk associated with younger age (Parise et al. [60] OR 1.21, 95% CI 1.14–1.29; Stead et al. [63] OR 1.40, 95% CI 0.81–2.4).

Race and ethnicity—As noted in Figure 2, descriptive epidemiologic data suggest that hormone receptor negative breast cancer is more common among Blacks than Whites. Trivers et al. [54] was the only case-control study to report on race as a risk factor for triple negative breast cancer (Table 3). They found that black women were more likely than white women to be diagnosed with triple negative cancer (OR 2.41, 95% CI 1.81–3.21) and less likely than white women to have a diagnosis of luminal A breast cancer (OR 0.73, 95% CI 0.56–0.95).

This association is supported by data from case-case analyses comparing triple negative cases with luminal A cases (Table 4). Each of the reports that compared black women with white women found an increased risk of triple negative cancer for black women: Shinde et al. [64], OR 2.17, 95% CI 1.54–3.05; Kwan et al. [59], OR 3.14, 95% CI 2.12–4.66; Trivers et al. [54], OR 2.98, 95% CI 2.12–4.20; Millikan et al. [51], OR 2.1, 95% CI 1.6–2.9; Stark et al. [61], OR 1.72, 95% CI 1.17–2.54. Both Stead et al. [63] and Parise et al. [60] observed the same increased risk for black women, comparing triple negative cases with all other cases of breast cancer (OR 3.0, 95% CI 1.6–5.4; OR 1.88, 95% CI 1.69–2.09, respectively).

There are limited data available from case-case studies for other races and ethnicities (Table 4). Both Shinde et al. [64] and Kwan et al. [59] compared triple negative to luminal A cases and found no association for Hispanic women compared with non-Hispanic women (OR 1.04, 95% CI 0.71–1.51 and OR 0.93, 95% CI 0.57–1.53, respectively); both studies also observed a decreased risk for Asians compared with whites, albeit only the results from Kwan et al. were statistically significant (OR 0.53, 95% CI 0.28–0.97). Conversely, a large study within the population-based California state cancer registry [60] found an increased risk of triple negative breast cancer for Hispanic compared with non-Hispanic white women (OR 1.19, 95% CI 1.10–1.29), and a similar decreased risk for Asian/Pacific Islanders compared with Whites (OR 0.81, 95% CI 0.74–0.90).

Family history of breast cancer—The evidence to date suggests that having a positive family history of breast cancer increases risk of both triple negative and luminal A breast cancers. In the largest prospective study to date [70], having a family history of breast

cancer in a first degree relative was associated with an increased risk triple negative breast cancer (RR 1.73, 95% CI 1.43–2.09), with a magnitude of association similar to that for luminal cancers (RR 1.62, 95% CI 1.54–1.70) (Table 5). We identified three case-control studies that examined this risk factor; each compared women who had a first-degree relative with breast cancer with women who did not (Table 3). Dolle et al. [49] evaluated the relation for triple negative cancers only, and observed that women with a positive family history had 3.5 times the risk of triple negative breast cancer (95% CI 2.1–5.9). In the Chinese case-control study [56], family history was associated with increased risk of luminal A (OR 2.24, 95% CI 1.35–3.72) and triple negative breast cancers, although the finding was not statistically significant for the latter (OR 1.53, 95% CI 0.75–3.15). Yang et al. [55] observed increased risks associated with having a positive family history for both triple negative (OR 3.17, 95% CI 0.69–5.92) and luminal A (OR 1.72, 95% CI 1.21–2.45) breast cancers. In support of these findings, the case-case studies that carried out similar comparisons failed to find a differential effect of family history on risk of triple negative versus luminal A cancers (Kwan et al. [59]: OR 0.95, 95% CI 0.69–1.29; Millikan et al. [51]: OR 1.0, 95% CI 0.7–1.5).

Modifiable/lifestyle risk factors

Education—Only two case-control studies reported data on education as a risk factor (Table 3). Dolle et al. [49] found no association with triple negative cancer, comparing college graduates with women with less education (OR 1.3, 95% CI 0.9–2.0). Trivers et al. [54] found that having less education was associated with a decreased risk of luminal A cancer (OR for < college vs. college graduate: 0.68, 95% CI 0.54–0.86), but no association with triple negative cancer (OR 0.93, 95% CI 0.69–1.26). In the case-case portion of their analysis [54], they also found no relationship between education and risk of triple negative cancer, with luminal A cases as the referent group (OR 1.35, 95% CI 0.97–1.89; Table 4).

Body mass index—The data regarding body mass index (BMI) as a risk factor for triple negative cancer are equivocal. All studies that reported on this risk factor compared obese women (BMI ≥ 30) to lean women (BMI < 25). Case-control analyses that evaluated BMI in all women (i.e., irrespective of age or menopausal status) found no association with triple negative breast cancers (Table 3), whereas Trivers et al. [54] found a decreased risk of luminal A cancer for obese women (OR 0.58, 95% CI 0.43–0.78), as did Millikan et al. [51] (OR 0.8, 95% CI 0.6–1.0). In a case-case analysis of triple negative versus luminal A (Table 4), only Trivers et al. [54] found a statistically significant increased risk of triple negative cancer for obese women (OR 1.89, 95% CI 1.22–2.92). The remaining case-case analyses of all women did not observe a relationship between BMI and triple negative breast cancer [51, 59, 62–63] (Table 4).

Stratification by menopausal status has shed some light on the relationship between BMI and triple negative cancer. Whereas premenopausal obesity appeared to decrease the risk of luminal A breast cancers in case-control analyses [51, 55] (Table 3), case-case analyses revealed an increased risk of triple negative breast cancers associated with premenopausal obesity in three studies [51, 59, 65], two of which were statistically significant (Yang et al. OR 1.80, 95% CI 1.42–2.29; Kwan et al. OR 1.97, 95% CI 1.03–3.77; Table 4). Among

postmenopausal women, BMI was not associated with triple negative breast cancer in either case-control [51, 53, 55] or case-case analyses [51, 59]. The Women's Health Initiative is the only prospective study to date to have evaluated the association between BMI and risk of triple negative breast cancer (Table 5). In contrast with both the case-control and case-case literature, obesity was associated with elevated risk of both triple negative (RR 1.37, 95% CI 0.98–1.93) and ER+ (RR 1.35, 95% CI 1.20–1.51) breast cancer in this postmenopausal cohort [68].

Alcohol intake—Whereas elevated alcohol intake does seem to be associated with increased risk of luminal A breast cancer [54], there is little evidence of an association with increased risk of triple negative cancer from the data available to date. In case-control analyses, Dolle et al. [49] compared women who consumed at least three units of alcohol per week with those who had none or less than one, and found no association (OR 1.1, 95% CI 0.7–1.6; Table 3). Trivers et al. [54] compared those who consumed seven or more drinks per week with those who had none, and also failed to see a relationship with risk (OR 1.22, 95% CI 0.79–1.89). They used the same comparison groups for their case-case analysis [54], and again found no association, although the direction of the point estimate changed (OR 0.72, 95% CI 0.44–1.17; Table 4). In case-case analyses, both Kwan et al. [59] and Millikan et al. [51] compared women who ever drank alcohol with those who never drank alcohol, but neither study found an association with triple negative cancer (OR 0.98, 95% CI 0.73–1.30; OR 0.9, 95% CI 0.6–1.2, respectively). Findings from the Women's Health Initiative (WHI) cohort (Table 5) are difficult to reconcile with those from the cross-sectional studies; in the WHI, women who consumed at least seven drinks per week had a reduced risk of triple negative cancer compared with never drinkers (RR 0.59, 95% CI 0.34–0.95) [66].

Reproductive risk factors

Age at menarche—Early age at menarche has been associated with increased risk of breast cancer in many epidemiologic studies [71]. Epidemiologic data are conflicting as to whether earlier age at menarche is also a risk factor for triple negative breast cancer. In the WHI (Table 5), age at menarche was not associated with risk of triple negative breast cancer (RR for 14+ vs. <12 years=0.96, 95% CI 0.67–1.39) [69]. With respect to case-control studies (Table 3), Dolle et al. [49] found a decreased risk of triple negative cancer among women who were aged 15 or older at menarche, compared with those aged 8–12 years at menarche (OR 0.4, 95% CI 0.2–1.0). Similarly, Trivers et al. [54] observed an increased risk of triple negative cancer, but not for luminal A cancers, when comparing women who reached menarche before the age of 12 with after 12 years (OR 1.60, 95% CI 1.17–2.19). In the Polish Breast Cancer Study, Yang et al. [55] estimated that for every two years that menarche is delayed, risk of triple negative cancer decreases by 22% (OR 0.78, 95% CI 0.68–0.89). Estimates to the contrary were observed by Millikan et al. [51], who found an increased risk of triple negative breast cancer for later age at menarche (13+ years compared with <13 years; OR 1.4, 95% CI 1.1–1.9). The Chinese hospital-based study [56] did not observe a relationship between age at menarche and risk of triple negative breast cancer, but later age at menarche was associated with an increased risk of luminal A breast cancers in this study (OR 2.35, 95% CI 1.45–3.81).

