Title: Risk Factors for Triple-Negative Breast Cancer in Women Under Age 45

Authors: Jessica M. Dolle, MPH,[1] Janet R. Daling, PhD,[1] Emily White, PhD,[1,3] Louise A. Brinton, MPH, PhD,[4] David R. Doody, MS,[1] Peggy L. Porter, MD,[2] Kathleen E. Malone, MPH, PhD[1,3]

Author affiliations: Divisions of Public Health Sciences[1] and Human Biology[2], Fred Hutchinson Cancer Research Center, Seattle, Washington; Department of Epidemiology[3], University of Washington, Seattle; Division of Cancer Epidemiology and Genetics[4], National Cancer Institute, Rockville, Maryland

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Request for reprints: Kathleen E. Malone, PhD
Fred Hutchinson Cancer Research Center
P.O. Box 19024, M4-C308
Seattle, Washington 98109-1024
United States
Tel: 206-667-4632
Fax: 206-667-5948
Email: kmalone@fhcrc.org

ABSTRACT

Little is known about the etiologic profile of triple-negative breast cancer (TNBC; ER-/PR-/HER2-), a breast cancer subtype associated with high mortality and inadequate therapeutic options. We undertook the study to assess the risk of TNBC among women 45 years of age and younger in relation to demographic/lifestyle factors, reproductive history, and oral contraceptive (OC) use. Study participants were ascertained in two prior population-based, case-control studies. Eligible cases included all primary invasive breast cancers among women ages 20-45 in the Seattle-Puget Sound area, diagnosed between January 1983 and December 1992 for whom complete data was obtained for ER, PR and HER2 status (n=897; including n=187 TNBC cases). Controls were age matched and ascertained via random digit dialing. OC use ≥1 year was associated with a 2.5-fold increased risk of TNBC (95% CI 1.4-4.3) and no significantly increased risk of non-TNBC ($P_{heterogeneity}$ .008). Further, the risk among OC users conferred by longer OC duration and by more recent use was significantly greater for TNBC than non-TNBC ($P_{heterogeneity}$ .02 and .01, respectively). Among women ≤40 years, the relative risk of TNBC associated with OC use ≥1 year was 4.2 (95% CI 1.9-9.3), whereas there was no significantly increased risk with OC use for non-TNBC among women ≤40 years, nor for TNBC or non-TNBC among women 41-45 years of age. In conclusion, significant heterogeneity exists for the association of OC use and breast cancer risk between TNBC and non-TNBC among young women, lending support to a distinct etiology.

INTRODUCTION

Breast cancer is a strikingly heterogeneous disease with variable clinical, pathologic, and molecular features. Microarray expression patterns and immunohistochemical signatures can distinguish breast cancer subtypes and likely reflect important differences in pathogenesis and etiology (1-4). Current breast cancer treatment strategies rely on the characterization of estrogen and progesterone hormone receptor (ER/PR) protein expression status and more recently, on human epidermal growth factor (HER2) protein expression or gene amplification. Breast tumors that fail to express ER/PR and HER2 (triple-negative breast cancer, or TNBC) account for 10-17% of all breast cancers (5-12).

Recently, five distinct gene expression profile-based 'intrinsic' subtypes were identified by cDNA microarray analysis, two derived from ER-positive subtypes (luminal A and B) and three from ER-negative subtypes (HER2-positive, basal-like and normal-like) (1, 2, 13). Over 90% of TNBC tumors fall within the basal-like subgroup, so called for its gene expression profile that mimics basal epithelial cells in other parts of the body (usually identified by immunohistochemical staining for the expression of cytokeratin 5/6, reduced ER/PR and HER2 expression), and a characteristic morphology that includes high proliferative rate, central necrosis, and a pushing border (14, 15). Basal-like breast cancer is associated with aggressive histology, unresponsiveness to typical endocrine therapies, poor prognosis, and BRCA1-related breast cancer (1-3, 16).

TNBC constitutes a clinically challenging type of breast cancer that occurs more frequently in younger women (<50 years) (6, 7, 9, 10) and African American women (10-12), and is associated with significant aggressiveness as compared to other subtypes (5-7, 9-11). Although TNBC is of growing interest in the clinical and research community, its etiology remains understudied. We undertook this study to evaluate the contribution of known and suspected breast cancer risk factors to TNBC in a large population-based study.

METHODS

The cases included in this study were originally ascertained for two prior studies through the population-based Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry. Eligible cases from the first study population included all primary, invasive breast cancers within the three county Seattle metropolitan area, diagnosed between January 1, 1983 and April 30, 1990, ages 21-45. The methods for this study have been described elsewhere (17, 18). The study was confined to Caucasians because of the small representation of minorities in the region. Of 898 eligible invasive cases, 744 (83%) were interviewed. Nine hundred and sixty-one controls were interviewed, representing a 76% overall response rate (97% of dialed known residential households successfully screened; 78% interviewed). For both studies, controls were identified by random digit dialing (RDD) and frequency matched to cases by 5-year age groups.

The second population included the Seattle site participants of the multicenter Women's Interview Study of Health (WISH), the methods for which have been described (19). Eligible cases included women in the Seattle area diagnosed with invasive breast cancer between May 1, 1990 and December 31, 1992, ages 20-44 years. In-person interviews were completed on 542 women (86% of eligible Seattle cases with invasive disease). Six hundred and eight Seattle controls were interviewed, representing a 71% overall response rate (90% of dialed known residential households successfully screened; 78% interviewed). Reference dates were assigned to all participants: age at diagnosis for cases and an assigned age for each control to result in an approximately similar age distribution for cases and controls. Because the present study focuses on invasive TNBC, in situ cases were excluded. The appropriate institutional review boards approved all protocols.

In-person interviews of comparable format, covering a broad range of risk factors that included lifestyle/demographic factors, reproductive history, and oral contraceptive (OCs) use, were administered to participants in both studies. Tumor specimens were obtained for 1019 of the 1286 cases with invasive breast cancer who were accrued in the two previous studies. Tissue collection, pathology review, and testing for prognostic markers have been discussed previously (20). Briefly, tumor tissue was sufficient for immunoperoxidase (IHC) assay on 907 (89.0%) of the tumors. Antibody staining for ER, PR, and HER2 was assessed as negative, 1+ (low positive), 2+ (intermediate positive) or 3+ (high positive). Scores above negative were considered positive for ER and PR. A distinct membranous staining pattern above 1+ (low-positive) was considered positive for HER2. The current study is restricted to cases for whom complete ER, PR, and HER2 results were obtained (n=897).

