Use of oral contraceptives (OC) and breast cancer risk among young women by OC formulation and breast cancer subtype

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Abstract

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Background:

Many studies suggest a modest increased breast cancer risk is associated with recent oral contraceptive (OC) use, but risks associated with contemporary OCs and molecular subtypes of breast cancer are less well known. Estrogen and progestin doses have declined and new progestins have been used since OCs were introduced. Furthermore, the vast majority of studies have relied on self-reported OC use, rather than pharmacy data.

Methods:

Two studies examining invasive breast cancer risk were conducted in western Washington state. The first was a population-based interview case-control study among women ages 20-44 from 2004-2010 (985 cases, 882 controls). Logistic regression was used to estimate associations between lifetime OC use, overall risk, and breast cancer risk by subtype (estrogen receptor positive (ER+), ER-, and triple-negative (ER-/PR-/HER2-)). The second study was a nested case-control study among Group Health Cooperative health plan enrollees. Cases were ages 20-49 at diagnosis from 1990-2009 (n=1102) and controls were randomly selected (n=21952). Associations between recent OC use (within 1 year of reference date) by OC formulation and ER status were evaluated using conditional logistic regression.

Results:

In the first study, recent OC use for ≥5 years increased breast cancer risk (odds ratio (OR)=1.6), as well as lifetime duration of use for ≥15 years (OR=1.5). There was no statistically significant risk heterogeneity by OC formulation. ORs were generally greater among women ages 20-39. ER- cancer ORs were greater than ER+ ORs. Triple-negative breast cancer ORs were especially elevated. In the second study, recent OC use increased breast cancer risk (OR=1.6). Risk was greater for ER+ (OR=1.7) than ER- cancer (OR=1.3). Risk varied by OC formulation, with some OCs associated with an increased risk and others not associated with risk.

Conclusions:

We found that recent use of contemporary OCs increases breast cancer risk among women ages 20-49 and that long durations of use increases risk among ages 20-44. Risks may be greater among younger women and for triple-negative breast cancer. Risks may also vary by OC formulation. Continued monitoring of breast cancer risk is essential as OC formulations and use patterns continue to evolve.

TABLE OF CONTENTS

Page

List of Tables....................ii

Chapter 1: Oral contraceptive use and breast cancer risk overall and by molecular subtype among women ages 20-44

Abstract....................1

Introduction....................2

Methods....................3

Results....................7

Discussion....................10

Chapter 2: Recent oral contraceptive use by formulation and breast cancer risk among young women

Abstract....................23

Introduction....................24

Methods....................25

Results 31

Discussion....................34

Bibliography....................52

LIST OF TABLES

Table Number and Title Page

1.1 Selected characteristics of controls and cases......16

1.2 Oral contraceptive (OC) use and risk of breast cancer......18

1.3 Risk of breast cancer associated with current use of specific combined oral contraceptive (OC) preparations for 5 years or longer......19

1.4 Risk of breast cancer associated with ever or current use of specific combined oral contraceptive (OC) preparations......20

1.5 Duration of oral contraceptive (OC) use, recency of use, and risk of estrogen receptor positive (ER+), ER negative (ER-), and triple-negative (ER-/PR-/HER2-) breast cancer......21

2.1 Descriptive characteristics of controls and cases......44

2.2 Additional descriptive characteristics among a subset of controls and cases ages 20-44 (reference years: 1995-2009)......45

2.3 Recent oral contraceptive (OC) use and invasive breast cancer risk by estrogen receptor (ER) status......46

2.4 Recent oral contraceptive (OC) use by number of scripts and pills and invasive breast cancer risk by estrogen receptor (ER) status......47

2.5 Recent oral contraceptive (OC) use and invasive breast cancer risk by age......48

2.6 Recent oral contraceptive (OC) use by estrogen dose and progestin type and invasive breast cancer risk, by all cases (left) and ER positive cases (right)......49

2.7 Recent oral contraceptive (OC) use by monophasic formulations and invasive breast cancer risk, by all cases (left) and ER positive cases (right)......50

2.8 Recent oral contraceptive (OC) use by triphasic formulations and invasive breast cancer risk, by all cases (left) and ER positive cases (right)......51

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DEDICATION

To my dad, Larry Beaber. In memory of his constant love and support, good cheer, and commitment to lifelong learning.

CHAPTER 1: Oral contraceptive use and breast cancer risk overall and by molecular subtype among women ages 20-44

ABSTRACT

Background: The majority of studies demonstrate recent oral contraceptive (OC) use is associated with a small increased breast cancer risk among young women; yet risks associated with modern OC formulations and by molecular subtype have not been well characterized.

Methods: We conducted a population-based case-control study of invasive breast cancer among women ages 20-44 residing in the Seattle-Puget Sound area from 2004-2010 (985 cases and 882 controls). We collected detailed 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: Current OC use (within 1 year of reference date) for ≥5 years was associated with an increased breast cancer risk (OR=1.6, 95% CI=1.1-2.5) and there were no statistically significant differences in risk by OC formulation. Lifetime duration of OC use for ≥15 years was associated with an increased risk (OR=1.5, 95% CI=1.1-2.2) and risk increased with each additional year of use. Risk magnitudes were generally greater among women ages 20-39 years and among women with triple-negative breast cancer. Women ages 20-39 who were current OC users for ≥5 years had a particularly elevated risk of triple-negative breast cancer relative to women who never used OCs (OR=3.7, 95% CI=1.1-11.7).

Conclusions: Our findings suggest that current use of modern OC formulations for ≥5 years and OC use for long durations confer an increased breast cancer risk among women ages 20-44, with possible stronger associations among younger women and for triple-negative breast cancer. These results support the continued surveillance of OC use and breast cancer risk as OC formulations continue to change.

INTRODUCTION

Although the relationship between oral contraceptive (OC) use and breast cancer risk has been extensively studied, the topic remains an important area of research 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 considerable molecular heterogeneity of breast cancer. OCs are the most common type of hormonal contraception used in the United States (US). Eighty-two percent of US women have ever used OCs and 10.7 million women are current users.[1] OCs entered the US market in the early 1960s and since then there have been dramatic decreases in estrogen dose, the addition of new progestin constituents, and changes in pattern of uses. Specifically, the mean ethinyl estradiol dose dropped from approximately 56 micrograms (mcg) per pill in 1972, to 34 mcg in 1994, and now OCs with <30 mcg of ethinyl estradiol account for an increasing proportion of hormonal contraception prescriptions.[2-5] In addition, multiple types of progestins have been used in OCs over time. For example, desogestrel and norgestimate began to be used in the US in 1988,[2] and more recently drospirenone was approved for use in 2001. Patterns of use have also changed with the introduction of extended and continuous cycle OCs.

Results from a pooled analysis of 54 epidemiologic studies worldwide suggest a modest increased risk of breast cancer associated with current or recent OC use that is no longer evident 10 or more years after ceasing OC use.[6] Since publication of these findings in 1996, results from other US studies have been mixed,[7-10] 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,[7] but no evidence of an association among women ages 35-44 from the Women's Contraceptive and Reproductive Experiences (CARE) Study, a large multi-center population-based case-control study.[8] However, the extent to which these differences may relate to changes in OC formulations, dosages, and patterns of use has not been well characterized.

Additionally, differing age distributions may account for some of the variation in results, as some studies suggest younger women may have a greater risk of breast cancer associated with OC use than older women.[11-16] Another aspect of the OC and breast cancer relationship that has been understudied is how this relationship may vary according to molecular subtype, specifically by joint estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) status, but confirmation of these findings is needed. The largest population-based study to date focusing on etiologic differences in breast cancer subtypes according to ER, PR, and HER2 status among young women found that current use of OCs was associated with a 3.1-fold (95% confidence interval (CI)=1.2-7.6) increased risk of ER-/PR-/HER2- (triple-negative) breast cancer but was not related to risk of non-triple-negative breast cancer (odds ratio (OR)=0.7, 95% CI=0.4-1.4).[17] So in order to better characterize the association between use of contemporary OCs and risk of different invasive breast cancer subtypes among young women, we analyzed data from a population-based case-control study limited to women 20-44 years of age.

METHODS

Study participants

We conducted a large population-based case-control study of invasive breast cancer among women 20 to 44 years of age residing in the Seattle-Puget Sound region. Details of this study's methods have been published previously.[18] Briefly, we identified cases through the Cancer Surveillance System, which is the population-based cancer registry covering 13 counties in western Washington state and a participant in the Surveillance, Epidemiology, and End Results program funded by the National Cancer Institute. Eligible cases included women ages 20-44 diagnosed with a first primary invasive breast cancer from June 2004 to June 2010 who resided in King, Pierce, or Snohomish counties at the time of diagnosis, had a landline home telephone, and did not have a prior history of *in situ* or invasive breast cancer. 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.

Eligible controls included women ages 20-44 who resided in King, Pierce, or Snohomish counties, had a landline home telephone, and did not have a prior history of *in situ* or invasive breast cancer. 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 age 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. The interview included detailed questions about contraceptive use, including contraceptive type, prescription name, dose, duration of use, and number of pills taken per month for every reported episode of use. The interview also collected information about demographic, anthropometric, reproductive, and behavioral factors, in addition to personal and family medical history. The interview only collected information prior to the reference date; this date was the diagnosis date for cases and an assigned date for controls based on the expected distribution of diagnosis dates among cases.

Oral contraceptive exposure variables

We defined ever use of OCs as use for at least 6 months and never use as never using OCs. Women who used OCs within the 1 year immediately prior to reference date were classified as current users, whereas women who last used OCs more than 1 year prior to reference date were categorized as former users. Combined OCs contain an estrogen and progestin component, while progestin-only OCs contain progestin alone. We classified OC episodes of use with an unknown generic or brand name as combined OCs given the low prevalence of progestin-only OC use in the US.[5] In sub-analyses, we assessed the estrogen dose and progestin type of specific combined OC preparations among women with available information. We defined ever use as use for at least 6 months of a specific OC preparation and current use as use within the prior year and for at least 6 months. We classified estrogen dose as low (<30 mcg ethinyl estradiol), moderate (30-35 mcg ethinyl estradiol or 50 mcg mestranol), or high (>35 mcg ethinyl estradiol or >50 mcg mestranol). We classified the progestin component into groups with similar chemical structures (estrane and gonane progestins[20-22], respectively), 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 includes 882 controls and 985 cases.

