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Research Article

Oral Contraceptives and Breast Cancer Risk Overall and by Molecular Subtype Among Young Women

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Abstract

Background: Evidence suggests that recent oral contraceptive (OC) use is associated with a small increased breast cancer risk; yet risks associated with contemporary OC preparations and by molecular subtype are not well characterized.

Methods: We conducted a population-based case–control study of invasive breast cancer among women ages 20 to 44 residing in the Seattle–Puget Sound area from 2004 to 2010 (985 cases and 882 controls). We collected information on contraceptive use and participant characteristics via an in-person interview. Multivariable-adjusted logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results: Lifetime duration of OC use for ≥15 years was associated with an increased breast cancer risk (OR, 1.5; 95% CI, 1.1–2.2). Current OC use (within 1 year of reference date) for ≥5 years was associated with an increased risk (OR, 1.6; 95% CI, 1.1–2.5) and there were no statistically significant differences in risk by OC preparation. Risk magnitudes were generally greater among women ages 20 to 39, and for estrogen receptor–negative (ER^-) and triple-negative breast cancer (current use for ≥5 years among ages 20–39: ER^- OR, 3.5; 95% CI, 1.3–9.0; triple-negative OR, 3.7; 95% CI, 1.2–11.8), although differences between groups were not statistically significant.

Conclusions: Long-term use of contemporary OCs and current use for ≥5 years was associated with an increased breast cancer risk among women ages 20 to 44. Risk may be greater among younger women and for ER^- and triple-negative breast cancer, but these findings require confirmation.

Impact: Continued surveillance and pooled analyses of OC use and breast cancer risk by molecular subtype are needed as OC preparations evolve. *Cancer Epidemiol Biomarkers Prev; 23(5); 755–64. ©2014 AACR.*

Introduction

Although the relationship between oral contraceptive (OC) use and breast cancer risk has been extensively studied, the topic remains an important research area as there are several key unanswered questions. These relate to changes in the hormonal components and patterns of use of OCs, and to our evolving understanding of the molecular heterogeneity of breast cancer. Since OCs became available in the United States, there have been dramatic decreases in estrogen dose, the addition of new progestins, and changes in patterns of use (1–4). It is challenging to predict the potential impact of these complex changes on breast cancer risk. For instance, while lower OC estrogen doses may decrease risk, longer durations of OC use could possibly increase risk, and the impact of new OC preparations on risk is not known.

Results from a pooled analysis of 54 epidemiologic studies worldwide suggest a modest increased breast cancer risk associated with current or recent OC use that is no longer evident 10 or more years after ceasing OC use (5). Since the 1996 publication of these findings, results from other U.S. studies have been mixed (6–9), including a 33% increased breast cancer risk associated with current OC use observed among women <55 years of age in the Nurses' Health Study II (6), but no evidence of an association among women ages 35 to 44 from the Women's Contraceptive and Reproductive Experiences (CARE) Study, a large multicenter population-based case–control study (7). However, the extent to which these differences may relate to changes in OC preparations, dosages, and patterns of use has not been well characterized. In addition, differing age distributions may account for some variation, as some studies suggest that younger women may have a greater breast cancer risk associated with OC use than older women (10–15).

Another understudied aspect of the association between OC use and breast cancer risk is the potential variation in risk by molecular subtype, specifically by joint estrogen receptor (ER), progesterone receptor (PR), and

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HER2-neu (HER2) status. The largest population-based study to date focusing on differences in risk by ER, PR, and HER2 status among young women found that current OC use was associated with a 3.1-fold [95% confidence interval (CI), 1.2–7.6] increased risk of triple-negative (ER^-/PR^-/$HER2^-$) breast cancer and not related to risk of non-triple-negative breast cancer [odds ratio (OR), 0.7; 95% CI, 0.4–1.4], but confirmation of these findings is needed (16).

Addressing these issues is of public health importance, given the high prevalence of use among U.S. women (82% have ever used OCs; ref. 17) and the greater aggressiveness of breast cancer in younger women. So, to better characterize the association between contemporary OC use, defined as use primarily during the 1980s through 2000s, and risk of different breast cancer subtypes among young women, we analyzed data from a population-based case–control study among women 20 to 44 years of age.

Materials and Methods

Study participants

Details of this study's methods have been published previously (18). Briefly, all cases and controls were ages 20 to 44 at reference date (diagnosis date for cases and a comparable date assigned to controls), resided in the Seattle-Puget Sound region (King, Pierce, or Snohomish counties), had a landline home telephone, and did not have a prior history of *in situ* or invasive breast cancer. Eligible cases included women diagnosed with a first primary invasive breast cancer from June 2004 to June 2010. We identified cases through the Cancer Surveillance System, which is the population-based cancer registry covering 13 counties in the western Washington state and is a participant in the Surveillance, Epidemiology, and End Results program funded by the National Cancer Institute (NCI). We interviewed 1,056 of the 1,359 women (78%) identified as eligible cases. Data on ER, PR, and HER2 status were ascertained via a centralized review of pathology reports by trained abstractors. We identified controls by random digit dialing using the Mitosky–Waksberg method with a clustering factor of 5 and a list-assisted approach (19). Controls were frequency matched 1:1 to cases by age (5-year groups) and reference year for reference dates from 2004 to 2007. We received supplemental funding to acquire additional cases from 2008 to 2010; therefore, during these years, controls were frequency matched 0.7:1 to cases. We interviewed 943 of the 1,489 women (63%) identified as eligible controls. This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board and all participants provided written informed consent.