Breast cancer risk factors were evaluated according to ER, PR and HER2 status. Classification by these three markers results in eight different subtype combinations, however, our analyses focus primarily on comparisons between TNBC (n=187 [20.8%]) and non-TNBC tumors, due in part to the small number of observations with dissimilar ER/PR status in our study population (e.g. ER+/PR-/HER2-, n=57 [6.4%]; ER-/PR+/HER2-, n=65 [7.2%]; ER+/PR-/HER2+, n=23 [2.6%]; ER-/PR+/HER2+, n=26 [2.9%]).

Secondary analyses focus on OC variables and breast cancer defined separately and jointly by ER and HER2 status (collapsed across PR status; ER/PR correlation coefficient r=.60), and also stratifed by age (≤40 and 41-44), allowing us to determine whether one or two marker classification methods produced associations similar to that of TNBC, and compare results with previous ER and HER2 findings. Further, analyses were repeated stratified by source study and also restricted to participants with reference dates after 1985 (the latter due to an ascertainment delay for women with a reference date prior to the study's start in 1986).

Unordered polytomous logistic regression (STATA mlogit; StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX) was used to determine odds ratios (OR; as an approximation of the relative risk) and 95 percent confidence intervals (CI) for the risk of TNBC and non-TNBC, as well as for ER and HER2 defined breast cancer. The following known and suspected breast cancer risk factors

were examined separately as potential confounders for the main effects of all other risk factors, in age-adjusted models: age (at reference), race, education, annual income, family history of breast cancer, body mass index (BMI; kg/m^2) one year prior to reference, smoking history, alcohol consumption, age at menarche, number of live births, age at first birth (still or live), lactation history (among parous women), abortion history (among gravid women), and OC use (never/<1 year versus ≥1 year, OC duration, age at first use, years since first use, and years since last use). Those variables that produced a 10% or greater change in the OR for any TNBC risk factor were considered as adjustment factors in the final model. All final risk estimates are adjusted for age, family history, lactation history, and OC duration (i.e. multivariate-adjusted). Trend tests for ordered categorical exposure variables were performed by including a single grouped linear variable in the polytomous logistic regression model. We excluded nulliparous women from the trend test for age at first birth to evaluate whether an association with breast cancer risk existed beyond the effect of parity alone. To explore whether characteristics of OC use were associated with breast cancer risk beyond any effect of never/<1 year versus ≥1 year use, we tested the trend of OC duration, age at first use, years since first use, and years since last use among the OC users (≥1year) only.

Odds ratio heterogeneity between tumor subtypes was evaluated by logistic regression restricted to cases. For ordered categorical exposure variables, the $P_{heterogeneity}$ value was based on the significance of a linear trend variable; for age at first birth and the characteristics of OC use, $P_{heterogeneity}$ was limited to parous women and OC users ≥1 year, respectively. For dichotomous and nominal exposure variables, $P_{heterogeneity}$ was derived from the significance of removing the variable from models based on log-likelihood ratio tests.

RESULTS

In analyses of all 897 breast cancer cases (subtypes combined), the multivariate-adjusted odds ratios for examined risk factors were consistent with the effects observed in prior studies of younger women (Table 1). Specifically, older age, family history of breast cancer, earlier menarche age, induced abortion, and OC use were associated with an increased risk of breast cancer. Risk was decreased in relation to greater number of births and younger age at first birth. OC use ≥1 year was associated with a modest increased risk of breast cancer, and among OC users only, earlier age at first use further elevated the risk.

Upon examination of the same risk factors in cases with (n=187) and without (n=710) TNBC (Table 1), we found that OC use ≥1 year ($P_{heterogeneity}$ .008), OC duration ($P_{heterogeneity}$ .02), and years since last OC use ($P_{heterogeneity}$ .01) conferred significantly different risk estimates by case group, and BMI ≥30 k/m^2 was associated with a borderline significant increased risk of TNBC (OR 1.3, 95% CI 0.8-2.2) and a non-significant decreased risk of non-TNBC (OR 0.8, 95% CI 0.6-1.2) in women of all ages. Upon restriction to women ages 41-45, the risk of TNBC in relation to BMI ≥30 k/m^2 was further elevated (OR 2.2, 95% CI .9-5.24) while that of non-TNBC did not change substantively (OR 0.9, 95% CI 0.5-1.6; results not presented). OC use ≥1 year was associated with a 2.5-fold increased risk of TNBC (95% CI 1.4-4.3) and no significantly increased risk of non-TNBC. Among OC users, risk of TNBC increased with longer duration of OC use (P_{trend} .05) and fewer years since last OC use (P_{trend} .04), relationships that were absent for non-TNBC. We attempted to disentangle the effect of OC duration versus recency via stratified and adjusted polytomous logistic regression analyses, and found that neither risk factor was a more important determinant of risk.

We also examined the effect of OC variables across HER2 and ER defined breast cancer risk to evaluate the influence of each marker separately (Table 2). We found a 2-fold increased risk of ER-negative breast cancer conferred by OC use ≥1 year (OR 2.0, 95% CI 1.3-2.9), which differed significantly from the absence of an association with ER-positive breast cancer (OR 1.1, 95% CI 0.8-1.4; $P_{heterogeneity}$ .005), as did the risk conferred by OC duration ($P_{heterogeneity}$ .004) and years since last use

($P_{heterogeneity}$ <.001). The risk of ER-negative breast cancer increased substantially with longer OC duration (P_{trend} .05) and recency of use (P_{trend} .02). For all aspects of OC use, risk estimates were far greater for ER- breast cancer than for HER2- breast cancer.

Ever use of OCs was associated with a modest increased risk of HER2-negative disease (OR 1.4, 95% CI 1.1-1.9) and a lower non-statistically significant risk of HER2-positive disease (OR 1.2, 95% CI 0.8-1.7). No significant trends across OC use features were observed in relation to the risk of HER2-negative breast cancer, but risk of HER2-positive disease did appear to increase with younger age at first use (P_{trend} .05). Heterogeneity between HER2 subtypes was not statistically significant for any OC use variable.

Upon further cross-classification by both ER and HER2 (Table 3), we observed significantly elevated risk of breast cancer across all OC variables consistently and almost exclusively in the ER-/HER2- subset; ORs were comparable, only slightly less than those seen in relation to the risk of TNBC. The risk of ER-/HER2- breast cancer increased with longer OC duration (P_{trend} .03) and fewer years since last OC use (P_{trend} .04). We observed a large degree of heterogeneity between HER2-negative ER subtypes according to OC use ≥ 1 year ($P_{heterogeneity}$ .01), as well as OC duration ($P_{heterogeneity}$ <.001) and years since last use ($P_{heterogeneity}$ <.001).