In a large pooled case-case analysis (Table 4), Yang et al. did not find a relationship between age at menarche and risk of triple negative breast cancer (OR for 12 vs. 15 years=1.08, 95% CI 0.92–1.28) [65]. In contrast, Trivers et al. [54] observed a statistically significant increased risk of triple negative breast cancer among cases who were younger than age 12 at menarche, compared with those who were older than 12 (OR 1.55, 95% CI 1.08–2.23). In case-case analyses, Millikan et al. [51] observed a similar increase in risk of triple negative breast cancer associated with menarche before age 13, although the effect was not statistically significant (OR 1.3, 95% CI 0.9–1.7).

Oral contraceptive use—Only one prospective ([69]; Table 5) and two case-control ([49–50]; Table 3) studies have examined oral contraceptive use as a risk factor for triple negative breast cancer. Phipps et al. [69] compared oral contraceptive users of 10 or more years to never users and found no association with triple negative breast cancer risk in the WHI (RR 1.02, 95% CI 0.68–1.52). Ma et al. [50] observed no association for ever users versus never users, both overall (OR 1.00, 95% CI 0.72–1.39) and following stratification by age (<44 years: OR 0.72, 95% CI 0.42–1.24; ≥45 years: OR 1.25, 95% CI 0.83–1.88). This study also found no relationship between oral contraceptives and risk of luminal A breast cancer in similar analyses. Conversely, Dolle et al. [49] found an increased risk of triple negative cancer in women who reported using oral contraceptives for at least one month, compared with never users or users for less than one month (OR 2.5, 95% CI 1.4–4.3). They also stratified analyses by age, and the association remained statistically significant only in the younger age group (<40 years: OR 4.2, 95% CI 1.9–9.3; 40+ years: OR 0.9, 95% CI 0.4–2.2).

Case-case analyses have failed to see an association between oral contraceptive use and risk of triple negative breast cancer ([51, 59]; Table 4). Both case-case analyses compared ever users to never users, and observed no difference in risk of triple negative cancer compared to luminal A cancer (Kwan et al. [59]: OR 0.97, 95% CI 0.72–1.31; Millikan et al. [51]: OR 0.9, 95% CI 0.6–1.3).

Parity and age at first birth—While the majority of case-control and cohort studies observed an inverse relationship between parity and risk of luminal breast cancer, most did not find an association between parity and risk of triple negative breast cancer (Tables 3 and 5). Among the case-control studies, only the Carolina Breast Study [51] found a statistically significant relationship between parity and risk of triple negative cancer: compared with nulliparous women, women who had 3 or more children were at an increased risk of triple negative breast cancer (OR 1.9, 95% CI 1.1–3.3). Using the same comparison, Phipps et al. observed an increased risk of triple negative breast cancer among WHI participants who had 3 or more children, but the finding was not statistically significant (RR 1.46, 95% CI 0.82–2.63) [69]. When comparing the risk of triple negative breast cancer among nulliparous to parous women, Phipps et al. observed a statistically significant reduced risk in prospective analyses within the WHI (RR 0.61, 95% CI 0.37–0.97) [69] but not within the BCSC population (RR 1.07, 95% CI 0.87–1.33) [67]. Several case-control studies that evaluated the risk of triple negative breast cancer associated with multiple births versus nulliparity found elevated odds ratios, but the results were not statistically significant and the

confidence intervals wide [52, 55–56]. Case-case analyses of triple negative versus luminal A cancers generally demonstrated that women with three or more births were at an increased risk of triple negative breast cancer compared with nulliparous women (Table 4; Shinde et al. [64]: OR 2.97, 95% CI 1.98–4.46; Millikan et al. [51]: OR 1.7, 95% CI 1.0–2.9; and Trivers et al. [54]: OR 2.40, 95% CI 1.24–4.64). Along those lines, in a large pooled case-case analysis nulliparous women were at a reduced risk of triple negative breast cancer as compared with parous women (OR 0.69, 0.59–0.81) [65].

Whereas early age at first birth is associated with reduced risk of luminal cancers in one case-control [54] and both prospective studies [67, 69], data from case-control and cohort studies largely suggest that age at first birth is not related to risk of triple negative cancer (Tables 3 and 5). A large pooled case-case analysis suggested a reduced risk of triple negative breast cancers per each 5-year increase in age at first birth (OR 0.89, 95% CI 0.83–0.95; Table 4); however, when the pooled analysis was restricted to participating case-control studies, age at first birth was not associated with risk of triple negative breast cancer (OR 0.95, 95% CI 0.86–1.05; case-control results are reported in [65]).

Breastfeeding—In the prospective WHI, breastfeeding for at least a year was associated with a reduced, albeit not statistically significant, risk of triple negative breast cancer (RR 0.81, 95% CI 0.53–1.26; Table 5) [69]. For the most part, case-control data are fairly consistent with a protective effect for breastfeeding in triple negative cancer (Table 3). Only one study, Dolle et al. [49], failed to observe a statistically significant association, comparing women who breastfed for at least one year to those who never breastfed (OR 1.0, 95% CI 0.6–1.7). For the remaining five studies that evaluated breastfeeding, the protective effect was observed irrespective of breastfeeding duration. In addition, several studies observed a statistically significant dose response relationship such that the effect appeared stronger in women who breastfed longer [50–52, 54]. For example, Trivers et al. [54] observed non-significant association when comparing women who ever to never breastfed (OR 0.84, 95% CI 0.62–1.13), but when restricted to women who breastfed at least a year compared with those who never breastfed, an inverse association was found (OR 0.53, 95% CI 0.32–0.85). Similar, although less striking, protective effects associated with breastfeeding were observed in case-control analyses of luminal A cancers. Case-case comparisons of triple negative versus luminal A cancer were suggestive of an inverse relationship, although only the findings from Shinde et al. were statistically significant (OR 0.56, 95% CI 0.41–0.76; Table 4) [64].

Menopause—In the prospective BCSC, age at menopause was not associated with risk of triple negative cancer [67]. Likewise, case-control studies conducted in China [56], Poland [55] and the U.S. [52] also found no association between age at menopause and triple negative breast cancer risk; in contrast, older age at menopause was associated with increased risk of luminal A breast cancers in these studies (Tables 3 and 5). Whereas surgical menopause was associated with a reduced risk of luminal A breast cancers in a pooled analysis of U.S. case-control studies of postmenopausal breast cancer, neither bilateral oophorectomy nor trans abdominal hysterectomy were associated with risk of triple negative breast cancer in the same study [52].

Data from case-case analyses regarding menopausal status are limited and equivocal (Table 4). Consistent with the idea that women with triple negative cancers tend to have a younger age at diagnosis, Stark et al. [61] observed increased risk of triple negative cancer, compared with luminal A cancer, when comparing pre- with postmenopausal women (OR 1.94, 95% CI 1.27–2.96). Kwan et al. [59] and Millikan et al. [51] found the opposite effect, but neither estimate was statistically significant.

Menopausal hormone therapy—Limited data from both case-control and case-case analyses do not provide support for a relationship between menopausal hormone therapy (HT) use and risk of triple negative breast cancer. A single case-control study [52] compared never users to former and current users of estrogen therapy or combined estrogen plus progestin therapy and observed no association with triple negative breast cancer (Table 3). Similar analyses also failed to find an association with risk of luminal A breast cancer [52]. Two case-case studies compared ever HT users to never users (Table 4): Kwan et al. [59] did not find an association with risk of triple negative versus luminal A cancer (OR 0.83, 95% CI 0.57–1.20), nor did Millikan et al. [51] in a similar comparison (OR 0.8, 95% CI 0.5–1.3).