Statistical analysis

For the main analyses we compared controls and cases using unconditional logistic regression and calculated ORs and 95% CIs as estimates of the relative risk due to the low prevalence of breast cancer in the study age range. The reference group for all results presented is 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 (5 year groups) and reference year (continuous), along with the *a priori* selected potential confounder, self-reported race/ethnicity (non-Hispanic white, African American, Asian/Pacific Islander, other). We systematically evaluated the following covariates as potential confounders between OC use (ever, lifetime duration, recency of use, combined recency and duration of use, and age at first use) and risk of breast cancer among women ages 20-44: education (high school or less, post high school/some college, college graduate, post college), annual household income (<$25,000, $25,000-49,999, $50,000-89,000, ≥$90,000), age at menarche (<12, 12-13, ≥14), parous (no, yes), number of live births (0, 1-2, ≥3), age at first live birth (none, <25, 25-29, 30-34, ≥35), lactation duration (<12 months, ≥12 months), first degree family history of breast cancer (no, yes), and body mass index one year prior to reference date (<25, 25-<30, ≥30 kg/m^2). We assessed receipt of a non-symptomatic screening mammogram in the prior 30 months (no, yes) as a potential confounder only among women ages 40-44 because screening mammography is not usually recommended in younger women. Since none of the covariates changed any of the ORs by ≥10%, the final statistical models are only adjusted for age, reference year, and race/ethnicity. We evaluated a linear trend in the ORs for lifetime duration of OC use as well as for duration of use in the prior 5 years among current users by creating models with the continuous linear form of each variable (years of use) including the reference group. Because of high risks observed among current OC users for 5 years or longer, we further examined use by specific combined OC preparations (by estrogen dose, progestin group, and progestin type) among those who used only one preparation in the 5 years prior to reference date using separate logistic regression models for each preparation type. We did not assess OC preparations among women who used OCs for at least 15 years because only 19 controls and 40 cases reported ever using just one preparation with adequate information for classification by OC constituents. We also evaluated ever using specific combined OC preparations for 6 months or longer and current use within the prior year.

Based on prior literature suggesting possible differences in the association between OC use and breast cancer risk by age,[11-16] we tested for potential effect modification by age (age groups: 20-39 and 40-44) for both lifetime duration of use and recency of use by creating interaction terms with age and comparing models. There was no evidence of statistically significant effect modification based on likelihood ratio tests. However, we present results stratified by age group where possible, along with all ages, because some age-specific risk estimates suggest a meaningful difference by age groups, albeit a non-statistically significant difference.

In order to evaluate potential differences by molecular subtype for duration of use and recency of use, we used polytomous logistic regression to compare controls to ER+ and ER- cases, as well as to triple-negative cases. One model contained controls, ER+ cases, and ER- cases and another model included only controls, ER+ cases, and triple-negative cases. We excluded 9 cases with unknown ER values from the ER analyses and 84 cases from the HER2 analyses (56 ER-/HER2+ cases and 28 cases with unknown or borderline values for ER, PR, and/or HER2). 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 case groups (ER+ versus ER- and ER+ versus triple-negative). We completed all analyses using Stata/MP version 12.0 (StataCorp LP, College Station, TX).

RESULTS

Race/ethnicity and education distributions were comparable between cases and controls (Table 1.1). The distribution of reference years reflects the control to case matching ratio for different years (1:1 for 2004-2007 and 0.7:1 for 2008-2010). Cases were somewhat more likely to be 40-44 years of age than controls. Cases were more likely than controls to have an annual household income of at least $90,000, to be nulliparous, to have a first degree family history of breast cancer, and to have a lower BMI. Cases were less likely than controls to have reached menarche at a later age, to have a first live birth at a later age, and to have lactated for at least one year. Among women ages 40-44, cases were more likely than controls to have received a non-symptomatic screening mammogram in the prior 2.5 years.

There was no association between ever using OCs and breast cancer risk (Table 1.2). 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 was stronger among younger women 20-39 years of age (OR=1.9, 95% CI=1.0-3.7) compared to older women 40-44 years of age (OR=1.4, 95% CI=0.9-2.2). Shorter durations of use were not associated with risk. However, there was a significant linear trend for each additional year of OC use among all women and women ages 20-39 (OR=1.02, 95% CI=1.0-1.03 and OR=1.03, 95% CI=1.0-1.06, respectively) relative to never users, but not among women ages 40-44 (OR=1.01, 95% CI=1.0-1.03). While former use of OCs overall was not related to breast cancer risk, current use for 5 years or longer was associated with a 1.6-fold (95% CI=1.1-2.5) increased risk of breast cancer among all women and a 2.5-fold (95% CI=1.2-5.1) increased risk among women ages 20-39. In contrast, current OC use among women ages 40-44 was not associated with risk. Neither time since last use among former OC users nor age at first use among ever users was associated with breast cancer risk.

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 to determine if either factor was driving the observed association of the other. 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, Table 1.2). In contrast, among current users the risk estimates stratified by lifetime duration of use were comparable to the overall OR for current use. This general pattern also occurred among women ages 20-39 and ages 40-44, though the stratified risk estimate among women ages 20-39 was greater for current users with ≥15 years of use than for those with <15 years of use. We conducted additional analyses stratifying current users for 5 years or longer by lifetime duration of use (data not shown). Among current users who used OCs for the entire 5 years immediately prior to reference date, the risk was similar regardless of lifetime duration of use for all women and among women ages 40-44. The analysis among women ages 20-39 was limited by small numbers, but the risk magnitude was greater for current users for 5 years or longer who used OCs for at least 15 total years (OR=3.8, 95% CI=1.4-10.5) than for those who used OCs for <15 total years (OR=1.7, 95% CI=0.7-4.0).

We assessed the impact of using specific combined OC preparations among current users who used only one preparation during the 5 years immediately preceding the reference date relative to those who never used OCs. Both current users who used OCs with a low estrogen dose (OR=2.2, 95% CI=0.8-6.0) or a moderate estrogen dose (OR=1.5, 95% CI=0.9-2.4) for the 5 years prior to reference date had a non-statistically significant elevated OR and these risk estimates were not statistically significantly different (Table 1.3). With respect to progestin type, current users of OCs with a gonane progestin for 5 years or longer had a 1.9-fold (95% CI=1.1-3.4) increased breast cancer risk and this risk was similar for the individual gonane progestins, levonorgestrel and norgestimate. Current users of OCs with an estrane progestin for 5 years or longer did not have a statistically significant increased breast cancer risk (OR=1.3, 95% CI=0.7-2.4) and it was not statistically significantly different than current use of OCs with a gonane progestin for 5 years or longer (p for difference=0.28). The ORs associated with current use of specific OC preparations tended to be greater than those for ever use, but none of the risk estimates were statistically significant (Table 1.4).

We also evaluated lifetime duration of OC use and recency of use by molecular subtype. Ever use of 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=0.7-4.1) increased risk of triple-negative breast cancer among women ages 20-39 (Table 1.5). Overall, the risk estimates for ER+ breast cancer associated with OC use for ≥15 years were comparable to those for any invasive breast cancer, while the risk estimates for ER- and triple-negative breast cancer were either similar or slightly greater than the risk of invasive breast cancer of any type. There was a statistically significant linear trend per additional year of OC use among ER- cases ages 20-39 (p=0.009) and among all triple-negative cases (p=0.045). Current users ages 20-39 who used OCs for 5 years or longer had a 3.5-fold (95% CI=1.3-9.0) increased risk of ER- breast cancer and a 3.7-fold (95% CI=1.1-11.7) increased risk of triple-negative breast cancer, though neither risk estimate was statistically different than their risk of ER+ cancer.

DISCUSSION

In this population-based study among women 20-44 years of age, we found that current users of OCs for 5 years or longer had a 60% increased risk of breast cancer and that OC use for at least 15 years duration was associated with a 50% increased breast cancer risk. The magnitude of both effects was greater among women ages 20-39 (2.5-fold and 1.9-fold increased risk, respectively) than among women ages 40-44. Both the large pooled analysis by the Collaborative Group on Hormonal Factors in Breast Cancer,[6] as well as a recent analysis from the Nurses' Health Study II,[7] also observed a modest increased risk associated with current OC use. Our study assessing contemporary OC formulations adds to the literature in the following important areas: 1) We did not find a statistically significant variation in breast cancer risk by OC constituents (estrogen dose or progestin type); however, OCs containing gonane progestins were associated with a statistically significant elevated risk among current users for 5 years or longer, whereas those containing estrane progestins were not. 2) In general, we observed stronger effects among women ages 20-39 relative to ages 40-44. 3) There was some suggestion of greater risks associated with triple-negative compared to ER+ breast cancer, though the differences were not statistically significant.

Our findings of a 1.5-fold elevated breast cancer risk associated with OC use for at least 15 years duration and a statistically significant trend for increasing years of use differ somewhat from the Collaborative Group results (relative risk (RR)=1.08 for ≥15 years duration and p=0.05 for increasing years of use).[6,23] Since the Collaborative Group analysis, the large CARE study found a non-statistically significant elevated risk for at least 15 years of OC use among a subset of women ages 35-44 (OR=1.3, 95% CI=0.9-1.8), but no association with lower duration of use categories.[8] Other studies focusing on breast cancer in women ≤57 years of age have found either an increased risk across all duration categories among all women[9] or only among women <35 years of age,[14] an increased risk associated with longer durations of use,[24] a non-statistically significant increased risk only for >12 years of use,[10] or no association between long-term OC use and breast cancer risk.[25,26] We found stronger effects when restricting to younger women. This difference has been observed in other studies assessing a variety of aspects of OC use,[11-16] and suggests younger women may be particularly susceptible to risks related to OC use, though it is unknown if this is related to different proliferative effects on the breast or to other reasons.

We attempted to separate the effects of recent use and duration of use through stratification. Our results suggest, regardless of having a longer total duration of use, current users have a modest, but non-statistically significant increased breast cancer risk and current users for 5 years or longer have an increased breast cancer risk. However, among former users, only those who used OCs for ≥15 years have an elevated breast cancer 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.[6,23] Many individual studies since then have not reported the combined effect of recency and lifetime duration of use among younger women;[9,10,14,24,26] however, the Nurses' Health Study II found an increased breast cancer risk among current users regardless of duration of use, but current users for 8 or more years had a slightly greater risk (RR=1.5, 95% CI=1.1-2.0) compared to those who used for <8 years (RR=1.2, 95% CI=0.8-1.7).[7] In contrast, the CARE study did not find an association among current users overall or after evaluating lifetime duration of use.[8] Our stratified results also suggest the impact of duration of use among current users may be greater in women ages 20-39 than ages 40-44, but these results should be interpreted with caution, as they are based on a small subset of women.

Our results evaluating the effect of specific OC preparations on the risk of breast cancer associated with either current use or current use of one preparation for 5 years or longer do not suggest marked heterogeneity in risk by OC constituents, though our analyses were constrained by sparse data for some preparations. Our results examining ever use of OC preparations are difficult to interpret because a substantial portion of episodes of OC use could not be classified. Specifically, among all OC users approximately 35% of both controls and cases reported at least one episode of OC use without an accompanying brand or generic name and an additional 9-10% of controls and cases reported at least one OC episode that could not be classified by estrogen dose because of incomplete brand or generic name information. Among current OC users, 13% of controls and 9% of cases reported at least one OC episode that could not be classified by estrogen dose and/or progestin type.

