Cancer Research

Recent Oral Contraceptive Use by Formulation and Breast Cancer Risk among Women 20 to 49 Years of Age

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Abstract

Previous studies of oral contraceptives and breast cancer indicate that recent use slightly increases risk, but most studies relied on self-reported use and did not examine contemporary oral contraceptive formulations. This nested case–control study was among female enrollees in a large U.S. integrated health care delivery system. Cases were 1,102 women ages 20 to 49 years diagnosed with invasive breast cancer from 1990 to 2009. Controls were randomly sampled from enrollment records ($n = 21{,}952$) and matched to cases on age, year, enrollment length, and medical chart availability. Detailed oral contraceptive use information was ascertained from electronic pharmacy records and analyzed using conditional logistic regression, ORs, and 95% confidence intervals (CI). Recent oral contraceptive use (within the prior year) was associated with an increased breast cancer risk (OR, 1.5; 95% CI, 1.3–1.9) relative to never or former OC use. The association was stronger for estrogen receptor–positive (ER^+; OR, 1.7; 95% CI, 1.3–2.1) than estrogen receptor–negative (ER^-) disease (OR, 1.2, 95% CI, 0.8–1.8), although not statistically significantly different ($P = 0.15$). Recent use of oral contraceptives involving high-dose estrogen (OR, 2.7; 95% CI, 1.1–6.2), ethynodiol diacetate (OR, 2.6; 95% CI, 1.4–4.7), or triphasic dosing with an average of 0.75 mg of norethindrone (OR, 3.1; 95% CI, 1.9–5.1; $P_{\text{heterogeneity}}$ compared with using other oral contraceptives = 0.004) was associated with particularly elevated risks, whereas other types, including low-dose estrogen oral contraceptives, were not (OR, 1.0; 95% CI, 0.6–1.7). Our results suggest that recent use of contemporary oral contraceptives is associated with an increased breast cancer risk, which may vary by formulation. If confirmed, consideration of the breast cancer risk associated with different oral contraceptive types could impact discussions weighing recognized health benefits and potential risks. *Cancer Res; 74(15); 4078–89. ©2014 AACR.*

Introduction

The relationship between oral contraceptive use and breast cancer risk has been extensively studied, yet the composition and patterns of oral contraceptive use have evolved considerably over time and more recent formulations have received relatively little scrutiny. Notably, there have been changes in oral contraceptive formulations since they were introduced in the United States in the 1960s, including decreased estrogen doses, the addition of new synthetic progestins, and the approval of extended cycle oral contraceptives (1–4). Given that oral contraceptives are the leading contraceptive method in the United States (5), ongoing evaluation of their benefits and harms is of critical public health importance.

In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer published a pooled analysis of about 90% of the world's studies consisting of 53,297 breast cancer cases and 100,239 women without breast cancer. It concluded that women have an increased breast cancer risk while taking oral contraceptives, but risk decreases with increasing time since last use and is no longer evident 10 years after ceasing use (6, 7). Risk was highest among current oral contraceptive users [in the preceding 12 months; relative risk (RR), 1.24; 95% confidence interval (CI), 1.15–1.33] and there was little impact of duration of use after accounting for recency of use, suggesting that recent use is a relevant period (6, 7). There was no statistically significant risk variation by oral contraceptive formulation; however, 74% of the cases in the pooled analysis were diagnosed during the 1980s, and thus more likely to be exposed to oral contraceptive formulations less commonly used today, and only half of the contributing studies had formulation data (6, 7). A recent smaller study, the Nurses' Health Study II, reported an excess breast cancer risk (RR, 1.3; 95% CI, 1.0–1.7) associated with current oral contraceptive use and a marked increased risk associated with current use of one triphasic oral contraceptive formulation (OR, 3.1; 95% CI, 2.0–4.7; ref. 8), whereas the Women's Contraceptive and Reproductive Experiences (CARE) Study found no elevated risk associated with current use of oral contraceptives (9) or with unique oral contraceptive formulations (i.e., considering

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doi: 10.1158/0008-5472.CAN-13-3400

estrogen and progestin components; ref. 10). Yet these studies and most other studies lack formulation data and/or are susceptible to exposure misclassification due to their reliance solely on participant recall. In addition, comparatively few studies assessing recent oral contraceptive use have stratified breast cancer risk by estrogen receptor status and existing results are mixed (11–16).

To evaluate recent use of contemporary oral contraceptive formulations used from 1989 to 2009, we conducted a study among women enrolled in a large U.S. health plan and used pharmacy dispensing records to determine whether various oral contraceptive types are associated with an increased breast cancer risk.

Patients and Methods

Study population

We conducted a nested case–control study among women ages 20 to 49 years enrolled continuously at Group Health Cooperative (GHC), an integrated health care delivery system serving the Seattle–Puget Sound area (17), for at least 12 months before diagnosis date (reference date) or a similar date for controls from January 1990 to October 2009. At reference date, all women were required to reside in one of the 13 counties in western Washington state monitored by the Cancer Surveillance System (CSS), the local population-based cancer registry that participates in the Surveillance, Epidemiology, and End Results (SEER) program funded by the National Cancer Institute. All first primary invasive breast cancer cases were identified using the CSS and those with a prior history of *in situ* breast cancer or mastectomy at reference date were excluded. We randomly sampled up to 20 controls per case from enrollment records, individually matched on age, year (enrolled on the case's diagnosis date), enrollment length before reference date (±1 month), and medical chart availability (no/yes). We expanded the matching criteria for a small number of cases with fewer available controls, allowing controls to be matched to cases on enrollment length (±2 months), case's birthdate (±365 days), and/or have a different medical chart availability than their case. A total of 1,105 cases and 22,100 matched controls met the eligibility criteria (21,755 of the 22,100 matched controls met the exact matching criteria). The Group Health Human Subjects Review Committee approved this study and a waiver of consent.

