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

Jessica M. Dolle,¹ Janet R. Daling,¹ Emily White,^{1,3} Louise A. Brinton,⁴ David R. Doody,¹ Peggy L. Porter,² and Kathleen E. Malone^{1,3}

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

Abstract

Little is known about the etiologic profile of triple-negative breast cancer (negative for estrogen receptor/progesterone receptor/human epidermal growth factor), a breast cancer subtype associated with high mortality and inadequate therapeutic options. We undertook this study to assess the risk for triple-negative breast cancer among women 45 years of age and younger in relation to demographic/lifestyle factors, reproductive history, and oral contraceptive use. Study participants were ascertained in two previous population-based, case-control studies. Eligible cases included all primary invasive breast cancers among women ages 20 to 45 years in the Seattle–Puget Sound area, diagnosed between January 1983 and December 1992, for whom complete data was obtained for estrogen receptor, progesterone receptor, and human epidermal growth factor status ($n = 897$; including $n = 187$ triple-negative breast cancer cases). Controls were age matched and ascertained via random digit dialing. Oral contraceptive use ≥ 1 year was associated with a 2.5-fold increased risk for triple-negative breast cancer (95% confidence

interval, 1.4–4.3) and no significantly increased risk for non-triple-negative breast cancer ($P_{\text{heterogeneity}} = 0.008$). Furthermore, the risk among oral contraceptive users conferred by longer oral contraceptive duration and by more recent use was significantly greater for triple-negative breast cancer than non-triple-negative breast cancer ($P_{\text{heterogeneity}} = 0.02$ and 0.01 , respectively). Among women ≤ 40 years, the relative risk for triple-negative breast cancer associated with oral contraceptive use ≥ 1 year was 4.2 (95% confidence interval, 1.9–9.3), whereas there was no significantly increased risk with oral contraceptive use for non-triple-negative breast cancer among women ≤ 40 years, nor for triple-negative breast cancer or non-triple-negative breast cancer among women 41 to 45 years of age. In conclusion, significant heterogeneity exists for the association of oral contraceptive use and breast cancer risk between triple-negative breast cancer and non-triple-negative breast cancer among young women, lending support to a distinct etiology. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1157–66)

Introduction

Breast cancer is a strikingly heterogeneous disease with variable clinical, pathologic, and molecular features. Microarray expression patterns and immunohistochemical (IHC) 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 [estrogen receptor (ER)/progesterone receptor (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) account for 10% to 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+ (estrogen receptor positive) subtypes (luminal A and B) and three from ER- (estrogen receptor negative) subtypes (HER2+; basal-like and normal-like; refs. 1, 2, 13). More than 90% of triple-negative breast cancer 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 IHC 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).

Triple-negative breast cancer constitutes a clinically challenging type of breast cancer that occurs more frequently in younger women (<50 years; refs. 6, 7, 9, 10) and African-American women (10–12) and is associated with significant aggressiveness as compared with other subtypes (5–7, 9–11). Although triple-negative breast cancer is of growing interest in the clinical and research community, its etiology remains understudied. We undertook this study to evaluate the

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Note: J.M. Dolle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Requests for reprints: Kathleen E. Malone, Fred Hutchinson Cancer Research Center, P.O. Box 19024, M4-C308 Seattle, WA 98109-1024. Phone: 206-667-4632; Fax: 206-667-5948. E-mail: kmalone@fhcrc.org