SUMMARY AND FUTURE DIRECTIONS

Women with triple negative breast cancer tend to have an earlier age at onset, are more likely to be African American, and portend a worse diagnosis. Characterizing risk factors for triple negative breast cancer is challenging as the few epidemiologic studies to date have focused on populations of varying ages and racial and ethnic distributions. Furthermore, population-based age-specific incidence and mortality rates by race are not well understood as information on HER2 status has not been routinely collected by most U.S. cancer registries. The incorporation of HER2 data collection into SEER will facilitate monitoring of population-based rates of this poorly understood breast cancer subtype in the years to come. Larger studies in diverse populations are needed to monitor and address disparities in breast cancer.

Along with case-control and cohort studies, case-case comparisons have assisted in providing clues for etiologic heterogeneity in risk factor associations. While case-case comparisons can serve as an important initial step in exploring etiologic heterogeneity between cancer subtypes, the results from such analyses simply indicate the degree to which risk associations between the case groups differ quantitatively. If case-case analyses show that the strength of association differs by cancer subtype, then etiologic heterogeneity may be confirmed through observations in case-control and cohort studies that suggest distinct causal factors for different subtypes (i.e., the risk estimates reflect differential directions of effect [58]). To date, case-case comparisons have consistently suggested that premenopausal BMI, parity and breastfeeding differentially influence the risk of triple negative as compared with Luminal A breast cancer. However, the few case-control and prospective studies have revealed mixed results for these and other risk factors.

In summary, relationships between alcohol intake, obesity and triple negative breast cancer remain uncertain, although the evidence to date is suggestive of a positive association

between obesity and increased risk of triple negative breast cancer among premenopausal women. Reproductive exposures occurring early in life, such as having a greater number of children and possibly a lack of breastfeeding, appear to be related to an increased risk of triple negative breast cancers. Similarly, there is some evidence to suggest that having an earlier age at menarche is associated with an increased risk of triple negative breast cancer; however, a large pooled case-control analysis and the only prospective study to date do not support this idea. In contrast, menopausal status, age at menopause and type of menopause all appear to be linked to risk of luminal A breast cancers and do not appear to be related to risk of triple negative breast cancer. In general, exogenous hormone use does not seem to influence risk of triple negative cancers; however, data are limited. One case-control study reported an adverse relationship between oral contraceptive use and risk of triple negative breast cancer in younger women; this finding has not yet been confirmed in other studies. A positive family history of breast cancer in a first degree relative is related to an increased risk of both triple negative and luminal A cancers; perhaps through its association with *BRCA1* mutation positive cancers, having a positive family history may even be a stronger risk factor for triple negative than other breast cancer subtypes. Consortial efforts, in which data from individual epidemiologic studies are combined in large-scale pooled analyses, hold promise for clarifying etiologic differences in breast cancer risk and identifying risk factors for triple negative breast cancer.

APPENDIX

Population-based incidence data

We obtained case and population data from the National Cancer Institute's Surveillance, Epidemiology, and End Results 13 Registries Database (SEER 13) during the years 1992–2007 [5], covering approximately 14% of the United States population. These 13 SEER registries included Connecticut, Iowa, New Mexico, Utah, Hawaii, Detroit, San-Francisco-Oakland, Atlanta, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry.

To date, the SEER Public-Use Database has recorded estrogen receptor and progesterone expression (ER+PR+ and ER–PR–) but has not reported human epidermal growth factor receptor-2 (HER2) data. Population-based HER2 expression data were obtained from a prepared tissue microarray (TMA) that resided in SEER's Residual Tissue Repository in Hawaii (Hawaii RTR) [23]. The Hawaii TMA included 354 cases from breast cancers diagnosed in 1995, which represented 51% of all breast cancers that were diagnosed in the Hawaii Tumor registry during that year. The HTR cases that were recorded in the main SEER database and the TMA cases were similar with respect to patient demographics and clinical characteristics (P values greater than 0.09 for the null hypothesis of no difference between the HTR and TMA). Population denominators for the calculation of rates were not directly available for the Hawaii TMA cases, but were estimated according to the fraction of 1995 HTR cases that were captured in the TMA and the population data in the SEER database for that year.

Survival methods

Cumulative breast cancer-specific survival was estimated with the Kaplan-Meier (KM) product-limit method [43]. Conditional breast cancer survival was calculated with hazard rates using spline functions [44]. The annual hazard rate for cancer-specific death described the instantaneous rate of cancer death in a specified time interval (percentage dying per year) following initial diagnosis among women who were alive at the beginning of the time interval. Hazard rate curves were modeled using cubic splines with joinpoints selected by Akaike's information criteria (AIC) [72]. 95% confidence intervals were applied with bootstrap resampling [73]

References

1. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron J, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou C, Lonning P, Brown P, Borresen-Dale A, Botstein D. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100:8418–8423. [PubMed: 12829800]
2. Mavaddat N, Rebbeck TR, Lakhani SR, Easton DF, Antoniou AC. Incorporating tumour pathology information into breast cancer risk prediction algorithms. *Breast Cancer Research*. 2010; 12:R28. [PubMed: 20482762]
3. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End results database. *Breast Cancer Research and Treatment*. 2002; 76:27–36. [PubMed: 12408373]
4. Asselin-Labat M-L, Vaillant F, Sheridan JM, Pal B, Wu D, Simpson ER, Yasuda H, Smyth GK, Martin TJ, Lindeman GJ, Visvader JE. Control of mammary stem cell function by steroid hormone signalling. *Nature*. 2010; 465:798–802. [PubMed: 20383121]
5. Surveillance Epidemiology and End Results (SEER) Program. (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 13 Regs Research Data, Nov 2009 Sub (1992–2007) <Katrina/Rita Population Adjustment> - Linked to County Attributes - Total U.S., 1969–2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission
6. Carey LA.; Perou, CM. Gene arrays, prognosis, and therapeutic interventions. In: Harris, JR., et al., editors. *Diseases of the Breast*. Lippincott Williams & Wilkins; Philadelphia: 2009. p. 458–472.
7. Perou C, Sorlie T, Eisen M, Rijn M, Jeffrey S, Rees C, Pollack J, Ross D, Johnsen H, Akslen L, Fluge O, Pergamenschikov A, Williams C, Zhu S, Lonning P, Borresen-Dale A, Brown P, Botstein D. Molecular portraits of human breast tumours. *Nature*. 2000; 406:747–752. [PubMed: 10963602]
8. Sorlie T, Perou C, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen M, Rijn M, Jeffrey S, Thorsen T, Quist H, Matese J, Brown P, Botstein D, Lonning Eystein P, Borresen-Dale A. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA*. 2001; 98:10869–10874. [PubMed: 11553815]
9. Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Molecular Oncology*. 2011; 5:5–23. [PubMed: 21147047]
10. Hu Z, Fan C, Oh DS, Marron JS, He X, Qaqish BF, Livasy C, Carey LA, Reynolds E, Dressler L, Nobel A, Parker J, Ewend MG, Sawyer LR, Wu J, Liu Y, Nanda R, Tretiakova M, Ruiz Orrico A, Dreher D, Palazzo JP, Perreard L, Nelson E, Mone M, Hansen H, Mullins M, Quackenbush JF, Ellis MJ, Olopade OI, Bernard PS, Perou CM. The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics*. 2006; 7:96. [PubMed: 16643655]
11. Perreard L, Fan C, Quackenbush JF, Mullins M, Gauthier NP, Nelson E, Mone M, Hansen H, Buys SS, Rasmussen K, Orrico AR, Dreher D, Walters R, Parker J, Hu Z, He X, Palazzo JP, Olopade OI, Szabo A, Perou CM, Bernard PS. Classification and risk stratification of invasive breast carcinomas using a real-time quantitative RT-PCR assay. *Breast Cancer Res*. 2006; 8:R23. [PubMed: 16626501]