Oral contraceptive prescriptions

The GHC electronic pharmacy database began in 1977 and contains detailed information about pharmacy dispensings including date dispensed, drug name, dose, administration route, pill quantity, and days of supply. Past GHC studies estimate that approximately 96% to 97% of GHC enrollees fill all or almost all of their prescriptions at GHC pharmacies (17), likely due to financial incentives. We focused on exposures in the 12 months before reference date due to the enrollment lengths of our study population and because of prior evidence indicating an increased breast cancer risk during this period (6, 7). We obtained all oral contraceptives filled in the 12 months before reference date and classified them by formulation by identifying unique combinations of estrogen and progestin components, doses, and dosing schedules (monophasic or triphasic). Monophasic oral contraceptives contain the same estrogen and progestin dose in each hormone pill, whereas triphasic oral contraceptives contain three phases of estrogen and progestin dose combinations. We supplemented these data with claims data in the 12 months before reference date; thus, oral contraceptives filled outside of GHC pharmacies with a claim submitted were also captured (3.9% of oral contraceptive prescriptions came from claims).

We categorized combined oral contraceptive formulations, which contain estrogen and progestin, as low [20 μg ethinyl estradiol (EE)], moderate (30–35 μg EE or 50 μg mestranol), or high (50 μg EE or 80 μg mestranol) dose estrogen. We examined progestin types individually and grouped by chemical structure (estranes included norethindrone, norethindrone acetate, and ethynodiol diacetate; gonanes included levonorgestrel, norgestimate, norgestrel, and desogestrel; refs. 18–20). For each woman, we summed all oral contraceptive hormone pills and pills by estrogen dose, progestin type, and formulation in the year before reference date. We classified the number of pills as <190 or ≥ 190 to estimate exposure for greater than half of the year prior and to assess a potential dose–response effect.

We defined recent users as women who filled at least one oral contraceptive prescription in the year before reference date and compared them with women who did not fill an oral contraceptive prescription in the year before reference date. Progestin-only oral contraceptive use was uncommon; therefore, we excluded women with exclusively progestin-only oral contraceptives filled in the year before reference date (3 cases and 148 controls). Our final analyses included the remaining 1,102 cases and 21,952 controls.

Additional data sources

Using SEER data, we classified cases as estrogen receptor–positive (ER^+) or -negative (ER^-). We determined race and Hispanic ethnicity from a combination of data sources including SEER, death files, and self-administered breast cancer screening questionnaires from the Group Health Breast Cancer Surveillance Project (21). The breast cancer screening questionnaire collects information about demographics and breast cancer risk factors (22).

To evaluate possible confounding by parity, oophorectomy history, breast and/or ovarian cancer family history, and body mass index, we completed medical record reviews for all cases ages 20 to 44 years with reference dates from May 1995 to October 2009 and two of their matched controls. Medical record reviews were restricted to this subset because of data abstracting costs and the greater likelihood of oral contraceptive exposure among younger women. Because GHC administers breast cancer screening questionnaires systematically among women ages 40 years and older, medical record data for women ages 40 to 49 years were additionally supplemented with data from these questionnaires as available.

Statistical analysis

We used conditional logistic regression on the matched case–control sets to calculate OR and 95% CIs as estimates

Table 1. Characteristics of controls and cases

	All controls ($n = 21,952$)	All cases ($n = 1,102$)	Medical record review subset[a]	
			Controls ($n = 682$)	Cases ($n = 344$)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Reference year[b]				
1990–94	6,454 (29.4)	323 (29.3)	0 (0.0)	0 (0.0)
1995–99	6,532 (29.8)	328 (29.8)	297 (43.5)	150 (43.6)
2000–04	4,772 (21.7)	240 (21.8)	202 (29.6)	102 (29.7)
2005–09	4,194 (19.1)	211 (19.1)	183 (26.8)	92 (26.7)
Age (case's age in years)[b]				
20–29	197 (0.9)	10 (0.9)	18 (2.6)	9 (2.6)
30–34	1,141 (5.2)	58 (5.3)	69 (10.1)	36 (10.5)
35–39	2,944 (13.4)	148 (13.4)	173 (25.4)	87 (25.3)
40–44	6,730 (30.7)	338 (30.7)	422 (61.9)	212 (61.6)
45–49	10,940 (49.8)	548 (49.7)	0 (0.0)	0 (0.0)
Length of continuous GHC enrollment before reference date[b], mo				
Median	35.0	36.0	36.0	36.0
Mean	42.4	42.4	43.4	43.4
Race[c]				
White	12,728 (80.0)	905 (82.1)	364 (77.1)	274 (79.7)
Asian	1,611 (10.1)	82 (7.4)	58 (12.3)	31 (9.0)
Black	826 (5.2)	60 (5.4)	31 (6.6)	20 (5.8)
Other	739 (4.6)	55 (5.0)	19 (4.0)	19 (5.5)
Missing	6,048	0	210	0
Ethnicity				
Non-Hispanic	16,511 (95.0)	1,038 (94.4)	464 (94.7)	314 (91.3)
Hispanic	860 (5.0)	61 (5.6)	26 (5.3)	30 (8.7)
Missing	4,581	3	192	0
Body mass index (kg/m^2, available for reference dates from June 1998 and later)[d]				
<25	3,196 (41.6)	224 (44.2)	188 (42.0)	107 (44.2)
25.0–29.9	2,097 (27.3)	148 (29.2)	122 (27.2)	62 (25.6)
30+	2,389 (31.1)	135 (26.6)	138 (30.8)	73 (30.2)
Missing	3,254	43	42	5
Recent screening mammogram (within 18 months before reference date, available for women ≥40 years of age with reference dates from June 1998 and later)[e]				
No	6,087 (70.4)	249 (57.4)	213 (75.8)	86 (61.0)
Yes	2,560 (29.6)	185 (42.6)	68 (24.2)	55 (39.0)
Parous				
No	—	—	168 (27.6)	95 (29.0)
Yes	—	—	441 (72.4)	233 (71.0)
Missing			73	16
Number of live births				
0	—	—	168 (28.6)	95 (29.3)
1	—	—	113 (19.3)	71 (21.9)
2	—	—	202 (34.4)	111 (34.3)
3+	—	—	104 (17.7)	47 (14.5)
Missing			95	20
Removal of both ovaries				
No	—	—	610 (97.3)	335 (99.1)
Yes	—	—	17 (2.7)	3 (0.9)
Missing			55	6

