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Recent Use of Oral Contraceptives and Risk of Luminal B, Triple-Negative, and HER2-Overexpressing Breast Cancer

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Abstract

Oral contraceptive use is a well-established risk factor for breast cancer and is common among reproductive-aged women in the USA. Its relationship with less common, more aggressive, molecular subtypes is less clear. A population-based case-case analysis was conducted comparing three less common molecular subtypes to luminal A breast cancer among 1701 premenopausal cases aged 21–49 diagnosed with a first primary invasive breast cancer between 2004 and 2015. Medical record reviews and structured interviewer-administered questionnaires were used to collect data on oral contraceptive use. Multinomial logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for recency of oral contraceptive use for each subtype of breast cancer. Current use of oral contraceptives and use within 5 years before diagnosis was associated with lower odds of H2E tumors compared with luminal A tumors [OR = 0.5, 95% CI: 0.3, 0.9 and OR = 0.5, 95% CI: 0.4, 0.8, respectively] with increasing duration associated with decreasing odds (p for trend < 0.05). Oral contraceptive use was not associated with risks of TN or luminal B breast cancer. Oral contraceptive use may be more strongly positively associated with risks of luminal A, luminal B, and TN breast cancer than with risk of H2E tumors. These findings contribute to the etiological understanding of different molecular subtypes of breast cancer.

Keywords Oral contraceptives · Breast cancer · Triple-negative · HER2-overexpressing · Luminal

Introduction

Oral contraceptive (OC) use is a well-studied risk factor for breast cancer [1]. Results from one large meta-analysis showed that current OC use during the year prior to diagnosis was associated with a 24% increase in breast cancer risk [1]. Breast cancer can be classified into four molecular subtypes, defined by joint estrogen receptor (ER)/progesterone receptor (PR)/HER2-neu (HER2) expression: luminal A (ER+/HER2−), luminal B (ER+/HER2+), HER2-overexpressing (H2E) (ER−/HER2+), and triple-negative (TN) (ER−/PR−/HER2−). The subtypes differ in etiology, treatment options, and prognosis [2]. Some studies have shown an increased risk of TN breast cancer associated with OC use [3–6], but others have not [7–11], and the association with other subtypes is less clear [3–12]. Recency [3–5], duration of use [3–5, 12], and the dosage and type of hormones in OCs [3, 12] have been shown to influence the association.

Investigating the heterogeneity in risk of breast cancer subtypes associated with OC use can increase understanding of their etiologic differences. This population-based case-case analysis compares the odds of luminal B, TN, and H2E breast cancers associated with OC use to the odds of luminal A breast cancers among premenopausal women in the Seattle-Puget Sound region and New Mexico to better understand the association between OC use and the less common, more aggressive molecular subtypes of breast cancer that disproportionately impact younger women.

Methods

Study Population

This study was approved by institutional review boards at the Fred Hutchinson Cancer Research Center and University of

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New Mexico. Patient identification and data collection methods have been described elsewhere [13]. Briefly, women aged 20–69 years and diagnosed with breast cancer between June 1, 2004, and June 30, 2012, in the Albuquerque, New Mexico greater metropolitan area and between June 1, 2004, and June 30, 2015, in the Seattle-Puget sound region were considered for study eligibility. Subtypes were defined by joint ER/PR/HER2 status based on clinical data abstracted from patient medical records: luminal A (ER+/HER2−), luminal B (ER+/HER2+), H2E (ER−/HER2+), and TN (ER−/PR−/HER2−). HER2/neu was determined by the combination of immunohistochemical stains (IHC) or fluorescent in situ hybridization (FISH). IHC was used to classify HER2 as positive or negative, but if IHC results were equivocal, FISH test was performed to clarify the result. All identified TN and H2E cases and a random, frequency-matched, sample of luminal A and luminal B were considered eligible. From the total 4557 pre- and postmenopausal breast cancer cases, this analysis was restricted to 1701 premenopausal breast cancer cases aged 21–49 years who were not current users of hormone replacement therapy and whose body mass index (BMI) and use of OCs in the 5 years before diagnosis could be ascertained through medical records or patient interview.

Data Collection and Exposure Variables

Medical record reviews and structured interviewer-administered questionnaires recorded information on demographic, epidemiologic, and clinical factors and were conducted by trained staff in Seattle and New Mexico using the same protocol and instruments. To ensure abstraction methods were consistent between study sites, a random 10% of completed abstracts were exchanged and reviewed by each study site. OC names and dates of use in the 5 years prior to breast cancer diagnosis were captured by medical records and questionnaires. Prioritizing medical records, OC use was categorized as current use (use within the year before diagnosis), use between 1 and 5 years before diagnosis, use within the 5 years before diagnosis, or no use in the 5 years before diagnosis. Current estrogen dose and progestin type was assigned using the current OC.