Some,[7,10,15,27,28] but not all,[13,29,30] 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, which included some of these studies, largely found no evidence of significant heterogeneity in risk by estrogen dose or progestin type.[6,23] 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 with the progestin levonorgestrel and varying doses of ethinyl estradiol.[7] We examined this preparation in our data and found no association between current use and breast cancer risk (OR=0.9, 95% CI=0.3-2.6, based on 8 controls and 8 cases, data not shown).

It is important to recognize that after stratifying by molecular subtype, there were no statistically significant differences between risk of ER+ breast cancer compared to ER- or triple-negative breast cancer for any characteristic of OC use. However, the risk estimates tended to be greater for ER- than for ER+ breast cancer and particularly elevated for triple-negative breast cancer. Specifically, we found a marked increased risk of triple-negative breast cancer among current users ages 20-39 who used OCs for 5 years or longer and a significant trend for increasing risk of triple-negative breast cancer with increasing duration of OC use. These findings are consistent with a large study among young women that found a greater risk of triple-negative compared to non-triple-negative breast cancer associated with more recent OC use and longer durations of use.[17] A sub-analysis from 2 of the 5 study sites in the CARE study did not find an elevated risk of triple-negative breast cancer relative to controls or to luminal A (ER+ or PR+/HER2-) breast cancer cases associated with either time since last use or duration of OC use among women ages 35-44, but this could be due to excluding women ages 20-34, who may have greater risks than older women.[31] We also found statistically significant elevated risks for ER- breast cancer among women ages 20-39 associated with current OC use for 5 years or longer and a trend of increasing risk with each additional year of use. Other studies among young women evaluating recency of use do not suggest significant differences in risk by ER and/or PR status and include risk estimates that are greater for ER- breast cancer,[32] in addition to risk estimates that are greater for ER+/PR+ breast cancer.[33] Two studies assessing duration of OC use did not find statistically significant differences between risk of ER+/PR+ versus ER-/PR- breast cancer,[34,35] though the risk estimate for ER-/PR- breast cancer was greater than ER+/PR+ breast cancer for ≥10 years of OC use in both studies, and for ≤4 years of use in one study.[34]

The limitations of our study should be noted when interpreting the results. We relied on participant recall to measure OC exposure and thus exposure misclassification could have impacted our results, especially related to specific OC preparations. However, this study was designed to assess hormonal contraceptive exposures and used a photo book and life calendar to improve participant recall. Prior studies comparing medical or pharmacy records and participant responses suggest women are reasonably good historians with respect to ever use, timing of use, and total duration of OC use overall (i.e., not considering variations in OC use by preparation).[36,37] Detection bias is a potential concern, but we believe it is unlikely to account for our results related to current OC use since adjusting for recent receipt of screening mammography among women ages 40-44 did not meaningfully change our risk estimates. This study is unique and provides novel contributions because we focused on modern OCs, analyzed the impact of OC constituents, and categorized risk by molecular subtype defined via a centralized review of pathology reports.

Although breast cancer is rare among young women, our findings suggest that both current use of modern OC preparations for 5 years or longer and using OCs for a total of 15 years or longer confer an increased risk of breast cancer among women ages 20-44. The observed recency effect supports a tumor promoter role for OCs, while the risk related to long durations of use suggests OCs may also have a threshold effect after 15 or more years of use. Laboratory data supports 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 non-use.[38-41] Our recency results are generally consistent with existing studies, but there is more heterogeneity in results related to long durations of use, and our findings require confirmation. Given the relatively modest increased breast cancer risk among young women observed to date related to recent OC use, continued research in this area will require large study populations to reach conclusions, especially when stratifying by molecular subtype. Future studies should continue to monitor breast cancer risk among young women as additional OC preparations are developed and as use patterns change. Results from future pooled or meta-analyses will help women and their prescribers make informed decisions about using OCs after weighing the associated health benefits against the risks.

Table 1.1: Selected characteristics of controls and cases

Characteristic	Controls n=882	%	Cases n=985	%
Age (yr)				
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 (yr)				
<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 (yr)				
None	185	21.0	255	25.9
<25	196	22.2	220	22.4
25-29	213	24.1	246	25.0
30-34	194	22.0	175	17.8
≥35	94	10.7	87	8.9
Missing	0		2	

Table 1.1, continued

Characteristic	Controls n=882	%	Cases n=985	%
Lactation duration*				
None	56	8.1	70	9.6
<12 months	285	41.0	311	42.7
≥12 months	354	50.9	347	47.7
Missing	2		2	
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 one year prior to 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†				
No	189	36.1	201	32.9
Yes	335	63.9	410	67.1
Missing	3		0	

* Among parous women.

† Among women ages 40-44. Excludes symptomatic and diagnostic mammograms.

Table 1.2: Oral contraceptive (OC) use and risk of breast cancer*

	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†	95% CI	n	%	n	%	OR†	95% CI	n	%	n	%	OR†	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 yr	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 yr	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	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 yr	100	11.4	174	17.7	1.5	(1.1-2.2)‡	27	7.6	51	13.7	1.9	(1.0-3.7)	73	13.9	123	20.2	1.4	(0.9-2.2)
Per year of use					1.02	(1.0-1.03)‡					1.03	(1.0-1.06)‡					1.01	(1.0-1.03)
Recency of use and duration of use in the prior 5 years																		
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)
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)
<3 yr	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 yr	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 yr	54	6.1	97	9.8	1.6	(1.1-2.5)‡	17	4.8	43	11.5	2.5	(1.2-5.1)‡	37	7.0	54	8.8	1.2	(0.7-2.1)
Per year of use					1.1	(1.0-1.1)					1.1	(1.0-1.3)					1.0	(0.9-1.1)
Recency of use and lifetime duration of use																		
Former use																		
<15 yr	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 yr	37	4.2	80	8.2	1.9	(1.2-3.1)‡	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 yr	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 yr	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)
Time since last use among former users (yr)																		
<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																		
<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)

Abbreviations: OR, odds ratio; CI, confidence interval.

* 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 oral contraceptives 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.

† Odds ratios are adjusted for age, year, and race/ethnicity.

‡ p-value <0.05

Table 1.3: Risk of breast cancer associated with current use of specific combined oral contraceptive (OC) preparations for 5 years or longer*

	Controls (n=882)		Cases (n=985)				
	n	**%**	**n**	**%**	**OR†**	**95% CI**	**P****
OC preparation							
Never use	103	11.7	119	12.1	1.0	Ref.	
Current use for ≥5 years	54	6.1	97	9.8	1.6	(1.1-2.5)‡	
Estrogen dose¶							0.44
Low	6	0.7	15	1.5	2.2	(0.8-6.0)	
Moderate	40	4.5	67	6.8	1.5	(0.9-2.4)	
Progestin group							0.28
Estrane progestins	19	2.2	26	2.6	1.3	(0.7-2.4)	
Norethindrone	15	1.7	17	1.7	1.1	(0.5-2.2)	
Gonane progestins	22	2.5	49	5.0	1.9	(1.1-3.4)‡	
Levonorgestrel	9	1.0	18	1.8	1.8	(0.8-4.2)	
Norgestimate	7	0.8	15	1.5	1.9	(0.7-4.8)	

Abbreviations: OR, odds ratio; CI, confidence interval.

* Current use is defined as use within the prior year. Only exclusive current users of one preparation for 5 years or longer are included in the estrogen and progestin groups (groups do not add up to the total because of women missing OC preparation information or using multiple preparations in the prior 5 years). Categories containing cells with <5 women are not displayed.

† Odds ratios are adjusted for age, year, and race/ethnicity.

‡ p-value <0.05

¶ Low dose: <30 micrograms (mcg) ethinyl estradiol (EE) and moderate dose: 30-35 mcg EE or 50 mcg mestranol.

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

Table 1.4: Risk of breast cancer associated with ever or current use of specific combined oral contraceptive (OC) preparations*

	Controls (n=882)		Cases (n=985)			
	n	%	n	%	OR†	95% CI
OC preparation						
Never use	103	11.7	119	12.1	1.0	Ref.
Estrogen dose‡						
Low						
Ever use	82	9.3	96	9.8	1.0	(0.7-1.5)
Current use	16	1.8	29	3.0	1.5	(0.8-3.0)
Moderate						
Ever use	573	65.1	625	63.8	1.0	(0.7-1.3)
Current use	96	10.9	149	15.2	1.4	(1.0-2.0)
High						
Ever use	25	2.8	20	2.0	0.7	(0.4-1.4)
Progestin group						
Estrane progestins						
Ever use	439	49.9	485	49.5	1.0	(0.7-1.3)
Current use	45	5.1	67	6.9	1.4	(0.9-2.2)
Norethindrone						
Ever use	369	41.9	407	41.8	1.0	(0.7-1.3)
Current use	30	3.4	42	4.3	1.3	(0.7-2.2)
Norethindrone acetate						
Ever use	77	8.7	98	10.0	1.1	(0.7-1.7)
Current use	11	1.2	23	2.3	1.9	(0.9-4.2)
Ethynodiol diacetate						
Ever use	21	2.4	19	1.9	0.8	(0.4-1.6)
Gonane progestins						
Ever use	332	37.8	390	39.9	1.0	(0.8-1.4)
Current use	63	7.2	94	9.6	1.3	(0.9-2.0)
Levonorgestrel						
Ever use	111	12.6	136	13.9	1.1	(0.8-1.6)
Current use	19	2.2	33	3.4	1.5	(0.8-2.9)
Norgestrel						
Ever use	68	7.7	90	9.2	1.2	(0.8-1.8)
Norgestimate						
Ever use	156	17.8	182	18.6	1.0	(0.7-1.5)
Current use	28	3.2	35	3.6	1.1	(0.6-2.0)
Desogestrel						
Ever use	63	7.2	61	6.2	0.9	(0.6-1.4)
Current use	15	1.7	12	1.2	0.7	(0.3-1.6)
Other progestin¶						
Drospirenone						
Ever use	19	2.2	31	3.1	1.4	(0.7-2.6)
Current use	9	1.0	22	2.2	2.1	(0.9-4.9)

Abbreviations: OR, odds ratio; CI, confidence interval.
* Ever use is defined as use for ≥6 months. Current use is defined as use within the prior year and for ≥6 months. Categories are not mutually exclusive and cells with <5 women are not displayed.
† Odds ratios are adjusted for age, year, and race/ethnicity.
‡ Low dose: <30 micrograms (mcg) ethinyl estradiol (EE), moderate dose: 30-35 mcg EE or 50 mcg mestranol, and high dose: >35 mcg EE or >50 mcg ME.
¶ Additional progestins are not listed because only one case used gestodene and one control used both gestodene and cyproterone acetate.