12. Sorlie T, Wang Y, Xiao C, Johnsen H, Naume B, Samaha RR, Borresen-Dale AL. Distinct molecular mechanisms underlying clinically relevant subtypes of breast cancer: Gene expression analyses across three different platforms. *BMC Genomics*. 2006; 7:127. [PubMed: 16729877]
13. Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, Martiat P, Fox SB, Harris AL, Liu ET. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100:10393–10398. [PubMed: 12917485]
14. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, Perou CM. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. *Modern Pathology*. 2006; 19:264–271. [PubMed: 16341146]
15. Livasy CA, Perou CM, Karaca G, Cowan DW, Maia D, Jackson S, Tse CK, Nyante S, Millikan RC. Identification of a basal-like subtype of breast ductal carcinoma in situ. *Human Pathology*. 2007; 38:197–204. [PubMed: 17234468]
16. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, Deitz AC, Connolly JL, Schnitt SJ, Colditz GA, Collins LC. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. *Breast Cancer Res*. 2008; 10:R67. [PubMed: 18681955]
17. Yu K, Lee CH, Tan PH, Tan P. Conservation of breast cancer molecular subtypes and transcriptional patterns of tumor progression across distinct ethnic populations. *Clinical Cancer Research*. 2004; 10:5508–5517. [PubMed: 15328190]
18. Calza S, Hall P, Auer G, Bjohle J, Klaar S, Kronenwett U, Liu ET, Miller L, Ploner A, Smeds J, Bergh J, Pawitan Y. Intrinsic molecular signature of breast cancer in a population-based cohort of 412 patients. *Breast Cancer Res*. 2006; 8:R34. [PubMed: 16846532]
19. Ithemelandu CU, Leffall LD Jr, Dewitty RL, Naab TJ, Mezgebe HM, Makambi KH, Adams-Campbell L, Frederick WA. Molecular breast cancer subtypes in premenopausal and postmenopausal African-American women: age-specific prevalence and survival. *Journal of Surgical Research*. 2007; 143:109–118. [PubMed: 17950079]
20. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Boussard T, Livasy C, Cowan D, Dressler L, Akslen LA, Ragaz J, Gown AM, Gilks CB, van de Rijn M, Perou CM. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clinical Cancer Research*. 2004; 10:5367–5374. [PubMed: 15328174]
21. Abd El-Rehim DM, Ball G, Pinder SE, Rakha E, Paish C, Robertson JF, Macmillan D, Blamey RW, Ellis IO. High-throughput protein expression analysis using tissue microarray technology of a large well-characterized series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analysis. *International Journal of Cancer*. 2005; 116:340–350.
22. Carey L, Perou C, Livasy C, Dressler L, Cowan D, Conway K, Karaca G, Troester M, Tse C, Edmiston S, Deming S, Geradts J, Cheang M, Nielsen T, Moorman P, Earp H, Millikan R. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006; 295:2492–2502. [PubMed: 16757721]
23. Anderson WF, Luo S, Chatterjee N, Rosenberg PS, Matsuno RK, Goodman MT, Hernandez BY, Reichman M, Dolled-Filhart MP, O'Regan RM, Garcia-Closas M, Perou CM, Jatoi I, Cartun RW, Sherman ME. Human epidermal growth factor receptor-2 and estrogen receptor expression, a demonstration project using the residual tissue repository of the Surveillance, Epidemiology, and End Results (SEER) program. *Breast Cancer Research and Treatment*. 2009; 113:189–196. [PubMed: 18256926]
24. Fan C, Oh D, Wessels L, Weigelt B, Nuyten D, Nobel A, van't Veer L, Perou C. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med*. 2006; 355:560–569. [PubMed: 16899776]
25. Jatoi I, Anderson WF, Jeong JH, Redmond CK. Breast cancer adjuvant therapy: time to consider its time-dependent effects. *J Clin Oncol*. 2011; 29:2301–2304. [PubMed: 21555693]
26. Winer, EP.; Carey, LA.; Dowsett, M.; Tripathy, D. Beyond anatomic staging: are we ready to take the leap to molecular classification?. In: Perry, MC., editor. *American Society of Clinical Oncology Education Book*. American Society of Clinical Oncology; Alexandria, VA: 2005. p. 46-59.
27. Symmans WF. A pathologist's perspective on emerging genomic tests for breast cancer. *Seminars in Oncology*. 2007; 34:S4–9. [PubMed: 17512433]

28. Pusztai L, Mazouni C, Anderson K, Wu Y, Symmans WF. Molecular classification of breast cancer: limitations and potential. *The Oncologist*. 2006; 11:868–877. [PubMed: 16951390]
29. Sorlie T. Introducing molecular subtyping of breast cancer into the clinic? *Journal of Clinical Oncology*. 2009; 27:1153–1154. [PubMed: 19204193]
30. Reis-Filho JS, Lakhani SR. Breast cancer special types: why bother? *Journal of Pathology*. 2008; 216:394–398. [PubMed: 18798222]
31. Reichman ME, Altekruse S, Li CI, Chen VW, Deapen D, Potts M, Wu XC, Morrell D, Hafterson J, Phipps AI, Harlan LC, Ries LG, Edwards BK. Feasibility Study for Collection of HER2 Data by National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program Central Cancer Registries. *Cancer Epidemiology Biomarkers & Prevention*. 2010; 19:144–147.
32. Clemmesen J. Carcinoma of the breast. *British Journal of Radiology*. 1948; 21:583–590. [PubMed: 18099749]
33. Thomas DB. Breast cancer in men. *Epidemiologic Reviews*. 1993; 15:220–231. [PubMed: 8405206]
34. Anderson WF, Jatoi I, Sherman ME. Qualitative age interactions in breast cancer studies: mind the gap. *Journal of Clinical Oncology*. 2009; 27:5308–5311. [PubMed: 19826117]
35. Anderson WF, Matsuno R. Breast Cancer Heterogeneity: A Mixture of At Least Two Main Types? *J Natl Cancer Inst*. 2006; 98:948–951. [PubMed: 16849671]
36. Clarke RB, Sims AH, Howell A. The origin of estrogen receptor alpha-positive and alpha-negative breast cancer. *Advances in Experimental Medicine and Biology*. 2008; 617:79–86. [PubMed: 18497032]
37. Yasui Y, Potter JD. The shape of age–incidence curves of female breast cancer by hormone-receptor status. *Cancer Causes and Control*. 1999; 10:431–437. [PubMed: 10530614]
38. Kurian A, Fish K, Shema S, Clarke C. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. *Breast Cancer Research*. 2010; 12:R99. [PubMed: 21092082]
39. Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women. *Cancer*. 2011; 117:2747–2753. [PubMed: 21656753]
40. Parise CA, Bauer KR, Caggiano V. Variation in breast cancer subtypes with age and race/ethnicity. *Critical Reviews in Oncology/Hematology*. 2010; 76:44–52. [PubMed: 19800812]
41. Huo D, Ikpat F, Khramtsov A, Dangou J, Nanda R, Dignam J, Zhang B, Grushko T, Zhang C, Oluwasola O, Malaka D, Malami S, Odetunde A, Adeoye A, Iyare F, Falusi A, Perou C, Olopade O. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol*. 2009; 27:4515–4521. [PubMed: 19704069]
42. Anderson W, Rosenberg P, Menashe I, Mitani A, Pfeiffer R. Age-related crossover in breast cancer incidence rates between black and white ethnic groups. *J Natl Cancer Inst*. 2008; 100:1804–1814. [PubMed: 19066264]
43. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of American Statistical Association*. 1958; 53:457–481.
44. Rosenberg PS. Hazard function estimation using B-splines. *Biometrics*. 1995; 51:874–887. [PubMed: 7548706]
45. Anderson WF, Schairer C, Chen BE, Hance KC, Levine PH. Epidemiology of inflammatory breast cancer (IBC). *Breast Dis*. 2005–2006; 22:9–23. [PubMed: 16735783]
46. Anderson WF, Chen BE, Jatoi I, Rosenberg PS. Effects of estrogen receptor expression and histopathology on annual hazard rates of death from breast cancer. *Breast Cancer Res Treat*. 2006; 100:121–126. [PubMed: 16685588]
47. Jatoi I, Chen BE, Anderson WF, Rosenberg PS. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *Journal of Clinical Oncology*. 2007; 25:1683–1690. [PubMed: 17404367]
48. Menashe I, Anderson WF, Jatoi I, Rosenberg PS. Underlying causes of the Black-White racial disparity in breast cancer mortality: a population-based analysis. *JNCI*. 2009; 101:993–1000. [PubMed: 19584327]

49. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, Malone KE. Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years. *Cancer Epidemiol Biomarkers Prev.* 2009 1055-9965.EPI-1008-1005.
50. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, Press MF, Bernstein L. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. *Cancer Res.* 2010; 70:575–587. [PubMed: 20068186]
51. Millikan R, Newman B, Tse C, Moorman P, Conway K, Dressler L, Smith L, Labbok M, Geradts J, Bensen J, Jackson S, Nyante S, Livasy C, Carey L, Earp H, Perou C. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat.* 2008; 109:123–139. [PubMed: 17578664]
52. Phipps A, Malone K, Porter P, Daling J, Li C. Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer. *Cancer.* 2008; 113:1521–1526. [PubMed: 18726992]
53. Phipps A, Malone K, Porter P, Daling J, Li C. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:2078–2086. [PubMed: 18664548]
54. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, Eley JW. The epidemiology of triple-negative breast cancer, including race. *Cancer Causes Control.* 2009; 20:1071–1082. [PubMed: 19343511]
55. Yang X, Sherman M, Rimm D, Lissowska J, Brinton L, Peplonska B, Hewitt S, Anderson W, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Cartun R, Mandich D, Rymkiewicz G, Ligaj M, Lukaszek S, Kordek R, Garcia-Closas M. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:439–443. [PubMed: 17372238]
56. Xing P, Li J, Jin F. A case-control study of reproductive factors associated with subtypes of breast cancer in Northeast China. *Med Oncol.* 2010; 27:926–931. [PubMed: 19771534]
57. Begg C, Zhang Z. Statistical analysis of molecular epidemiology studies employing case-series. *Cancer Epidemiol Biomarkers Prev.* 1994; 3:173–175. [PubMed: 8049640]
58. Martinez ME, Cruz GI, Brewster AM, Bondy ML, Thompson PA. What can we learn about disease etiology from case-case analyses? Lessons from breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:2710–2714. [PubMed: 20870734]
59. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, Lee MM, Ambrosone CB, Caan BJ. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res.* 2009; 11:R31. [PubMed: 19463150]
60. Parise C, Bauer K, Brown M, Caggiano V. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) among women with invasive breast cancer in California, 1999–2004. *Breast J.* 2009; 15:593–602. [PubMed: 19764994]
61. Stark A, Kapke A, Schultz D, Brown R, Linden M, Raju U. Advanced stages and poorly differentiated grade are associated with an increased risk of HER2/neu positive breast carcinoma only in White women: findings from a prospective cohort study of African-American and White-American women. *Breast Cancer Res Treat.* 2008; 107:405–414. [PubMed: 17431759]
62. Stark A, Schultz D, Kapke A, Nadkarni P, Burke M, Linden M, Raju U. Obesity and risk of the less commonly diagnosed subtypes of breast cancer. *Eur J Surg Oncol.* 2009; 35:928–935. [PubMed: 19121564]
63. Stead L, Lash T, Sobieraj J, Chi D, Westrup J, Charlot M, Blanchard R, Lee J, King T, Rosenberg C. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res.* 2009; 11:R18. [PubMed: 19320967]
64. Shinde SS, Forman MR, Kuerer HM, Yan K, Peintinger F, Hunt KK, Hortobagyi GN, Pusztai L, Symmans WF. Higher parity and shorter breastfeeding duration: Association with triple-negative phenotype of breast cancer. *Cancer.* 2010; 116:4933–4943. [PubMed: 20665494]
65. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, Gaudet M, Schmidt MK, Broeks A, Cox A, Fasching PA, Hein R, Spurdle AB, Blows F, Driver K, Flesch-Janys D, Heinz J, Sinn P, Vrieling A, Heikkinen T, Aittomäki K, Heikkilä P, Blomqvist C, Lissowska J,

Peplonska B, Chanock S, Figueroa J, Brinton L, Hall P, Czene K, Humphreys K, Darabi H, Liu J, Van 't Veer LJ, van Leeuwen FE, Andrulis IL, Glendon G, Knight JA, Mulligan AM, O'Malley FP, Weerasooriya N, John EM, Beckmann MW, Hartmann A, Weihbrecht SB, Wachter DL, Jud SM, Loehberg CR, Baglietto L, English DR, Giles GG, McLean CA, Severi G, Lambrechts D, Vandrope T, Weltens C, Paridaens R, Smeets A, Neven P, Wildiers H, Wang X, Olson JE, Cafourek V, Fredericksen Z, Kosel M, Vachon C, Cramp HE, Connley D, Cross SS, Balasubramanian SP, Reed MWR, Dörk T, Bremer M, Meyer A, Karstens JH, Ay A, Park-Simon T-W, Hillemanns P, Arias Pérez JI, Rodríguez PM, Zamora P, Benítez J, Ko Y-D, Fischer H-P, Hamann U, Pesch B, Brüning T, Justenhoven C, Brauch H, Eccles DM, Tapper WJ, Gerty SM, Sawyer EJ, Tomlinson IP, Jones A, Kerin M, Miller N, McInerney N, Anton-Culver H, Ziogas A, Shen C-Y, Hsiung C-N, Wu P-E, Yang S-L, Yu J-C, Chen S-T, Hsu G-C, Haiman CA, Henderson BE, Marchand L Le, Kolonel LN, Lindblom A, Margolin S, Jakubowska A, Lubinski J, Huzarski T, Byrski T, Górski B, Gronwald J, Hooning MJ, Hollestelle A, van den Ouweland AMW, Jager A, Kriege M, Tilanus-Linthorst MMA, Collée M, Wang-Gohrke S, Pykäs K, Jukkola-Vuorinen A, Mononen K, Grip M, Hirvikoski P, Winqvist R, Mannermaa A, Kosma V-M, Kauppinen J, Kataja V, Auvinen P, Soini Y, Sironen R, Bojesen SE, Ørsted D Dynnes, Kaur-Knudsen D, Flyger H, Nordestgaard BG, Holland H, Chenevix-Trench G, Manoukian S, Barile M, Radice P, Hankinson SE, Hunter DJ, Tamimi R, Sangrajrang S, Brennan P, McKay J, Odefrey F, Gaborieau V, Devilee P, Huijts PEA, Tollenaar R, Seynaeve C, Dite GS, Apicella C, Hopper JL, Hammet F, Tsimiklis H, Smith LD, Southey MC, Humphreys MK, Easton D, Pharoah P, Sherman ME, Garcia-Closas M. Associations of Breast Cancer Risk Factors With Tumor Subtypes: A Pooled Analysis From the Breast Cancer Association Consortium Studies. *Journal of the National Cancer Institute*. 2011; 103:250–263. [PubMed: 21191117]

66. Kabat G, Kim M, Phipps A, Li C, Messina C, Wactawski-Wende J, Kuller L, Simon M, Yasmeen S, Wassertheil-Smoller S, Rohan T. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. *Cancer Causes and Control*. 2011;1–9.
67. Phipps A, Buist D, Malone K, Barlow W, Porter P, Kerlikowske K, Li C. Reproductive history and risk of three breast cancer subtypes defined by three biomarkers. *Cancer Causes and Control*. 2011; 22:399–405. [PubMed: 21184265]
68. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Stefanick ML, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Vitolins M, Kabat GC, Rohan TE, Li CI. Body Size, Physical Activity, and Risk of Triple-Negative and Estrogen Receptor–Positive Breast Cancer. *Cancer Epidemiology Biomarkers & Prevention*. 2011; 20:454–463.
69. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, Li CI. Reproductive History and Oral Contraceptive Use in Relation to Risk of Triple-Negative Breast Cancer. *Journal of the National Cancer Institute*. 2011; 103:470–477. [PubMed: 21346227]
70. Phipps A, Buist D, Malone K, Barlow W, Porter P, Kerlikowske K, Li C. Family history of breast cancer in first-degree relatives and triple-negative breast cancer risk. *Breast Cancer Research and Treatment*. 2011; 126:671–678. [PubMed: 20814817]
71. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1558–1568. [PubMed: 15466970]
72. Akaike, H. 2nd International Symposium on Information Theory. Budapest: Akademiai Kiado; 1973. Information Theory and an extension of the maximum likelihood principle; p. 267-281.
73. Efron B. The Jackknife, the bootstrap, and other resampling plans Society for Industrial and Applied Mathematics, Philadelphia. 1982

Figure 1.
 Age-specific incidence rates by ERPR expression

Figure 2.
Age-specific incidence rates by ERPR expression and Race (Black-White)

Figure 3.
Cumulative and Conditional breast cancer survival

Table 1

A standard immunohistochemistry (IHC) panel for the three main clinical biomarkers ER, PR, and HER2 can approximate the four intrinsic breast cancer molecular subtypes.