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

| | Controls (n = 1,569) | | All breast cancer (n = 897) | | Triple-negative status | | | | | | | | P* | | |
|--|----------------------|--------|-----------------------------|--------|---------------------------|-----------|-----|----------|-------------------------------|-----------|-----|----------|-------|-----------|------|
| | | | | | Triple-negative (n = 187) | | | | Non-triple-negative (n = 710) | | | | | | |
| | | | | | n | (%) | OR | (95% CI) | n | (%) | OR | (95% CI) | | n | (%) |
| <i>Demographic/lifestyle factors</i> | | | | | | | | | | | | | | | |
| <i>Age (y)</i> | | | | | | | | | | | | | | | |
| <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 | | | | | 0.006 | | | | 0.81 | | | | 0.002 | 0.13 | |
| <i>Race</i> | | | | | | | | | | | | | | | |
| White | 1,482 | (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) | 0.05 |
| <i>Education</i> | | | | | | | | | | | | | | | |
| <College graduate | 1,035 | (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) | 0.61 |
| <i>Annual income[†]</i> | | | | | | | | | | | | | | | |
| <15,000 | 184 | (11.9) | 81 | (9.1) | 1.0 | Reference | 14 | (7.5) | 1.0 | Reference | 67 | (9.5) | 1.0 | Reference | |
| 15,000-45,000/50,000 | 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) | |
| 45,000/50,000+ | 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 | | | | | 0.39 | | | | 0.24 | | | | 0.64 | 0.55 | |
| <i>Family history of breast cancer</i> | | | | | | | | | | | | | | | |
| 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) | 0.70 |
| <i>BMI (k/m²)[§]</i> | | | | | | | | | | | | | | | |
| <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 | | | | | 0.99 | | | | 0.18 | | | | 0.54 | 0.12 | |
| <i>Smoking</i> | | | | | | | | | | | | | | | |
| 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) | 0.29 |
| <i>Alcohol use (drinks/wk)</i> | | | | | | | | | | | | | | | |
| 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 | | | | | 0.54 | | | | 0.84 | | | | 0.54 | 0.49 | |
| <i>Reproductive factors</i> | | | | | | | | | | | | | | | |
| <i>Age at menarche (y)</i> | | | | | | | | | | | | | | | |
| 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 | | | | | 0.03 | | | | 0.05 | | | | 0.11 | 0.33 | |
| <i>Number of live births</i> | | | | | | | | | | | | | | | |
| None | 396 | (25.2) | 232 | (25.9) | 1.0 | Reference | 53 | (28.3) | 1.0 | Reference | 179 | (25.2) | 1.0 | Reference | |
| 1-3 | 1,057 | (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 | | | | | 0.04 | | | | 0.38 | | | | 0.04 | 0.83 | |
| <i>Age at first birth (y)</i> | | | | | | | | | | | | | | | |
| 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 [¶] | | | | | 0.002 | | | | 0.03 | | | | 0.009 | 0.49 | |
| <i>Lactation**</i> | | | | | | | | | | | | | | | |
| 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 | | | | | 0.97 | | | | 0.99 | | | | 0.98 | 0.78 | |
| <i>Abortion^{††}</i> | | | | | | | | | | | | | | | |
| 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) | 0.82 |

(Continued on the following page)

Table 1. Multivariate adjusted case-control odds ratios and 95% CIs for all breast cancer cases, triple-negative and non-triple-negative cases, in relation to known and suspected risk factors among women 45 y of age and younger, 1983-1992 (Cont'd)