Data collection

All cases and controls completed an in-person interview administered by a trained interviewer through which they were queried about their lifetime contraceptive use before reference date, including contraceptive type, prescription name, dose, and duration of use for every reported episode of use. Interviewers used a photo book containing color photos of numerous OC pills and packaging, along with a life-events calendar, to aid participants' recall of the timing and type of OCs used. Data on demographic, anthropometric, reproductive, and lifestyle factors, medical history, and family history of cancer were also collected.

OC exposure variables

We defined ever use as OC use for at least 6 months and never use as never using OCs. Women who used OCs within the 1 year immediately before the reference date were classified as current users, whereas women who last used OCs more than 1 year before the reference date were categorized as former users. We classified OC episodes of use with an unknown generic or brand name as combined OCs (i.e., containing estrogen and progestin), given the low prevalence of progestin-only OC use in the United States (20, 21). In subanalyses, we assessed the estrogen dose and progestin type of specific OC preparations among women with available information. We classified estrogen dose as low (<30 μg ethinyl estradiol), moderate (30–35 μg ethinyl estradiol or 50 μg mestranol), or high (>35 μg ethinyl estradiol or >50 μg mestranol). We classified the progestin component into groups with similar chemical structures (estrane and gonane progestins; refs. 22–24), along with examining each progestin type individually. We excluded women who used OCs for <6 months (52 controls, 64 cases), only used progestin-only OCs (7 controls, 5 cases), and with unknown OC use (2 controls, 2 cases) from all analyses; therefore, the final study population included 882 controls and 985 cases.

Statistical analysis

We compared controls and cases using unconditional logistic regression and calculated ORs and 95% CIs. The reference group for all results was women who never used OCs. We used two-sided tests and interpreted P values <0.05 as statistically significant. All analyses were adjusted for the matching variables, age and reference year, and for race/ethnicity. We systematically evaluated a variety of covariates (listed in Table 1) as potential confounders between OC use and breast cancer risk. None of the covariates changed any of the ORs by ≥10%; therefore, the final statistical models are only adjusted for age, reference year, and race/ethnicity.

We further examined use by specific combined OC preparations (grouped by estrogen dose, progestin group, and progestin type) among exclusive current users of one OC preparation for 5 years or longer immediately before the reference date. We also evaluated current use by OC preparation. We used separate logistic regression models for each preparation type. On the basis of prior literature suggesting possible differences in the association between OC use and breast cancer risk by age (10–15), we tested for effect modification by age group (ages 20–39 and 40–44) for lifetime duration of use and recency of use.

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Table 1. Selected characteristics of controls and cases

Characteristic	Controls $n = 882$ (%)	Cases $n = 985$ (%)
Age (y)		
20–29	24 (2.7)	22 (2.2)
30–34	82 (9.3)	77 (7.8)
35–39	249 (28.2)	275 (27.9)
40–44	527 (59.8)	611 (62.0)
Reference year		
2004–2005	283 (32.1)	283 (28.7)
2006–2007	338 (38.3)	340 (34.5)
2008–2010	261 (29.6)	362 (36.8)
Race/ethnicity		
Non-Hispanic White	721 (82.1)	785 (80.6)
African-American	27 (3.1)	47 (4.8)
Asian/Pacific Islander	78 (8.9)	103 (10.6)
Other	52 (5.9)	39 (4.0)
Missing	4	11
Education		
High school or less	89 (10.1)	107 (10.9)
Post high school/some college	279 (31.7)	321 (32.8)
College graduate	340 (38.7)	363 (37.1)
Post college	171 (19.5)	187 (19.1)
Missing	3	7
Annual household income		
<$25,000	64 (7.3)	67 (6.9)
$25,000–49,999	116 (13.3)	152 (15.7)
$50,000–89,999	327 (37.4)	310 (32.1)
≥$90,000	368 (42.1)	437 (45.2)
Missing	7	19
Age at menarche (y)		
<12	178 (20.2)	218 (22.2)
12–13	489 (55.6)	558 (56.7)
≥14	213 (24.2)	208 (21.1)
Missing	2	1
Number of live births		
0	185 (21.0)	255 (25.9)
1–2	530 (60.1)	570 (57.9)
≥3	167 (18.9)	159 (16.2)
Missing	0	1
Age at first live birth (y)		
<25	196 (28.1)	220 (30.2)
25–29	213 (30.6)	246 (33.8)
30–34	194 (27.8)	175 (24.0)
≥35	94 (13.5)	87 (12.0)
Missing	0	2
Lactation duration (mo)[a]		
None	56 (8.1)	70 (9.6)
<6	150 (21.6)	169 (23.2)
6–11	135 (19.4)	142 (19.5)
≥12	354 (50.9)	347 (47.7)
Missing	2	1
First-degree family history of breast cancer		
No	765 (89.8)	766 (80.3)
Yes	87 (10.2)	188 (19.7)
Missing	30	31
BMI 1 year before reference date (kg/m^2)		
<25	502 (57.2)	588 (60.2)
25–<30	218 (24.9)	228 (23.4)
≥30	157 (17.9)	160 (16.4)
Missing	5	9
Screening mammogram in prior 30 months[b]		
No	189 (36.1)	201 (32.9)
Yes	335 (63.9)	410 (67.1)
Missing	3	0