Finally, we examined the effect of OC use according to TNBC status stratified by age at breast cancer diagnosis ≤40 and 41-45 years (Table 4). Among women 41 to 45 years of age, there was no significantly increased risk of breast cancer for any aspect of OC use, overall and within TNBC-defined subgroups, however we did find significant heterogeneity between the risk of TNBC and non-TNBC according to years since last use ($P_{heterogeneity}$ .01). Among TNBC cases ≤40 years of age, all risk estimates for OC use variables were approximately two times greater than those in the combined TNBC age group estimates. In women ≤40 years of age, OC use ≥1 year was associated with an over 4-fold increased risk of TNBC (OR 4.2, 95% CI 1.9-9.3) and no increased risk of non-TNBC (OR 1.2, 95% CI 0.9-1.7; $P_{heterogeneity}$ <.001). Also among women ≤40 years of age, we found that the risk of breast cancer overall and of non-TNBC increased with younger age at first use (P_{trend} .02 and .04 respectively).

Results did not vary substantively when examined separately by original study source or in those with a reference year after 1985. Characteristics of the women from whom we were able to obtain sufficient tissue for tumor marker assays differed on a number of factors from those of women for whom we were unable to obtain tissue (data not presented). The women whose tumors were not tested were younger, more likely to be white, and more likely to have a low annual income. AJCC stage and tumor grade did not differ significantly between the tumors available for assay and those unavailable.

DISCUSSION

In this population-based study of breast cancer in women under 45 years of age, the risk conferred by OC use varied significantly between TNBC and non-TNBC. OC use ≥1 year was associated with a 2.7-fold increased risk of TNBC. The risk of TNBC was further heightened in relation to longer OC duration and fewer years since last use. Among women ≤40 years the strength of the OC use association with TNBC was further magnified. Similar relationships were not observed in relation to non-TNBC, providing support for an etiologic distinction.

The relationship between OC use and breast cancer risk has been the subject of extensive research (17, 19, 21-23). Unlike well-established risk factors such as family history, early menarche, nulliparity, and lack of breastfeeding (24-27), the relationship between OC use and breast cancer risk has remained less clear. A large pooled analysis (28) and recent meta-analysis (29) have both reported an increased risk of breast cancer (approximately 20-30%) in relation to OC use among premenopausal women. Previous studies have also shown risk in relation to OC use to be concentrated among younger premenopausal women (30, 31). These findings are compatible with the present study and consistent with our prior reports on OC use effects in the two study populations from which our study population was drawn (17, 19).

The mechanism through which OC use impacts breast cancer risk in young women is unknown. Studies of estrogen's role in promoting the growth and vascularization of cancer cells have focused largely on the transcriptional effects of estrogen binding to its receptor in ER-positive mammary and ovarian cancer cells. However, a recent publication has proposed a second mechanism whereby estrogen promotes the growth of ER-negative and ER-positive cancer by systematically enhancing angiogenesis and stromal cell recruitment (32).

Interest in the clinical and pathologic characterization of TNBC has grown tremendously in recent years, related in part to its poor prognosis and higher frequency in younger and African-American women. Although basal-like/TNBC tends to have a poor prognosis compared to other subtypes, it is unclear whether this is due to inherent aggressiveness or resistance to systemic therapy. Trastuzumab

(Herceptin) and tamoxifen effectively target HER2+ (33, 34) and ER+ (35) breast cancer, respectively, but targeted therapies for basal-like/TNBC patients are lacking. Carey et al. reported that TNBC (and less common HER2+/ER-) patients had worse survival than luminal subtypes (5), despite higher chemosensitivity to conventional anthracycline-based therapy.

Few studies to date have focused on etiologic risk factors for basal-like/TNBC, and none have focused on young women. Millikan et al. (36) examined common breast cancer risk factors across 'intrinsic' breast cancer subtypes in the population-based Carolina Breast Cancer Study of women ages 20-74. Among women of all ages, they observed an increased risk of basal-like breast cancer in relation to increasing number of live births and younger age at first full-term pregnancy. In a case-only comparison of basal-like versus luminal A breast cancer subtypes among women of all ages in relation to OC use, no differences were observed. Yang et al. (37) evaluated established breast cancer etiologic factors by subtype within the Polish Breast Cancer Study. Among premenopausal women, increasing BMI (per 5 units) was associated with a borderline-significant increased risk of basal-like breast cancer (OR 1.2, 95% CI 0.9-1.6) and a reduced risk of luminal A breast cancer (OR .7, 95% CI 0.6-0.9; $P_{heterogeneity}$ .003). OC use was rare in this population (>60% of participants were postmenopausal) and not significantly associated with breast cancer risk overall or within subtypes.

Hormone receptor and HER2 defined breast cancers have been the subject of a more extensive literature. ER-negative breast cancer is known to be more frequent among young women (38), African American women (39), and BRCA1 carriers (40). ER-positive breast cancer is associated with improved response to hormonal therapy, longer disease-free intervals, and improved survival (41). Previous studies of etiologic heterogeneity among hormone receptor defined breast cancer have reported risk factor differences with mixed results. In a systematic literature review, Althuis et al. (42) reported that delayed childbearing, nulliparity, and early menarche were commonly associated with an increased risk among ER-positive breast cancer only. Several studies that have examined elevated BMI in premenopausal women by hormone receptor status have discerned an increased risk of ER-/PR- breast cancer but not ER+/PR+ breast cancer (43, 44), while others have not (38, 45, 46). The relationship between OC use and

risk of ER-defined breast cancer is somewhat ambiguous. Several studies have reported an increased risk of ER-negative breast cancer in young women associated with ever using OCs (38, 47), and long duration of use (43, 44), but with varying levels of magnitude and statistical significance.

Evidence that breast cancer risk factors operate through HER2 is inconsistent. Within the Carolina Breast Cancer Study, Huang et al. (48) found that most recognized breast cancer risk factors did not vary by HER2 status; neither high BMI nor OC use were associated with a significantly increased risk of HER+ or HER2- breast cancer in premenopausal women. In contrast, Sherman et al. (49) found that high BMI was associated with low HER2 levels in premenopausal women (P_{trend} .01) within the Polish Breast Cancer Study. Some studies of premenopausal women have found an increased risk of HER2-positive breast cancer in relation to early OC use (50, 51), while others have found no association between OC use and either HER2 subtype (48, 52).