<i>Breast cancer subtype</i>	<i>ER</i>	<i>PR</i>	<i>HER2</i>	<i>Triple designation</i>
Luminal A	+	±	–	ER+PR±HER2–
Luminal B	+	±	+	ER+PR±HER2+
HER2+	–	–	+	ER–PR–HER2+
Basal-like	–	–	–	ER–PR–HER2–

Table 2

Design features and population characteristics of case-control, case-case, and prospective studies examining epidemiologic risk factors for triple negative breast cancer

First author: Publication year (reference)	Country (State)	Study-design	Age range (y) or mean/median (SD) age at diagnosis	% Post- menopausal	% Invasive cases	% non- Hispanic White	Sample size			IHC markers used for subtype definitions		
							Luminal A	Triple negative	Controls	Matching factors‡	ER/PR/ HER2	HER1 /ck5
<u>Case-control studies</u>												
Ma: 2010 [50]	United States (CA and MI)	Population-based	35–64	DNS	100%	56%	645	335	2,015	1, 2, 3	Yes	No
Xing: 2010 [56]	China	Hospital-based	21–85 (cases), 30–72 (controls)	46%	100%	0%	722	327	1,587	1	Yes	No
Dolle: 2009 [49]	United States (WA)	Population-based	21–45	DNS	100%	94%	710	187	1,569	None. Adjusted for 1	Yes	No
Trivers: 2009 [54]	United States (GA)	Population-based	20–54	DNS	100%	74%	272	135	913	None. Adjusted for 1, 2	Yes	No
Phipps: 2008 –I [53]†	United States (WA)	Population-based	55–74	100%	100%	92%	1,008	77	1,447	1	Yes	No
Phipps: 2008 –2 [52]†	United States (WA)	Population-based	55–74	100%	100%	92%	1,023	78	1,476	1	Yes	No
Millikan: 2008 [51]	United States (NC)	Population-based	20–74	57%	78%	61%	796	225	2,022	1, 2	No	Yes
Yang: 2007 [55]	Poland	Population-based	20–74	67%	100%	100%	552	95	2,502	1, 3	No	Yes
<u>Case-case studies</u>												
Yang: 2011 [65]	International consortium	Pooled analysis of 34 studies	18+	DNS	100%	92% of European ancestry	9,534	1,997	N/A	N/A	Yes	No
Shinde: 2010 [64]	United States (TX)	Hospital-based case series	DNS	67%	100%	73%	1,616	468	N/A	N/A	Yes	No
Kwan: 2009 [59]	United States (CA and UT)	Pooled analysis of two cohort studies of breast cancer survivors	18+	66%	100%	76%	1,868	288	N/A	N/A	Yes	No
Parise: 2009 [60]	United States (CA)	Population-based state cancer registry	DNS	DNS	100%	71%	34,646	7,370	N/A	N/A	Yes	No
Stark: 2009 [62]*	United States (MI)	HMO-based case series	Mean (SD) age at diagnosis = 61.5 (13.7)	78%	100%	61%	711	285	N/A	N/A	Yes	No
Stead: 2009 [63]	United States (MA)	Hospital-based case series	Median age at diagnosis = 58 years	DNS	100%	36%	DNS	81	N/A	N/A	No	Yes
Trivers: 2009 [54]	United States (GA)	Population-based case-control	20–54	DNS	100%	76%	272	135	N/A	N/A	Yes	No
Millikan: 2008 [51]	United States (NC)	Population-based case-control	20–74	55%	78%	59%	796	225	N/A	N/A	No	Yes
Stark: 2008 [61]*	United States (MI)	HMO-based case series	Mean (SD) age at diagnosis = 61.8 (13.8)	78%	100%	65%	733	225	N/A	N/A	Yes	No

First author; Publication year (reference)	Country (State)	Study-design	Age range (y) or mean/median (SD) age at diagnosis	% Post- menopausal	% Invasive cases	% non- Hispanic White	Sample size			IHC markers used for subtype definitions		
							Luminal A	Triple negative	Controls	Matching factors [‡]	ER/PR/ HER2	ER/PR /HER1 /ck5
<i>Prospective studies</i>												
Kabat: 2011 [66] [‡]	United States (Multi-center)	Prospective clinical trial and observational study	50–79	100%	100%	84%	2,479	300	145,251	N/A	Yes	No
Phipps: 2011 - 1 [67] [‡]	United States (Multi-center)	Mammography registries	40–84	DNS	100%	74%	8,203	645	732,727	N/A	Yes	No
Phipps: 2011 - 2 [69] [‡]	United States (Multi-center)	Prospective clinical trial and observational study	50–79	100%	100%	86%	2,610	307	150,529	N/A	Yes	No
Phipps: 2011 - 3 [68] [‡]	United States (Multi-center)	Prospective clinical trial and observational study	50–79	100%	100%	82%	2,610	307	150,705	N/A	Yes	No
Phipps: 2011 - 4 [70] [‡]	United States (Multi-center)	Mammography registries	40–84	DNS	100%	74%	10,026	705	1,043,427	N/A	Yes	No

DNS, data not shown; IHC, immunohistochemistry; N/A, not applicable; SD, standard deviation

[‡]*[‡]€ Same study populations

[‡] Matching factors coded as follows: 1=age, 2=race, 3=study site/city

[‡] Prospective studies did not distinguish between luminal A and luminal B breast cancers

Table 3

Odds ratios and 95% confidence intervals from case-control studies of luminal A (ER+PR±HER2-) and triple negative (ER-PR-HER2-) breast cancers

<i>Risk factor</i>	<i>Comparison</i>	<i>Luminal A</i>	<i>Triple negative</i>	<i>References</i>
Age at diagnosis	20–39 vs. 50+	0.80 (0.58–1.12)	1.77 (1.18–2.64)	Trivers et al. (2009)
	40–49 vs. 50+	1.05 (0.81–1.37)	1.14 (0.78–1.65)	Trivers et al. (2009)
	40–45 vs. <30 yrs		2.2 (0.7–7.4)	Dolle et al. (2009)
Race/ethnicity	Black vs. white	0.73 (0.56–0.95)	2.41 (1.81–3.21)	Trivers et al. (2009)
Family history	First-degree relative vs. none		3.5 (2.1–5.9)	Dolle et al. (2009)
	First-degree relative vs. none	2.24 (1.35–3.72)	1.53 (0.75–3.15)	Xing et al. (2010)
	First-degree relative vs. none	1.72 (1.21–2.45)	3.17 (1.69–5.92)	Yang et al. (2007)
Education	<College grad vs. college grad+	0.68 (0.54–0.86)	0.93 (0.69–1.26)	Trivers et al. (2009)
	College grad vs. <college grad		1.3 (0.9–2.0)	Dolle et al. (2009)
Body mass index (BMI) [‡]	BMI overall		1.3 (0.8–2.2)	Dolle et al. (2009)
	30+ vs. <25	0.58 (0.43–0.78)	1.25 (0.87–1.79)	Trivers et al. (2009)
	30+ vs. <25	0.8 (0.6–1.0)	0.8 (0.6–1.2)	Millikan et al. (2008)
BMI premenopausal	30+ vs. <25	0.7 (0.5–1.0)	1.0 (0.6–1.8)	Millikan et al. (2008)
	Per 5 unit increase	0.71 (0.57–0.88)	1.18 (0.86–1.64)	Yang et al. (2007)
BMI postmenopausal	30+ vs. <25	0.8 (0.6–1.1)	0.6 (0.3–1.1)	Millikan et al. (2008)
	30+ vs. <25	1.1 (0.9–1.3)	1.4 (0.8–2.5)	Phipps et al. (2008) - 1
	Per 5 unit increase	1.00 (0.90–1.12)	0.87 (0.66–1.14)	Yang et al. (2007)
Alcohol	3+ drinks/week vs. none/<1		1.1 (0.7–1.6)	Dolle et al. (2009)
	7+ drinks/week vs. none	1.86 (1.34–2.60)	1.22 (0.79–1.89)	Trivers et al. (2009)
Age at menarche	<12 vs. 12+	1.09 (0.84–1.42)	1.60 (1.17–2.19)	Trivers et al. (2009)
	13–14 vs. 8–12 years		0.8 (0.6–1.2)	Dolle et al. (2009)
	15+ vs. 8–12 years		0.4 (0.2–1.0)	Dolle et al. (2009)
	13+ vs. <13 years	1.1 (0.9–1.3)	1.4 (1.1–1.9)	Millikan et al. (2008)
	13+ vs. <13 years	1.0 (0.9–1.2)	1.1 (0.7–1.7)	Phipps et al. (2008) - 2
	13+ vs. <13 years	2.35 (1.45–3.81)	1.55 (0.79–3.03)	Xing et al. (2010)
	per 2 year increase	0.90 (0.95–1.08)	0.78 (0.68–0.89)	Yang et al. (2007)
Oral contraceptives	Ever vs. never	0.93 (0.74–1.17)	1.00 (0.72–1.39)	Ma et al. (2010)
	1+ months vs. never/<1 month		2.5 (1.4–4.3)	Dolle et al. (2009)
	<40 yrs: 1+ months vs. never/<1 month		4.2 (1.9–9.3)	Dolle et al. (2009)