Abbreviation: BMI, body mass index.

[a]Among parous women.

[b]Among women ages 40 to 44. Excludes symptomatic and diagnostic mammograms.

To evaluate risk by molecular subtype for duration of use and recency of use, we used polytomous logistic regression to compare controls to ER-positive (ER^+) and ER^- cases and to compare controls to triple-negative ($ER^-/PR^-/HER2^-$), HER2-overexpressing ($ER^-/HER2^+$), and ER^+ cases. We excluded 9 cases with unknown ER values from ER analyses and an additional 19 cases with unknown or borderline HER2 values from HER2 analyses. We evaluated OR heterogeneity between tumor subtypes using unconditional logistic regression limited to cases and calculated *P* values to assess the difference in risk estimates between the predominant case groups (ER^+ versus ER^- and ER^+ versus triple-negative). We completed all analyses using Stata/MP version 12.0 (StataCorp LP).

Results

Age, race/ethnicity, and education distributions were generally comparable between cases and controls (Table 1). The reference year distribution reflects the control-to-case matching ratio for different years. Cases were more likely than controls to be nulliparous, have a family history of breast cancer, a lower body mass index, a recent screening mammogram, and the highest annual household income. Cases were less likely than controls to have a later age at menarche, later age at first birth, and to have lactated for at least 1 year.

Ever using OCs was not associated with breast cancer risk (Table 2). There was no evidence of statistically significant effect modification by age group for lifetime duration of use and recency of use based on likelihood ratio tests. However, we present results stratified by age group along with all ages because some risk estimates

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Table 2. Oral contraceptive use and risk of breast cancer[a]

