

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

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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.

Keywords: Triple-negative breast cancer, oral contraceptives

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 stratified 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 (≥ 1 year) only.

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

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. ([more ...](#))

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 ($P_{\text{heterogeneity}} .008$), OC duration ($P_{\text{heterogeneity}} .02$), and years since last OC use ($P_{\text{heterogeneity}} .01$) conferred significantly different risk estimates by case group, and BMI ≥ 30 k/m² 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/m² 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 ($P_{\text{trend}} .05$) and fewer years since last OC use ($P_{\text{trend}} .04$), 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. ...

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References

1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406:747–52. [[PubMed](#)]
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98:10869–74. [[PubMed](#)]
3. Sorlie T, Tibshirani R, Parker J, et al. 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;100:8418–23. [[PubMed](#)]
4. Sotiriou C, Neo SY, McShane LM, et al. 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;100:10393–8. [[PubMed](#)]
5. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes. *Clinical Cancer Research*. 2007;13:2329–34. [[PubMed](#)]
6. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. *Clinical Cancer Research*. 2007;13:4429–34. [[PubMed](#)]
7. Haffty BG, Yang QF, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *Journal of Clinical Oncology*. 2006;24:5652–7. [[PubMed](#)]
8. Rakha EA, El-Sayed ME, Green AR, Lee AHS, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. *Cancer*. 2007;109:25–32. [[PubMed](#)]
9. Tischkowitz M, Brunet JS, Begin LR, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. *Bmc Cancer*. 2007;7
10. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype - A population-based study from the California Cancer Registry. *Cancer*. 2007;109:1721–8. [[PubMed](#)]
11. Harris LN, Broadwater G, Lin NU, et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. *Breast Cancer Research*. 2006;8

12. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients - A single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results Database. *Cancer*. 2007;110:876–84. [[PubMed](#)]
13. Perou CM, Jeffrey SS, Van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;96:9212–7. [[PubMed](#)]
14. Livasy CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. *Modern Pathology*. 2006;19:264–71. [[PubMed](#)]
15. Kreike B, van Kouwenhove M, Horlings H, et al. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. *Breast Cancer Research*. 2007;9:R65. [[PubMed](#)]
16. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *Journal of the National Cancer Institute*. 2003;95:1482–5. [[PubMed](#)]
17. White E, Malone KE, Weiss NS, Daling JR. Breast cancer among young United States women in relation to oral contraceptive use. *Journal of the National Cancer Institute*. 1994;86:505–14. [[PubMed](#)]
18. Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of breast cancer among young women: relationship to induced abortion. *Journal of the National Cancer Institute*. 1994;86:1584–92. [[PubMed](#)]
19. Brinton LA, Daling JR, Liff JM, et al. Oral contraceptives and breast cancer risk among younger women. *Journal of the National Cancer Institute*. 1995;87:827–35. [[PubMed](#)]
20. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. *Cancer Epidemiology Biomarkers & Prevention*. 2002;11:235–41.
21. Harris NV, Weiss NS, Francis AM, Polissar L. Breast cancer in relation to patterns of oral contraceptive use. *American Journal of Epidemiology*. 1982;116:643–51. [[PubMed](#)]
22. Malone KE, Daling JR, Weiss NS. Oral contraceptives in relation to breast cancer. *Epidemiologic Reviews*. 1993;15:80–97. [[PubMed](#)]
23. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *New England Journal of Medicine*. 2002;346:2025–32. [[PubMed](#)]
24. Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a reduced risk of premenopausal breast cancer. *New England Journal of Medicine*. 1994;330:81–7. [[PubMed](#)]
25. McTiernan A, Thomas DB. Evidence for a protective effect of lactation on risk of breast cancer in young women: results from a case-control study. *American Journal of Epidemiology*. 1986;124:353–8. [[PubMed](#)]
26. Lowe CR, Macmahon B. Breast cancer and reproduction. *Lancet*. 1970;2:1137–&. [[PubMed](#)]
27. Mirra AP, Cole P, Macmahon B. Breast cancer in an area of high parity: Sao Paulo, Brazil. *Cancer Research*. 1971;31:77–&. [[PubMed](#)]
28. Calle EE, Heath CW, MiracleMcMahill HL, et al. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53297 women with breast cancer and 100239 women without breast cancer from 54 epidemiological studies. *Lancet*. 1996;347:1713–27. [[PubMed](#)]
29. Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: A meta-analysis. *Mayo Clinic Proceedings*. 2006;81:1290–302. [[PubMed](#)]
30. Rookus MA, van Leeuwen FE. Oral contraceptives and risk of breast cancer in women aged 20-54 years. *Netherlands Oral Contraceptives and Breast Cancer Study Group. Lancet*. 1994;344:844–51. [[PubMed](#)]
31. Rosenberg L, Palmer JR, Rao RS, et al. Case-control study of oral contraceptive use and risk of breast cancer. *Am J Epidemiol*. 1996;143:25–37. [[PubMed](#)]
32. Gupta PB, Proia D, Cingoz O, et al. Systemic stromal effects of estrogen promote the growth of estrogen receptor-negative cancers. *Cancer Research*. 2007;67:2062–71. [[PubMed](#)]
33. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine*. 2005;353:1659–72. [[PubMed](#)]
34. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*. 2005;353:1673–84. [[PubMed](#)]
35. Tamoxifen for early breast cancer: an overview of the randomised trials. *Early Breast Cancer Trialists' Collaborative Group. Lancet*. 1998;351:1451–67. [[PubMed](#)]
36. Millikan R, Newman B, Tse CKT, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*. 2007
37. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiology Biomarkers & Prevention*. 2007;16:439–43.
38. Britton JA, Gammon MD, Schoenberg JB, et al. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20–44 years of age. *Am J Epidemiol*. 2002;156:507–16. [[PubMed](#)]
39. Furberg H, Millikan R, Dressler L, Newman B, Geradts J. Tumor characteristics in African American and white women. *Breast Cancer Res Treat*. 2001;68:33–43. [[PubMed](#)]
40. Armes JE, Trute L, White D, et al. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2