Table 1.5: Duration of oral contraceptive (OC) use, recency of use, and risk of estrogen receptor positive (ER+), ER negative (ER-), and triple-negative (ER-/PR-/HER2-) breast cancer*

	Controls		ER+				ER-				ER-/PR-/HER2-			
	n	%	n	%	OR†	95% CI	n	%	OR†	95% CI	n	%	OR†	95% CI
All (age 20-44)	n=882		n=730				n=246				n=171			
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.
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)
<15 yr	677	76.9	499	68.5	0.9	(0.6-1.2)	183	75.0	1.0	(0.7-1.7)	131	77.5	1.4	(0.7-2.4)
≥15 yr	100	11.4	137	18.8	1.6	(1.0-2.3)‡	35	14.3	1.5	(0.8-2.7)	23	13.6	1.7	(0.8-3.6)
Per year of use					1.01	(1.0-1.03)			1.02	(1.0-1.04)			1.03	(1.0-1.1)‡
Recency of use and duration of use in the prior 5 years														
Former use	635	72.0	488	66.8	0.9	(0.6-1.2)	171	69.5	1.1	(0.7-1.7)	122	71.3	1.4	(0.7-2.5)
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)
<3 yr	31	3.5	33	4.5	1.3	(0.7-2.3)	10	4.1	1.2	(0.5-2.7)	9	5.3	1.9	(0.8-4.9)
3-4.9 yr	58	6.6	47	6.4	0.9	(0.6-1.6)	12	4.9	0.7	(0.3-1.6)	9	5.3	1.0	(0.4-2.5)
≥5 yr	54	6.1	70	9.6	1.5	(1.0-2.4)	27	11.0	2.0	(1.1-3.9)‡	16	9.4	2.2	(1.0-4.7)
Per year of use					1.1	(1.0-1.1)			1.1	(1.0-1.3)			1.1	(1.0-1.3)
Age 20-39	n=355		n=249				n=122				n=82			
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.
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	(0.7-4.1)
<15 yr	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)
≥15 yr	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)
Per year of use					1.02	(1.0-1.1)			1.05	(1.0-1.1)‡			1.04	(1.0-1.1)
Recency of use and duration of use in the prior 5 years														
Former use	239	67.3	149	59.8	0.8	(0.5-1.4)	80	65.6	1.2	(0.6-2.4)	56	68.3	1.6	(0.7-4.0)
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	1.9	(0.7-4.9)
<3 yr	21	5.9	17	6.8	1.1	(0.5-2.4)	6	4.9	1.1	(0.4-3.3)	5	6.1	1.7	(0.5-6.2)
3-4.9 yr	34	9.6	23	9.2	1.0	(0.5-2.0)	8	6.6	0.8	(0.3-2.3)	5	6.1	1.0	(0.3-3.6)
≥5 yr	17	4.8	27	10.8	2.2	(1.0-4.7)	16	13.1	3.5	(1.3-9.0)‡	9	11.0	3.7	(1.1-11.7)‡
Per year of use					1.1	(1.0-1.3)			1.2	(1.0-1.4)			1.2	(1.0-1.5)

Table 1.5, continued*

	Controls		ER+				ER-				ER-/PR-/HER2-			
	n	%	n	%	OR†	95% CI	n	%	OR†	95% CI	n	%	OR†	95% CI
Age 40-44	n=527		n=481				n=124				n=89			
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.
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	(0.5-2.6)
<15 yr	393	74.9	320	66.5	0.8	(0.6-1.3)	90	73.2	0.9	(0.5-1.7)	65	73.9	1.1	(0.5-2.5)
≥15 yr	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)
Per year of use					1.0	(1.0-1.03)			1.0	(1.0-1.03)			1.0	(1.0-1.1)
Recency of use and duration of use in the prior 5 years														
Former use	396	75.1	339	70.5	0.9	(0.6-1.3)	91	73.4	0.9	(0.5-1.7)	66	74.2	1.1	(0.5-2.5)
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	(0.6-3.6)
<3 yr	10	1.9	16	3.3	1.5	(0.6-3.6)	4	3.2	1.4	(0.4-5.1)	4	4.5	2.4	(0.6-9.7)
3-4.9 yr	24	4.6	24	5.0	0.9	(0.5-1.8)	4	3.2	0.6	(0.2-2.2)	4	4.5	1.1	(0.3-4.2)
≥5 yr	37	7.0	43	8.9	1.2	(0.7-2.2)	11	8.9	1.2	(0.5-3.0)	7	7.9	1.3	(0.4-4.1)
Per year of use					1.0	(0.9-1.1)			1.0	(0.9-1.2)			1.1	(0.9-1.3)

Abbreviations: OR, odds ratio; CI, confidence interval.

* Current use is defined as use of OCs within the prior year.

† Odds ratios are adjusted for age, year, and race/ethnicity.

‡ p-value <0.05

CHAPTER 2: Recent oral contraceptive use by formulation and breast cancer risk among young women

ABSTRACT

Background: Most studies show recent oral contraceptive (OC) use is associated with a modest increase in breast cancer risk, but the majority relied on self-reported use and did not examine risks associated with newer OC formulations.

Methods: We conducted a nested case-control study among health plan enrollees at a large health maintenance organization. Cases consisted of 1,102 women ages 20-49 diagnosed with invasive breast cancer from 1990-2009. We randomly selected 21,952 controls matched on age, year, and enrollment length. Detailed information on recent OC use was ascertained from electronic pharmacy records and analyzed using conditional logistic regression.

Results: Recent OC use (within 1 year of diagnosis) was associated with an increased risk of breast cancer (odds ratio (OR)=1.6, 95% confidence interval (CI)=1.3-1.9) relative to non-use. The association was slightly stronger for estrogen receptor (ER) positive (OR=1.7, 95% CI=1.3-2.1) compared to ER negative disease (OR=1.3, 95% CI=0.9-1.9), though this difference was not statistically significant. Risk varied by OC formulation, with recent use of OCs containing the progestin ethynodiol diacetate (OR=2.6, 95% CI=1.4-4.7) or high dose estrogen (OR=2.7, 95% CI=1.2-6.4) associated with particularly elevated risk estimates. In contrast, recent use of OCs with the progestin norgestimate or low dose estrogen were not associated with breast cancer risk (OR=1.2, 95% CI=0.6-2.2 and OR=1.0, 95% CI=0.6-1.7, respectively).

Conclusions: These results suggest that recent use of contemporary OC formulations is associated with an elevated risk of breast cancer among women ages 20-49 overall, but that associations vary somewhat by OC formulation. Given the multitude of available OC formulations and other contraceptive options, if confirmed, consideration of the risk of breast cancer associated with different types of OCs could impact contraceptive decision making.

INTRODUCTION

The association between oral contraceptive (OC) use and breast cancer risk has been extensively studied, yet the composition and patterns of use of OCs continues to evolve and more recent formulations have been less well studied. There have been striking changes in OC formulations since they first entered the US market in the 1960s, including a decrease in estrogen dose, the addition of new synthetic progestins such as norgestimate, desogestrel, and drospirenone, and the approval of extended and continuous cycle OCs.[2-5] Given that 10.7 million women in the United States (US) currently use OCs, ongoing evaluation of the benefits and harms associated with OC use is of critical public health importance.[1]

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 a modest increased breast cancer risk while taking OCs, but risk decreases with increasing time since last use and is no longer evident 10 years after ceasing use.[6,23] Breast cancer risk was highest among current OC users (users in the preceding 12 months; relative risk (RR)=1.24, 95% confidence interval (CI)=1.15-1.33) and there was no statistically significant variation in risk by OC formulation.[6,23] However, 74% of the breast cancer cases included were diagnosed during the 1980s,[23] and thus the majority of women were exposed to OC formulations not commonly used today. More recent large US studies assessing OC formulations report differing results.[7,30] One study among women <55 years of age found a 1.3-fold excess risk (95% CI=1.0-1.7) associated with current use of any OC and a 3.1-fold increased breast cancer risk (95% CI=2.0-4.7) associated with current use of a triphasic formulation with the progestin levonorgestrel.[7] Another study found no overall association with current use among women ages 35-44[8] or with use of unique OC formulations among women ages 35-64.[30] Yet these studies, along with the majority of other studies examining this topic, are susceptible to exposure misclassification because they relied on participant recall of the specific OC formulations used. Additionally, comparatively few studies of recent OC use have stratified breast cancer risk according to estrogen receptor (ER) status and existing data on associations between OC use and ER positive (ER+) and ER negative (ER-) breast cancer are mixed.[17,31,33,42] In order to evaluate recent use of contemporary OC formulations, we conducted a study among young women enrolled in a large health maintenance organization and used electronic pharmacy dispensing records to determine how various types of OCs are associated with breast cancer risk overall and by ER status.

METHODS

Study subjects

We conducted a nested case-control study among women ages 20-49 enrolled continuously within the integrated group practice at Group Health Cooperative (GHC) for at least 12 months prior to diagnosis date (reference date) or a similar date for controls from January 1990 to October 2009 (ignoring any 1-month gaps in enrollment). GHC is an integrated health care delivery system serving the Seattle-Puget Sound area. At reference date all study subjects were also 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. Study subjects had no prior history of breast cancer (*in situ* or invasive) or mastectomy (unilateral or bilateral) at reference date. Among eligible women, all first primary invasive breast cancer cases were then identified using the CSS. We randomly selected with replacement up to 20 controls per case from enrollment files, individually matched on age, year (enrolled at the time of the case’s diagnosis), 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 +/-2 months of enrollment, +/-365 days of the case's birthdate, and/or to have a different medical chart availability than their case. A control could be matched to multiple cases and be eligible as a case at a later date. A total of 1,105 cases and 22,100 matched controls met the study eligibility criteria (21,755 controls met the exact matching criteria). This study was approved by the Group Health Human Subjects Review Committee.

Oral contraceptive prescriptions

GHC has an electronic pharmacy database containing detailed information about individual pharmacy dispensings from 1977 to present including date dispensed, drug name (generic and brand), dose, administration route, pill quantity, and days supply. We obtained all OC fills in the 12 months prior to reference date and classified OCs by formulation by identifying unique combinations of estrogen and progestin components, doses, and dosing schedules (monophasic or triphasic). We supplemented these data with OC fills from outside claims data in the 12 months prior to reference date.

Combined OCs include both an estrogen and progestin and most are packaged with 21 hormone pills and 7 placebo pills per pack. Monophasic OCs contain the same dose of estrogen and progestin in each hormone pill, whereas triphasic OCs contain 3 phases of estrogen and progestin dose combinations. Progestin-only OCs contain progestin alone and are taken continuously without the addition of placebo pills. Only one pill is taken per day for all OC types. Combined OCs in the US contain either ethinyl estradiol or mestranol as the estrogen component, with ethinyl estradiol comprising the majority of OC preparations.[43] Mestranol has approximately 67% of the estrogenic activity of ethinyl estradiol, making preparations with 35 micrograms (mcg) ethinyl estradiol bioequivalent to those with 50 mcg mestranol.[44,45]

We categorized combined OC formulations as low (20 mcg ethinyl estradiol), moderate (30-35 mcg ethinyl estradiol or 50 mcg mestranol), or high (50 mcg ethinyl estradiol or 80 mcg mestranol) dose estrogen. We examined progestin types individually, as well as grouped by chemical structure (estrane and gonane progestins).[20-22] Estrane progestins included norethindrone, norethindrone acetate, and ethynodiol diacetate, and gonane progestins included levonorgestrel, norgestimate, norgestrel, and desogestrel.