	All women (age 20–44)				Age 20–39				Age 40–44			
	Controls ($n = 882$)	Cases ($n = 985$)			Controls ($n = 355$)	Cases ($n = 374$)			Controls ($n = 527$)	Cases ($n = 611$)		
	n (%)	*n* (%)	OR[b]	95% CI	*n* (%)	*n* (%)	OR[b]	95% CI	*n* (%)	*n* (%)	OR[b]	95% CI
Lifetime duration of use												
Never	103 (11.7)	119 (12.1)	1.0	(ref)	44 (12.4)	45 (12.0)	1.0	(ref)	59 (11.2)	74 (12.1)	1.0	(ref)
Ever	779 (88.3)	866 (87.9)	1.0	(0.7–1.3)	311 (87.6)	329 (88.0)	1.0	(0.7–1.7)	468 (88.8)	537 (87.9)	0.9	(0.6–1.4)
<5 years	280 (31.8)	306 (31.2)	1.0	(0.7–1.3)	115 (32.4)	107 (28.8)	0.9	(0.5–1.5)	165 (31.4)	199 (32.6)	1.0	(0.6–1.5)
5–9.9 years	219 (24.9)	213 (21.7)	0.9	(0.6–1.2)	86 (24.2)	88 (23.7)	1.1	(0.6–1.8)	133 (25.3)	125 (20.5)	0.7	(0.5–1.2)
10–14.9 years	178 (20.2)	169 (17.2)	0.9	(0.6–1.2)	83 (23.4)	80 (21.6)	1.0	(0.6–1.7)	95 (18.1)	89 (14.6)	0.8	(0.5–1.2)
≥15 years	100 (11.4)	174 (17.7)	1.5	(1.1–2.2)[c]	27 (7.6)	51 (13.7)	1.9	(1.0–3.7)	73 (13.9)	123 (20.2)	1.4	(0.9–2.2)
Time since last use (y)												
Current use	144 (16.3)	201 (20.4)	1.3	(0.9–1.8)	72 (20.3)	99 (26.5)	1.4	(0.8–2.4)	72 (13.7)	102 (16.7)	1.1	(0.7–1.8)
Former use	635 (72.0)	665 (67.5)	0.9	(0.7–1.2)	239 (67.3)	230 (61.5)	0.9	(0.6–1.5)	396 (75.1)	435 (71.2)	0.9	(0.6–1.3)
>1 to <5	133 (15.1)	132 (13.4)	0.9	(0.6–1.3)	72 (20.3)	73 (19.5)	1.0	(0.6–1.8)	61 (11.6)	59 (9.7)	0.8	(0.5–1.3)
5–9.9	161 (18.3)	186 (18.9)	1.0	(0.7–1.4)	72 (20.3)	76 (20.3)	1.0	(0.6–1.8)	89 (16.9)	110 (18.0)	1.0	(0.6–1.6)
10–14.9	151 (17.1)	133 (13.5)	0.8	(0.5–1.1)	56 (15.8)	48 (12.8)	0.8	(0.4–1.5)	95 (18.0)	85 (13.9)	0.7	(0.5–1.2)
≥15	190 (21.5)	214 (21.7)	0.9	(0.7–1.3)	39 (11.0)	33 (8.8)	0.7	(0.4–1.4)	151 (28.7)	181 (29.6)	1.0	(0.6–1.5)
Age at first use (y)												
<18	284 (32.2)	323 (32.8)	1.0	(0.7–1.4)	131 (36.9)	138 (36.9)	1.0	(0.6–1.7)	153 (29.0)	185 (30.3)	0.9	(0.6–1.5)
18–20	279 (31.6)	288 (29.2)	0.9	(0.7–1.3)	106 (29.9)	115 (30.7)	1.1	(0.7–1.9)	173 (32.8)	173 (28.3)	0.8	(0.5–1.2)
≥21	216 (24.5)	255 (25.9)	1.0	(0.7–1.4)	74 (20.8)	76 (20.3)	1.0	(0.6–1.7)	142 (26.9)	179 (29.3)	1.0	(0.7–1.5)
Duration of use in the prior 5 years among current users												
Current use												
<3 years	31 (3.5)	44 (4.5)	1.3	(0.7–2.2)	21 (5.9)	24 (6.4)	1.1	(0.6–2.4)	10 (1.9)	20 (3.3)	1.4	(0.6–3.3)
3–4.9 years	58 (6.6)	60 (6.1)	0.9	(0.6–1.4)	34 (9.6)	32 (8.6)	1.0	(0.5–1.8)	24 (4.6)	28 (4.6)	0.9	(0.4–1.6)
≥5 years	54 (6.1)	97 (9.8)	1.6	(1.1–2.5)[c]	17 (4.8)	43 (11.5)	2.5	(1.2–5.1)[c]	37 (7.0)	54 (8.8)	1.2	(0.7–2.1)
Recency of use and lifetime duration of use												
Former use												
<15 years	598 (68.0)	585 (59.6)	0.9	(0.6–1.2)	232 (65.4)	213 (57.4)	0.9	(0.6–1.5)	366 (69.7)	372 (61.0)	0.8	(0.6–1.2)
≥15 years	37 (4.2)	80 (8.2)	1.9	(1.2–3.1)[c]	7 (2.0)	17 (4.6)	2.4	(0.9–6.6)	30 (5.7)	63 (10.3)	1.7	(1.0–3.0)
Current use												
<15 years	79 (9.0)	103 (10.5)	1.2	(0.8–1.8)	52 (14.6)	62 (16.7)	1.2	(0.7–2.2)	27 (5.1)	41 (6.7)	1.2	(0.6–2.1)
≥15 years	63 (7.2)	94 (9.6)	1.3	(0.9–2.0)	20 (5.6)	34 (9.2)	1.7	(0.8–3.4)	43 (8.2)	60 (9.8)	1.1	(0.7–1.9)

Abbreviations: OC, oral contraceptive; OR, odds ratio; CI, confidence interval.

[a]Ever use is defined as OC use for ≥6 months and current use is defined as use of OCs within the prior year. Women who used OCs for <6 months (52 controls, 64 cases), only used progestin-only OC pills (7 controls, 5 cases), and with unknown OC use (2 controls, 2 cases) are excluded from all analyses. The reference group for all models is women who never used OCs.

[b]ORs are adjusted for age, year, and race/ethnicity.

[c]$P < 0.05$.

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were suggestive of an age-group difference. Total lifetime duration of OC use for 15 or more years relative to never using OCs was associated with a 50% increased breast cancer risk among all women (OR, 1.5; 95% CI, 1.1–2.2) and there was some suggestion that this risk may be stronger among women ages 20 to 39 compared with ages 40 to 44. Shorter durations of use were not associated with risk. Neither time since last use among former OC users nor age at first use among ever users was associated with risk. Although current use was not associated with a statistically significant elevated risk, current use for 5 years or longer was associated with a 1.6-fold (95% CI, 1.1–2.5) increased breast cancer risk among all women and a 2.5-fold (95% CI, 1.2–5.1) increased risk among women ages 20 to 39. We conducted sensitivity analyses including women who used OCs for <6 months as either ever or never OC users, and neither classification substantially altered our results.

Because we observed positive associations between breast cancer risk and both recency of OC use and lifetime duration of use, we stratified former and current users by lifetime duration of use. Former users with <15 years of lifetime OC use had no elevated breast cancer risk, whereas former users with at least 15 years of use had a 1.9-fold increased risk (95% CI, 1.2–3.1). In contrast, among current users the risk estimates stratified by lifetime duration of use were comparable with the overall OR for current use and were of low magnitude and not statistically different. This general pattern also occurred among women ages 20 to 39 and ages 40 to 44.