Statistical Analysis

Medical record data were used for 1285, but for 416 cases (24%), medical review data was missing or incomplete and interview data was used instead. Thirty-four cases (2%) used OCs in the 5 years before diagnosis but use within the year before diagnosis could not be determined. The final analytic set included 1701 cases.

Multinomial logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for each subtype of breast cancer in analyses for recency, duration, and progestin type. For all analyses, cases with no use of OCs in the 5 years before diagnosis were the unexposed group and luminal A cases were the reference outcome. Due to limited numbers of luminal B and H2E cases, a separate logistic regression model was used to estimate ORs for TN breast cancer in analyses for current estrogen dose and progestin. Effect modification by other breast cancer risk factors was assessed using a likelihood ratio test, and none was observed. All models were adjusted for matching variables: age at diagnosis (in 5-year groups, youngest group < 30 years), study site, and year of diagnosis (as a continuous variable). Race (non-Hispanic white, Hispanic white, African American, Asian/Pacific Islander, American Indian) and BMI (continuous) were also included in the model, as adjustment for each variable changed risk estimates by more than 10%. p values for trend, using duration of use in the 5 years before diagnosis (in months) and estrogen dose of the current OC (in micrograms) as continuous variables, were computed using a likelihood ratio test. p values less than 0.05 were considered significant.

Results

Distribution of breast cancer risk factors did not differ greatly across subtypes, except that TN cases were somewhat more frequently Hispanic white, African American, and obese and H2E cases were more likely to be nulliparous (Table 1). Current use of OCs and use within the 5 years before diagnosis, relative to no use in the 5 years before diagnosis, was associated with lower odds of H2E, compared with luminal A breast cancer (Table 2) (current use OR = 0.5 and 95% CI: 0.3, 0.9; use within 5 years OR = 0.5 and 95% CI: 0.4–0.8). Among current users and users within the 5 years before diagnosis, increasing duration of use was associated with lower odds of H2E breast cancer, compared with luminal A (p for trend < 0.05). There was no statistically significant association between OC use and TN or luminal B breast cancer.

Although OR estimates for current use of gonane progestins were lower than estimates for estranes in a multinomial logistic regression model (data not shown), there was no statistically significant relationship between progestin type (estranes, gonanes, and drospirenone) and subtype. In separate logistic regression models, there was no statistically significant association between current estrogen dose or current progestin and TN breast cancer (Table 3).

Discussion

In this population-based case-case study, we found heterogeneity in risk of breast cancer associated with OC use by molecular subtype. H2E cancer risk differed from that for luminal

Table 1 Distribution of patient characteristics and known breast cancer risk factors by molecular subtype

Variable	Luminal A ($N = 778$) *n*, %	Luminal B ($N = 179$) *n*, %	Triple-negative ($N = 556$) *n*, %	HER2-overexpressing ($N = 188$) *n*, %
Year of breast cancer diagnosis				
2004–2006	234 (30.1)	48 (26.8)	173 (31.1)	49 (26.1)
2007–2009	250 (32.1)	55 (30.7)	188 (33.8)	55 (29.3)
2010–2012	162 (20.8)	50 (27.9)	121 (21.8)	52 (27.7)
2013–2015	132 (17.00)	26 (14.5)	74 (13.3)	32 (17.0)
Age at breast cancer diagnosis (years)				
< 30	19 (2.4)	12 (6.7)	21 (3.8)	6 (3.2)
30–34	71 (9.1)	25 (14.0)	68 (12.2)	20 (10.6)
35–39	175 (22.5)	37 (20.7)	119 (21.4)	44 (23.4)
40–44	278 (35.7)	53 (29.6)	190 (34.2)	54 (28.7)
45–49	235 (30.2)	52 (29.1)	158 (28.4)	64 (34.0)
Study site				
Seattle-Puget Sound	721 (92.7)	163 (91.1)	452 (81.3)	158 (84.1)
Albuquerque	57 (7.3)	16 (8.9)	104 (18.7)	30 (16.0)
Race/ethnicity				
Non-Hispanic white	590 (75.8)	131 (73.2)	396 (71.2)	133 (70.7)
Hispanic white	60 (7.7)	18 (10.1)	65 (11.7)	19 (10.1)
African American	34 (4.4)	7 (3.9)	52 (9.4)	13 (6.9)
Asian/Pacific Islander	81 (10.4)	18 (10.1)	31 (5.6)	21 (11.2)
American Indian	13 (1.7)	5 (2.8)	12 (2.2)	2 (1.1)
First-degree family history				
No	606 (80.0)	149 (85.1)	441 (80.8)	167 (89.3)
Yes	152 (20.1)	26 (14.9)	105 (19.2)	20 (10.7)
Missing	20	4	10	1
Number of full-term pregnancies				
0	225 (28.9)	43 (24.0)	150 (27.0)	36 (19.2)
1	138 (17.7)	40 (22.4)	110 (19.8)	36 (19.2)
2	281 (36.1)	57 (31.8)	182 (32.7)	72 (38.3)
3+	134 (17.2)	39 (21.8)	114 (20.5)	44 (23.4)
Smoking status at breast cancer diagnosis				
Never	499 (64.2)	102 (57.0)	341 (61.4)	121 (64.4)
Current	79 (10.2)	25 (14.0)	78 (14.1)	21 (11.2)
Former	166 (21.4)	44 (24.6)	124 (22.3)	36 (19.2)
Not current/NOS	33 (4.3)	8 (4.5)	12 (2.2)	10 (5.3)
Missing	1	0	1	0
Body mass index				
< 25	396 (50.9)	94 (52.5)	204 (36.7)	82 (43.6)
25–29	212 (27.3)	48 (26.8)	156 (28.1)	53 (28.2)
30+	170 (21.9)	37 (20.7)	196 (35.3)	53 (28.2)