To determine the total number of OC hormone pills dispensed on each fill date, we first classified formulations by the number of hormone pills contained in each pack (21, 24, 28, or 84) using the brand and/or generic name and formulation packaging knowledge. We assumed OCs were taken per the label instructions (i.e., combined OCs were taken with the placebo pills and progestin-only pills were taken continuously). Next, within each group we coded the appropriate number of hormone pills if the values for the days supply and quantity variables corresponded (e.g., days supply=56 and quantity=2). If the days supply value was missing, we used the quantity (values 1-6) to determine number of packs and imputed the corresponding number of hormone pills for the given formulation. Finally, if there were conflicting days supply and quantity values for combined OC formulations, then we coded as the value provided for days supply for values <28 days and as 75% of the days supply value for values ≥28 days to account for the placebo pills included in the days supply value.

For each woman, we summed all OC hormone pills in the year prior to reference date, as well as summing pills by estrogen dose, progestin type, and OC formulation (i.e., considering dose and type of estrogen and progestin in each pill). We categorized the number of hormone pills as <190 or 190+ to approximate ≤9 months and >9 months supply of OC packs with 7 placebo pills per pack, respectively. We chose not to adjust for a compliance factor when calculating total number of hormone pills because we expected high compliance for this therapeutic class of drugs among women in the age range included. We defined recent users as women who filled at least one OC prescription in the year prior to reference date and compared them to the reference group of non-users, comprised of both never and past OC users, who did not fill an OC prescription in the year prior to reference date. We lacked data on OC use during time frames when subjects were not enrolled at GHC, so while we could assess recent use we could not distinguish between never users and former OC users. Progestin-only OC use was uncommon; therefore, the 3 cases and 148 controls with only progestin-only OC fills in the year prior to reference date (or controls matched to a case with progestin-only fills) were excluded. Our final analyses included the remaining 1,102 cases and 21,952 controls.

Other data sources

We determined race and ethnicity from a combination of data sources including SEER, death files, and self-administered breast cancer screening questionnaires from the Breast Cancer Surveillance Project at GHC.[46] The breast cancer screening questionnaire collects information about demographics, breast cancer risk factors, and mammography history among women at least 40 years of age enrolled at GHC.[47] Information is updated at the time of each mammogram. We classified breast cancer cases as either ER+ or ER- using SEER data. Borderline ER values were coded as ER+ cases (n=4). Data on HER2-neu (HER2) status from abstracted pathology reports were only available on 368 cases of which 47 were triple-negative (ER-/PR-/HER2-) and 20 were HER2-overexpressing (ER-/HER2+). Thus due to sample size limitations we could not assess associations between recent OC use and risk of triple-negative or HER2-overexpressing breast cancer.

Statistical analysis

We used conditional logistic regression on the matched sets of each case to their controls to calculate odds ratios (OR) and 95% confidence intervals (CI) as estimates of the relative risk for each OC use category because of the low prevalence of breast cancer among women ages 20-49. We used two-sided tests. ORs with a p-value <0.05 were considered statistically significant. The reference group for all analyses consisted of women who did not fill an OC prescription in the year prior to reference date. To test for a linear trend in the number of hormone pills dispensed in the prior year we used the continuous linear form of variables including the reference group.

In order to evaluate possible confounding by parity, oophorectomy history, family history of cancer, and body mass index (BMI) we obtained data on these factors from all cases 20-44 years of age with reference dates on or after May 1995 and two of their matched controls through medical record reviews. If a breast cancer screening questionnaire was available within the two years prior to reference date among the 40-44 year-old women, then we used these data rather than medical record data. Potential confounder information was restricted to this subset of cases and controls because of the considerable costs of abstracting data from medical records and because this age group was more likely to be exposed than women ages 45-49. The potential confounders were categorized as follows: parous (no/yes), parity (0, 1, 2, 3+), removal of both ovaries (no/yes), first degree breast cancer family history (no/yes), first and/or second degree breast cancer family history (no/yes), first degree ovarian cancer family history (no/yes), and BMI closest to one year prior to reference date (<25, 25.0-29.9, and 30+ kg/m^2). In addition, data on race (white, Asian, Black, other) and Hispanic ethnicity (no/yes) were compiled through a variety of sources and available for all reference years and age groups.

When assessed systematically among women with available data, none of these potential confounders changed the OR for OC 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. We also conducted a sensitivity analysis to evaluate the possibility of confounding due to prior history of breast cancer screening. We obtained non-symptomatic screening mammography data from Group Health's breast cancer surveillance data for all cases and matched controls who were 40-49 years of age with reference dates on or after June 1998. This analysis was limited to women 40-49 years of age because systematic screening mammography is not recommended among younger women. Inclusion of recent screening mammogram receipt (within 18 months prior to reference date) in our statistical model only changed the OR for OC use in the prior year and breast cancer risk by 5% among women ages 40-49 and thus was not incorporated into our final statistical models.

We examined potential effect modification on a multiplicative scale by age (20-39, 40-44, and 45-49) and by year (in 5 and 10 year intervals) among all women by creating interaction terms with the variable for OC use in the prior year. We used likelihood ratio tests to compare regression models with and without the interaction terms and test for interaction. All p-values for interaction were >0.05. However, we present our overall results by age group because some prior studies indicate possible differences in risk by age.[11-16]

The OC formulation analyses used separate regression models for each exposure category; therefore, the exposure categories were not mutually exclusive. For example, our estrogen dose analyses used 3 separate models for low, moderate, and high dose estrogen and women could be exposed in multiple models if they used OCs with different estrogen doses in the year prior to reference date. Similarly, we used separate regression models for each OC formulation (defined by estrogen/progestin dose and type, and dosing schedule) and women could be exposed in multiple models.

To calculate ORs by ER status we used two separate conditional logistic regression models restricted to either ER+ cases and matched controls or ER- cases and matched controls. We excluded 91 cases and matched controls from ER-specific analyses because of unknown ER status. To test for a difference in the ORs between ER+ and ER- case groups we calculated a p-value using an unconditional logistic regression model adjusted for the matching factors and limited to only cases (ER+ versus ER-). We performed all analyses using Stata/MP version 12.0 (StataCorp LP, College Station, TX).

RESULTS

Distributions of reference year, age, and months of GHC enrollment prior to reference date were similar among cases and controls due to the matching criteria (Table 2.1). Cases were somewhat more likely to be white, more likely to be leaner, and more likely to have had a screening mammogram during the one year interval prior to reference date than controls. Among women with available information, cases were slightly less likely than controls to be parous, less likely to have three or more live births, and somewhat less likely to have both ovaries removed prior to reference date (Table 2.2). Family history of breast (first and/or second degree) and ovarian cancer (first degree) was more common among cases than controls.

Among recent OC users the number of combined OC prescriptions filled during the year prior to reference date was similar for controls and cases (controls: median=4.0, mean=3.7; cases: median=4.0, mean=3.9), but the number of combined OC hormone pills dispensed differed somewhat (controls: median=231, mean=195; cases: median=252, mean=215). Recent OC use was associated with a 60% elevated breast cancer risk (95% CI=1.3-1.9) relative to never or former OC use (Table 2.3). When stratified by ER status, OC use was more strongly related to ER+ compared to ER- breast cancer, though 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 (p for trend <0.001 for both). Since results were comparable when defining recent users as women who filled at least two OC prescriptions in the year prior to reference date (Table 2.4), all of our analyses define recent use as filling at least one prescription in the prior year. We examined risk by age group; women ages 20-39 had the greatest risk associated with recent OC use (OR=1.7, 95% CI=1.3-2.4), followed by ages 40-44 (OR=1.5, 1.1-2.2), and ages 45-49 (OR=1.4, 95% CI=1.0-1.9), but confidence intervals overlapped (Table 2.5). We also stratified our main results among all women by stage at diagnosis. The ORs associated with recent OC use and risk of stage 2 cancer or risk of either stage 3 or 4 cancer were not statistically significantly different than the OR associated with recent OC use and risk of stage 1 cancer (p=0.92 and p=0.26, respectively, data not shown).

Low dose estrogen OCs were not associated with breast cancer risk (OR=1.0, 95% CI=0.6-1.7). However, moderate dose and high dose OC use were associated with 1.6-fold (95% CI=1.3-2.0) and 2.7-fold (95% CI=1.2-6.4) elevations in risk, respectively (Table 2.6). Furthermore, risk increased with increasing number of pills dispensed of moderate (p for trend <0.001) and high dose estrogen OCs (p for trend=0.02).

Estrane progestin OCs were associated with a 60% increased risk (95% CI=1.3-2.0) and there was a statistically significant trend associated with number of pills dispensed (p for trend <0.001). All of the individual estrane progestins (norethindrone, norethindrone acetate, and ethynodiol diacetate) were also associated with elevated risks and statistically significant trends, except for norethindrone acetate which did not exhibit a trend in risk associated with number of pills. Ethynodiol diacetate OCs were associated with a particularly elevated risk (OR=2.6, 95% CI=1.4-4.7), though this progestin was infrequently used (12 cases and 100 controls exposed).

There was a 1.4-fold increased risk (95% CI=1.0-2.0) associated with recent use of OCs containing a gonane progestin. Risk did not increase with additional pills dispensed for either any gonane use or use of the individual gonane progestins. Among the separate gonane progestins, norgestimate did not appear to be associated with risk, while levonorgestrel was associated with an elevated risk. Analyses of the gonane progestin desogestrel suggested an increased risk (OR=2.6, 95% CI=0.8-8.6), but this was based on only 3 cases (data not shown). Most risk estimates by estrogen dose and progestin type were slightly greater in analyses limited to ER+ cases, though the confidence intervals were wider.

We further assessed risk according to use of unique monophasic and triphasic OC formulations stratified by dose and type of estrogen and progestin. Monophasic OCs were associated with a similar risk as using any type of OC (Table 2.7). One specific monophasic OC (low dose estrogen and 1.0 milligram (mg) of norethindrone acetate) comprised most of our low dose users so these results were comparable to those for low dose estrogen users overall. Among monophasic moderate dose estrogen users, there was considerable variation in estimates; 0.50 mg of norethindrone was not associated with risk (OR=0.8, 95% CI=0.4-1.6), and 1.0 mg of ethynodiol diacetate was associated with the greatest risk (OR=2.8, 95% CI=1.5-5.2). There was some suggestion that risk was greater with a higher norethindrone dose (1.0 mg) than lower dose (0.50 mg). Most, but not all, risk estimates for monophasic formulations increased somewhat after restricting to ER+ cases. We could only evaluate one specific high dose estrogen formulation containing 0.50 mg of norgestrel due to limited use of high dose estrogen OCs. This formulation was associated with a particularly increased risk (OR=3.1, 95% CI=1.1-8.8), but it was based on only 4 exposed cases (data not shown).