We examined specific OC preparations among current users and among current users who used only one preparation for 5 years or longer immediately preceding the reference date relative to those who never used OCs. Only current users of OCs with a gonane progestin for 5 years or longer had a statistically significant increased risk (OR, 1.9; 95% CI, 1.1–3.4; Table 3), and this risk was similar for the individual gonane progestins, levonorgestrel and norgestimate. Current users of OCs with low estrogen dose, moderate estrogen dose, estrane progestins, and the progestin drospirenone had elevated, but non-statistically significant risk estimates. We assessed current use of a triphasic OC preparation containing levonorgestrel and varying doses of ethinyl estradiol in response to a report from the Nurses' Health Study II demonstrating an elevated breast cancer risk (6), but we found no association in our data (OR, 0.9; 95% CI, 0.3–2.6; 8 controls and 8 cases, data not shown).

We also evaluated lifetime duration of OC use and recency of use by molecular subtype. Ever using OCs was not associated with risk of ER^+ or ER^- breast cancer, but was associated with a non-statistically significant 1.7-fold (95% CI, 0.7–4.0) increased risk of triple-negative breast cancer among women ages 20 to 39 (Table 4). The risk estimates for ER^+ cancer associated with OC use for ≥15 years were comparable with those for any invasive breast cancer. For example, among all ages, OC users for ≥15 years had a 1.6-fold (95% CI, 1.0–2.3) increased risk of ER^+ cancer. The risk estimates for ER^- and triple-negative cancer were either similar or slightly greater than the risk of any invasive cancer and did not achieve statistical significance. There was a statistically significant linear trend per additional lifetime year of OC use relative to never using OCs among ER^- cases ages 20 to 39 ($P = 0.009$) and among all triple-negative cases ($P = 0.045$). Current users ages 20 to 39 who used OCs for 5 years or longer had a 3.5-fold (95% CI, 1.3–9.0) increased ER^- cancer risk and a 3.7-fold (95% CI, 1.2–11.8) increased triple-negative cancer risk, although neither risk estimate was statistically different than their risk of ER^+ cancer (P value for difference = 0.34 and 0.37, respectively). The risk estimates for HER2-overexpressing cancer tended to be close to or less than 1.0, but were difficult to interpret due to small numbers.

Discussion

Our overall results evaluating use of any type of OCs are consistent with the large pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (5), as well as a recent analysis from the Nurses' Health Study II (6), which both suggested a modest increased risk associated with current OC use. Our duration of use findings are less consistent with the Collaborative Group results (5, 25) and add to the mixed evidence related to duration of use among women ≤57 years of age (7–9, 13, 26–28). After stratifying recency of use by duration, our results suggest that both aspects of exposure may impact risk. This diverges from the Collaborative Group results, as it found no additional effect of duration of use after accounting for time since last use (5, 25). Many individual studies since then have not reported a combined effect of recency and lifetime duration of use among younger women (8, 9, 13, 27, 28); however, the Nurses' Health Study II found a slightly greater risk among current users for ≥8 years [relative risk (RR), 1.5; 95% CI, 1.1–2.0) than current users for <8 years (RR, 1.2, 95% CI, 0.8–1.7; ref. 6). In contrast, the CARE study did not find an association among current users overall or after evaluating lifetime duration of use (7), but this could be due to excluding women <35 years of age who may have greater risks associated with OC use. Differences across studies, although, can also potentially be explained by the substantial changes in both the constituents and patterns of use of OCs across time and place. For example, the proportion of low estrogen dose (<30 μg ethinyl estradiol) OC prescriptions has increased (3, 4), progestins such as drospirenone have been added to OCs, and extended and continuous cycle OCs with an increased number of days of hormone exposure continue to enter the U.S. market. The cumulative impact of the numerous changes in OC use on breast cancer risk is presently unclear; thus, continued evaluation of the risks and benefits of currently used OC preparations remains of public health importance.

Although the relationship between OC use and breast cancer risk has been extensively researched, our study

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Table 3. Risk of breast cancer associated with current use of combined oral contraceptive preparations and use for 5 years or longer immediately before reference date[a]