A, in that current users and users within 5 years before diagnosis had a lower risk of H2E cancer relative to cases with no use. Estrogen and progestin influence cell proliferation in breast cancer cells that are HR+ [14, 15] and progesterone has been shown to increase proliferation and amount of progenitor cells in a mouse model of the human breast, potentially influencing the proliferation and differentiation of breast epithelial cells [16]. Combined OCs have also been shown to increase proliferation of luminal epithelial breast tissue, compared with a natural menstrual cycle [17]. The luminal A subtype is more similar to mature luminal cells than the TN or H2E subtype, and under the cancer stem cell hypothesis, the luminal A subtype likely arises from luminal progenitor cells [18–20]. So, OCs may increase the proliferation of

Table 2 Association between oral contraceptive use, by recency of use and duration of use, and breast cancer subtype, adjusted for age at diagnosis (5-year groups), study site, year of diagnosis (continuous), race, and body mass index at diagnosis (continuous)

	Luminal A ($N = 778$)	Luminal B ($N = 179$)		Triple-negative ($N = 556$)		HER2-overexpressing ($N = 188$)	
Time since last oral contraceptive use in 5 years before diagnosis	*N* (%)	*N* (%)	OR (95% CI)	*N* (%)	OR (95% CI)	*N* (%)	OR (95% CI)
No use	532 (68.4)	127 (71.0)	1.0 (ref)	381 (68.5)	1.0 (ref)	149 (79.3)	1.0 (ref)
≤ 5 years	246 (31.6)	52 (29.1)	0.8 (0.5, 1.1)	175 (31.5)	1.0 (0.7, 1.3)	39 (20.7)	*0.5 (0.4, 0.8)*
< 3 years duration	93 (12.0)	23 (12.9)	0.9 (0.5, 1.5)	71 (12.8)	0.9 (0.6, 1.3)	17 (9.0)	0.6 (0.3, 1.0)
3+ years duration	144 (18.5)	25 (14.0)	0.6 (0.4, 1.0)	93 (16.7)	1.0 (0.7, 1.4)	22 (11.7)	*0.6 (0.3, 0.9)*
p for trend[a]			0.085		0.859		*0.009*
> 1 and ≤ 5 years	78 (10.0)	21 (11.7)	1.0 (0.6, 1.7)	66 (11.9)	1.1 (0.7, 1.6)	17 (9.0)	0.7 (0.4, 1.3)
Current use[b]	155 (19.9)	30 (16.8)	0.7 (0.5, 1.2)	90 (16.2)	0.9 (0.6, 1.3)	21 (11.2)	*0.5 (0.3, 0.9)*
< 3 years duration	37 (4.8)	8 (4.5)	0.8 (0.3, 1.7)	22 (4.0)	0.6 (0.3, 1.1)	5 (2.7)	*0.3 (0.1, 1.0)*
3+ years duration	115 (14.8)	22 (12.3)	0.7 (0.4, 1.2)	67 (12.1)	1.1 (0.7, 1.6)	16 (8.5)	0.6 (0.3, 1.1)
p for trend			0.130		0.782		*0.013*

Four current users and 24 users within 5 years were missing information on duration of use

[a] *p* value for trend, using duration of use in the 5 years before diagnosis (in months) as a continuous variable, and cases with no use as the referent category (duration = 0 months), computed using a likelihood ratio test

[b] Current use defined as any oral contraceptive use within the year before diagnosis

Italicized results indicate statistical significance ($p<0.05$)

cells most similar to luminal A breast cancer cells and the amount of cells from which luminal A breast cancer is thought to arise, which is consistent with our finding that OC use is less strongly associated with H2E breast cancer than with hormone receptor positive luminal A, breast cancer. However, we did not observe the same association with TN breast cancer, so this mechanism may not fully explain our findings.