| | Controls (n = 1,569) | | All breast cancer (n = 897) | | Triple-negative status | | | | | | | | P* | | |
|---------------------------------|----------------------|--------|-----------------------------|--------|---------------------------|-----------|-----|--------|-------------------------------|-----------|------|--------|------|-----------|----------|
| | | | | | Triple-negative (n = 187) | | | | Non-triple-negative (n = 710) | | | | | | |
| | n | (%) | n | (%) | OR | (95% CI) | n | (%) | OR | (95% CI) | n | (%) | | OR | (95% CI) |
| <i>Oral contraception</i> | | | | | | | | | | | | | | | |
| <i>OC use (y)</i> | | | | | | | | | | | | | | | |
| Never/<1 | 407 | (25.9) | 197 | (22.0) | 1.0 | Reference | 22 | (11.8) | 1.0 | Reference | 175 | (24.7) | 1.0 | Reference | 0.008 |
| 1+ | 1,162 | (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) | |
| <i>OC duration (y) **</i> | | | | | | | | | | | | | | | |
| 1 to <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) | 0.02 |
| 3 to <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) | |
| <i>P for trend</i> | | | | | 0.85 | | | | | | 0.05 | | 0.45 | | |
| <i>Age at first use (y) **</i> | | | | | | | | | | | | | | | |
| 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) | 0.84 |
| 18 to <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) | |
| <i>P for trend</i> | | | | | 0.05 | | | | | | 0.13 | | 0.10 | | |
| <i>Years since first use **</i> | | | | | | | | | | | | | | | |
| 1 to <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) | 0.74 |
| 15 to <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) | |
| <i>P for trend</i> | | | | | 0.27 | | | | | | 0.74 | | 0.25 | | |
| <i>Years since last use **</i> | | | | | | | | | | | | | | | |
| 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) | 0.01 |
| 1 to <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 to <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 to <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) | |
| <i>P for trend</i> | | | | | 0.86 | | | | | | 0.04 | | 0.39 | | |

NOTE: Risk factors adjusted for age, family history of breast cancer, breastfeeding history, and oral contraceptive duration.

Abbreviations: OR, odds ratio; OC, oral contraceptive.

* $P_{\text{heterogeneity}}$ (association of risk factor with triple-negative versus non-triple-negative breast cancer).

† Because of missing data, race was adjusted for age, breastfeeding history, and oral contraceptive duration but not family history of breast cancer.

‡ Income categories reflect the fact that the two studies combined for the present study used different cutoffs.

§ One year before reference date.

|| Still and live births.

¶ P for trend among parous women only.

** Among parous women.

†† Among gravid women.

‡‡ P_{trend} and $P_{\text{heterogeneity}}$ among oral contraceptive users >1 y only.

contribution of known and suspected breast cancer risk factors to triple-negative breast cancer in a large population-based study.

Materials and Methods

The cases included in this study were originally ascertained for two previous studies through the population-based Seattle-Puget Sound Surveillance, Epidemiology, and End Results 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 y). 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 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 and frequency matched to cases by 5-y age groups.

The second population included the Seattle site participants of the multicenter Women's Interview Study of Health, 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 21-44 y). In-person interviews were completed on 542 women (86% of eligible Seattle cases with invasive disease). Six hundred 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 triple-negative breast cancer, *in situ* cases were excluded. The appropriate institutional review boards approved all protocols.

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

| | ER status | | | | | | | | P* | HER2 status | | | | | | P† | | | | |
|------------------------|-------------------------|--------|---------------|--------|------|-----------|---------------|--------|-----|-----------------|----------|--------|-----------------|-----------|-----------|--------|--------|-----------|-----------|------|
| | Controls (n = 1,569) | | ER- (n = 364) | | | | ER+ (n = 533) | | | HER2- (n = 608) | | | HER2+ (n = 289) | | | | | | | |
| | n | (%) | n | (%) | OR | (95% CI) | n | (%) | | OR | (95% CI) | n | (%) | OR | (95% CI) | | | | | |
| OC use (y) | | | | | | | | | | | | | | | | | | | | |
| 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+ | 1,162 | (74.1) | 305 | (83.8) | 2.0 | (1.3-2.9) | 394 | (74.1) | 1.1 | (0.8-1.4) | 0.005 | 483 | (79.6) | 1.4 | (1.1-1.9) | 216 | (74.7) | 1.2 | (0.8-1.7) | 0.27 |
| OC duration (y)‡ | | | | | | | | | | | | | | | | | | | | |
| 1 to <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 to <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 | | | | | 0.05 | | | | | 0.15 | 0.004 | 0.94 | | | 0.79 | | | | 0.89 | |
| Age at first use (y)‡ | | | | | | | | | | | | | | | | | | | | |
| 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 to <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 | | | | | 0.10 | | | | | 0.14 | 0.96 | 0.18 | | | 0.05 | | | | 0.40 | |
| Years since first use‡ | | | | | | | | | | | | | | | | | | | | |
| 1 to <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 to <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 | | | | | 0.80 | | | | | 0.17 | 0.40 | 0.78 | | | 0.07 | | | | 0.12 | |
| 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 to <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 to <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 to <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 | | | | | 0.02 | | | | | 0.07 | <0.001 | 0.95 | | | 0.62 | | | | 0.65 | |

NOTE: Risk factors adjusted for age, family history of breast cancer, and breastfeeding history.