	Controls ($n = 882$)	Cases ($n = 985$)			
	n (%)	*n* (%)	OR[b]	95% CI	*P*[e]
Current use and duration of use in the prior 5 years					
Never use	103 (11.7)	119 (12.1)	1.0	(ref)	
Current use	144 (16.3)	201 (20.4)	1.3	(0.9–1.8)	
≥5 years	54 (6.1)	97 (9.8)	1.6	(1.1–2.5)[c]	
Estrogen dose[d]					0.44
Low					
Current use	16 (1.8)	29 (3.0)	1.5	(0.8–3.0)	
≥5 years	6 (0.7)	15 (1.5)	2.2	(0.8–6.0)	
Moderate					
Current use	96 (10.9)	149 (15.2)	1.4	(1.0–2.0)	
≥5 years	40 (4.5)	67 (6.8)	1.5	(0.9–2.4)	
Progestin group					0.28
Estrane progestins					
Current use	45 (5.1)	67 (6.9)	1.4	(0.9–2.2)	
≥5 years	19 (2.2)	26 (2.6)	1.3	(0.7–2.4)	
Norethindrone					
Current use	30 (3.4)	42 (4.3)	1.3	(0.7–2.2)	
≥5 years	15 (1.7)	17 (1.7)	1.1	(0.5–2.2)	
Norethindrone acetate					
Current use	11 (1.2)	23 (2.3)	1.9	(0.9–4.2)	
Gonane progestins					
Current use	63 (7.2)	94 (9.6)	1.3	(0.9–2.0)	
≥5 years	22 (2.5)	49 (5.0)	1.9	(1.1–3.4)[c]	
Levonorgestrel					
Current use	19 (2.2)	33 (3.4)	1.5	(0.8–2.9)	
≥5 years	9 (1.0)	18 (1.8)	1.8	(0.8–4.2)	
Norgestimate					
Current use	28 (3.2)	35 (3.6)	1.1	(0.6–2.0)	
≥5 years	7 (0.8)	15 (1.5)	1.9	(0.7–4.8)	
Desogestrel					
Current use	15 (1.7)	12 (1.2)	0.7	(0.3–1.6)	
Other progestin					
Drospirenone					
Current use	9 (1.0)	22 (2.2)	2.1	(0.9–4.9)	

Abbreviations: OC, oral contraceptive; OR, odds ratio; CI, confidence interval.

[a]Current use indicates use within the prior year and for ≥6 months. Only exclusive current users of one preparation for 5 years or longer are included in the estrogen and progestin groups for current use for ≥5 years (groups do not add up to the total because of women missing OC preparation information or using multiple preparations in the prior 5 years). Cells with <5 women are not displayed. Among current OC users, 13% controls and 9% cases could not be classified by estrogen dose and/or progestin type.

[b]ORs are adjusted for age, year, and race/ethnicity.

[c]$P < 0.05$.

[d]Low dose, <30 μg ethinyl estradiol (EE); moderate dose, 30–35 μg EE or 50 μg mestranol.

[e]*P* for difference (low versus moderate estrogen dose and estrane versus gonane progestins).

assessing contemporary OC preparations adds to the literature in three primary respects. First, we did not identify distinct differences in breast cancer risk when comparing OC constituents (estrogen doses or progestin types). Second, there was some suggestion that OC use may be more strongly related to risk of ER^- and triple-negative cancer compared with ER^+ cancer, although the differences were not statistically significant. Finally, we observed more pronounced elevations in breast cancer risk associated with OCs among women ages 20 to 39

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Table 4. Duration of oral contraceptive use, current use, and risk of ER^+, ER^-, triple-negative ($ER^-/PR^-/HER2^-$), and HER2-overexpressing ($ER^-/HER2^+$) breast cancer[a]