All triphasic OCs contained moderate dose estrogen and the risk estimate for recent use was slightly greater than for monophasic OCs (Table 2.8). Three of the 4 most commonly used triphasic OCs were associated with 1.8 to 3.1-fold increased risks of breast cancer overall and 2.1-3.5-fold increased risks of ER+ breast cancer. The least commonly used triphasic OC containing norgestimate was not associated with risk. Triphasic OCs containing an average dose of 0.75 mg norethindrone were associated with the greatest risk among all OC formulations (OR=3.1, 95% CI=1.9-5.1). Triphasic OCs containing levonorgestrel were associated with a greater risk estimate than the monophasic levonorgestrel OC for overall breast cancer and ER+ breast cancer. This pattern did not apply to OCs with norgestimate, which had lower risk estimates associated with the triphasic than the monophasic formulation.

We also examined non-oral hormonal contraceptive use (e.g., contraceptive shot, transdermal patch, vaginal ring, intrauterine device, and subdermal implant), but <1% of controls and cases filled a prescription for these contraceptive types in the year prior to reference date (data not shown).

DISCUSSION

To our knowledge this is the first study to examine associations between specific OC formulations used in the US during the 1990s and 2000s, determined by electronic pharmacy dispensing records, and breast cancer risk among young women. We found a 1.6-fold increased breast cancer risk among women ages 20-49 who used any type of OC during the year prior to reference date relative to never or former users and this risk increased with the number of hormone pills dispensed, suggesting a possible effect of duration during the year prior. Our results are consistent with those from the Nurses' Health Study II[7] and the pooled analysis by the Collaborative Group,[6] though other studies have either found no association between recent OC use and breast cancer risk,[8] found the greatest risk among women who last used OCs 5 to 9 years ago,[9] or only found the suggestion of an increased risk associated with recent use among women ages 36-40 and among parous women.[10] A prospective cohort study in Norway and Sweden in the 1990s also found an increased breast cancer risk associated with recent OC use among women ages 30-39 at study enrollment (RR=1.7, 95% CI=1.1-2.7), but recent use was defined as OC use at study enrollment or within one year before the beginning of the approximately 9 year follow-up period, rather than anchored by diagnosis or a comparable date.[24] The magnitude of our risk estimate is greater than from the Collaborative Group analysis; this could be due to our study including only younger women ages 20-49 and eliminating non-differential exposure misclassification due to participant recall through the use of pharmacy data.

We used number of hormone pills as a proxy for cumulative exposure, or duration of use, during the prior year. The Collaborative Group analysis did not find any additional statistically significant impact of duration of use among current OC users.[6,23] However, the Collaborative Group analysis, along with almost all other studies of this topic, evaluated lifetime duration of OC use, while our analysis focused only on duration of use in the prior year. We also found stronger associations between recent OC use and risk among younger women than older women, which has been shown in some previous studies.[11-16]

Our results by OC formulation suggest that the relationship between recent OC use and breast cancer risk varies by estrogen dose. Specifically, low dose estrogen was not associated with risk, high dose was associated with an increased risk, and risk varied among moderate dose estrogen according to the type of progestin used. Additional support for variations in risk by estrogen dose includes the increased risk associated with the formulation containing norethindrone acetate and moderate dose estrogen after removing the most commonly used low dose estrogen formulation (norethindrone acetate 1.0 mg and ethinyl estradiol 20 mcg) relative to recent use of norethindrone acetate overall.

Estrane and gonane progestins were associated with generally similar risks, while the individual progestins exhibited greater risk heterogeneity. The progestin ethynodiol diacetate was associated with a particularly elevated risk, while the progestin norgestimate was not associated with risk. The ethynodiol diacetate risk appeared to be independent of the high dose estrogen risk, as even the OC formulation with ethynodiol diacetate and moderate dose estrogen was associated with a statistically significantly elevated risk.

Our results considering unique OC formulations suggest that risk varies according to formulation and that progestin dose may also impact risk. Among moderate dose estrogen users, a higher norethindrone dose was associated with a greater breast cancer risk. Additionally, our findings suggest possible differences by dosing schedule (monophasic versus triphasic) and that particular triphasic OC formulations may be associated with an elevated risk.

Our results by estrogen dose, progestin type, and dosing schedule differ from the Collaborative Group, which overall did not find variations in risk by OC formulation among recent users, but this could be due to two important reasons. First, 21 of the 27 studies with available OC formulation data included in the Collaborative Group analysis relied only on self-reported data, while the remaining 6 relied on either medical records or a combination of interview and medical record data.[23] Though validation studies suggest women are able to recall ever using OCs, duration of use, and timing of use relatively well, recall of specific OC brand names is less accurate and thus prone to misclassification.[37,48,49] For example, ever using OCs was reported accurately (99% exact agreement) among a subset of women participating in the Nurses' Health Study II, but only 75% of the reported OC episodes were confirmed with an equivalent formulation in prescription records.[48] One might expect nurses to have an even better recall than the general population with regard to prior medication use and indeed studies with participants not restricted to health care providers suggest poorer recall for the most recently used OC formulation (53 to 70% percent agreement) when comparing interview data to either medical records[36] or to a combination of prescription records and prospectively collected self-reported data.[50] Additionally, 89% of the studies with OC formulation data in the Collaborative Group analysis were case-control studies, rather than prospective, and thus possibly more susceptible to exposure misclassification due to variable lengths of time between reference date and interview date.[6,23]

A second possible reason for differences in our results compared to the results from the Collaborative Group pooled analysis relates to the older OC formulations examined in the pooled analysis, many of which are no longer comparable to modern OCs. In particular, estrogen doses have declined dramatically over time such that 50% of controls and 48% of cases in the Collaborative Group analysis who had recently used a combined OC (<5 years ago) that was used frequently enough to permit dose analyses last used a high dose estrogen OC based on our definition, whereas in our study only 2% of controls and 4% of cases who had used OCs in the last year used high dose estrogen OCs.[23] Furthermore, we were able to evaluate low dose estrogen OCs (<30 mcg of ethinyl estradiol), which were not specifically assessed in the Collaborative Group analysis, rather than combining these formulations with moderate dose estrogen OCs as most other studies have done. Comparing results related to progestin type is also problematic because of the more frequent use of high dose estrogen OCs in earlier years and the addition and removal of progestin types over time.

Three studies conducted in the 1990s, including a Norwegian cohort study,[28] a US cohort study,[7] and a large US case-control study[8,30] have assessed the relationship between breast cancer risk and specific OC formulations in detail since the Collaborative Group analysis, though the Norwegian cohort study included women ages 30-70 and therefore is less comparable to our study.[28] One US multisite case-control study included in the Collaborative Group analysis is more relevant to our results because it had more recent diagnosis dates and conducted a thorough OC formulation analysis.[27] The authors assessed the OC formulation used for the longest duration during the 5 years prior to reference date among women ages 20-44.[27] They found a greater breast cancer risk (*in situ* or invasive) among women using high dose ethinyl estradiol OCs (>35 mcg) in the 5 years prior to reference date than those using lower ethinyl estradiol dose OCs (RR=2.0 and 1.3, respectively), similar to the estrogen dose trend we observed. Risk estimates among all women by progestin type ranged from 1.1 to 1.9 and use of OCs containing norethindrone or levonorgestrel in the prior 5 years was associated with borderline statistically significant elevated risks. Though data were sparse among women ages <35, ethynodiol diacetate use in the prior 5 years was associated with a large increased risk (RR=12.0, 95% CI=2.4-59.2; 12 cases and 3 controls exposed).[27] Our results also suggest a large increased risk associated with recent use of ethynodiol diacetate, but some of our progestin-specific analyses were also constrained by sparse data.

The Nurses' Health Study II (NHS II) also examined risk by specific OC formulations. The authors found an increased breast cancer risk only among current OC users and, as mentioned earlier, one triphasic formulation containing levonorgestrel accounted for much of the excess risk (RR=3.1, 95% CI=2.0-4.7).[7] We found a 1.8-fold excess risk (95% CI=1.0-3.3) associated with this formulation, but in our study the triphasic OC containing norethindrone (average dose=0.75 mg) was associated with the greatest risk estimate. In the NHS II current use of a non-triphasic OC with norgestrel was also associated with an elevated risk, while a non-triphasic OC with levonorgestrel was not, but these analyses were limited by small numbers and the range of estrogen doses associated with these formulations was not reported.

Another large US multisite case-control study assessing specific OC formulations among women ages 35-64 did not find an overall association between current OC use and breast cancer risk.[8] Among women ages 35-44 high dose estrogen OCs were not associated with risk. The authors found no difference in risk associated with current use of estrane versus gonane progestins among all women, though current use of OCs containing ethynodiol diacetate was associated with an elevated risk (OR=3.5, 95% CI=1.1-10.7; 15 cases and 4 controls exposed), similar to our findings. Unlike the NHS II, the authors did not find an association between current use of a triphasic OC containing levonorgestrel and breast cancer risk (OR=1.0, 95% CI=0.6-1.7).[30] The authors could only examine current use of one OC formulation (norethindrone 1.0 mg and ethinyl estradiol 35 mcg) after limiting analyses to women who either never used OCs or exclusively used one formulation and they found no elevated risk associated with this formulation, while we found a 1.6-fold increased risk.[30]

In summary, our estrogen dose and progestin type results are consistent with some, but not all, studies and our findings related to some unique OC formulations have not been observed previously. However, prior studies may have been limited in their ability to detect any differences in risk according to OC formulation because of relying on self-reported OC information.

Our findings add to the heterogeneity of prior study results on recent OC use and ER+ cancer in young women—our results suggest a stronger association between OC use and ER+ breast cancer than ER- breast cancer, though this difference was not significant. A North Carolina case-control study observed that OC use in the previous 4 years among pre-/perimenopausal women was more strongly associated with risk of ER+/PR+ compared to ER-/PR- breast cancer, though the confidence intervals overlapped.[33] In a multisite US case-control study the opposite was observed where OC use was more strongly related to risk of ER- compared to ER+ breast cancer among women ages 20-44[42] and among women <35 years of age.[32] A Seattle-based case-control study, which included some of the cases from the multisite study, found a statistically significantly greater risk of ER- than ER+ breast cancer associated with fewer years since last OC use,[17] while another multisite US case-control study found no overall association between <5 years since last OC use and risk of any breast cancer or of luminal A (ER+ or PR+/HER2-) or triple-negative breast cancer.[31] Differences in results may be due to varying age distributions, changes in laboratory methods, or to changes in the prevalence of use of different OC formulations over time. However, in the absence of a large difference in the true risk by ER status, it is likely that many individual studies lacked power to detect modest differences, and thus contributed to the overall heterogeneity of results. Overall, the association between recent OC use and breast cancer risk by ER status remains unclear, and additional studies with detailed ER, PR, and HER2 data are needed to clarify how risk potentially varies by molecular subtype.