(Continued on the following page)

Table 1. Characteristics of controls and cases (Cont'd)

	All controls (n = 21,952)	All cases (n = 1,102)	Medical record review subset[a] Controls (n = 682)	Medical record review subset[a] Cases (n = 344)
	n (%)	n (%)	n (%)	n (%)
First-degree family history of breast cancer (includes mother, sisters, and daughters)				
No	—	—	497 (91.5)	271 (86.0)
Yes	—	—	46 (8.5)	44 (14.0)
Missing			139	29
First-degree family history of ovarian cancer (includes mother, sisters, and daughters)				
No	—	—	475 (97.7)	284 (96.3)
Yes	—	—	11 (2.3)	11 (3.7)
Missing			196	49

NOTE: Demographic, anthropometric, and screening mammography among all controls and cases and reproductive and breast and ovarian cancer family history characteristics among a subset.

[a]Includes all cases ages 20–44 years with reference dates from May 1995 and later and up to two of their matched controls. Information came from medical records and breast cancer screening questionnaires.

[b]Matching variables. All 1-month enrollment gaps were considered administrative and ignored.

[c]The other race category includes women classified as multiple races.

[d]Body mass index before reference date (closest to 1 year prior) from medical records and breast cancer screening questionnaires. Months between weight value and reference month: all controls (median, 12; range, 0–60), all cases (median, 12; range, 0–54).

[e]Among women with 18+ months of enrollment before reference date. Excludes symptomatic and diagnostic mammograms. Mammography data were complete for all women with reference dates from June 1998 and later.

of the relative risk. We used 2-sided tests and ORs with $P < 0.05$ were considered statistically significant. The reference group for all analyses was women who did not fill an oral contraceptive prescription in the year before reference date. Because results were comparable when defining recent users as filling at least 2 oral contraceptive prescriptions in the year before reference date, all of our analyses defined recent use as filling at least one oral contraceptive prescription in the prior year. The oral contraceptive formulation analyses used separate regression models for each oral contraceptive exposure category. Therefore, the exposure categories were not mutually exclusive and women could be exposed in multiple models. We used unconditional logistic regression adjusted for the matching factors to test for heterogeneity between oral contraceptive exposure groups by calculating a P value comparing recent users of a specific oral contraceptive formulation to recent users of any other oral contraceptive formulation. In addition, we examined risk by age group (ages 20–39, 40–44, 45–49 years) but found no evidence of effect modification when comparing regression models using a likelihood ratio test ($P = 0.35$); thus, results were not stratified by age.

We systematically assessed potential confounders (in Tables 1 and 2) among women with available data. We also conducted a sensitivity analysis to evaluate possible confounding due to prior breast cancer screening among women ages 40 to 49 years, as systematic screening is not recommended for younger women. We obtained nonsymptomatic screening mammography data from GHC's Breast Cancer Surveillance Project for all women ages 40 to 49 years with reference dates beginning in June 1998.

We used 2 conditional logistic regression models restricted to either ER^+ or ER^- cases and their matched controls to calculate ER-specific ORs. We classified borderline ER results as positive ($n = 4$) and excluded cases with unknown ER status ($n = 91$) from these analyses. To test for a difference between ER case groups, we calculated a P value using unconditional logistic regression limited to cases and adjusted for the matching factors. We performed all analyses using Stata/MP version 12.0 (StataCorp LP).

Results

Distributions of reference year, age, and months of GHC enrollment were similar among cases and controls (Table 1). As expected, cases were more likely than controls to have a screening mammogram during the 18 months before the reference date because screening mammograms closer to the reference date were likely to lead to cancer detection in cases. Cases were somewhat more likely to be white and leaner than controls. Among women with available information, a first-degree family history of breast cancer among female relatives was more common among cases than controls. Cases were somewhat less likely than controls to have 3 or more live births and have both ovaries removed. Among control women, recent oral contraceptive users were more likely to be younger than 40 years of age, leaner, to have a screening mammogram in the 18 months before reference date, and somewhat more likely to be white compared with never or former oral contraceptive users (Table 2). Among controls with reproductive and family history of cancer information, recent oral contraceptive users were less likely than never or former oral contraceptive users to be

Table 2. Selected characteristics among controls who were never/former oral contraceptive users and recent oral contraceptive users