	Controls	ER^+			ER^-			$ER^-/PR^-/HER2^-$			$ER^-/HER2^+$		
	n (%)	*n* (%)	OR[b]	95% CI	*n* (%)	OR[b]	95% CI	*n* (%)	OR[b]	95% CI	*n* (%)	OR[b]	95% CI
All (age 20–44)	*n* = 882	*n* = 730			*n* = 246			*n* = 171			*n* = 56		
Lifetime duration of use													
Never	103 (11.7)	92 (12.6)	1.0	(ref)	26 (10.6)	1.0	(ref)	15 (8.8)	1.0	(ref)	11 (19.6)	1.0	(ref)
Ever	779 (88.3)	638 (87.4)	1.0	(0.7–1.3)	220 (89.4)	1.1	(0.7–1.8)	156 (91.2)	1.4	(0.8–2.5)	45 (80.4)	0.5	(0.3–1.1)
<15 years	677 (76.9)	499 (68.5)	0.9	(0.6–1.2)	183 (75.0)	1.0	(0.7–1.7)	131 (77.5)	1.3	(0.7–2.4)	38 (67.9)	0.5	(0.2–1.1)
≥15 years	100 (11.4)	137 (18.8)	1.6	(1.0–2.3)[c]	35 (14.3)	1.5	(0.8–2.7)	23 (13.6)	1.7	(0.8–3.6)	7 (12.5)	0.7	(0.2–1.9)
Current use and duration of use in the prior 5 years													
Current use	144 (16.3)	150 (20.5)	1.2	(0.9–1.8)	49 (19.9)	1.3	(0.7–2.2)	34 (19.9)	1.6	(0.8–3.2)	11 (19.6)	0.7	(0.3–1.6)
<5 years	89 (10.1)	80 (11.0)	1.1	(0.7–1.6)	22 (8.9)	0.9	(0.5–1.7)	18 (10.5)	1.3	(0.6–2.8)	4 (7.1)	—	—
≥5 years	54 (6.1)	70 (9.6)	1.5	(1.0–2.4)	27 (11.0)	2.0	(1.1–3.9)[c]	16 (9.4)	2.2	(1.0–4.7)	7 (12.5)	1.2	(0.4–3.4)
Age 20–39	*n* = 355	*n* = 249			*n* = 122			*n* = 82			*n* = 30		
Lifetime duration of use													
Never	44 (12.4)	33 (13.3)	1.0	(ref)	12 (9.8)	1.0	(ref)	7 (8.5)	1.0	(ref)	5 (16.7)	1.0	(ref)
Ever	311 (87.6)	216 (86.7)	1.0	(0.6–1.6)	110 (90.2)	1.3	(0.6–2.6)	75 (91.5)	1.7	(0.7–4.0)	25 (83.3)	0.6	(0.2–1.7)
<15 years	284 (80.0)	179 (72.5)	0.9	(0.5–1.5)	93 (76.9)	1.2	(0.6–2.4)	66 (81.5)	1.6	(0.7–3.9)	20 (66.7)	0.5	(0.2–1.6)
≥15 years	27 (7.6)	35 (14.2)	1.8	(0.9–3.7)	16 (13.2)	2.2	(0.9–5.6)	8 (9.9)	2.1	(0.7–7.0)	5 (16.7)	1.4	(0.3–5.8)
Current use and duration of use in the prior 5 years													
Current use	72 (20.3)	67 (26.9)	1.3	(0.7–2.3)	30 (24.6)	1.5	(0.7–3.4)	19 (23.2)	1.8	(0.7–4.9)	8 (26.7)	0.8	(0.3–2.9)
<5 years	55 (15.5)	40 (16.1)	1.0	(0.5–1.9)	14 (11.5)	0.9	(0.4–2.3)	10 (12.2)	1.3	(0.4–3.7)	4 (13.3)	—	—
≥5 years	17 (4.8)	27 (10.8)	2.2	(1.0–4.7)	16 (13.1)	3.5	(1.3–9.0)[c]	9 (11.0)	3.7	(1.2–11.8)[c]	4 (13.3)	—	—
Age 40–44	*n* = 527	*n* = 481			*n* = 124			*n* = 89			*n* = 26		
Lifetime duration of use													
Never	59 (11.2)	59 (12.3)	1.0	(ref)	14 (11.3)	1.0	(ref)	8 (9.0)	1.0	(ref)	6 (23.1)	1.0	(ref)
Ever	468 (88.8)	422 (87.7)	0.9	(0.6–1.4)	110 (88.7)	0.9	(0.5–1.7)	81 (91.0)	1.2	(0.5–2.7)	20 (76.9)	0.4	(0.1–1.0)
<15 years	393 (74.9)	320 (66.5)	0.8	(0.6–1.3)	90 (73.2)	0.9	(0.5–1.7)	65 (73.9)	1.2	(0.5–2.6)	18 (69.2)	0.4	(0.1–1.1)
≥15 years	73 (13.9)	102 (21.2)	1.4	(0.9–2.4)	19 (15.4)	1.0	(0.5–2.3)	15 (17.0)	1.5	(0.6–3.8)	2 (7.7)	—	—
Current use and duration of use in the prior 5 years													
Current use	72 (13.7)	83 (17.3)	1.2	(0.7–1.9)	19 (15.3)	1.0	(0.5–2.2)	15 (16.9)	1.4	(0.6–3.7)	3 (11.5)	—	—
<5 years	34 (6.5)	40 (8.3)	1.1	(0.6–2.0)	8 (6.5)	0.9	(0.3–2.3)	8 (9.0)	1.5	(0.5–4.6)	0 (0.0)	—	—
≥5 years	37 (7.0)	43 (8.9)	1.3	(0.7–2.2)	11 (8.9)	1.2	(0.5–3.0)	7 (7.9)	1.4	(0.5–4.2)	3 (11.5)	—	—

Abbreviations: OC, oral contraceptive; OR, odds ratio; CI, confidence interval; ER, estrogen receptor.

[a]Ever use is defined as OC use for ≥6 months and current use is defined as use of OCs within the prior year. ORs resulting from cells with <5 women are not displayed.

[b]ORs are adjusted for age, year, and race/ethnicity.

[c]$P < 0.05$.

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relative to ages 40 to 44. These observations are discussed in turn below.

Our results do not suggest marked heterogeneity in risk by OC constituents; however, our analyses were constrained by sparse data for some preparations and we could only classify preparations recalled by participants. Some (6, 9, 14, 29, 30), but not all (12, 31, 32), previous studies have found variations in risk among different OC preparations related to estrogen and/or progestin dose, type, or potency. The Collaborative Group analysis largely found no evidence of substantial heterogeneity in risk by estrogen dose or progestin type (5, 25). However, a recent report from the Nurses' Health Study II found a 3.1-fold (95% CI, 2.0–4.7) elevated breast cancer risk associated with current use of a triphasic OC containing levonorgestrel and varying doses of ethinyl estradiol, which accounted for much of the increased risk associated with current OC use overall (6). We did not find an increased risk associated with current use of this preparation, but we had limited power to evaluate OC preparations.