- mutation carriers: a population-based study. *Cancer Res.* 1999;59:2011–7. [[PubMed](#)]
41. Wittliff JL. Steroid-hormone receptors in breast cancer. *Cancer.* 1984;53:630–43. [[PubMed](#)]
42. 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;13:1558–68. [[PubMed](#)]
43. Ma HY, Bernstein L, Ross RK, Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. *Breast Cancer Research.* 2006;8
44. Cotterchio M, Kreiger N, Theis B, Sloan M, Bahl S. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiology Biomarkers & Prevention.* 2003;12:1053–60.
45. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *American Journal of Epidemiology.* 2000;151:703–14. [[PubMed](#)]
46. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: Results from two case-control studies. *Cancer Epidemiology Biomarkers & Prevention.* 2000;9:681–7.
47. Althuis MD, Brogan DD, Coates RJ, et al. Breast cancers among very young premenopausal women (United States). *Cancer Causes Control.* 2003;14:151–60. [[PubMed](#)]
48. Huang WY, Newman B, Millikan RC, et al. Risk of breast cancer according to the status of HER-2/neu oncogene amplification. *Cancer Epidemiol Biomarkers Prev.* 2000;9:65–71. [[PubMed](#)]
49. Sherman ME, Rimm DL, Yang XHR, et al. Variation in breast cancer hormone receptor and HER2 levels by etiologic factors: A population-based analysis. *International Journal of Cancer.* 2007;121:1079–85.
50. Olsson H, Borg A, Ferno M, Ranstam J, Sigurdsson H. HER-2/NEU and INT2 protooncogene amplification in malignant breast tumors in relation to reproductive factors and exposure to exogenous hormones. *Journal of the National Cancer Institute.* 1991;83:1483–7. [[PubMed](#)]
51. Gammon MD, Hibshoosh H, Terry MB, et al. Oral contraceptive use and other risk factors in relation to HER-2/neu overexpression in breast cancer among young women. *Cancer Epidemiol Biomarkers Prev.* 1999;8:413–9. [[PubMed](#)]
52. Swede H, Moysich KB, Freudenheim JL, et al. Breast cancer risk factors and HER2 over-expression in tumors. *Cancer Detection and Prevention.* 2001;25:511–9. [[PubMed](#)]
53. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* 3RD. Philadelphia: Lippincott Williams & Wilkins; 2008.
-

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J Natl Cancer Inst. 1994 Apr 6; 86(7):505-14.
[*J Natl Cancer Inst.* 1994]
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[*Contraception.* 1997]
- [ReviewBreast cancer and hormonal contraceptives: further results. Collaborative Group on Hormonal Factors in Breast Cancer.](#)
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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							P Value**	
	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)		
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)		
			.39		.24		.64	.55	

Triple-negative (ER-/PR-/HER2-) status

	Controls (N=1,569)		All breast cancer (N=897)		Triple-negative (N=187)		Non triple-negative (N=710)		P Value**
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)		
P for trend									
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		
1 st 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)		
2 nd 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	

Triple-negative (ER-/PR-/HER2-) status

	Controls (N=1,569)		All breast cancer (N=897)		Triple-negative (N=187)		Non triple-negative (N=710)		P Value ^{**}
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)		
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

Triple-negative (ER-/PR-/HER2-) status

	Controls (N=1,569)		All breast cancer (N=897)		Triple-negative (N=187)		Non triple-negative (N=710)		P Value ^{**}
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)		
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
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

Triple-negative (ER-/PR-/HER2-) status

	Controls (N=1,569)		All breast cancer (N=897)		Triple-negative (N=187)		Non triple-negative (N=710)		P Value**
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)		
OC									
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

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