The results of this study should be considered in light of several limitations. Our study population contained few non-Caucasians, and given that TNBC is more than twice as common among African Americans, similar research is needed in a racially heterogeneous population to evaluate the generalizability of our results. Our ability to evaluate age-specific effects was constrained by the small number of TNBC cases ages 41-45. It is worth noting that the diagnosis years in this study pre-date the incorporation of HER2 and routine ER/PR clinical testing, thus requiring direct testing of samples, which was limited by the availability of tumor specimens. We obtained specimens for 1019 of the 1286 women in our study (79.2%). To the extent that the availability of tumor specimens was related to features that are also related to TNBC, our results may be biased. As with all studies of TNBC, there is also potential for misclassification of TNBC due to false negative or false positive IHC results. In particular, our study used IHC to assess HER2 expression levels, the accepted standard for HER2 assessment at the time assays were completed. Since then, fluorescence in situ hybridization (FISH) has become the standard for discrimination of HER2 intermediate IHC scores. Because a portion of the 2+ (intermediate positive) tumors would not show amplification by FISH analysis, we may have misclassified some true HER2-negative cases as HER2 positive. In addition a small number of tumors that exhibit only 1+ (low positive)

immunostaining could be falsely low by IHC. For the analyses presented in this study we used the standard clinical definition of HER2-negative, which included negative and low positive staining. We also repeated all analyses with a purer HER2-negative definition by excluding low positives from the TNBC group; results were of similar magnitude, but with wider confidence intervals (data not shown).

Our study has the strength of being population-based and is the largest of its kind to evaluate breast cancer subtypes and etiologic differences in young women. In contrast to the few other studies that have examined risk factors by tumor subtype, OC use was common in our study population and extensive detail on OC usage patterns was collected, allowing us to assess OC use associations in a thorough manner. By excluding non-OC users from trend tests, we were able to discern differences in OC use above and beyond ever use, thereby providing additional support for dose-response relationships (53). The centralized, blinded nature of tumor specimen testing removed the potential for inter-reviewer bias.

The strong association between OC use and the risk of TNBC observed in this study and the relative scarcity of such studies to date, emphasize the need for future research. Given that we have yet to understand whether the poor prognosis associated with TNBC is a reflection of fewer treatment options, or is intrinsic to the biology of the disease, the results of etiologic studies such as the present one may ultimately play an important role in elucidating the etiologic pathways of TNBC, and in facilitating the development of strategies for prevention, treatment, and management of TNBC.

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Table 1. Multivariate adjusted* case-control odds ratios and 95% confidence intervals for all breast cancer cases, triple-negative and non triple-negative cases in relation to known and suspected risk factors among women 45 years of age and younger, 1983-1992.

				Triple–negative (ER-/PR-/HER2-) status			
	Controls (N=1,569)	All breast cancer (N=897)		Triple-negative (N=187)		Non triple-negative (N=710)	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	P Value**
Demographic/Lifestyle factors								
Age (yrs)								
<30	155 (9.9)	35 (3.9)	1.0 Reference	9 (4.8)	1.0 Reference	26 (3.7)	1.0 Reference	
30-34	297 (18.9)	140 (15.6)	2.1 (1.1-3.9)	38 (20.3)	2.6 (0.8-9.1)	102 (14.4)	2.0 (1.0-3.9)	
35-39	573 (36.5)	335 (37.3)	2.4 (1.3-4.3)	79 (42.2)	2.9 (0.9-9.8)	256 (36.1)	2.2 (1.2-4.2)	
40-45	544 (34.7)	387 (43.1)	2.6 (1.4-4.6)	61 (32.6)	2.2 (0.7-7.4)	326 (45.9)	2.7 (1.4-5.1)	
P for trend			**.006**		**.81**		**.002**	**.13**
Race§§								
White	1482 (94.6)	836 (93.7)	1.0 Reference	178 (95.7)	1.0 Reference	658 (93.2)	1.0 Reference	
Black	27 (1.7)	20 (2.2)	0.9 (0.4-2.5)	3 (1.6)	0.0 N/A	17 (2.4)	1.2 (0.5-3.2)	
Other	58 (3.7)	36 (4.0)	0.9 (0.5-1.7)	5 (2.7)	0.9 (0.3-3.1)	31 (4.4)	0.9 (0.4-1.8)	**.05**
Education								
<College graduate	1035 (66.0)	572 (63.8)	1.0 Reference	119 (63.6)	1.0 Reference	453 (63.8)	1.0 Reference	
College graduate	533 (34.0)	325 (36.2)	1.2 (1.0-1.6)	68 (36.4)	1.3 (0.9-2.0)	257 (36.2)	1.2 (1.0-1.6)	**.61**
Annual income‡‡								
<15,000	184 (11.9)	81 (9.1)	1.0 Reference	14 (7.5)	1.0 Reference	67 (9.5)	1.0 Reference	
15-45/50,000	863 (55.9)	471 (52.9)	1.3 (0.8-1.9)	99 (52.9)	1.2 (0.6-2.6)	372 (52.9)	1.3 (0.8-1.9)	
45/50,000+	496 (32.1)	338 (38.0)	1.3 (0.8-1.9)	74 (39.6)	1.5 (0.7-3.2)	264 (37.6)	1.2 (0.8-1.9)	
P for trend			**.39**		**.24**		**.64**	**.55**
Family history of breast cancer								
None	807 (67.8)	363 (50.3)	1.0 Reference	78 (47.6)	1.0 Reference	285 (51.1)	1.0 Reference	
1st degree	95 (8.0)	150 (20.8)	3.0 (2.1-4.1)	37 (22.6)	3.5 (2.1-5.9)	113 (20.3)	2.8 (2.0-4.0)	
2nd degree only	289 (24.3)	209 (28.9)	1.7 (1.3-2.2)	49 (29.9)	1.8 (1.2-2.8)	160 (28.7)	1.7 (1.3-2.2)	**.70**
Body mass index (k/m^2)†								
<18.5	87 (5.6)	35 (4.0)	0.7 (0.4-1.2)	6 (3.2)	0.5 (0.2-1.7)	29 (4.2)	0.8 (0.4-1.4)	
18.5 – 24.9	977 (63.4)	578 (65.6)	1.0 Reference	121 (65.1)	1.0 Reference	457 (65.8)	1.0 Reference	
25.0-29.9	269 (17.4)	151 (17.1)	1.0 (0.7-1.3)	33 (17.7)	1.1 (0.6-1.8)	118 (17.0)	0.9 (0.7-1.3)	
30+	209 (13.6)	117 (13.3)	0.9 (0.7-1.3)	26 (14.0)	1.3 (0.8-2.2)	91 (13.1)	0.8 (0.6-1.2)	
P for trend			**.99**		**.18**		**.54**	**.12**
Smoking								
Never	801 (51.4)	464 (52.2)	1.0 Reference	100 (54.6)	1.0 Reference	364 (51.6)	1.0 Reference	
Former	332 (21.3)	189 (21.3)	0.9 (0.7-1.2)	34 (18.6)	0.8 (0.5-1.3)	155 (22.0)	0.9 (0.7-1.3)	
Current	424 (27.2)	236 (26.5)	0.9 (0.7-1.2)	49 (26.8)	1.0 (0.6-1.6)	187 (26.5)	0.9 (0.7-1.2)	**.29**
Alcohol use (drinks/wk)								
None/<1	771 (49.2)	442 (49.3)	1.0 Reference	88 (47.1)	1.0 Reference	354 (49.9)	1.0 Reference	
1-3	288 (18.4)	152 (17.0)	1.0 (0.7-1.3)	29 (15.5)	0.8 (0.5-1.4)	123 (17.3)	1.0 (0.7-1.4)	
3+	507 (32.4)	302 (33.7)	1.1 (0.9-1.4)	70 (37.4)	1.1 (0.7-1.6)	232 (32.7)	1.1 (0.8-1.4)	
P for trend			**.54**		**.84**		**.54**	**.49**
Reproductive factors								
Age at menarche								
8-12	737 (47.1)	471 (52.5)	1.0 Reference	98 (52.4)	1.0 Reference	373 (52.5)	1.0 Reference	
13-14	690 (44.1)	351 (39.1)	0.8 (0.6-1.0)	77 (41.2)	0.8 (0.6-1.2)	274 (38.6)	0.7 (0.6-1.0)	
15+	139 (8.9)	75 (8.4)	0.8 (0.5-1.2)	12 (6.4)	0.4 (0.2-1.0)	63 (8.9)	0.9 (0.6-1.4)	
P for trend			**.03**		**.05**		**.11**	**.33**
Number of live births								
None	396 (25.2)	232 (25.9)	1.0 Reference	53 (28.3)	1.0 Reference	179 (25.2)	1.0 Reference	
1-3	1057 (67.4)	621 (69.2)	0.8 (0.5-1.3)	127 (67.9)	0.9 (0.4-1.9)	494 (69.6)	0.8 (0.5-1.3)	
4+	116 (7.4)	44 (4.9)	0.5 (0.3-1.0)	7 (3.7)	0.6 (0.2-1.9)	37 (5.2)	0.5 (0.3-1.0)	
P for trend			**.04**		**.38**		**.04**	**.83**
Age at first birth (yrs)‡								
None	390 (24.9)	230 (25.7)	1.0 Reference	53 (28.3)	1.0 Reference	177 (25.0)	1.0 Reference	
<20	264 (16.8)	116 (12.9)	0.6 (0.3-1.0)	19 (10.2)	0.6 (0.2-1.4)	97 (13.7)	0.6 (0.3-1.0)	
20-29	745 (47.5)	419 (46.8)	0.8 (0.5-1.3)	86 (46.0)	0.9 (0.4-2.0)	333 (47.0)	0.8 (0.5-1.3)	
30+	170 (10.8)	131 (14.6)	1.0 (0.6-1.8)	29 (15.5)	1.2 (0.5-3.0)	102 (14.4)	1.0 (0.6-1.8)	
P for trend§			**.002**		**.03**		**.009**	**.49**
Lactation‖								
Never	313 (26.9)	189 (28.5)	1.0 Reference	33 (24.6)	1.0 Reference	156 (29.4)	1.0 Reference	
<12	494 (42.5)	279 (42.0)	1.1 (0.8-1.4)	63 (47.0)	1.1 (0.7-1.8)	216 (40.8)	1.1 (0.8-1.5)	
12+	356 (30.6)	196 (29.5)	1.0 (0.7-1.4)	38 (28.4)	1.0 (0.6-1.7)	158 (29.8)	1.0 (0.7-1.4)	
P for trend			**.97**		**.99**		**.98**	**.78**
Abortion¶								
Never	950 (72.9)	510 (67.3)	1.0 Reference	98 (64.5)	1.0 Reference	412 (68.0)	1.0 Reference	
Ever	354 (27.1)	248 (32.7)	1.4 (1.1-1.8)	54 (35.5)	1.4 (0.9-2.2)	194 (32.0)	1.4 (1.1-1.8)	**.82**