*P_{heterogeneity} (association of risk factor with ER- versus ER+ breast cancer).

† P_{heterogeneity} (association of risk factor with HER2- versus HER2+ breast cancer).

‡ P_{trend} and P_{heterogeneity} among oral contraceptive users >1 y only.

In-person interviews of comparable format, covering a broad range of risk factors that included lifestyle/demographic factors, reproductive history, and oral contraceptive use, were administered to participants in both studies. Tumor specimens were obtained for 1,019 of the 1,286 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+ 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 triple-negative breast cancer (n = 187, 20.8%) and non-triple-negative breast cancer tumors partly because of 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 oral contraceptive variables and breast cancer defined separately and jointly by ER and HER2 status (collapsed across PR status; ER/PR r = 0.60) 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 triple-negative breast cancer and compare our results with ER and HER2 findings from previous studies. Furthermore, analyses were repeated stratified by source study and also restricted to participants with reference dates after 1985 (the latter because of an ascertainment delay for women with a reference date before the start of the study in 1986).

Unordered polytomous logistic regression (STATA mlogit; Stata Statistical Software: Release 9, StataCorp) was used to determine odds ratios (as an approximation of the relative risk) and 95% confidence interval (95% CI) for the risk for triple-negative breast cancer and non-triple-negative breast cancer, 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; kilogram per square meter) 1 y before 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 oral contraceptive use (never/<1 y versus ≥ 1 y, oral contraceptive duration, age at first use, years since first use, and years since last use). Those variables that produced $\geq 10\%$ change in the odds ratio for any triple-negative breast cancer risk factor were considered as adjustment factors in the final model. All final risk estimates are adjusted for age, family history, lactation history, and oral contraceptive duration (that is, multivariate adjusted). Trend tests for ordered catego-

rical exposure variables were done 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 oral contraceptive use were associated with breast cancer risk beyond any effect of never/<1 y versus ≥ 1 y use, we tested the trend of oral

Table 3. Multivariate adjusted case-control odds ratios and 95% CIs for ER- and ER+ breast cancer in relation to oral contraceptive use, stratified by HER2 status among women age 45 y and younger, 1983-1992

