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A prospective cohort study of oral contraceptive use and ovarian cancer among women in the United States born from 1947 to 1964

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Abstract

Purpose—Oral contraceptives (OCs) have been consistently associated with a reduced ovarian cancer risk; however, most previous studies included women in older birth cohorts using high-dose OC formulations. We assessed OC use, including type and dose, and ovarian cancer risk among women born between 1947 and 1964 using more recent formulations.

Methods—We included 110,929 Nurses' Health Study II participants. Women reported duration of OC use and brands used from age 13 to baseline (1989) and every two years thereafter through 2009. We categorized brands by estrogen and progestin type, dose, and potency, and used Cox proportional hazards models, adjusted for age, calendar time, reproductive factors and body mass index, to assess associations with ovarian cancer.

Results—Over 2,178,679 person-years of follow-up, we confirmed 281 cases. At baseline, 83% of participants reported ever using OCs. Compared to never use, we observed an increased risk of ovarian cancer with 6 months of OC use (HR: 1.82; 95%CI: 1.13-2.93) but a non-significant 57% (95%CI: 0.18-1.03) decreased risk with 15 years of OC use. The increased risk among short-term

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users (1 year) was restricted to OCs containing mestranol (HR: 1.83; 95%CI: 1.16-2.88) and first generation progestin (HR: 1.72; 95%CI: 1.11-2.65).

Conclusion—The associations between OCs and ovarian cancer observed for this younger birth cohort differ substantially from the results of previous cohort studies, possibly reflecting changes in OC formulations and use patterns over time, although these results could be due to chance. Additional studies should evaluate newer OC formulations and ovarian cancer risk.

Keywords

oral contraceptives; ovarian cancer; ethinyl estradiol; mestranol

Introduction

Oral contraceptive (OC) use is common among reproductive age women, particularly in recent years; therefore, understanding the influence of OC use on future cancer risk has important public health implications. While current OC use may increase the risk of breast and cervical cancers (1-4), OCs are among the strongest preventive factors known for ovarian cancer, with an approximately 30% decreased risk of ovarian cancer with ever OC use compared to never use reported in a recent pooled analysis of 45 studies (5).

The majority of studies that have reported on the relationship between OC use and ovarian cancer risk were conducted in older birth cohorts among women who primarily used higher dose OC formulations (5). The dose of estrogen has decreased from ~50 µg in the 1970s to ~35 µg in the 1980s and is as low as 20 µg in current combination OC pills. The progestin dose has also slightly decreased over time (6-8). Few data are available on associations of lower dose OC pills with ovarian cancer particularly among cohort studies. Several case-control studies among younger birth cohorts observed an inverse association for OC duration (9-14), and the only cohort study among a younger birth cohort observed a 40% (95% CI: 0.5-0.8) decreased risk of ovarian cancer with ever OC use compared to never use.(15).

In this study, we conducted a detailed assessment of the association between oral contraceptives and ovarian cancer risk in the Nurses' Health Study II (NHSII), a prospective cohort study of women who were aged 25-42 in 1989. The reproductive years of NHSII participants spanned the transition from higher to lower dose combination OCs. Women reported their OC duration and OC brand from age 13 years until age at baseline (1989) and every two years after baseline, enabling us to examine not only duration of OC use but also estrogen and progestin dose and potency in relation to ovarian cancer risk.

Methods

Study population

The Nurses' Health Study II (NHSII) began in 1989 when 116,429 US female nurses, aged 25-42 completed a baseline questionnaire on health, lifestyle and disease diagnoses. Follow-up questionnaires were mailed to study participants biennially to obtain updated information on exposures and disease diagnoses, with a follow-up rate through June 2013 of 94% of the potential person-years. At baseline we excluded women with a previous diagnosis of cancer

except for non-melanoma skin cancer (n=1,045), previous bilateral oophorectomy (n=2,232), or menopause due to radiation (n=31), resulting in an analytic sample of 110,929 participants. The study protocol was approved by the institutional review board of Brigham and Women's Hospital.