	Combined OC use[b]		Medical record review subset[a] Combined OC use[b]	
	Never/former use (n = 19,953)	Recent use (n = 1,999)	Never/former use (n = 579)	Recent use (n = 103)
	n (%)	n (%)	n (%)	n (%)
Age[c], y				
19–29	132 (0.7)	65 (3.3)	13 (2.3)	5 (4.9)
30–34	839 (4.2)	302 (15.1)	49 (8.5)	20 (19.4)
35–39	2,518 (12.6)	426 (21.3)	140 (24.2)	33 (32.0)
40–44	6,185 (31.0)	549 (27.5)	377 (65.1)	45 (43.7)
45–50	10,279 (51.5)	657 (32.9)	0 (0.0)	0 (0.0)
Race				
White	11,519 (79.8)	1,209 (82.6)	311 (76.8)	53 (79.1)
Asian	1,490 (10.3)	121 (8.3)	51 (12.6)	7 (10.4)
Black	757 (5.2)	69 (4.7)	27 (6.7)	4 (6.0)
Other	674 (4.7)	65 (4.4)	16 (4.0)	3 (4.5)
Missing	5,513	535	174	36
Ethnicity				
Non-Hispanic	15,083 (95.1)	1,428 (94.4)	401 (95.0)	63 (92.6)
Hispanic	775 (4.9)	85 (5.6)	21 (5.0)	5 (7.4)
Missing	4,095	486	157	35
Body mass index (kg/m^2, available for reference dates from June 1998 and later)[d]				
<25	2,771 (40.9)	425 (46.8)	148 (40.4)	40 (48.8)
25.0–29.9	1,862 (27.5)	235 (25.9)	100 (27.3)	22 (26.8)
30+	2,140 (31.6)	249 (27.4)	118 (32.2)	20 (24.4)
Missing	2,869	385	38	4
Recent screening mammogram (within 18 months before reference date, available for women ≥40 years of age with reference dates from June 1998 and later)[e]				
No	5,580 (71.2)	507 (62.5)	186 (75.6)	27 (77.1)
Yes	2,256 (28.8)	304 (37.5)	60 (24.4)	8 (22.9)
Parous				
No	—	—	126 (24.7)	42 (42.4)
Yes	—	—	384 (75.3)	57 (57.6)
Missing			69	4
First-degree family history of breast cancer (includes mother, sisters, and daughters)				
No	—	—	416 (91.0)	81 (94.2)
Yes	—	—	41 (9.0)	5 (5.8)
Missing			122	17
First-degree family history of ovarian cancer (includes mother, sisters, and daughters)				
No	—	—	399 (98.0)	76 (96.2)
Yes	—	—	8 (2.0)	3 (3.8)
Missing			172	24

Abbreviation: OC, oral contraceptive.

[a]Includes up to two of the controls matched to all cases ages 20–44 years with reference dates from May 1995 and later. Information came from medical records and breast cancer screening questionnaires.

[b]Recent use is defined as filling at least one combined oral contraceptive script in the year before reference date.

[c]Some controls are outside of the 20–49 age range due to expanded matching criteria.

[d]Body mass index before reference date (closest to 1 year prior) from medical records and breast cancer screening questionnaires.

[e]Among women with 18+ months of enrollment before reference date. Excludes symptomatic and diagnostic mammograms. Mammography data were complete for all women with reference dates from June 1998 and later.

parous and somewhat less likely to have a first-degree family history of breast cancer but slightly more likely to have a first-degree family history of ovarian cancer.

None of the potential confounders assessed (in Tables 1 and 2) changed the OR for any oral contraceptive use in the prior year and breast cancer risk by ≥10% when individually

added to the model. Thus, none were adjusted for in our final statistical models. Inclusion of recent screening mammogram receipt in our model only changed the OR for oral contraceptive use and breast cancer risk by 5%; therefore, it was not included in our final statistical models.

Recent oral contraceptive use was associated with a 50% elevated breast cancer risk (95% CI, 1.3–1.9) relative to never or former oral contraceptive use (Table 3). Recent oral contraceptive use was more strongly related to ER^+ than to ER^- cancer, although this difference was not statistically significant ($P = 0.15$). Risk of overall breast cancer and ER^+ cancer increased with increasing number of hormone pills dispensed over the past year ($P_{trend} < 0.001$ for both).

The proportions of use of different oral contraceptive types varied by oral contraceptive estrogen dose, progestin type, and reference year among controls who were recent oral contraceptive users (Table 4). Low-dose estrogen oral contraceptives were not associated with an increased breast cancer risk (OR, 1.0; 95% CI, 0.6–1.7), whereas moderate- and high-dose oral contraceptives were associated with elevations in risk (OR, 1.6; 95% CI, 1.3–2.0 and OR, 2.7; 95% CI, 1.1–6.2, respectively; Table 5). None of the estrogen dose risk estimates were statistically significantly different than the risk estimates for using other estrogen doses, although low-dose estrogen oral contraceptives approached statistical significance ($P_{heterogeneity} = 0.08$). Risk increased with increasing number of pills dispensed of moderate ($P_{trend} < 0.001$) and high-dose estrogen oral contraceptives ($P_{trend} = 0.01$) in the prior year, although few women used high-dose estrogen oral contraceptives.

Estrane progestin oral contraceptives were associated with a 60% increased risk (95% CI, 1.3–2.0) and a greater number of pills dispensed increased this risk ($P_{trend} < 0.001$). All of the individual estrane progestins were associated with elevated risks and had statistically significant trends for increasing number of pills, except for norethindrone acetate. Ethynodiol diacetate oral contraceptives were infrequently used but were associated with an elevated risk (OR, 2.6; 95% CI, 1.4–4.7). Gonane progestin oral contraceptives were associated with an increased risk (OR, 1.4; 95% CI, 1.0–2.0), but risk did not increase with additional pills dispensed. While norgestimate oral contraceptives did not appear to be associated with an increased risk (OR, 1.2; 95% CI, 0.6–2.2), levonorgestrel oral contraceptives were (OR, 1.5; 95% CI, 1.0–2.3), although neither OR was statistically significantly different than using other progestin types.

We further assessed risk by the most commonly used oral contraceptive formulations. One monophasic formulation (low-dose estrogen and norethindrone acetate 1.0 mg) composed most of the low-dose users (Table 6). Among monophasic moderate-dose estrogen users, there was considerable variation in risk estimates and some neared statistical significance when compared with users of other oral contraceptive formulations. Norethindrone 0.50 mg was not associated with an increased risk (OR, 0.8; 95% CI, 0.4–1.6; $P_{heterogeneity} = 0.05$), whereas norethindrone acetate 1.5 mg was associated with an increased risk (OR, 2.1; 95% CI, 1.4–3.1; $P_{heterogeneity} = 0.08$), and ethynodiol diacetate 1.0 mg was associated with the greatest risk (OR, 2.8; 95% CI, 1.5–5.2;

Table 3. Recent oral contraceptive use and invasive breast cancer risk by ER status