* Risk factors adjusted for age, family history of breast cancer, breastfeeding history and OC duration
† 1 yr prior to reference date
‡ Still and live births
§ P for trend among parous women only
‖ Among parous women
¶ Among gravid women
** $P_{heterogeneity}$ (association of risk factor with triple-negative vs. non triple-negative breast cancer)
†† P_{trend} and $P_{heterogeneity}$ among OC users >1 year only
‡‡ Income categories reflect the fact that the two studies combined for the present study used different cut-offs
§§ Due to missing data, race was adjusted for age, breastfeeding history and OC duration, but not family history of breast cancer

Table 1 continued. Multivariate adjusted* case-control odds ratios and 95% confidence intervals for all breast cancer cases, triple-negative and non triple-negative cases in relation to known and suspected risk factors among women 45 years of age and younger, 1983-1992.

				Triple –negative (ER-/PR-/HER2-) status			
	Controls (N=1,569)	**All breast cancer (N=897)**		**Triple-negative (N=187)**		**Non triple-negative (N=710)**	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	**P Value****
Oral contraceptive use								
OC use (yrs)								
Never/<1	407 (25.9)	197 (22.0)	1.0 Reference	22 (11.8)	1.0 Reference	175 (24.7)	1.0 Reference	
1+	1162 (74.1)	699 (78.0)	1.3 (1.0-1.7)	165 (88.2)	2.5 (1.4-4.3)	534 (75.3)	1.2 (0.9-1.5)	**.008**
OC duration (yrs)††								
1-<3	327 (20.8)	184 (20.5)	1.3 (0.9-1.7)	35 (18.7)	1.6 (0.9-3.3)	149 (21.0)	1.2 (0.9-1.7)	
3-<6	357 (22.8)	220 (24.6)	1.4 (1.0-2.0)	51 (27.3)	2.8 (1.5-5.3)	169 (23.8)	1.2 (0.9-1.7)	
6+	478 (30.5)	295 (32.9)	1.3 (1.0-1.8)	79 (42.2)	2.9 (1.6-5.3)	216 (30.5)	1.1 (0.8-1.5)	
P for trend			**.85**		**.05**		**.45**	**.02**
Age at first use (yrs)††								
22+	260 (16.6)	159 (17.7)	1.2 (0.9-1.7)	31 (16.6)	2.0 (1.0-4.1)	128 (18.1)	1.1 (0.8-1.6)	
18-<22	674 (43.0)	390 (43.5)	1.2 (0.9-1.6)	92 (49.2)	2.3 (1.3-4.1)	298 (42.0)	1.1 (0.8-1.4)	
<18	228 (14.5)	150 (16.7)	1.9 (1.3-2.7)	42 (22.5)	3.7 (1.9-7.2)	108 (15.2)	1.6 (1.1-2.3)	
P for trend			**.05**		**.13**		**.10**	**.84**
Years since first use††								
1-<15	313 (19.9)	132 (14.7)	1.3 (0.8-1.9)	36 (19.3)	2.4 (1.1-5.1)	96 (13.5)	1.1 (0.7-1.6)	
15-<20	462 (29.4)	277 (30.9)	1.3 (1.0-1.8)	78 (41.7)	3.0 (1.6-5.4)	199 (28.1)	1.1 (0.8-1.5)	
20+	387 (24.7)	290 (32.4)	1.4 (1.0-1.9)	51 (27.3)	2.0 (1.1-4.0)	239 (33.7)	1.3 (0.9-1.8)	
P for trend			**.27**		**.74**		**.25**	**.74**
Years since last use††								
Current	120 (7.6)	43 (4.8)	1.0 (0.6-1.8)	16 (8.6)	3.1 (1.2-7.6)	27 (3.8)	0.7 (0.4-1.4)	
1-<5	190 (12.1)	116 (12.9)	1.9 (1.3-2.9)	31 (16.6)	4.2 (2.0-8.6)	85 (12.0)	1.6 (1.1-2.5)	
5-<10	255 (16.3)	136 (15.2)	1.2 (0.8-1.7)	41 (21.9)	3.0 (1.6-5.9)	95 (13.4)	0.9 (0.6-1.3)	
10-<15	339 (21.6)	213 (23.8)	1.3 (1.0-1.8)	55 (29.4)	2.6 (1.4-4.8)	158 (22.3)	1.2 (0.8-1.6)	
15+	258 (16.4)	191 (21.3)	1.3 (0.9-1.8)	22 (11.8)	1.2 (0.6-2.6)	169 (23.8)	1.3 (0.9-1.8)	
P for trend			**.86**		**.04**		**.39**	**.01**