Oral contraceptive use

At baseline, women were asked to report if they had ever used OCs and if they were currently using OCs. A life-events calendar was used to ascertain OC use starting at age 13 years. For each year of age, women were asked: (1) if they had used OCs for at least 2 months in that year, (2) if they had used OCs for at least 10+ months in that year, and (3) the brand of OC used during that year (women indicated the brand used the longest at each age if more than one brand was used). If women reported using OCs for at least 2 months but not 10 months in a year, then they were coded as having 6 months of use in that year while women who reported 10+ months in a year were coded as 12 months of use in that year. At each follow-up questionnaire cycle, women reported (1) if they were currently using OCs, (2) if they had used OCs since the last questionnaire, (3) their duration of OC use since the last questionnaire in pre-specified categories: 1 or less months, 2-4, 5-9, 10-14, 15-19, 20 or more months, and (4) the OC brand they had used for the longest during the last two years. To aid in recall, a booklet with names and color photographs of all OC brands available during the relevant time period was sent with each questionnaire. We only considered OC use during the premenopausal period, i.e. any OC use reported during the postmenopausal period was not included in the OC variables.

Hunter and colleagues (1997) assessed the reproducibility of ever OC use and duration of OC use and evaluated the validity of OC formulation reporting in 1989 in NHSII (16). In a telephone interview conducted approximately 11 months after the baseline questionnaire, women had excellent recall of ever OC use (sensitivity: 99%; specificity: 97%) and duration of OC use (spearman correlation: 0.94) reported on the self-administrated baseline questionnaire. Compared to medical records for 150 women, the exact OC brand reported at baseline was in agreement 42% of the time but, when brands that had the exact same estrogen and progestin type and dose were collapsed, the percent agreement increased to 75%, suggesting that women were fairly good at recalling OC formulation.

Assessment of OC dose and potency

We classified OC brands by estrogen type, dose and potency, and by progestin type, dose and potency using published categories (17-19). The estrogenic potency (μg ethinyl estradiol equivalents per day) was based on mouse uterine assays, while the progestin potency (mg norethindrone equivalents per day) was based on the induction of glycogen vacuoles in human endometrium (17). For OC brands not included in our reference book, information was obtained on estrogen and progestin type and dose from the Physician's Desk Reference, American Drug Index and other sources (20-24) and these brands were matched to a brand in the reference book with the same OC formulation to obtain potency. For women reporting a known OC brand but unknown formulation (i.e. dose), the dose of estrogen and progestin was set as the average of the known formulations within that brand; however, potency was left as missing as potency depends on the exact estrogen and progestin type and dose.

We classified OC brands according to estrogen type: mestranol (ME) or ethinyl estradiol (EE). As 12 different progestins were reported during follow-up, the progestin types were grouped by generation based on the compound from which each progestin was derived (25). First generation progestins included norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, medroxyprogesterone acetate, and chlormadinone acetate, while second generation progestins included levonorgestrel and norgestrel (25). Too few women used third (desogestrel and norgestimate) and fourth (drospirenone) generation OC brands to be analyzed separately. Among women who reported the specific OC brand(s) they had used for at least 85% of their total OC duration, we calculated (1) duration of OC use by estrogen type and progestin generation and (2) cumulative dose and potency of estrogen and progestin. Further, we estimated average dose and potency over the entire period of prior known OC duration by dividing the cumulative total dose or potency by total duration of use.

Ovarian cancer cases and deaths

Incident cases of epithelial ovarian cancer were identified on biennial questionnaires from 1989 to 2013 or, for deceased participants, from linkage to the National Death Index (26), the U.S. Postal Service, or family members. For all ovarian cancer cases we attempted to obtain pathology reports. A gynecological pathologist, blinded to exposure status, reviewed the reports to confirm the diagnosis of epithelial ovarian cancer and classify the tumors by behavior (invasive and borderline), histologic type (serous/poorly differentiated, mucinous, endometrioid, clear cell, and other) and stage. If medical records could not be obtained, pathology information was acquired through linkage with cancer registries. The analyses included ovarian cancer cases that were confirmed either through pathology reports or registries.