| | Controls (n = 1,569) | | ER- (n = 364) | | | | ER+ (n = 533) | | | | P* |
|------------------------------------|----------------------|--------|---------------|--------|------|-----------|---------------|--------|------|-----------|--------|
| | n | (%) | n | (%) | OR | (95% CI) | n | (%) | OR | (95% CI) | |
| <i>Among HER2-</i> | | | n = 252 | | | | n = 356 | | | | |
| OC use (y) | | | | | | | | | | | |
| Never/<1 | 407 | (25.9) | 32 | (12.7) | 1.0 | Reference | 92 | (25.9) | 1.0 | Reference | 0.01 |
| 1+ | 1,162 | (74.1) | 220 | (87.3) | 2.2 | (1.4-3.5) | 263 | (74.1) | 1.1 | (0.8-1.6) | |
| OC duration (y) [†] | | | | | | | | | | | |
| 1 to <3 | 327 | (20.8) | 45 | (17.9) | 1.4 | (0.8-2.6) | 81 | (22.8) | 1.3 | (0.9-2.0) | <0.001 |
| 3 to <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 | | | | | 0.03 | | | | 0.05 | | |
| 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) | 0.80 |
| 18 to <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 | | | | | 0.17 | | | | 0.51 | | |
| Years since first use [†] | | | | | | | | | | | |
| 1 to <15 | 313 | (19.9) | 50 | (19.8) | 2.1 | (1.1-4.0) | 39 | (11.0) | 1.0 | (0.6-1.9) | 0.67 |
| 15 to <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 | | | | | 0.88 | | | | 0.58 | | |
| 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) | <0.001 |
| 1 to <5 | 190 | (12.1) | 41 | (16.3) | 3.5 | (1.9-6.6) | 35 | (9.9) | 1.3 | (0.7-2.2) | |
| 5 to <10 | 255 | (16.3) | 56 | (22.2) | 2.6 | (1.5-4.6) | 44 | (12.4) | 0.8 | (0.4-1.3) | |
| 10 to <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 | | | | | 0.04 | | | | 0.03 | | |
| <i>Among HER2+</i> | | | n = 112 | | | | n = 177 | | | | |
| OC use (y) | | | | | | | | | | | |
| Never/<1 | 407 | (25.9) | 27 | (24.1) | 1.0 | Reference | 46 | (26.0) | 1.0 | Reference | 0.18 |
| 1+ | 1,162 | (74.1) | 85 | (75.9) | 1.6 | (0.8-3.0) | 131 | (74.0) | 1.0 | (0.6-1.5) | |
| OC duration (y) [†] | | | | | | | | | | | |
| 1 to <3 | 327 | (20.8) | 21 | (18.8) | 1.5 | (0.7-3.2) | 37 | (20.9) | 1.0 | (0.5-1.7) | 0.83 |
| 3 to <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 | | | | | 0.73 | | | | 0.91 | | |
| Age at first use (y) [†] | | | | | | | | | | | |
| 22+ | 260 | (16.6) | 19 | (17.0) | 1.4 | (0.6-3.2) | 28 | (15.8) | 0.8 | (0.4-1.5) | 0.79 |
| 18 to <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 | | | | | 0.26 | | | | 0.09 | | |
| Years since first use [†] | | | | | | | | | | | |
| 1 to <15 | 313 | (19.9) | 20 | (17.9) | 1.3 | (0.5-3.4) | 23 | (13.0) | 0.9 | (0.4-1.8) | 0.62 |
| 15 to <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 | | | | | 0.42 | | | | 0.08 | | |
| 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) | 0.36 |
| 1 to <5 | 190 | (12.1) | 22 | (19.6) | 3.5 | (1.5-8.1) | 18 | (10.2) | 1.2 | (0.6-2.6) | |
| 5 to <10 | 255 | (16.3) | 15 | (13.4) | 1.3 | (0.6-3.1) | 21 | (11.9) | 0.7 | (0.4-1.4) | |
| 10 to <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 | | | | | 0.24 | | | | 0.84 | | |

NOTE: Risk factors adjusted for age, family history of breast cancer, and breastfeeding history.

*P_{heterogeneity} (association of risk factor with ER- versus ER+ breast cancer).

†P_{trend} and P_{heterogeneity} among oral contraceptive users >1 y only.