* Risk factors adjusted for age, family history of breast cancer, breastfeeding history and OC duration
† 1 yr prior to reference date
‡ Still and live births
§ P for trend among parous women only
|| Among parous women
¶ Among gravid women
** $P_{heterogeneity}$ (association of risk factor with triple-negative vs. non triple-negative breast cancer)
†† P_{trend} and $P_{heterogeneity}$ among OC users >1 year only
‡‡ Income categories reflect the fact that the two studies combined for the present study used different cut-offs
§§ Due to missing data, race was adjusted for age, breastfeeding history and OC duration, but not family history of breast cancer

Table 2. Multivariate adjusted* case-control odds ratios and 95% confidence intervals for all breast cancer cases defined by HER2 and ER status in relation to OC use among women 45 years of age and younger, 1983-1992.

		ER status					HER2 status				
	Controls (N=1,569)	ER-negative (N=364)		ER-positive (N=533)			HER2-negative (N=608)		HER2-positve (N=289)		
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	P Value†	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	P Value§
Oral contraceptive use											
OC use (yrs)											
Never/<1	407 (25.9)	59 (16.2)	1.0 Reference	138 (25.9)	1.0 Reference		124 (20.4)	1.0 Reference	73 (25.3)	1.0 Reference	
1+	1162 (74.1)	305 (83.8)	2.0 (1.3-2.9)	394 (74.1)	1.1 (0.8-1.4)	**.005**	483 (79.6)	1.4 (1.1-1.9)	216 (74.7)	1.2 (0.8-1.7)	**.27**
OC duration (yrs)‡											
1-<3	327 (20.8)	66 (18.1)	1.5 (0.9-2.4)	118 (22.2)	1.2 (0.8-1.7)		126 (20.8)	1.4 (0.9-2.0)	58 (20.1)	1.1 (0.7-1.8)	
3-<6	357 (22.8)	98 (26.9)	2.2 (1.4-3.4)	122 (22.9)	1.1 (0.8-1.6)		159 (26.2)	1.6 (1.1-2.3)	61 (21.1)	1.2 (0.7-1.9)	
6+	478 (30.5)	141 (38.7)	2.2 (1.4-3.4)	154 (28.9)	0.9 (0.6-1.3)		198 (32.6)	1.4 (1.0-2.0)	97 (33.6)	1.2 (0.8-1.8)	
P for trend			**.05**		**.15**	**.004**		**.94**		**.79**	**.89**
Age at first use (yrs)‡											
22+	260 (16.6)	64 (17.6)	1.7 (1.1-2.9)	95 (17.9)	1.0 (0.7-1.5)		112 (18.5)	1.4 (0.9-2.0)	47 (16.3)	1.0 (0.6-1.6)	
18-<22	674 (43.0)	170 (46.7)	1.8 (1.2-2.8)	220 (41.4)	1.0 (0.7-1.3)		270 (44.5)	1.3 (1.0-1.8)	120 (41.5)	1.1 (0.7-1.6)	
<18	228 (14.5)	71 (19.5)	2.8 (1.7-4.6)	79 (14.8)	1.4 (0.9-2.2)		101 (16.6)	1.9 (1.3-2.9)	49 (17.0)	1.8 (1.1-2.9)	
P for trend			**.10**		**.14**	**.96**		**.18**		**.05**	**.40**
Years since first use‡											
1-<15	313 (19.9)	70 (19.2)	1.8 (1.1-3.2)	62 (11.7)	1.0 (0.6-1.6)		89 (14.7)	1.4 (0.9-2.2)	43 (14.9)	1.0 (0.6-1.8)	
15-<20	462 (29.4)	137 (37.6)	2.3 (1.5-3.6)	140 (26.3)	0.9 (0.6-1.3)		200 (32.9)	1.5 (1.1-2.2)	77 (26.6)	1.0 (0.6-1.6)	
20+	387 (24.7)	98 (26.9)	1.7 (1.1-2.8)	192 (36.1)	1.2 (0.9-1.7)		194 (32.0)	1.4 (0.9-2.0)	96 (33.2)	1.4 (0.9-2.2)	
P for trend			**.80**		**.17**	**.40**		**.78**		**.07**	**.12**
Years since last use‡											
Current	120 (7.6)	24 (6.6)	1.9 (0.9-3.9)	19 (3.6)	0.6 (0.3-1.4)		27 (4.4)	0.9 (0.5-1.8)	16 (5.5)	1.2 (0.5-2.6)	
1-<5	190 (12.1)	63 (17.3)	3.6 (2.1-6.0)	53 (10.0)	1.3 (0.8-2.0)		76 (12.5)	2.0 (1.3-3.1)	40 (13.8)	1.9 (1.1-3.3)	
5-<10	255 (16.3)	71 (19.5)	2.2 (1.3-3.6)	65 (12.2)	0.7 (0.5-1.2)		100 (16.5)	1.3 (0.9-2.0)	36 (12.5)	0.9 (0.5-1.5)	
10-<15	339 (21.6)	91 (25.0)	2.0 (1.3-3.2)	122 (22.9)	1.0 (0.7-1.5)		155 (25.5)	1.6 (1.1-2.2)	58 (20.1)	1.0 (0.6-1.5)	
15+	258 (16.4)	56 (15.4)	1.2 (0.7-2.0)	135 (25.4)	1.3 (0.9-1.9)		125 (20.6)	1.3 (0.9-1.9)	66 (22.8)	1.2 (0.8-2.0)	
P for trend			**.02**		**.07**	**< .001**		**.95**		**.62**	**.65**

*Risk factors adjusted for age, family history of breast cancer, and breastfeeding history

† $P_{heterogeneity}$ (association of risk factor with ER-negative vs. ER-positive breast cancer)

‡ P_{trend} and $P_{heterogeneity}$ among OC users >1 year only

§ $P_{heterogeneity}$ (association of risk factor with HER2-negative vs. HER2-positive breast cancer)

Table 3. Multivariate adjusted* case-control odds ratios and 95% confidence intervals for ER-negative and ER-positive breast cancer in relation to OC use, stratified by HER2 status among women age 45 years and younger, 1983-1992.