Statistical analysis

We classified OC use using several different methods. For all analyses, person-years were calculated from 1989 to the date of ovarian or other cancer diagnosis (except for non-melanoma skin cancer), death, bilateral oophorectomy, menopause due to radiation, missing OC duration, or end of study follow-up (June 2013). Cox proportional hazards models stratified by age in months and calendar time were used to obtain hazard ratios (HR) and 95% confidence intervals (CI). Analyses were adjusted for number of pregnancies (continuous), tubal ligation (yes/no), duration of breastfeeding (continuous in months, indicator for missing), and laparoscopically-confirmed endometriosis (yes/no). Analyses were further adjusted for body mass index (BMI; continuous in kg/m^2 , indicator for missing) in a separate model as BMI was thought to be a potential effect modifier. We additionally assessed potential confounding by the following covariates: use of IUD or diaphragm (yes/no), use of male contraception (yes/no), use of other contraceptives (yes/no), smoking status (past/current/never), race (Asian/White/Other), age at menarche (per year), age at natural menopause (continuous), postmenopausal hormone therapy use (ever/never), infertility (defined as trying to get pregnant for >1 year: yes/no/missing), marital status (married/divorced or widowed/never married), and family history of breast and/or ovarian cancer (yes/no). None of these covariates changed the relative risk estimates substantially and as such were not included in the final models.

Total duration of OC use—Duration of OC use was categorized as never, 6 months or less, >6 months to 1 year, >1 to <5 years, 5 to <10 years, 10-<15 years, 15 or more years of OC use. Tests for trend were conducted by treating OC duration as an ordinal variable with values set to the median duration within each category and calculated using the Wald statistic. In sensitivity analyses, we stratified by age (<50 vs. ≥50), parity (nulliparous vs. parous) and BMI (<25 kg/m² vs. ≥25 kg/m²), using a likelihood ratio test of a multiplicative interaction term to assess effect modification. Additionally, we conducted sensitivity analyses (1) considering total OC duration up to 2-4 years before diagnosis to assess the impact of subclinical disease, (2) excluding borderline ovarian cancer cases and (3) excluding women with a simple hysterectomy. In secondary analyses, we assessed time since last OC use cross-classified with duration of OC use among never and past OC users categorized as never OC use, <1 year OC use/<20 years since last use, 1-5 years OC use/<20 years since last use, >5 years OC use/<20 years since last use, >1-5 years OC use/>20 years since last use, 5-10 years OC use/>20 years since last use, and >10 years OC use/>20 years since last use.

Duration of OC use by estrogen and progestin type—Duration for each estrogen (ME and EE) and progestin type (first generation and second generation) was categorized as never OC use, 1 year or less, >1 to <5 years and 5-<10 years and 10 or more years of use. Each hormone type was analyzed in separate models. Hormone variables were not mutually exclusive, i.e. women who used both ME and EE were included in the analyses. Women who were exclusive users of only one type of estrogen or progestin were excluded from analyses of the other type (n=36,687 for first generation progestin, n=11,948 for second generation progestin, n=16,183 for mestranol, n=32,944 for ethinyl estradiol).

For total OC duration and duration of OC use by estrogen and progestin type, we assessed potential differences in the associations by histologic subtype (serous vs. non-serous) using competing risk models (27). Additionally, we examined the possible non-linear relationship between total OC duration and ovarian cancer non-parametrically using restricted cubic splines (28). A likelihood ratio test was used to assess non-linearity by comparing the model with only the linear term in the model with the cubic spline terms. A significant p-value indicated a non-linear relationship. We could not assess the possible non-linear relationship duration of OC use by estrogen and progestin type and ovarian cancer due to small sample sizes, particularly for mestranol.