	Controls ($n = 21,952$)	All cases ($n = 1,102$)		Controls ($n = 14,704$)	ER^+ cases[a] ($n = 738$)		Controls ($n = 5,433$)	ER^- cases[a] ($n = 273$)	
	n (%)	*n* (%)	OR (95% CI)[b]	*n* (%)	*n* (%)	OR (95% CI)[b]	*n* (%)	*n* (%)	OR (95% CI)[b]
Combined OC use[c]									
Never/former use	19,953 (90.9)	957 (86.8)	Reference	13,394 (91.1)	637 (86.3)	Reference	4,889 (90.0)	240 (87.9)	Reference
Recent use	1,999 (9.1)	145 (13.2)	1.5 (1.3–1.9)	1,310 (8.9)	101 (13.7)	1.7 (1.3–2.1)	544 (10.0)	33 (12.1)	1.2 (0.8–1.8)
Total number of combined OC hormone pills									
<190	899 (4.1)	50 (4.5)	1.2 (0.9–1.6)	582 (4.0)	33 (4.5)	1.2 (0.8–1.8)	254 (4.7)	14 (5.1)	1.1 (0.6–2.0)
190+	1,082 (4.9)	93 (8.5)	1.8 (1.5–2.3)	714 (4.9)	66 (9.0)	2.0 (1.5–2.6)	288 (5.3)	19 (7.0)	1.4 (0.8–2.2)
Missing	18	2		14	2		2	0	
P_{trend}[d]			<0.001			<0.001			0.16

Abbreviation: OC, oral contraceptive.

[a]Ninety-one cases were excluded because of unknown ER status. Cases with borderline ER results were coded as positive ($n = 4$). There was no statistically significant difference between recent oral contraceptive use and risk of ER^+ compared with ER^- breast cancer ($P = 0.15$).

[b]All ORs are implicitly adjusted for the matching factors (age, year, months of enrollment before reference date, and medical chart availability).

[c]Recent use is defined as filling at least one combined oral contraceptive script in the year before reference date.

[d]P_{trend} in the prior year (maximum number of pills = 365) using the continuous linear variable and a reference group comprised of never/former oral contraceptive users).

Table 4. Proportions of use of different types of oral contraceptives over time among controls who were recent oral contraceptive users

	Reference year			
	1990–1994	1995–1999	2000–2004	2005–2009
OC type[a]	%	%	%	%
Low estrogen dose	6.4	19.5	19.2	23.8
Moderate estrogen dose	91.5	81.7	82.8	78.2
High estrogen dose	6.1	3.6	0.8	0.4
Progestin types				
Estrane progestin	83.6	80.8	71.2	62.2
Norethindrone	59.7	44.1	36.5	30.8
Norethindrone acetate	23.3	34.6	32.3	28.5
Ethynodiol diacetate	3.9	6.8	5.2	3.5
Gonane progestin	20.3	22.9	35.6	36.8
Levonorgestrel	15.8	17.4	16.9	19.9
Norgestimate	0.0	3.1	16.7	13.8
Norgestrel	4.6	2.3	1.3	1.4
Desogestrel	0.0	0.5	1.5	2.5

NOTE: Percent of controls filling at least one combined oral contraceptive script among recent oral contraceptive users by reference year. Recent use is defined as filling at least one combined oral contraceptive script in the year prior.

Abbreviation: OC, oral contraceptive.

[a]Oral contraceptive types are not mutually exclusive. Low estrogen dose = 20 μg ethinyl estradiol, moderate estrogen dose = 30–35 μg ethinyl estradiol or 50 μg mestranol, and high estrogen dose = 50 μg ethinyl estradiol or 80 μg mestranol. Estrane progestins include norethindrone, norethindrone acetate, and ethynodiol diacetate. Gonane progestins include levonorgestrel, norgestimate, norgestrel, and desogestrel.

$P_{\text{heterogeneity}} = 0.08$). There was some suggestion that risk increased as norethindrone dose increased (1.0 vs. 0.50 mg). Triphasic oral contraceptives with an average dose of 0.75 mg norethindrone were associated with the greatest risk of all formulations (OR, 3.1; 95% CI, 1.9–5.1). This formulation was the only oral contraceptive exposure (by estrogen dose, progestin type, or unique formulation) that was statistically significantly different than using other oral contraceptive formulations ($P_{\text{heterogeneity}} = 0.004$). Most risk estimates by estrogen dose, progestin type, and unique oral contraceptive formulation increased somewhat after limiting to ER^+ cases, although confidence intervals widened.

Discussion

To our knowledge, this is the first study evaluating specific oral contraceptive formulations used in the United States during the 1990s and 2000s, determined by high-quality electronic pharmacy dispensing records, and breast cancer risk among young women. Our findings suggest that recent use of contemporary oral contraceptive formulations is associated with an increased breast cancer risk among women ages 20 to 49 years. This risk may be more strongly associated with ER^+ than ER^- breast cancer and may increase with increasing number of pills dispensed. Our results also suggest that risk may vary by oral contraceptive formulation. High-dose estrogen, ethynodiol diacetate, higher dose norethindrone, and specific triphasic oral contraceptives are possibly associated with increased breast cancer risks, whereas low-dose estrogen oral contraceptives and other formulations may not be associated with elevated risks.

The increased breast cancer risk associated with recent oral contraceptive use that we observed is consistent with some studies, including the large Collaborative Group pooled analysis that found the greatest breast cancer risk associated with oral contraceptive use in the prior year (6), and the Nurses' Health Study II (8), although not consistent with all studies (9, 23, 24). Collectively, these results suggest that oral contraceptives may act as tumor promoters, which is supported by evidence demonstrating increased breast cell proliferation among oral contraceptive users (25–28).