	Controls (N=1569)	ER-negative (N=364)		ER-positive (N=533)		
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	P Value†
Among HER2-negative						
Oral contraceptive use		*n*=252		*n*=356		
OC use (yrs)						
Never/<1	407 (25.9)	32 (12.7)	1.0 Reference	92 (25.9)	1.0 Reference	
1+	1162 (74.1)	220 (87.3)	2.2 (1.4-3.5)	263 (74.1)	1.1 (0.8-1.6)	**.01**
OC duration (yrs)‡						
1-<3	327 (20.8)	45 (17.9)	1.4 (0.8-2.6)	81 (22.8)	1.3 (0.9-2.0)	
3-<6	357 (22.8)	72 (28.6)	2.5 (1.5-4.4)	87 (24.5)	1.2 (0.8-1.8)	
6+	478 (30.5)	103 (40.9)	2.5 (1.5-4.2)	95 (26.8)	0.9 (0.6-1.3)	
P for trend			**.03**		**.05**	**<.001**
Age at first use‡						
22+	260 (16.6)	45 (17.9)	2.0 (1.1-3.6)	67 (18.9)	1.1 (0.7-1.8)	
18-<22	674 (43.0)	122 (48.4)	2.0 (1.2-3.3)	148 (41.7)	1.0 (0.7-1.5)	
<18	228 (14.5)	53 (21.0)	3.1 (1.7-5.5)	48 (13.5)	1.3 (0.8-2.2)	
P for trend			**.17**		**.51**	**.80**
Years since first use‡						
1-<15	313 (19.9)	50 (19.8)	2.1 (1.1-4.0)	39 (11.0)	1.0 (0.6-1.9)	
15-<20	462 (29.4)	104 (41.3)	2.7 (1.6-4.5)	96 (27.0)	1.0 (0.7-1.5)	
20+	387 (24.7)	66 (26.2)	1.7 (1.0-3.0)	128 (36.1)	1.2 (0.8-1.8)	
P for trend			**.88**		**.58**	**.67**
Years since last use‡						
Current	120 (7.6)	19 (7.5)	2.2 (1.0-5.2)	8 (2.3)	0.3 (0.1-1.1)	
1-<5	190 (12.1)	41 (16.3)	3.5 (1.9-6.6)	35 (9.9)	1.3 (0.7-2.2)	
5-<10	255 (16.3)	56 (22.2)	2.6 (1.5-4.6)	44 (12.4)	0.8 (0.4-1.3)	
10-<15	339 (21.6)	72 (28.6)	2.4 (1.4-4.1)	83 (23.4)	1.2 (0.8-1.8)	
15+	258 (16.4)	32 (12.7)	1.1 (0.6-2.1)	93 (26.2)	1.3 (0.9-2.1)	
P for trend			**.04**		**.03**	**<.001**
Among HER2-positive						
Oral contraceptive use		*n* =112		*n* =177		
OC use (yrs)						
Never/<1	407 (25.9)	27 (24.1)	1.0 Reference	46 (26.0)	1.0 Reference	
1+	1162 (74.1)	85 (75.9)	1.6 (0.8-3.0)	131 (74.0)	1.0 (0.6-1.5)	**.18**
OC duration (yrs)‡						
1-<3	327 (20.8)	21 (18.8)	1.5 (0.7-3.2)	37 (20.9)	1.0 (0.5-1.7)	
3-<6	357 (22.8)	26 (23.2)	1.5 (0.7-3.3)	35 (19.8)	1.0 (0.6-1.8)	
6+	478 (30.5)	38 (33.9)	1.7 (0.8-3.4)	59 (33.3)	1.0 (0.6-1.7)	
P for trend			**.73**		**.91**	**.83**
Age at first use (yrs)‡						
22+	260 (16.6)	19 (17.0)	1.4 (0.6-3.2)	28 (15.8)	0.8 (0.4-1.5)	
18-<22	674 (43.0)	48 (42.9)	1.4 (0.7-2.8)	72 (40.7)	0.9 (0.5-1.4)	
<18	228 (14.5)	18 (16.1)	2.3 (1.0-5.1)	31 (17.5)	1.5 (0.8-2.8)	
P for trend			**.26**		**.09**	**.79**
Years since first use‡						
1-<15	313 (19.9)	20 (17.9)	1.3 (0.5-3.4)	23 (13.0)	0.9 (0.4-1.8)	
15-<20	462 (29.4)	33 (29.5)	1.6 (0.8-3.2)	44 (24.9)	0.8 (0.5-1.4)	
20+	387 (24.7)	32 (28.6)	1.7 (0.8-3.7)	64 (36.2)	1.3 (0.7-2.2)	
P for trend			**.42**		**.08**	**.62**
Years since last use‡						
Current	120 (7.6)	5 (4.5)	1.2 (0.3-4.6)	11 (6.2)	1.2 (0.5-2.9)	
1-<5	190 (12.1)	22 (19.6)	3.5 (1.5-8.1)	18 (10.2)	1.2 (0.6-2.6)	
5-<10	255 (16.3)	15 (13.4)	1.3 (0.6-3.1)	21 (11.9)	0.7 (0.4-1.4)	
10-<15	339 (21.6)	19 (17.0)	1.3 (0.6-2.8)	39 (22.0)	0.8 (0.5-1.5)	
15+	258 (16.4)	24 (21.4)	1.3 (0.6-3.0)	42 (23.7)	1.2 (0.7-2.1)	
P for trend			**.24**		**.84**	**.36**

*Risk factors adjusted for age, family history of breast cancer, and breastfeeding history

† $P_{heterogeneity}$ (association of risk factor with ER-negative vs. ER-positive breast cancer)

‡ P_{trend} and $P_{heterogeneity}$ among OC users >1 year only

Table 4. Multivariate adjusted* case-control odds ratios and 95% confidence intervals for all breast cancer cases, triple-negative and non triple-negative cases in relation to OC risk factors, stratified by age at diagnosis ≤40 and 41-45 years, 1983-1992.