Average dose and potency—Average dose and potency analyses for both estrogen and progestin were conducted among ever OC users with a known dose or potency. Exclusive users of progestin-only OCs were excluded from these analyses. We created cross-classified variables for average dose and potency for estrogen and progestin, using median cutpoints for each 2-year follow-up period. For average dose, the following categories were used: both estrogen and progestin dose <median, estrogen dose <median and progestin dose ≥median, estrogen dose ≥median and progestin dose <median, and both estrogen and progestin dose ≥median. A similar classification was used for average potency. The average dose and potency analyses were further adjusted for total OC duration (continuous in months).

Cumulative dose and potency—In secondary analyses, we assessed cumulative dose and potency among ever OC users with known dose or potency. As these variables were highly correlated with total OC duration ($\rho=0.88$ for cumulative estrogen dose, 0.90 for cumulative estrogen potency, 0.64 for cumulative progestin dose, 0.78 for cumulative progestin potency), we used the residuals from generalized linear models in our analyses. To calculate the residuals, we natural log-transformed the cumulative dose and potency variables as well as total OC duration. We then regressed the natural log of each of the cumulative dose and potency variables on the natural log of total OC duration. The residuals represent the difference between a woman's predicted cumulative dose/potency based on her total OC duration and her actual value. We cross-classified estrogen and progestin dose residuals using a cutpoint of below or at/above the median for each follow-up cycle. A similar cross-classification was used for the potency residuals. We additionally adjusted these analyses for total duration of OC use (continuous in months).

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). P-values were 2-sided and considered statistically significant if less than 0.05.

Results

Study population characteristics

In 1989, 83% of women in NHSII had ever used OCs and 14% of ever users were currently using OCs. Among ever OC users at baseline, most women had used OCs for either >1 to <5 years (39%) or 5 to <10 years (30%) (Table 1). Mean BMI was lower among those with longer OC duration except for women who used OCs for ≤ 15 years. Never OC users and women with 10- <15 or ≤ 15 years of OC use were the least likely to have children, 61%, 58%, and 34%, respectively, were parous and the least likely to have reported infertility, 15%, 11%, and 6%, respectively. However, among parous women, never OC users had a higher mean number of pregnancies lasting 6 months or more than women with 15 or more years of OC use. Additionally, duration of breastfeeding was lower among those with longer length of OC use.

Oral contraceptive use characteristics

Among ever OC users in 1989, 43% had ever used ME while 66% had ever used EE. At baseline, the proportion of women using an OC brand containing ME was higher among those with longer total duration; these women were also more likely to have used multiple brands of OCs, while short-term OC users were more likely to have used only 1 brand (Table 2). Additionally, women with short-term OC use were less likely to know the specific OC brand they had used compared to women with longer durations. Ever OC users at baseline were more likely to have used first generation (72%) as opposed to second generation (37%) progestins. The median cumulative dose was 47,939 μg for estrogen (10th – 90th percentile: 8,903 – 136,969 μg) and 822 mg for progestin (10th – 90th percentile: 137 – 2,465 mg), while the median cumulative potency was 36,708 μg EE equivalent for estrogen (10th – 90th percentile: 6,848 – 97,795 μg EE equivalent) and 1,011 mg norethindrone equivalent for progestin (10th – 90th percentile: 215 – 2,968 mg norethindrone equivalent). Finally, there

was relatively little variation in average dose and potency for estrogen and progestin across categories of duration.