<i>Risk factor</i>	<i>Comparison</i>	<i>Luminal A</i>	<i>Triple negative</i>	<i>References</i>
Parity	40+ yrs: 1+ months vs. never/<1 month		0.9 (0.4–2.2)	Dolle et al. (2009)
	44 yrs: Ever vs. never	0.97 (0.57–1.64)	0.72 (0.42–1.24)	Ma et al. (2010)
	45+ yrs: Ever vs. never	0.92 (0.71–1.20)	1.25 (0.83–1.88)	Ma et al. (2010)
	Parous vs. nulliparous	0.8 (0.6–1.0)	1.1 (0.5–2.3)	Phipps et al. (2008) - 2
	2+ vs. none	0.42 (0.21–0.84)	1.80 (0.37–8.85)	Yang et al. (2007)
	3+ vs. none	0.7 (0.5–0.9)	1.9 (1.1–3.3)	Millikan et al. (2008)
	3+ vs. none	1.64 (0.74–3.62)	3.02 (0.99–9.17)	Xing et al. (2010)
	3+ vs. one	0.8 (0.6–1.1)	0.8 (0.3–1.7)	Phipps et al. (2008) - 2
	4+ vs. none	0.28 (0.17–0.46)	0.62 (0.36–1.07)	Trivers et al. (2009)
	4+ vs. none		0.6 (0.2–1.9)	Dolle et al. (2009)
	4+ vs. none	0.55 (0.38–0.79)	1.00 (0.60–1.67)	Ma et al. (2010)
	44 yrs: 4+ vs. none	0.56 (0.26–1.17)	0.76 (0.35–1.67)	Ma et al. (2010)
	45+ yrs: 4+ vs. none	0.56 (0.36–0.86)	1.48 (0.68–3.21)	Ma et al. (2010)
	Age at 1st birth			
Age at 1st birth	18+ vs. none	0.75 (0.57–1.00)	0.79 (0.55–1.14)	Trivers et al. (2009)
	26+ vs. none	0.9 (0.6–1.2)	1.5 (0.8–2.8)	Millikan et al. (2008)
	30+ vs. none		1.2 (0.5–3.0)	Dolle et al. (2009)
	30+ vs. 19	1.03 (0.67–1.57)	1.32 (0.80–2.17)	Ma et al. (2010)
	30+ vs. 20	1.2 (0.8–1.7)	0.7 (0.2–2.3)	Phipps et al. (2008) - 2
	30+ vs. 24	0.96 (0.67–1.40)	0.74 (0.42–1.29)	Xing et al. (2010)
	44 yrs: 30+ vs. 19	0.92 (0.45–1.90)	1.43 (0.66–3.09)	Ma et al. (2010)
	45+ yrs: 30+ vs. 19	1.22 (0.71–2.09)	1.41 (0.71–2.80)	Ma et al. (2010)
	Per 5-year increase	1.08 (0.95–1.23)	0.95 (0.71–1.27)	Yang et al. (2007)
	Breastfeeding			
	Ever vs. never	0.90 (0.72–1.13)	0.84 (0.62–1.13)	Trivers et al. (2009)
	Ever vs. never	0.44 (0.31–0.63)	0.48 (0.30–0.77)	Xing et al. (2010)
	Ever vs. never	0.9 (0.7–1.0)	0.7 (0.5–1.0)	Millikan et al. (2008)
	4 months vs. never	0.9 (0.7–1.1)	0.7 (0.4–0.9)	Millikan et al. (2008)
Breastfeeding	6 months vs. never	0.8 (0.6–1.0)	0.5 (0.3–0.9)	Phipps et al. (2008) - 2
	12+ months vs. never	0.68 (0.48–0.96)	0.53 (0.32–0.85)	Trivers et al. (2009)
	12+ months vs. never		1.0 (0.6–1.7)	Dolle et al. (2009)
	7–23 months vs. never	0.78 (0.58–1.05)	0.58 (0.38–0.89)	Ma et al. (2010)
	44 yrs: 7–23 months vs. never	0.60 (0.34–1.05)	0.45 (0.24–0.87)	Ma et al. (2010)
	45+ yrs: 7–23 months vs. never	0.86 (0.60–1.23)	0.60 (0.34–1.07)	Ma et al. (2010)
	Menopausal status			
	Post- vs. premenopause	0.72 (0.55–0.94)	0.89 (0.62–1.28)	Xing et al. (2010)
	Age at menopause			
	55 vs. <45	1.6 (1.1–2.2)	1.2 (0.5–3.0)	Phipps et al. (2008) - 2
	55 vs. <45	1.76 (0.83–3.75)	2.24 (0.77–6.54)	Xing et al. (2010)
	Per 5-year increase	1.13 (1.01–1.28)	1.02 (0.82–1.28)	Yang et al. (2007)
	Type of menopause			

<i>Risk factor</i>	<i>Comparison</i>	<i>Luminal A</i>	<i>Triple negative</i>	<i>References</i>
Menopausal hormone therapy	BSO vs. natural	0.7 (0.6–0.9)	0.8 (0.4–1.6)	Phipps et al. (2008) - 2
	TAH vs. natural	0.8 (0.7–1.0)	1.3 (0.7–2.1)	Phipps et al. (2008) - 2
	Former vs. never	1.0 (0.8–1.3)	0.8 (0.4–1.6)	Phipps et al. (2008) - 2
	Current ET vs. never	0.9 (0.7–1.1)	0.7 (0.4–1.4)	Phipps et al. (2008) - 2
	Current EPT vs. never	1.7 (1.3–2.1)	0.6 (0.3–1.3)	Phipps et al. (2008) - 2

[‡]BMI, body mass index in kg/m²

Table 4

Odds ratios and 95% confidence intervals from case-case studies of triple negative (ER–PR–HER2–) breast cancers