Our results by estrogen dose, progestin type, and dosing schedule differ from the Collaborative Group analysis, which overall did not find risk variations by oral contraceptive formulation among recent users (6, 7), but this could be due to two important study design differences. First, 21 of the 27 studies with oral contraceptive formulation data in the Collaborative Group analysis relied only on self-report and the remaining 6 relied partially or exclusively on medical records (7), whereas our study used pharmacy records. Although validation studies suggest that women recall ever using oral contraceptives, duration of use, and timing of use relatively well, recall of specific oral contraceptive brand names is less accurate (29–33). Second, many of the oral contraceptive formulations examined in the Collaborative Group analysis are not comparable to oral contraceptives used today. In particular, the mean ethinyl

Table 5. Recent oral contraceptive use by estrogen dose and progestin type and invasive breast cancer risk by all cases (left) and ER^+ cases (right)

	Controls ($n = 21,952$)	All cases ($n = 1,102$)		Controls ($n = 14,704$)	ER^+ cases ($n = 738$)	
Number of pills[a]	*n* (%)	*n* (%)	OR (95% CI)[b]	*n* (%)	*n* (%)	OR (95% CI)[b]
Never/former use	19,953 (90.9)	957 (86.8)	Reference	13,394 (91.1)	637 (86.3)	Reference
Low estrogen dose	367 (1.7)	18 (1.6)	1.0 (0.6–1.7)	256 (1.7)	14 (1.9)	1.2 (0.7–2.0)
<190	228 (1.0)	11 (1.0)	1.0 (0.6–1.9)	155 (1.1)	10 (1.4)	1.4 (0.7–2.6)
190+	138 (0.6)	7 (0.6)	1.1 (0.5–2.3)	100 (0.7)	4 (0.5)	0.9 (0.3–2.3)
P_{trend}[c]			0.94			0.81
Moderate estrogen dose	1,654 (7.5)	126 (11.4)	1.6 (1.3–2.0)	1,063 (7.2)	86 (11.7)	1.8 (1.4–2.2)
<190	734 (3.3)	45 (4.1)	1.3 (1.0–1.8)	463 (3.2)	29 (3.9)	1.4 (0.9–2.0)
190+	919 (4.2)	81 (7.4)	1.9 (1.5–2.4)	600 (4.1)	57 (7.7)	2.1 (1.5–2.8)
P_{trend}[c]			<0.001			<0.001
High estrogen dose	47 (0.2)	6 (0.5)	2.7 (1.1–6.2)	32 (0.2)	6 (0.8)	3.9 (1.6–9.4)
P_{trend}[c]			0.01			0.01
Progestin types[d]						
Estrane progestin[d]	1,472 (6.7)	111 (10.1)	1.6 (1.3–2.0)	973 (6.6)	76 (10.3)	1.7 (1.3–2.2)
<190	741 (3.4)	43 (3.9)	1.2 (0.9–1.7)	487 (3.3)	28 (3.8)	1.2 (0.8–1.8)
190+	729 (3.3)	68 (6.2)	2.0 (1.5–2.6)	485 (3.3)	48 (6.5)	2.1 (1.6–2.9)
P_{trend}[c]			<0.001			<0.001
Norethindrone	819 (3.7)	59 (5.4)	1.5 (1.2–2.0)	519 (3.5)	35 (4.7)	1.5 (1.0–2.1)
<190	415 (1.9)	20 (1.8)	1.0 (0.7–1.6)	252 (1.7)	9 (1.2)	0.8 (0.4–1.5)
190+	403 (1.8)	39 (3.5)	2.1 (1.5–2.9)	267 (1.8)	26 (3.5)	2.1 (1.4–3.2)
P_{trend}[c]			<0.001			<0.001
Norethindrone acetate	609 (2.8)	46 (4.2)	1.6 (1.2–2.2)	425 (2.9)	36 (4.9)	1.8 (1.3–2.6)
<190	339 (1.5)	27 (2.5)	1.7 (1.1–2.5)	240 (1.6)	22 (3.0)	2.0 (1.3–3.1)
190+	269 (1.2)	19 (1.7)	1.5 (0.9–2.4)	184 (1.3)	14 (1.9)	1.6 (0.9–2.8)
P_{trend}[c]			0.06			0.06
Ethynodiol diacetate	100 (0.5)	12 (1.1)	2.6 (1.4–4.7)	64 (0.4)	9 (1.2)	3.1 (1.5–6.2)
<190	59 (0.3)	2 (0.2)	0.7 (0.2–3.0)	38 (0.3)	1 (0.1)	0.6 (0.1–4.2)
190+	41 (0.2)	10 (0.9)	5.2 (2.6–10.5)	26 (0.2)	8 (1.1)	6.7 (3.0–15.1)
P_{trend}[c]			<0.001			<0.001
Gonane progestin[d]	597 (2.7)	40 (3.6)	1.4 (1.0–2.0)	385 (2.6)	29 (3.9)	1.6 (1.1–2.4)
<190	269 (1.2)	17 (1.6)	1.4 (0.8–2.3)	165 (1.1)	12 (1.6)	1.6 (0.9–2.9)
190+	312 (1.4)	21 (1.9)	1.4 (0.9–2.3)	207 (1.4)	15 (2.0)	1.6 (0.9–2.7)
P_{trend}[c]			0.12			0.11
Levonorgestrel	352 (1.6)	25 (2.3)	1.5 (1.0–2.3)	222 (1.5)	16 (2.2)	1.6 (0.9–2.6)
<190	141 (0.6)	14 (1.3)	2.2 (1.2–3.8)	80 (0.5)	9 (1.2)	2.4 (1.2–4.9)
190+	211 (1.0)	11 (1.0)	1.1 (0.6–2.1)	142 (1.0)	7 (1.0)	1.1 (0.5–2.3)
P_{trend}[c]			0.45			0.61
Norgestimate	188 (0.9)	10 (0.9)	1.2 (0.6–2.2)	130 (0.9)	8 (1.1)	1.4 (0.6–2.8)
<190	112 (0.5)	4 (0.4)	0.8 (0.3–2.1)	80 (0.5)	4 (0.5)	1.1 (0.4–3.1)
190+	76 (0.4)	6 (0.5)	1.7 (0.7–3.9)	50 (0.3)	4 (0.5)	1.7 (0.6–4.9)
P_{trend}[c]			0.22			0.20

[a]Recent use is defined as filling at least one combined oral contraceptive script in the year before reference date. Includes mono- and triphasic oral contraceptives. Categories are not mutually exclusive and numbers may not add up to column totals because of missing values. Low estrogen dose = 20 μg ethinyl estradiol, moderate estrogen dose = 30–35 μg ethinyl estradiol or 50 μg mestranol, and high estrogen dose = 50 μg ethinyl estradiol or 80 μg mestranol.