				Triple–negative status			
	Controls (N=1,569)	**All breast cancer (N=897)**		**Triple-negative (N=187)**		**Non triple-negative (N=710)**	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	**P Value**†
				Among women ≤ 40 years of age				
Oral contraceptive use	*n*=1156	*n*=590		*n*=141		*n*=449		
OC use (yrs)								
Never/<1	299 (25.9)	121 (20.5)	1.0 Reference	11 (7.8)	1.0 Reference	110 (24.5)	1.0 Reference	
1+	857 (74.1)	469 (79.5)	1.6 (1.1-2.1)	130 (92.2)	4.2 (1.9-9.3)	339 (75.5)	1.2 (0.9-1.7)	**<.001**
OC duration (yrs)‡								
1-<3	242 (20.9)	126 (21.4)	1.5 (1.0-2.2)	31 (22.0)	3.0 (1.2-7.3)	95 (21.2)	1.3 (0.9-2.0)	
3-<6	261 (22.6)	141 (23.9)	1.6 (1.1-2.4)	39 (27.7)	4.9 (2.1-11.6)	102 (22.7)	1.2 (0.8-1.9)	
6+	354 (30.6)	202 (34.2)	1.5 (1.1-2.2)	60 (42.6)	4.7 (2.0-10.8)	142 (31.6)	1.2 (0.8-1.7)	
P for trend			**.86**		**.17**		**.58**	**.10**
Age at first use (yrs)‡								
22+	166 (14.4)	79 (13.4)	1.3 (0.8-2.1)	20 (14.2)	3.5 (1.4-9.1)	59 (13.1)	1.1 (0.7-1.8)	
18-<22	499 (43.2)	270 (45.8)	1.4 (1.0-2.0)	75 (53.2)	3.7 (1.7-8.5)	195 (43.4)	1.1 (0.8-1.6)	
<18	192 (16.6)	120 (20.3)	2.3 (1.5-3.5)	35 (24.8)	6.4 (2.6-15.6)	85 (18.9)	1.8 (1.2-2.8)	
P for trend			**.02**		**.12**		**.04**	**.93**
Years since first use‡								
<20	721 (62.4)	368 (62.4)	1.5 (1.1-2.1)	108 (76.6)	4.2 (1.9-9.5)	260 (57.9)	1.2 (0.8-1.7)	
20+	136 (11.8)	101 (17.1)	1.8 (1.2-2.9)	22 (15.6)	4.2 (1.6-10.8)	79 (17.6)	1.6 (1.0-2.5)	**.45**
Years since last use‡								
Current	117 (10.1)	43 (7.3)	1.2 (0.6-2.1)	16 (11.3)	4.5 (1.6-13.1)	27 (6.0)	0.8 (0.4-1.5)	
1-<10	388 (33.6)	210 (35.6)	1.7 (1.2-2.4)	62 (44.0)	5.1 (2.2-11.6)	148 (33.0)	1.3 (0.9-1.9)	
10-<15	240 (20.8)	148 (25.1)	1.7 (1.1-2.4)	41 (29.1)	4.2 (1.7-9.9)	107 (23.8)	1.4 (0.9-2.1)	
15+	112 (9.7)	68 (11.5)	1.3 (0.8-2.1)	11 (7.8)	2.1 (0.7-6.2)	57 (12.7)	1.2 (0.7-2.0)	
P for trend			**.95**		**.15**		**.46**	**.07**
				Among women 41-45 years of age				
Oral contraceptive use	*n*=413	*n*=307		*n*=46		*n*=261		
OC use (yrs)								
Never/<1	108 (26.2)	76 (24.8)	1.0 Reference	11 (23.9)	1.0 Reference	65 (25.0)	1.0 Reference	
1+	305 (73.8)	230 (75.2)	1.0 (0.7-1.5)	35 (76.1)	0.9 (0.4-2.2)	195 (75.0)	1.0 (0.7-1.6)	**.93**
OC duration (yrs)‡								
1-<3	85 (20.6)	58 (19.0)	0.9 (0.5-1.6)	4 (8.7)	0.4 (0.1-1.6)	54 (20.8)	1.0 (0.6-1.8)	
3-<6	96 (23.2)	79 (25.8)	1.2 (0.7-2.0)	12 (26.1)	1.1 (0.4-3.0)	67 (25.8)	1.2 (0.7-2.1)	
6+	124 (30.0)	93 (30.4)	0.9 (0.6-1.6)	19 (41.3)	1.3 (0.5-3.3)	74 (28.5)	0.9 (0.5-1.5)	
P for trend			**.91**		**.11**		**.65**	**.06**
Age at first use (yrs)‡								
22+	94 (22.8)	80 (26.1)	1.0 (0.6-1.8)	11 (23.9)	0.8 (0.3-2.5)	69 (26.5)	1.1 (0.6-1.9)	
18-<22	175 (42.4)	120 (39.2)	1.0 (0.6-1.6)	17 (37.0)	0.9 (0.4-2.3)	103 (39.6)	1.0 (0.6-1.6)	
<18	36 (8.7)	30 (9.8)	1.1 (0.6-2.3)	7 (15.2)	1.3 (0.4-4.9)	23 (8.8)	1.1 (0.5-2.3)	
P for trend			**.85**		**.57**		**1.0**	**.59**
Years since first use‡								
<20	54 (13.1)	41 (13.4)	1.0 (0.5-1.9)	6 (13.0)	1.0 (0.3-3.6)	35 (13.5)	1.0 (0.5-1.9)	
20+	251 (60.8)	189 (61.8)	1.0 (0.7-1.6)	29 (63.0)	0.9 (0.4-2.2)	160 (61.5)	1.0 (0.7-1.6)	**.77**
Years since last use‡								
Current	3 (0.7)	0 (0.0)	0.0 N/A	0 (0.0)	0.0 N/A	0 (0.0)	0.0 N/A	
1-<10	57 (13.8)	42 (13.7)	1.0 (0.5-1.9)	10 (21.7)	1.8 (0.6-5.4)	32 (12.3)	0.8 (0.4-1.6)	
10-<15	99 (24.0)	65 (21.2)	0.8 (0.5-1.5)	14 (30.4)	1.0 (0.4-2.8)	51 (19.6)	0.8 (0.5-1.5)	
15+	146 (35.4)	123 (40.2)	1.1 (0.7-1.8)	11 (23.9)	0.7 (0.2-1.8)	112 (43.1)	1.2 (0.8-2.0)	
P for trend			**.33**		**.08**		**.10**	**.01**

*Risk factors adjusted for age, family history of breast cancer, and breastfeeding history

† $P_{heterogeneity}$ (association of risk factor with triple-negative vs. non triple-negative breast cancer)

‡ P_{trend} and $P_{heterogeneity}$ among OC users >1 year only