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

| | Controls (n = 1,569) | | All breast cancer (n = 897) | | Triple-negative status | | | | | | | | P* | |
|-----------------------------------|----------------------|--------|-----------------------------|--------|---------------------------|-----------|-----|--------|-------------------------------|------------|-----|--------|------|-----------|
| | | | | | Triple-negative (n = 187) | | | | Non-triple-negative (n = 710) | | | | | |
| | n | (%) | n | (%) | OR | (95% CI) | n | (%) | OR | (95% CI) | n | (%) | | OR |
| <i>Among women ≤40 y of age</i> | | | | | | | | | | | | | | |
| | n = 1,156 | | n = 590 | | n = 141 | | | | n = 449 | | | | | |
| OC use (y) | | | | | | | | | | | | | | |
| 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) |
| OC duration (y) † | | | | | | | | | | | | | | |
| 1 to <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 to <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 | | | | | 0.86 | | | | 0.17 | | | | 0.58 | |
| Age at first use (y) † | | | | | | | | | | | | | | |
| 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 to <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 | | | | | 0.02 | | | | 0.12 | | | | 0.04 | |
| 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) |
| 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 to <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 to <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 | | | | | 0.95 | | | | 0.15 | | | | 0.46 | |
| <i>Among women 41-45 y of age</i> | | | | | | | | | | | | | | |
| | n = 413 | | n = 307 | | n = 46 | | | | n = 261 | | | | | |
| OC use (y) | | | | | | | | | | | | | | |
| 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) |
| OC duration (y) † | | | | | | | | | | | | | | |
| 1 to <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 to <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 | | | | | 0.91 | | | | 0.11 | | | | 0.65 | |
| Age at first use (y) † | | | | | | | | | | | | | | |
| 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 to <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 | | | | | 0.85 | | | | 0.57 | | | | 1.0 | |
| 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) |
| 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 to <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 to <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 | | | | | 0.33 | | | | 0.08 | | | | 0.10 | |

NOTE: Risk factors adjusted for age, family history of breast cancer, and breastfeeding history.

*P_{heterogeneity} (association of risk factor with triple-negative versus non-triple-negative breast cancer).

† P_{trend} and P_{heterogeneity} among oral contraceptive users >1 y only.

contraceptive duration, age at first use, years since first use, and years since last use among the oral contraceptive users (≥1 y) 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 oral contraceptive use, P_{heterogeneity} was limited to parous women and oral contraceptive users ≥1 y, 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 previous studies on younger women (Table 1). Specifically, older age, family history of breast cancer, earlier menarche age, induced abortion, and oral contraceptive use were associated with an increased risk for breast cancer. Risk was decreased in relation to greater number of births and younger age at first birth. Oral contraceptive use ≥ 1 year was associated with a modest increased risk for breast cancer, and among oral contraceptive 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 ($n = 710$) triple-negative breast cancer (Table 1), we found that oral contraceptive use ≥ 1 year ($P_{\text{heterogeneity}} = 0.008$), oral contraceptive duration ($P_{\text{heterogeneity}} = 0.02$), and years since last oral contraceptive use ($P_{\text{heterogeneity}} = 0.01$) conferred significantly different risk estimates by case group, and BMI ≥ 30 kg/m² was associated with a borderline significant increased risk for triple-negative breast cancer (odds ratio, 1.3; 95% CI, 0.8-2.2) and a nonsignificant decreased risk for non-triple-negative breast cancer (odds ratio, 0.8; 95% CI, 0.6-1.2) in women of all ages. Upon restriction to women ages 41 to 45 years, the risk for triple-negative breast cancer in relation to BMI ≥ 30 kg/m² was further elevated (odds ratio, 2.2; 95% CI, 0.9-5.24) whereas that of non-triple-negative breast cancer did not change substantively (odds ratio, 0.9; 95% CI, 0.5-1.6; results not presented). Oral contraceptive use ≥ 1 year was associated with a 2.5-fold increased risk for triple-negative breast cancer (95% CI, 1.4-4.3) and no significantly increased risk for non-triple-negative breast cancer. Among oral contraceptive users, risk for triple-negative breast cancer increased with longer duration of oral contraceptive use ($P_{\text{trend}} = 0.05$) and fewer years since last oral contraceptive use ($P_{\text{trend}} = 0.04$), relationships that were absent for non-triple-negative breast cancer. We attempted to disentangle the effect of oral contraceptive 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 oral contraceptive 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 for ER-breast cancer conferred by oral contraceptive use ≥ 1 year (odds ratio, 2.0; 95% CI, 1.3-2.9), which differed significantly from the absence of an association with ER+ breast cancer (odds ratio, 1.1; 95% CI, 0.8-1.4; $P_{\text{heterogeneity}} = 0.005$), as did the risk conferred by oral contraceptive duration ($P_{\text{heterogeneity}} = 0.004$) and years since last use ($P_{\text{heterogeneity}} < 0.001$). The risk for ER- breast cancer increased substantially with longer oral contraceptive duration ($P_{\text{trend}} = 0.05$) and fewer years since use ($P_{\text{trend}} = 0.02$).