[b]All ORs are implicitly adjusted for the matching factors.

[c]P_{trend} in the prior year (maximum number of pills = 365) using the continuous linear variable and a reference group comprised of never/former oral contraceptive users.

[d]Estrane progestins include norethindrone, norethindrone acetate, and ethynodiol diacetate. Gonane progestins include levonorgestrel, norgestimate, norgestrel, and desogestrel. ORs for recent use of norgestrel and desogestrel are not displayed because <5 cases were exposed to these progestin types.

Table 6. Recent oral contraceptive use by monophasic and triphasic formulations and invasive breast cancer risk by all cases (left) and ER^+ cases (right)

	Controls ($n = 21,952$)	All cases ($n = 1,102$)		Controls ($n = 14,704$)	ER^+ cases ($n = 738$)	
OC formulation[a]	***n* (%)**	***n* (%)**	**OR (95% CI)[b]**	***n* (%)**	***n* (%)**	**OR (95% CI)[b]**
Never/former use	19,953 (90.9)	957 (86.8)	Reference	13,394 (91.1)	637 (86.3)	Reference
Monophasic OCs						
Any monophasic OC	1,614 (7.4)	114 (10.3)	1.5 (1.2–1.9)	1,068 (7.3)	79 (10.7)	1.6 (1.2–2.0)
By estrogen dose and progestin type and dose						
Low estrogen dose						
Norethindrone acetate						
1.00 mg	328 (1.5)	17 (1.5)	1.1 (0.7–1.8)	228 (1.6)	13 (1.8)	1.2 (0.7–2.1)
Moderate estrogen dose	1,259 (5.7)	95 (8.6)	1.6 (1.3–2.0)	816 (5.6)	64 (8.7)	1.7 (1.3–2.2)
Any norethindrone	616 (2.8)	40 (3.6)	1.4 (1.0–1.9)	398 (2.7)	22 (3.0)	1.2 (0.8–1.9)
0.50 mg	229 (1.0)	9 (0.8)	0.8 (0.4–1.6)	148 (1.0)	5 (0.7)	0.7 (0.3–1.8)
1.00 mg	358 (1.6)	27 (2.5)	1.6 (1.1–2.4)	230 (1.6)	13 (1.8)	1.2 (0.7–2.2)
1.00 mg[c]	46 (0.2)	5 (0.5)	2.3 (0.9–5.9)	26 (0.2)	5 (0.7)	4.2 (1.6–11.1)
Norethindrone acetate						
1.50 mg	300 (1.4)	30 (2.7)	2.1 (1.4–3.1)	205 (1.4)	24 (3.3)	2.5 (1.6–3.9)
Ethynodiol diacetate						
1.00 mg	86 (0.4)	11 (1.0)	2.8 (1.5–5.2)	55 (0.4)	8 (1.1)	3.2 (1.5–6.7)
Levonorgestrel						
0.15 mg	166 (0.8)	10 (0.9)	1.3 (0.7–2.5)	104 (0.7)	5 (0.7)	1.0 (0.4–2.6)
Norgestimate						
0.25 mg	96 (0.4)	6 (0.5)	1.4 (0.6–3.2)	67 (0.5)	5 (0.7)	1.7 (0.7–4.2)
Triphasic OCs						
Any triphasic OC	456 (2.1)	37 (3.4)	1.8 (1.2–2.5)	283 (1.9)	25 (3.4)	1.9 (1.3–3.0)
By progestin type and dose[d]						
Moderate estrogen dose						
Norethindrone						
0.71 mg	97 (0.4)	8 (0.7)	1.8 (0.9–3.7)	54 (0.4)	6 (0.8)	2.4 (1.0–5.7)
0.75 mg	132 (0.6)	19 (1.7)	3.1 (1.9–5.1)[e]	76 (0.5)	12 (1.6)	3.5 (1.9–6.4)
Levonorgestrel						
0.09 mg	153 (0.7)	13 (1.2)	1.8 (1.0–3.3)	94 (0.6)	9 (1.2)	2.1 (1.0–4.2)
Norgestimate						
0.22 mg	96 (0.4)	5 (0.5)	1.1 (0.5–2.8)	67 (0.5)	4 (0.5)	1.3 (0.5–3.7)

Abbreviation: OC, oral contraceptive.

[a]Recent use is defined as filling at least one combined oral contraceptive script in the year before reference date. Categories are not mutually exclusive and numbers may not add up to column totals because of missing values. Oral contraceptive formulations with <5 controls or invasive cases as recent users are not displayed. Low estrogen dose = 20 μg ethinyl estradiol and moderate estrogen dose = 30–35 μg ethinyl estradiol or 50 μg mestranol.

[b]All ORs are implicitly adjusted for the matching factors.

[c]Contains the estrogen mestranol rather than ethinyl estradiol.

[d]All triphasic formulations contain moderate estrogen dose. Average progestin doses are listed. The dosing schedules are as follows: (i) Norethindrone 0.71 mg = 35 μg ethinyl estradiol/0.5 mg (7 days), 1.0 mg (9 days), 0.5 mg (5 days) norethindrone; (ii) norethindrone 0.75 mg = 35 μg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone; (iii) levonorgestrel 0.09 mg = 30 μg ethinyl estradiol/0.05 mg levonorgestrel (6 days), 40 μg ethinyl estradiol/0.075 mg levonorgestrel (5 days), 30 μg ethinyl estradiol/0.125 mg levonorgestrel (10 days); (iv) norgestimate 0.22 mg = 35 μg ethinyl estradiol/0.18 mg (7 days), 0.215 mg (7 days), 0.25 mg (7 days) norgestimate.