Table 3 Association between current oral contraceptive use, by estrogen dose and progestin type, and triple-negative breast cancer, adjusted for age at diagnosis (5-year groups), study site, year of diagnosis (continuous), race, and body mass index at diagnosis (continuous)

	Luminal A ($N = 778$)	Triple-negative ($N = 556$)	
Oral contraceptive use in 5 years before diagnosis	*N* (%)	*N* (%)	OR (95% CI)
No use	532 (68.4)	381 (68.5)	1.0 (ref)
Current[a] estrogen dose			
< 30 mcg	16 (2.1)	12 (2.2)	1.2 (0.5, 2.8)
30–35 mcg	63 (8.1)	51 (9.2)	1.3 (0.8, 2.1)
p for trend[b]			0.214
Current[a] progestin type			
Estranes			
Norethindrone	20 (2.6)	15 (2.7)	1.0 (0.4, 2.3)
Norethindrone acetate	19 (2.4)	13 (2.3)	1.1 (0.5, 2.6)
Gonanes			
Norgestimate	26 (3.3)	13 (2.3)	0.9 (0.4, 1.9)
Levonorgestrel	29 (3.7)	15 (2.7)	0.7 (0.3, 1.5)
Other			
Drospirenone	15 (1.9)	11 (2.0)	1.6 (0.6, 4.2)

Of triple-negative cases, 27 current oral contraceptive users were missing current estrogen dose and 15 were missing progestin type; of luminal A cases, 76 current oral contraceptive users were missing current estrogen dose and 39 were missing progestin type

[a] Current use defined as any oral contraceptive use within the year before diagnosis

[b] *p* value for trend, using current estrogen dose (in mcg) as a continuous variable, and cases with no use as the referent category (dose = 0 mcg), computed using a likelihood ratio test

OC use may also contribute to decreased parity, and increasing parity is associated with a lower risk of breast cancer [21]. As H2E cases in this study were less likely to be nulliparous than women with other subtypes, differences in parity between H2E cases and luminal A cases may also partially explain the lower risk of H2E associated with OC use, relative to luminal A cases. Parity did not differ greatly between TN cases and luminal A cases, potentially explaining the similar risk of TN and luminal A breast cancer associated with OC use. However, we found no evidence of effect modification by parity and adjustment for parity did not change our estimates by more than 10%.

Few studies have evaluated the relationship between OC use and risk of molecular subtypes of breast cancer. Some of these found that OC use is associated with increased risks of TN [3–6], H2E [22], ER+ [4, 12, 23], and ER− [23], and others reporting null associations with ER+ [3, 5, 8], ER− [12], luminal A [7, 9], luminal B [7, 9], TN [7, 9], and H2E [3, 5, 7, 9] breast cancers. However, three did not restrict analyses to premenopausal women [4, 7, 8].

Of two other case-case analyses, one found a lower odds of luminal B breast cancer compared with luminal A among ever users of OC, relative to never users [11], and the other did not find an association between ever OC use at any duration and molecular subtype, using all other cases as the reference group [10]. These results may differ from ours because neither case-only study restricted analyses to premenopausal women.

This study differs from previous studies in multiple ways. First, our study used a case-case study design, as did two others [10, 11], where luminal A cases served as our reference outcome. While this study design is a limitation of the present study, as it prevented comparison with cancer-free controls as many other studies have done [3–9, 12, 22, 23], it allowed us to examine the heterogeneity in the established association between OC use and breast cancer risk, by molecular subtype. We also restricted analyses to younger, premenopausal women, while others did not [4, 7, 8, 10, 11] which may explain inconsistencies with previous findings. Additionally, by considering all identified TN and H2E cases eligible for this study, we were able to obtain larger sample of these less common subtypes than other studies of young women [3, 5, 9]. Further, this study built on previous work [3, 12] by examining the association of current use with TN breast cancer, compared with luminal A, by estrogen dose and progestin type. Finally, we utilized data abstracted from medical records for 76% of patients to limit recall bias, with no variations in the associations observed in sensitivity analyses limited to those with medical record data (data not shown), while previous studies have mainly relied on self-reported data [3–5, 7–11]. Overall, the main strengths of this study are its population-based sample of premenopausal women, and its large number of TN and H2E breast cancer cases.

Conclusions

These results suggest heterogeneity in risk of breast cancer associated with OC use by molecular subtype in that OC use may be more strongly positively associated with risks of luminal A and TN breast cancer than with risk of H2E tumors.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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