<i>Risk factor</i>	<i>Comparison</i>	<i>Comparison group</i>	<i>Triple negative</i>	<i>References</i>
Age at diagnosis	20–39 vs. 50+	Luminal A	2.13 (1.34–3.39)	Trivers et al. (2009)
	40–49 vs. 50+	Luminal A	1.09 (0.72–1.64)	Trivers et al. (2009)
	40 vs. >60	Luminal A	4.2 (2.76–6.39)	Shinde et al. (2010)
	40–59 vs. >60	Luminal A	1.54 (1.16–2.04)	Shinde et al. (2010)
	<40 vs. 60+	Luminal A	4.5 (2.7–7.3)	Millikan et al. (2008)
	40–49 vs. 60+	Luminal A	2.6 (1.7–3.9)	Millikan et al. (2008)
	50–59 vs. 60+	Luminal A	1.8 (1.1–2.8)	Millikan et al. (2008)
	<50 vs. 65+	Luminal A	2.78 (1.99–3.90)	Kwan et al. (2009)
	50–64 vs. 65+	Luminal A	1.99 (0.85–1.62)	Kwan et al. (2009)
	Age in decades	Luminal A	0.84 (0.74–0.95)	Stark et al. (2009)
	50 vs. 50+	All other subtypes	1.21 (1.14–1.29)	Parise et al. (2009)
	50 vs. 50+	All other subtypes	1.40 (0.81–2.4)	Stead et al. (2009)
Race/ethnicity	Black vs. white	Luminal A	2.17 (1.54–3.05)	Shinde et al. (2010)
	Black vs. white	Luminal A	3.14 (2.12–4.66)	Kwan et al. (2009)
	Black vs. white	Luminal A	2.98 (2.12–4.20)	Trivers et al. (2009)
	Black vs. white	Luminal A	2.1 (1.6–2.9)	Millikan et al. (2008)
	Black vs. white	Luminal A	1.72 (1.17–2.54)	Stark et al. (2008)
	Hispanic vs. non-Hispanic white	Luminal A	1.04 (0.71–1.51)	Shinde et al. (2010)
	Hispanic vs. non-Hispanic white	Luminal A	0.93 (0.57–1.53)	Kwan et al. (2009)
	Asian vs. white	Luminal A	0.69 (0.35–1.36)	Shinde et al. (2010)
	Asian vs. white	Luminal A	0.53 (0.28–0.97)	Kwan et al. (2009)
	Black vs. white	All other subtypes	3.0 (1.6–5.4)	Stead et al. (2009)
	Black vs. white	All other subtypes	1.88 (1.69–2.09)	Parise et al. (2009)
	Hispanic vs. white	All other subtypes	0.83 (0.28–2.4)	Stead et al. (2009)
	Hispanic vs. non-Hispanic white	All other subtypes	1.19 (1.10–1.29)	Parise et al. (2009)
	Asian/Pacific Islander vs. white	All other subtypes	0.81 (0.74–0.90)	Parise et al. (2009)
Family history	First-degree relative vs. none	Luminal A	0.95 (0.69–1.29)	Kwan et al. (2009)
	First-degree relative vs. none	Luminal A	1.0 (0.7–1.5)	Millikan et al. (2008)
Education				
	<College grad vs. college grad+	Luminal A	1.35 (0.97–1.89)	Trivers et al. (2009)
Body mass index (BMI) [‡]				
	BMI overall			
	30+ vs. <25	Luminal A	1.04 (0.75–1.45)	Kwan et al. (2009)
	30+ vs. <25	Luminal A	0.67 (0.44–1.02)	Stark et al. (2009)
	30+ vs. <25	Luminal A	1.89 (1.22–2.92)	Trivers et al. (2009)
	30+ vs. <25	Luminal A	1.3 (0.8–1.9)	Millikan et al. (2008)

<i>Risk factor</i>	<i>Comparison</i>	<i>Comparison group</i>	<i>Triple negative</i>	<i>References</i>
BMI premenopausal	30–34.9 vs. <25	All other subtypes	0.69 (0.33–1.5)	Stead et al. (2009)
	30+ vs. <25	Luminal A	1.80 (1.42–2.29)	Yang et al. (2011)
	30+ vs. <25	Luminal A	1.97 (1.03–3.77)	Kwan et al. (2009)
	30+ vs. <25	Luminal A	1.6 (0.9–2.7)	Millikan et al. (2008)
BMI postmenopausal	30+ vs. <25	Luminal A	1.09 (0.91–1.29)	Yang et al. (2011)
	30+ vs. <25	Luminal A	0.76 (0.49–1.17)	Kwan et al. (2009)
	30+ vs. <25	Luminal A	1.0 (0.5–1.7)	Millikan et al. (2008)
Alcohol	Ever vs. never	Luminal A	0.98 (0.73–1.30)	Kwan et al. (2009)
	Ever vs. never	Luminal A	0.9 (0.6–1.2)	Millikan et al. (2008)
	7+ drinks/week vs. none	Luminal A	0.72 (0.44–1.17)	Trivers et al. (2009)
Age at menarche	12 vs. 15	Luminal A	1.08 (0.92–1.28)	Yang et al. (2011)
	<12 vs. 12+	Luminal A	1.55 (1.08–2.23)	Trivers et al. (2009)
	<13 vs. 13+	Luminal A	1.3 (0.9–1.7)	Millikan et al. (2008)
Oral contraceptives	Ever vs. never	Luminal A	0.97 (0.72–1.31)	Kwan et al. (2009)
	Ever vs. never	Luminal A	0.9 (0.6–1.3)	Millikan et al. (2008)
Parity	Nulliparous vs. parous	Luminal A	0.69 (0.59–0.81)	Yang et al. (2011)
	3+ vs. none	Luminal A	2.97 (1.98–4.46)	Shinde et. al. (2010)
	3+ vs. none	Luminal A	1.18 (0.81–1.72)	Kwan et al. (2009)
	3+ vs. none	Luminal A	1.7 (1.0–2.9)	Millikan et al. (2008)
	4+ vs. none	Luminal A	2.40 (1.24–4.64)	Trivers et al. (2009)
Age at 1st birth	18+ vs. none	Luminal A	0.99 (0.67–1.48)	Trivers et al. (2009)
	26+ vs. none	Luminal A	0.93 (0.63–1.38)	Kwan et al. (2009)
	26+ vs. none	Luminal A	1.2 (0.7–2.1)	Millikan et al. (2008)
	Per 5-year increase	Luminal A	0.89 (0.83–0.95)	Yang et al. (2011)
Breastfeeding	Ever vs. never	Luminal A	0.97 (0.69–1.36)	Trivers et al. (2009)
	>2 months vs. never	Luminal A	0.56 (0.41–0.76)	Shinde et. al. (2010)
	4 months vs. never	Luminal A	0.78 (0.59–1.03)	Kwan et al. (2009)
	4 months vs. never	Luminal A	0.7 (0.5–1.1)	Millikan et al. (2008)
	12+ months vs. never	Luminal A	0.83 (0.48–1.43)	Trivers et al. (2009)
Menopausal status	Pre- vs. postmenopause	Luminal A	0.84 (0.55–1.27)	Kwan et al. (2009)
	Pre- vs. postmenopause	Luminal A	1.94 (1.27–2.96)	Stark et al. (2008)
	Pre- vs. postmenopause	Luminal A	0.8 (0.5–1.3)	Millikan et al. (2008)
Menopausal hormone therapy				

<i>Risk factor</i>	<i>Comparison</i>	<i>Comparison group</i>	<i>Triple negative</i>	<i>References</i>
	Ever vs. never	Luminal A	0.83 (0.57–1.20)	Kwan et al. (2009)
	Ever vs. never	Luminal A	0.8 (0.5–1.3)	Millikan et al. (2008)

[‡]BMI, body mass index in kg/m²; Yang et al. (2011) reported BMI associations for women 50 years of age (reported here as “premenopausal” BMI) and women > 50 years of age (reported here as “postmenopausal” BMI).

Table 5

Relative risks and 95% confidence intervals from prospective studies of luminal and triple negative (ER–PR–HER2–) breast cancers

<i>Risk factor</i>	<i>Comparison</i>	<i>Luminal*</i>	<i>Triple negative</i>	<i>References</i>
Family history				
	First-degree relative vs. none	1.62 (1.54–1.70)	1.73 (1.43–2.09)	Phipps et al. (2011) - 4
Body mass index (BMI) [‡] postmenopausal				
	30+ vs. <25	1.35 (1.20–1.51)	1.37 (0.98–1.93)	Phipps et al. (2011) - 3
Alcohol				
	7+ drinks/week vs. none	1.26 (1.06–1.50)	0.57 (0.34–0.95)	Kabat et al. (2011)
Age at menarche				
	14+ vs. <12 years	0.89 (0.79–1.00)	0.96 (0.67–1.39)	Phipps et al. (2011) - 2
Oral contraceptives				
	10+ years vs. never	0.80 (0.68–0.94)	1.11 (0.72–1.70)	Phipps et al. (2011) - 2
Parity				
	Nulliparous vs. parous	1.31 (1.23–1.39)	1.07 (0.87–1.33)	Phipps et al. (2011) - 1
	Nulliparous vs. parous	1.35 (1.20–1.52)	0.61 (0.37–0.97)	Phipps et al. (2011) - 2
	3+ vs. 1	0.88 (0.74–1.04)	1.46 (0.82–2.63)	Phipps et al. (2011) - 2
Age at 1st birth				
	30+ vs. <20	1.36 (1.10–1.67)	1.05 (0.53–2.06)	Phipps et al. (2011) - 2
	30+ vs. <30	1.37 (1.28–1.47)	1.18 (0.93–1.51)	Phipps et al. (2011) - 1
Breastfeeding				
	12+ months vs. never	0.98 (0.85–1.13)	0.81 (0.53–1.26)	Phipps et al. (2011) - 2
Age at menopause				
	55 vs. 45–54	1.13 (1.00–1.27)	1.02 (0.68–1.52)	Phipps et al. (2011) - 1

* ER+ breast cancers; these studies did not distinguish between luminal A and luminal B breast cancers.

[‡] BMI, body mass index in kg/m²