Ever use of oral contraceptives was associated with a modest increased risk for HER2- disease (odds ratio, 1.4; 95% CI, 1.1-1.9) and a lower nonstatistically significant risk for HER2+ disease (odds ratio, 1.2; 95% CI, 0.8-1.7). No significant trends across oral contraceptive use features were observed in relation to the risk for HER2- breast cancer, but risk for HER2+ disease did seem to increase with younger age at first use ($P_{\text{trend}} = 0.05$). Heterogeneity between HER2 subtypes was not

statistically significant for any oral contraceptive use variable. For all aspects of oral contraceptive use, risk estimates were greater for ER- breast cancer than for HER2- breast cancer.

Upon further cross-classification by both ER and HER2 status (Table 3), we observed significantly elevated risk for breast cancer across all oral contraceptive variables consistently and almost exclusively in the ER-/HER2-subset; odds ratios were comparable, only slightly less than those seen in relation to the risk for triple-negative breast cancer. The risk for ER-/HER2- breast cancer increased with longer oral contraceptive duration ($P_{\text{trend}} = 0.03$) and fewer years since last use ($P_{\text{trend}} = 0.04$). We observed a large degree of heterogeneity between HER2-ER subtypes according to oral contraceptive use ≥ 1 year ($P_{\text{heterogeneity}} = 0.01$), as well as oral contraceptive duration ($P_{\text{heterogeneity}} < 0.001$) and years since last use ($P_{\text{heterogeneity}} < 0.001$).

Finally, we examined the effect of oral contraceptive use according to triple-negative breast cancer status stratified by age at breast cancer diagnosis ≤ 40 and 41 to 45 years (Table 4). Among women 41 to 45 years of age, there was no significantly increased risk for breast cancer for any aspect of oral contraceptive use, overall and within triple-negative breast cancer-defined subgroups; however, we did find significant heterogeneity between the risk for triple-negative breast cancer and non-triple-negative breast cancer according to years since last use ($P_{\text{heterogeneity}} = 0.01$). Among triple-negative breast cancer cases ≤ 40 years of age, all risk estimates for oral contraceptive use variables were approximately two times greater than those in the combined triple-negative breast cancer age group estimates. In women ≤ 40 years of age, oral contraceptive use ≥ 1 year was associated with a >4-fold increased risk for triple-negative breast cancer (odds ratio, 4.2; 95% CI, 1.9-9.3) and no increased risk for non-triple-negative breast cancer (odds ratio, 1.2; 95% CI, 0.9-1.7; $P_{\text{heterogeneity}} < 0.001$). Also, among women ≤ 40 years of age, we found that the risk for breast cancer overall and of non-triple-negative breast cancer increased with younger age at first use ($P_{\text{trend}} = 0.02$ and 0.04, 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. American Joint Committee on Cancer stage and tumor grade did not differ significantly between the tumors available for assay and those unavailable.

Discussion

In this population-based study on breast cancer in women under 45 years of age, the risk conferred by oral contraceptive use varied significantly between triple-negative breast cancer and non-triple-negative breast cancer. Oral contraceptive use ≥ 1 year was associated with a 2.7-fold increased risk for triple-negative breast cancer. The risk for triple-negative breast cancer was

further heightened in relation to longer oral contraceptive duration and fewer years since last use. Among women ≤ 40 years, the strength of the oral contraceptive use association with triple-negative breast cancer was further magnified. Similar relationships were not observed in relation to non-triple-negative breast cancer, providing support for an etiologic distinction.