Duration of total OC use

Compared to never use, only 15 years of OC use was associated with a non-significant decreased risk of ovarian cancer (HR: 0.43; 95% CI: 0.18, 1.03; Table 3), with a significant trend across categories of OC duration including never OC users (p-trend=0.006). Short-term OC use of 6 months or less was associated with a significant 82% increased risk of ovarian cancer compared to never OC use in the full multivariate model (HR: 1.82; 95% CI: 1.13, 2.93). Among ever OC users, the risk of ovarian cancer decreased by 5% for each year of use (HR: 0.95; 95% CI: 0.92, 0.98) with a significant trend across OC duration categories (p-trend=0.0005). No significant difference in the association between duration of OC use and ovarian cancer risk were observed by tumor histology (p-heterogeneity=0.85). In sensitivity analyses, the relative risk estimates among invasive ovarian cancer cases (n=229) were stronger than observed in the main analyses (Supplemental Table S1). Women with 6 months or less of OC use had over twice the risk (HR: 2.13; 95% CI: 1.25, 3.61) of developing invasive ovarian cancer compared to never OC users while women with 15 or more years of OC use had a significant 71% (95% CI: 0.09, 0.95) decreased risk of ovarian cancer compared to never OC users. Additionally, among ever OC users there was a significant decreasing trend across OC duration categories (p-trend=0.0002). In analyses using OC duration ending 2-4 years before diagnosis and in analyses excluding women with a simple hysterectomy, the results were similar to the main findings (data not shown). The test of non-linearity for total OC duration and ovarian cancer was non-significant among all NHSII participants and ever OC users (p-value for non-linearity=0.17 and 0.35, respectively; Supplemental Tables 1 & 2).

In stratified analyses by parity, a significant decreased risk of ovarian cancer was observed among nulliparous women with 10 or more years of OC use (HR: 0.39; 95% CI: 0.16, 0.96), while no association was observed for parous women with 10 or more years of OC use (HR: 1.28; 95% CI: 0.69, 2.40); however, this difference was not statistically significant (p-interaction=0.22; Supplemental Table S1). Nulliparous women who had never used OCs were much less likely to have ever been married than parous women who had never used OCs (66% vs. 1%, respectively) and the parous never OC users were more likely to have used other forms of contraception. However, adjusting for these factors did not change the results. Additionally, the increased risk among short-term OC users was suggestively stronger for women aged ≤ 50 years (HR: 2.26; 95% CI: 1.26, 4.04 for 1 year vs. never use) compared to women aged >50 years (HR: 1.13; 95% CI: 0.61, 2.09 for 1 year vs. never use; Supplemental Table S1), although the interaction was not significant (p-int=0.28). No differences were observed between the relative risk estimates for OC duration when stratified by BMI (p-int=0.88; data not shown).

Time since last OC use

In cross-classified analyses of time since last OC use and duration of OC use compared to never use, the risk estimates among short-term OC users (≤ 1 year) were similar between women who had stopped using OCs <20 years ago and women who had stopped using OCs

20 or more years ago (HR: 1.68; 95% CI: 0.90, 3.12 for 1 yr OC use/<20 yrs since last OC use vs. HR: 1.78; 95% CI: 1.10, 2.86 for 1 yr OC use/ 20 yrs since last OC use) (Supplemental Table S3). Additionally, compared to never users, women with 5 years of OC use and <20 years since last use had a non-significant 9% (95% CI: 0.53, 1.55) decreased risk of ovarian cancer, while women with 5 years of OC use and 20 years since last use had a non-significant 26% (95% CI: 0.75, 2.12) increased risk.

OC duration by estrogen and progestin type

We further investigated the relationship between duration of OC use and ovarian cancer by estrogen and progestin type. The increased risk among women who used OCs for 1 year or less was most apparent for duration of ME and first generation progestins (Table 4). Women who used ME for one year or less had a significant 83% (95% CI: 1.16, 2.88) increased risk of ovarian cancer compared to never OC users, while women who used first generation progestins for one year or less had a significant 72% (95% CI: 1.11, 2.65) increased risk of ovarian cancer compared to never OC users. The comparable relative risk estimates for EE and second generation progestins were both 1.22. The association between duration of OC use by estrogen and progestin type and ovarian cancer risk did not appear to vary by tumor histology ($p_{\text{het}}=0.40$ for EE, 0.69 for ME, 0.43 for first generation progestin, 0.49 for second generation progestin).