Although there were no statistically significant differences between ER^+ cancer risk compared with ER^- or triple-negative cancer risk for any characteristic of OC use, the risk estimates tended to be greater for ER^- and triple-negative cancer than for ER^+ cancer. Our results suggest that the elevated risks may be due to an increased risk of triple-negative cancer, rather than all ER^- cancers, but the small number of HER2-overexpressing cases precluded comparative analyses. Our triple-negative findings are consistent with a large study among young women that found a greater risk of triple-negative compared with non-triple-negative cancer associated with more recent OC use and longer durations of use (16). The only other report assessing OC use and triple-negative cancer risk among young women did not find an elevated risk of triple-negative cancer relative to controls or to luminal A (ER^+ or $PR^+/HER2^-$) cases associated with either time since last use or duration of use among women ages 35 to 44 (33), but this could be due to excluding women <35 years of age.

Other studies classifying only by ER and/or PR status among pre-/perimenopausal women or women <50 years of age provide context for our results by ER status among young women and generally do not suggest distinct differences in risk associated with recency of use or duration of use (34–37). However, making comparisons across these studies is challenging due to the wide range in sample sizes (121–854 cases of ER^+ breast cancer and 105–385 cases of ER^- breast cancer; refs. 34–37). Three more recently published studies including pre- and postmenopausal women and evaluating risk by ER and/or PR status may include more relevant OC exposures, but they report differing findings. One study among African-American women and another study in the southwestern U.S. found that recent OC use and long durations of use were more strongly related to ER^- or ER^-/PR^- cancer than ER^+ or ER^+/PR^+ cancer (38, 39). Furthermore, risk of ER^-/PR^- cancer increased among recent users with increasing duration of use (38). In contrast, the Shanghai Breast Cancer Study did not find any statistically significant differences in duration of OC use and risk of ER^-/PR^- or ER^+/PR^+ cancer (40).

Age group was not a statistically significant effect modifier of the association between OC use and breast cancer risk in our study, yet we generally observed stronger effects when restricting to younger women. This difference has been observed in other studies assessing a variety of aspects of OC use (10–15), and suggests that younger women may be particularly susceptible to risks related to OC use, although it is unknown if this is related to different proliferative effects on the breast or to other reasons.

The study limitations should be noted when interpreting our results. We measured OC exposure through participant self-report and thus exposure misclassification could have impacted results. We expect that our results by OC preparation are most susceptible to exposure misclassification, as validation studies of self-reported OC use report fairly accurate recall of any OC use and timing of use, but less precise reporting of the specific OC preparations used (41–45). However, our study was designed specifically to evaluate hormonal contraceptive exposures and thus a photo book, life events calendar, and structured ordering of questions were all used to optimize recall of OC usage. Recall bias is possible due to the case–control study design, but it is unlikely to have impacted our main results considerably (43, 44), and we would not expect recall to vary by molecular subtype or OC preparation. Another potential source of bias is our study's restriction to women with landline telephones, but our recent publication demonstrating no variation in OC use by landline telephone status suggests that this is not a concern (46). Nevertheless, selection bias due to other factors is still possible. Detection bias is a potential concern, as OC users might be more apt to be screened, but we believe it is unlikely to account for our recency results as adjusting for recent screening mammography among women ages 40 to 44 did not meaningfully change our estimates and the strongest signals of increased risk were seen in age groups not routinely screened. Finally, we were limited by small sample sizes in some molecular subtype–specific and OC preparation–based analyses and given the number of associations examined, we cannot rule out the possibility that some statistically significant effects are due to chance.

Our findings suggest that both current use of contemporary OC preparations for 5 years or longer and lifetime OC durations of use of 15 years or longer confer an increased breast cancer risk among women ages 20 to 44. The observed recency effect supports a tumor promoter role for OCs, and the risk related to duration of use suggests that length of OC exposure also impacts risk and could play a role in tumorigenesis. Laboratory data support the proliferative effect of OCs in breast tissue; most notably, studies among premenopausal women demonstrate an increase in breast epithelial cell proliferation when using OCs relative to nonuse (47–50). Our results support the continued monitoring of OC use and breast

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cancer risk with particular attention to possible differences in risk by molecular subtype. Meta-analyses or updated pooled analyses stratifying risk by molecular subtype are needed to confirm potential risk differences due to the large sample sizes required. In addition, future studies evaluating risk by OC preparations should be conducted in settings with available pharmacy data, such as managed health care organizations or nations with prescription databases, to minimize OC exposure misclassification and improve the quality of subsequent pooled analyses. Although breast cancer is rare among young women, our results, if confirmed, could contribute to the risk-benefit profile considered by women and their prescribers when making informed decisions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Oral Contraceptives and Breast Cancer Risk Overall and by Molecular Subtype Among Young Women

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