The relationship between oral contraceptive 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 oral contraceptive use and breast cancer risk has remained less clear. A large pooled analysis (28) and recent meta-analysis (29) have reported an increased risk for breast cancer (~20-30%) in relation to oral contraceptive use among premenopausal women. Previous studies have also shown risk in relation to oral contraceptive use to be concentrated among younger premenopausal women (30, 31). These findings are compatible with the present study and consistent with our previous reports on oral contraceptive use effects in the two study populations from which our study population was drawn (17, 19).

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

Interest in the clinical and pathologic characterization of triple-negative breast cancer 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/triple-negative breast cancer tends to have a poor prognosis compared with 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/triple-negative breast cancer patients are lacking. Carey et al. (5) reported that triple-negative breast cancer (and less common HER2+/ER-) patients had worse survival than luminal subtypes despite higher chemosensitivity to conventional anthracycline-based therapy.

Few studies to date have focused on etiologic risk factors for basal-like/triple-negative breast cancer, 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 on women ages 20 to 74 years. Among women of all ages, they observed an increased risk for 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 oral contraceptive use, no differences were observed. Yang et al. (37) evaluated established breast cancer etiologic factors by subtype within the Polish Breast Cancer Study. Among premen-

opausal women, increasing BMI (per five units) was associated with a borderline-significant increased risk for basal-like breast cancer (odds ratio, 1.2; 95% CI, 0.9-1.6) and a reduced risk of luminal A breast cancer (odds ratio, 0.7; 95% CI, 0.6-0.9; $P_{\text{heterogeneity}} = 0.003$). Oral contraceptive 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- breast cancer is known to be more frequent among young women (38), African-American women (39), and *BRCA1* carriers (40). ER+ breast cancer is associated with improved response to hormonal therapy, longer disease-free intervals, and improved survival (41). Previous studies on 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+ breast cancer only. Several studies that have examined elevated BMI in premenopausal women by hormone receptor status have discerned an increased risk for ER-/PR- breast cancer but not ER+/PR+ breast cancer (43, 44), whereas others have not (38, 45, 46). The relationship between oral contraceptive use and risk for ER-defined breast cancer is somewhat ambiguous. Several studies have reported an increased risk for ER- breast cancer in young women associated with ever using oral contraceptives (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 oral contraceptive use were associated with a significantly increased risk for 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 ($P_{\text{trend}} = 0.01$) within the Polish Breast Cancer Study. Some studies on premenopausal women have found an increased risk for HER2+ breast cancer in relation to early oral contraceptive use (50, 51), whereas others have found no association between oral contraceptive 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 triple-negative breast cancer 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 triple-negative breast cancer cases ages 41 to 45 years. It is worth noting that the diagnosis years in this study predate 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 1,019 (79.2%) of the 1,286 women in our study. To the extent that the

availability of tumor specimens was related to features that are also related to triple-negative breast cancer, our results may be biased. As with all studies on triple-negative breast cancer, there is also potential for misclassification of triple-negative breast cancer 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 has become the standard for discrimination of HER2 intermediate IHC scores. Because a portion of the 2+ tumors would not show amplification by fluorescence *in situ* hybridization analysis, we may have misclassified some true HER2- cases as HER2+. In addition, a small number of tumors that exhibit only 1+ immunostaining could be falsely low by IHC. For the analyses presented in this study, we used the standard clinical definition of HER2-, which included negative and low-positive staining. We also repeated all analyses with a purer HER2- definition by excluding low positives from the triple-negative breast cancer 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, oral contraceptive use was common in our study population and extensive detail on usage patterns was collected, allowing us to assess associations in a thorough manner. By excluding non-oral contraceptive users from trend tests, we were able to discern differences 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 interviewer bias.

The strong association between oral contraceptive use and the risk for triple-negative breast cancer 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 triple-negative breast cancer 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 triple-negative breast cancer and in facilitating the development of strategies for prevention, treatment, and management of triple-negative breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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