A key strength of this study is the utilization of detailed pharmacy dispensing records and screening mammography data. By using pharmacy records instead of self-reported episodes of OC use we limited the amount of misclassification by formulation and the number of episodes with an unknown formulation. The availability of electronic mammography data allowed us to identify non-symptomatic screening mammography receipt without relying on subject recall. These data, along with the young ages of the study women, the exclusion of *in situ* breast cancer cases, and evidence from past studies suggesting detection bias does not account for the recency effect observed between OCs and breast cancer,[11,51] increase our confidence about the validity of our findings. Additional strengths of this study include the large number of controls available and the inclusion of all eligible women, since no direct contact was required.

The two main limitations of this study relate to the time frame for exposure measurement and some limitations of covariate data available. Our analyses were constrained by the relatively short durations of continuous GHC enrollment prior to the reference date. We only allowed 1-month enrollment gaps in an effort to limit the opportunity for filling prescriptions outside of GHC, but this restriction, along with frequent changes in health insurance coverage among young women, limited our ability to assess long durations of use or past OC use. We therefore restricted our main analyses to exposure in the year prior to reference date. Yet, we believe our findings are germane because prior evidence suggests current and/or recent OC use is the exposure period associated with the greatest risk.[6] Additionally, our reference group was comprised of both never and former OC users since we did not have data about lifetime OC use. We would expect this to attenuate our observed risk estimates as the Collaborative Group found a statistically significant increased risk among current users, as well as those who last used OCs 1, 2, 4, and 5 years earlier.[23] Consequently, our ORs are likely underestimates of the association between recent OC use and breast cancer risk relative to never using OCs.

Another limitation is that data on potentially relevant confounders were not available for the entire study population, though we collected data on a sizeable subset of our cases as well as two of their matched controls. We found that each had a minimal impact on our risk estimates when adjusted for in our statistical models. While some degree of residual confounding may still be present, residual confounding of any appreciable magnitude is unlikely because prior studies reporting both age-adjusted and multivariable-adjusted risk estimates generally do not suggest strong confounders of the association between recent OC use and breast cancer among young women,[7,15] and we would not expect covariates to be strongly associated with recent use of particular OC formulations. Our OC formulation categories were not mutually exclusive and the results may be obscured due to exposure to other formulations during the year prior to reference date or earlier. We also made a large number of comparisons and some models were less robust than others; therefore, the results should be interpreted with caution.

Other limitations of our study include our inability to confirm if OC dispensings were consumed and to identify OC dispensings from non-GHC pharmacies without a filed claim. To address these issues we conducted our main analyses defining recent users as women who filled at least two OC prescriptions in the year prior to reference date and results were similar. We do not expect that OC fills at non-GHC pharmacies without a claim would significantly impact our results because of the financial incentive to use GHC pharmacies, the wide range of OCs included in GHC's formulary, and because only 0.9% of our cases were in the youngest age group (ages 20-29), which is a group that may be more likely to obtain OCs outside of GHC pharmacies without filing a claim. Furthermore, it is unlikely that OC fills outside of GHC or compliance patterns would be differential between controls and cases, so any misclassification would bias our results towards the null.

Our findings suggest recent use of modern OC formulations is associated with an increased breast cancer risk among women ages 20-49. This risk may be more strongly associated with ER+ than ER- breast cancer and may increase with increasing number of pills dispensed. The increased breast cancer risk associated with the short time frame prior to reference date suggests that OCs may promote growth of existing tumors which may or may not have been detected otherwise. Our results also suggest risk may vary by OC formulation with high dose estrogen, ethynodiol diacetate, higher dose norethindrone, and specific triphasic OCs possibly associated with increased risks. Just as important though, may be our findings of an absence of an association with low dose estrogen OCs, and perhaps other specific formulations (e.g., OCs containing norgestimate). Our results require replication, as the existing epidemiologic and laboratory evidence about the association of OC use with breast cancer is conflicting and does not consistently implicate particular estrogen doses or progestin types. However if confirmed, these results may contribute to evidence-based discussions between women and their providers regarding risks and benefits of the various commonly prescribed hormonal contraceptive options. Future studies will require substantial sample sizes, possibly by using pharmacy data from multiple health maintenance organizations, conducting research in settings with national health insurance and pharmacy records, or by completing additional pooled analyses.

Although evidence suggests that recent OC use increases breast cancer risk among young women and our findings indicate possible variations in risk by OC formulation, the absolute risk of breast cancer in this age group is quite small and the many established health benefits associated with OC use, including reproductive planning, menses regulation, decreased dysmenorrhea, a decreased risk of benign breast conditions,[43,45] and a reduction in endometrial and ovarian cancer risk,[52] should also be considered when making individual decisions.

Table 2.1: Descriptive characteristics of controls and cases

	Controls (n=21952)		Cases (n=1102)	
All reference dates	**n**	**%**	**n**	**%**
Reference year*				
1990-94	6454	29.4	323	29.3
1995-99	6532	29.8	328	29.8
2000-04	4772	21.7	240	21.8
2005-09	4194	19.1	211	19.1
Age (years)*				
20-29	197	0.9	10	0.9
30-34	1141	5.2	58	5.3
35-39	2944	13.4	148	13.4
40-44	6734	30.7	338	30.7
45-49	10936	49.8	548	49.7
Length of GHC enrollment prior to reference date (months)*				
Median	35.0		36.0	
Mean	42.4		42.4	
Race†				
White	12728	80.0	905	82.1
Asian	1611	10.1	82	7.4
Black	826	5.2	60	5.4
Other	739	4.6	55	5.0
Missing	6048		0	
Hispanic ethnicity	860	5.0	61	5.6
Missing	4581		3	
Among June 1998-October 2009 reference dates				
	Controls (n=10936)		**Cases (n=550)**	
	n	**%**	**n**	**%**
Body mass index (kg/m^2)‡				
<25	3196	41.6	224	44.2
25.0-29.9	2097	27.3	148	29.2
30+	2389	31.1	135	26.6
Missing	3254		43	
	Controls (n=8647)		**Cases (n=434)**	
	n	**%**	**n**	**%**
Screening mammogram during 1 year interval (18 months prior to reference date)¶				
No	6087	70.4	249	57.4
Yes	2560	29.6	185	42.6

* Matching variables.

† The other race category includes women classified as multiple races.

‡ Body mass index (BMI) prior to reference date (closest to 1 year prior). Information from medical records and breast cancer screening questionnaires. Months between weight value and reference month: controls (median=12, range=0-60), cases (median=12, range=0-54). Electronic BMI data were consistently available from 1998-2009.

¶ Among women ages 40-49 with 18+ months of enrollment prior to reference date. Excludes symptomatic and diagnostic mammograms. Screening mammography data were only available from 1996-2009.

Table 2.2: Additional descriptive characteristics among a subset of controls and cases ages 20-44 (reference years: 1995-2009)*

	Controls (n=682)		Cases (n=344)	
	n	%	n	%
Age (y)				
20-29	18	2.6	9	2.6
30-34	69	10.1	36	10.5
35-39	173	25.4	87	25.3
40-44	422	61.9	212	61.6
Parity				
Nulliparous	168	27.6	95	29.0
Parous	441	72.4	233	71.0
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	
1st degree breast cancer family history†				
No	497	91.5	271	86.0
Yes	46	8.5	44	14.0
Missing	139		29	
1st and/or 2nd degree breast cancer family history†				
No	373	74.6	194	64.7
Yes	127	25.4	106	35.3
Missing	182		44	
1st degree ovarian cancer family history†				
No	475	97.7	284	96.3
Yes	11	2.3	11	3.7
Missing	196		49	
Body mass index (kg/m^2)‡				
<25	267	43.3	159	47.6
25.0-29.9	165	26.7	86	25.7
30+	185	30.0	89	26.6
Missing	65		10	

* Information from medical records and breast cancer screening questionnaires. Includes cases and up to 2 of their matched controls.

† First degree relatives include mothers, sisters, and daughters. Second degree relatives include aunts and grandmothers.

‡ Body mass index prior to reference date (closest to 1 year prior). Months between weight value and reference month: controls (median=12, range=0-59), cases (median=13, range=0-52).

Table 2.3: Recent oral contraceptive (OC) use and invasive breast cancer risk by estrogen receptor (ER) status

	Controls (n=21952)		All cases (n=1102)				Controls (n=14704)		ER+ cases[¶] (n=738)				Controls (n=5433)		ER- cases[¶] (n=273)			
	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI
Combined OC use[†]																		
Never/former use	19953	90.9	957	86.8	1.0	Ref.	13394	91.1	637	86.3	1.0	Ref.	4889	90.0	240	87.9	1.0	Ref.
Recent use	1999	9.1	145	13.2	1.6	(1.3- 1.9)‡	1310	8.9	101	13.7	1.7	(1.3- 2.1)‡	544	10.0	33	12.1	1.3	(0.9- 1.9)
Total number of combined OC hormone pills																		
<190	897	4.1	50	4.5	1.2	(0.9- 1.6)	581	4.0	33	4.5	1.2	(0.9- 1.8)	253	4.7	14	5.1	1.1	(0.7- 2.0)
190+	1085	4.9	93	8.5	1.8	(1.5- 2.3)‡	716	4.9	66	9.0	2.0	(1.5- 2.6)‡	289	5.3	19	7.0	1.4	(0.8- 2.2)
Missing	17		2				13		2				2		0			
p for trend**					<0.001						<0.001						0.16	

* All odds ratios (ORs) are implicitly adjusted for the matching factors (age, year, months of enrollment prior to reference date, and medical chart availability).

† Recent use is defined as filling at least one combined OC script in the year prior to reference date.

‡ p-value <0.05

¶ 91 cases were excluded because of unknown ER status. Cases with borderline ER results were coded as positive (n=4).

** P for trend using the continuous linear variable (reference group=never/former users).

Table 2.4: Recent oral contraceptive (OC) use by number of scripts and pills and invasive breast cancer risk by estrogen receptor (ER) status

	Controls (n=21952)		All cases (n=1102)				Controls (n=14704)		ER+ cases¶ (n=738)				Controls (n=5433)		ER- cases¶ (n=273)			
	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI
Number of combined OC scripts†																		
None	19953	90.9	957	86.8	1.0	Ref.	13394	91.1	637	86.3	1.0	Ref.	4889	90.0	240	87.9	1.0	Ref.
Only 1	433	2.0	24	2.2	1.2	(0.8-1.8)	291	2.0	18	2.4	1.3	(0.8-2.2)	112	2.1	5	1.8	0.9	(0.4-2.3)
At least 2	1566	7.1	121	11.0	1.7	(1.4-2.0)‡	1019	6.9	83	11.2	1.8	(1.4-2.3)‡	432	8.0	28	10.3	1.3	(0.9-2.0)
Total number of combined OC hormone pills																		
<190	474	2.2	27	2.5	1.2	(0.8-1.8)	299	2.0	16	2.2	1.2	(0.7-1.9)	141	2.6	9	3.3	1.3	(0.7-2.7)
190+	1085	4.9	93	8.4	1.8	(1.5-2.3)‡	716	4.9	66	9.0	2.0	(0.7-2.6)‡	289	5.3	19	7.0	1.4	(0.8-2.2)
Missing	7		1				4		1				2		0			
p for trend**					<0.001						<0.001						0.15	

* All odds ratios (ORs) are implicitly adjusted for the matching factors (age, year, months of enrollment prior to reference date, and medical chart availability).