[e]$P_{heterogeneity} < 0.05$ comparing recent users of the formulation to recent users of other formulations.

estradiol dose dropped from approximately 56 μg per pill in 1972, to 34 μg in 1994, and now oral contraceptives with <30 μg ethinyl estradiol account for an increasing proportion of hormonal contraception prescriptions (1–4). This change allowed us to evaluate 20 μg ethinyl estradiol oral contraceptives, which was not possible in earlier studies.

Some of our oral contraceptive formulation results are consistent with studies after the Collaborative Group analysis, although all of these studies relied exclusively on self-report. The Nurses' Health Study II reported an increased breast cancer risk among women younger than 55 years who were current oral contraceptive users and one triphasic formulation containing levonorgestrel accounted for much of the excess risk (RR, 3.1; 95% CI, 2.0–4.7; ref. 8). We also found an increased risk associated with this formulation (OR, 1.8; 95% CI, 1.0–3.3). However, another triphasic oral contraceptive (average dose of 0.75 mg norethindrone) was associated with the greatest risk in our study and was the only oral contraceptive formulation with a statistically significantly different risk compared with using other oral contraceptive formulations. In contrast, the CARE study found no increased risk associated with unique oral contraceptive formulations, high-dose estrogen oral contraceptives, or progestin types among women ages 35 to 64 years, with the exception of an elevated risk associated with current use of ethynodiol diacetate oral contraceptives (OR, 3.5; 95% CI, 1.1–10.7), yet numbers were quite small (9, 10). Another study included in the Collaborative Group analysis, but with more recent diagnosis dates, reported nonstatistically significant risk estimates of similar magnitudes to our progestin type results, a greater risk associated with higher than lower dose estrogen oral contraceptives, and an elevated risk associated with ethynodiol diacetate oral contraceptives among the youngest women, but data were sparse (34). Future studies are necessary to identify mechanisms explaining possible differences in risk by estrogen dose, progestin type, dosing schedule, and specific oral contraceptive formulation.

Although we did not find statistically significant differences between ER case groups, our ER status findings add to the varying results on recent oral contraceptive use and breast cancer risk among young women. While one prior study observed a stronger association between recent oral contraceptive use and risk of ER^+/PR^+ than ER^-/PR^- cancer (13), others found the opposite where oral contraceptive use was more strongly related to ER^- than to ER^+ cancer (11, 12), and another study found no association between recent use and luminal A or triple-negative breast cancer risk (14). Two studies including both pre- and postmenopausal women observed greater risks of ER^- than ER^+ cancer associated with recent use, although the differences were not statistically significant (15, 16). Differences in results may be due to varying age distributions or to having insufficient power to detect modest differences. Additional studies with ER, PR, and HER2-neu data are needed to clarify how risk potentially varies by molecular subtype.

Our main study limitation was the relatively short durations of continuous GHC enrollment before reference date, which restricted the exposure length we could evaluate. While the large Collaborative Group analysis did not find any significant impact of duration of oral contraceptive use after accounting for recency of use (6, 7), some individual studies since then have found long durations of oral contraceptive use associated with increased risk among women younger than 60 years (23, 24, 35). In addition, never and former oral contraceptive users comprised our reference group, because we did not have lifetime oral contraceptive use data. Data on potentially relevant confounders were unavailable for all women, although we collected information on a sizeable subset of matched sets and found that each had a minimal impact. While some residual confounding may still be present, confounding of any appreciable magnitude is unlikely because prior studies reporting age-adjusted and multivariable-adjusted results generally do not suggest strong confounders (8, 36), and we would not expect strong associations between covariates and specific oral contraceptive formulations. Several of our analyses by oral contraceptive type, such as for low- and high-dose estrogen, were limited by a small number of exposed cases, and some of the statistically significant findings may be due to chance as a result of the number of analyses performed.

A key strength of this study is the utilization of electronic pharmacy data that reduced misclassification and allowed all oral contraceptive episodes to be categorized by formulation. Electronic mammography data enabled the accurate identification of screening mammograms without relying on participant recall. These data, along with the minimal impact of adjustment for recent screening mammography on the OR, equal opportunity for screening among all women ages 40 to 49 years, and excluding *in situ* breast cancer cases, increase our confidence that our findings are not due to detection bias. Additional strengths include the large number of controls and including all eligible women, as no direct contact was required.

Our results indicating possible variations in risk by oral contraceptive formulation require replication in larger studies and should be interpreted cautiously. In addition, prior evidence indicates that the increased risk associated with recent oral contraceptive use declines after ceasing use (6, 7). However if confirmed, these results could contribute to evidence-based discussions between women and their providers regarding the benefits and harms of the various commonly prescribed hormonal contraceptive options. Although these results suggest an increased risk of breast cancer, the many established health benefits associated with oral contraceptive use, including reproductive planning, menses regulation, decreased dysmenorrhea, and decreased risk of benign breast conditions (37, 38), must also be considered when making individual choices.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The study sponsors had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; and the decision to submit the article for publication. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NCI, NIH.

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Acknowledgments

The authors acknowledge and thank the efforts of numerous Group Health Research Institute staff members who contributed to the medical record review, data extraction, and project management aspects of this research study.

Grant Support

This study was funded by grant number R03CA141485 from the NCI at the NIH and through the NCI-funded Group Health Breast Cancer Surveillance Registry (U01CA063731). Dr. E.F. Beaber and this publication were also supported by grant number T32CA09168 from the NCI, NIH. The collection of cancer incidence data used in this study was supported by the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, which is funded by Contract No. N01-CN-67009 and N01-PC-35142 from the Surveillance, Epidemiology and End Results (SEER) Program of the NCI with additional support from the Fred Hutchinson Cancer Research Center and the State of Washington.

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Received November 26, 2013; revised April 30, 2014; accepted May 24, 2014; published online August 1, 2014.

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Cancer Res 2014;74:4078-4089.