† Recent use is defined as filling at least one combined OC script in the year prior to reference date.

‡ p-value <0.05

¶ 91 cases were excluded because of unknown ER status. Cases with borderline ER results were coded as positive (n=4).

** P for trend using the continuous linear variable (reference group=never/former users).

Table 2.5: Recent oral contraceptive (OC) use and invasive breast cancer risk by age

	Ages 20-39						Ages 40-44						Ages 45-49					
	Controls (n=4282)		Cases (n=216)				Controls (n=6730)		Cases (n=338)				Controls (n=10940)		Cases (n=548)			
	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI	n	%	n	%	OR*	95% CI
Combined OC use†																		
Never/former use	3489	81.5	156	72.2	1.0	Ref.	6181	91.8	298	88.2	1.0	Ref.	10283	94.0	503	91.8	1.0	Ref.
Recent use	793	18.5	60	27.8	1.7	(1.3- 2.4)‡	549	8.2	40	11.8	1.5	(1.1- 2.2)‡	657	6.0	45	8.2	1.4	(1.0- 1.9)‡
Total number of combined OC hormone pills																		
<190	368	8.6	23	10.6	1.4	(0.9- 2.3)	247	3.7	10	3.0	0.8	(0.4- 1.6)	282	2.6	17	3.1	1.2	(0.8- 2.0)
190+	420	9.8	37	17.1	2.0	(1.4- 3.0)‡	298	4.4	30	8.9	2.1	(1.4- 3.2)‡	367	3.4	26	4.8	1.5	(1.0- 2.2)
Missing	5		0				4		0				8		2			
p for trend¶					<0.001						0.001						0.06	

* All odds ratios (ORs) are implicitly adjusted for the matching factors (age, year, months of enrollment prior to reference date, and medical chart availability).

† Recent use is defined as filling at least one combined OC script in the year prior to reference date. When defining recent use as filling at least two combined OC scripts in the year prior to reference date the risk estimates are as follows: ages 20-39 (OR=1.8, 95% CI=1.3-2.5), ages 40-44 (OR=1.8, 95% CI=1.2-2.6), ages 45-49 (1.5, 95% CI=1.0-2.1).

‡ p-value <0.05

¶ P for trend using the continuous linear variable (reference group=never/former users).

Table 2.6: Recent oral contraceptive (OC) use by estrogen dose and progestin type and invasive breast cancer risk, by all cases (left) and ER positive cases (right)

	Controls (n=21952)		All cases (n=1102)				Controls (n=14704)		ER+ cases (n=738)			
Number of pills[†]	**n**	**%**	**n**	**%**	**OR***	**95% CI**	**n**	**%**	**n**	**%**	**OR***	**95% CI**
Never/former use	19953	90.9	957	86.8	1.0	Ref.	13394	91.1	637	86.3	1.0	Ref.
Estrogen dose												
Low dose	366	1.7	18	1.6	1.0	(0.6- 1.7)	255	1.7	14	1.9	1.2	(0.7- 2.0)
<190	227	1.0	11	1.0	1.0	(0.6- 1.9)	154	1.1	10	1.4	1.4	(0.7- 2.7)
190+	138	0.6	7	0.6	1.1	(0.5- 2.3)	100	0.7	4	0.5	0.9	(0.3- 2.4)
p for trend					0.89						0.81	
Moderate dose	1653	7.5	126	11.4	1.6	(1.3- 2.0)‡	1062	7.2	86	11.7	1.8	(1.4- 2.2)‡
<190	730	3.3	45	4.1	1.3	(1.0- 1.8)	460	3.1	29	3.9	1.4	(0.9- 2.0)
190+	922	4.2	81	7.4	1.9	(1.5- 2.4)‡	602	4.1	57	7.7	2.1	(1.5- 2.8)‡
p for trend					<0.001						<0.001	
High dose	46	0.2	6	0.5	2.7	(1.2- 6.4)‡	31	0.2	6	0.8	4.0	(1.7- 9.7)‡
p for trend					0.02						0.01	
Progestin types[¶]												
Estrane progestin	1472	6.7	111	10.1	1.6	(1.3- 2.0)‡	973	6.6	76	10.3	1.7	(1.3- 2.2)‡
<190	740	3.4	43	3.9	1.2	(0.9- 1.7)	486	3.3	28	3.8	1.2	(0.8- 1.8)
190+	730	3.3	68	6.2	2.0	(1.5- 2.6)‡	486	3.3	48	6.5	2.1	(1.6- 2.9)‡
p for trend					<0.001						<0.001	
Norethindrone	818	3.7	59	5.4	1.5	(1.2- 2.0)‡	518	3.5	35	4.7	1.5	(1.0- 2.1)‡
<190	413	1.9	20	1.8	1.0	(1.2- 1.6)	250	1.7	9	1.2	0.8	(1.0- 1.5)
190+	404	1.8	39	3.5	2.1	(1.2- 2.9)‡	268	1.8	26	3.5	2.1	(1.0- 3.2)‡
p for trend					<0.001						<0.001	
Norethindrone acetate	608	2.8	46	4.2	1.6	(1.2- 2.2)‡	424	2.9	36	4.9	1.8	(1.3- 2.6)‡
<190	338	1.5	27	2.5	1.7	(1.1- 2.5)‡	239	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 for trend					0.07						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+	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 for trend					<0.001						<0.001	
Gonane progestin	596	2.7	40	3.6	1.4	(1.0- 2.0)‡	384	2.6	29	3.9	1.7	(1.1- 2.4)‡
<190	267	1.2	17	1.6	1.4	(0.8- 2.3)	164	1.1	12	1.6	1.6	(1.1- 3.0)
190+	314	1.4	21	1.9	1.4	(0.9- 2.2)	208	1.4	15	2.0	1.6	(1.1- 2.7)
p for trend					0.13						0.12	
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	0.9	1.1	(0.5- 2.3)
p for trend					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	(0.7- 2.8)
190+	77	0.4	6	0.5	1.7	(0.7- 3.9)	51	0.3	4	0.5	1.7	(0.6- 4.8)
p for trend					0.23						0.21	

* All odds ratios (ORs) are implicitly adjusted for the matching factors. Includes mono- and triphasic OCs.

† Recent use is defined as filling at least one combined OC script in the year prior to reference date. Categories are not mutually exclusive and numbers may not add up to column totals because of missing values. Categories with <5 controls or invasive cases are not displayed. The p for trend uses the continuous linear variable (reference group=never/former OC users). Low dose=20 micrograms (mcg) ethinyl estradiol (EE), moderate dose=30-35 mcg EE or 50 mcg mestranol (ME), and high dose=50 mcg EE or 80 mcg ME.

‡ p-value <0.05

¶ Estrane progestins include norethindrone, norethindrone acetate, and ethynodiol diacetate. Gonane progestins include levonorgestrel, norgestimate, norgestrel, and desogestrel.

Table 2.7: Recent oral contraceptive (OC) use by monophasic formulations and invasive breast cancer risk, by all cases (left) and ER positive cases (right)

	Controls (n=21952)		All cases (n=1102)				Controls (n=14704)		ER+ cases (n=738)			
OC formulation†	**n**	**%**	**n**	**%**	**OR***	**95% CI**	**n**	**%**	**n**	**%**	**OR***	**95% CI**
Never/former use	19953	90.9	957	86.8	1.0	Ref.	13394	91.1	637	86.3	1.0	Ref.
Any monophasic OC	1613	7.3	114	10.3	1.5	(1.2- 1.9)‡	1067	7.3	79	10.7	1.6	(1.3- 2.1)‡
By estrogen dose and progestin type/dose												
Low dose estrogen												
Norethindrone acetate												
1.0 mg	327	1.5	17	1.5	1.1	(0.7- 1.8)	227	1.5	13	1.8	1.2	(0.7- 2.2)
Moderate dose estrogen	1257	5.7	95	8.6	1.6	(1.3- 2.0)‡	814	5.5	64	8.7	1.7	(1.3- 2.2)‡
Any norethindrone	615	2.8	40	3.6	1.4	(1.0- 1.9)	397	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)
1.0 mg	357	1.6	27	2.5	1.6	(1.1- 2.4)‡	229	1.6	13	1.8	1.2	(0.7- 2.2)
1.0 mg¶	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												
1.5 mg	300	1.4	30	2.7	2.1	(1.5- 3.1)‡	205	1.4	24	3.3	2.5	(1.6- 3.9)‡
Ethynodiol diacetate												
1.0 mg	86	0.4	11	1.0	2.8	(1.5- 5.2)‡	55	0.4	8	1.1	3.2	(1.5- 6.8)‡
Levonorgestrel												
0.15 mg	165	0.8	10	0.9	1.3	(0.7- 2.5)	103	0.7	5	0.7	1.1	(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)

* All odds ratios (ORs) are implicitly adjusted for the matching factors.
† Recent use is defined as filling at least one combined OC script in the year prior to reference date. Categories are not mutually exclusive and numbers may not add up to column totals because of missing values. OC formulations with <5 controls or invasive cases as recent users are not displayed. Low dose=20 micrograms (mcg) ethinyl estradiol (EE), moderate dose=30-35 mcg EE or 50 mcg mestranol (ME), and mg=milligrams.
‡ p-value <0.05
¶ Contains the estrogen mestranol rather than ethinyl estradiol.

Table 2.8: Recent oral contraceptive (OC) use by triphasic formulations and invasive breast cancer risk, by all cases (left) and ER positive cases (right)

	Controls (n=21952)		All cases (n=1102)				Controls (n=14704)		ER+ cases (n=738)			
OC formulation†	**n**	**%**	**n**	**%**	**OR***	**95% CI**	**n**	**%**	**n**	**%**	**OR***	**95% CI**
Never/former use	19953	90.9	957	86.8	1.0	Ref.	13394	91.1	637	86.3	1.0	Ref.
Any triphasic OC	455	2.1	37	3.4	1.8	(1.2- 2.5)‡	282	1.9	25	3.4	2.0	(1.3- 3.0)‡
By progestin type¶												
Norethindrone												
0.714 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)‡	76	0.5	12	1.6	3.5	(1.9- 6.4)‡
Levonorgestrel												
0.092 mg	152	0.7	13	1.2	1.8	(1.0- 3.3)‡	93	0.6	9	1.2	2.1	(1.1- 4.2)‡
Norgestimate												
0.215 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)

* All odds ratios (ORs) are implicitly adjusted for the matching factors.

† Recent use is defined as filling at least one combined OC script in the year prior to reference date. Categories are not mutually exclusive and numbers may not add up to column totals because of missing values. Mg=milligrams.

‡ p-value <0.05

¶ All triphasic formulations contain moderate estrogen dose. Average progestin doses are listed.

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