Dose and potency

To assess if risk differed by the estrogen or progestin content, we conducted a cross-classification analysis of average estrogen and progestin dose and potency (Table 5). Women with average estrogen and progestin doses above the median had a non-significant 34% (95% CI: 0.92, 1.95) increased risk of ovarian cancer compared to women with average estrogen and progestin doses below the median. The association for estrogen above and progestin below the median versus both below the median was similar (HR: 1.24; 95% CI: 0.77, 2.00). However, no association was observed for women with average estrogen dose below the median but average progestin dose above the median (HR: 0.91; 95% CI: 0.54, 1.52). The analyses for average estrogen and progestin potency were null. In secondary analyses, we observed similar results for the cross-classification of estrogen and progestin dose and potency residuals (data not shown).

Discussion

In a prospective cohort study with 24 years of follow-up among women born between 1947 and 1964 who used more recent OC formulations, we observed that OC use of six months or less was associated with a significant increased risk of ovarian cancer compared to never use. Additionally, we did not observe a decreased risk of ovarian cancer with 10-<15 years of use compared to never use, although there was a suggestion of a decreased risk with 15 or more years of OC use. This is the first cohort study to assess duration of OC use and ovarian cancer by estrogen and progestin type. The significant increased risk of ovarian cancer for short-term use was restricted to users of ME and first generation progestins. By considering cross-classification of estrogen and progestin dose, we observed that estrogen, and not progestin content, may be driving this association.

The ovulation hypothesis is one mechanism through which oral contraceptives are thought to decrease ovarian cancer risk (29). During ovulation, the ovary undergoes trauma and associated wound healing, exposing the ovaries and fallopian tubes to high levels of hormonal and inflammatory agents. It has been known since the 1950s that, during pregnancy, high levels of progesterone suppress ovulation, which led to the development of synthetic progestins to be used for contraception (30). Individually, high doses of estrogen decrease the mid-cycle follicular stimulating hormone surge and moderate doses of progestin decrease the mid-cycle luteinizing hormone surge, both leading to inhibition of ovulation (7). However, in combination, lower doses of both hormones can be used, as estrogen and progestin have a synergistic effect on ovulation inhibition (30, 31).

Alternatively, OCs may influence ovarian cancer development through mechanisms other than ovulation inhibition as, for example, OCs decrease ovarian production of androgens and higher levels of androgens may be associated with increased ovarian cancer risk (32, 33). Previous studies have reported that a portion of the potential protective effect of OCs on ovarian cancer risk is likely independent of ovulation suppression (34-36).

The majority of studies on OC use and ovarian cancer observed a linear decreased risk of ovarian cancer with increasing duration of use (9, 10, 15, 37-41). A recent pooled analysis of 45 cohort and case-control studies reported an almost 45% decreased risk of ovarian cancer for 10 to 14 years of use compared to never users and a 58% decreased risk for 15 or more years of OC use compared to never OC users (5). Of note, the decreased risk per 5 years of OC use was stronger among the 32 population- and hospital-based case-control studies compared to the 13 cohort studies (25.6%, 24.7%, and 16.2% per 5 years among ever OC users, respectively). We did not observe a lower risk of ovarian cancer among participants using OCs for 10-<15 years; however, we did observe a non-significant 57% decreased risk of ovarian cancer with 15 or more years of OC use compared to never OC use; the association was stronger when considering only invasive cases. Among ever users of OCs, we observed a 24% decreased risk for every 5 additional years of use, although this decreased risk was largely driven by the higher risk for short-term users observed in our study.

Most studies that assessed short-term use of OCs observed no significant association between short-term OC use and ovarian cancer, including the pooled analysis of 45 studies (5, 10, 13, 38, 42, 43). However, some studies reported a suggestive (9, 12, 35) or significant (34, 44) decreased risk of ovarian cancer with short-term OC use. These results are in stark contrast to the results observed in our study and the other studies on OCs and ovarian cancer risk within this issue (references); we observed that short-term (≤ 6 months) OC use was associated with a significant 82% increased risk of ovarian cancer, which again was higher for invasive tumors.

Unique to our study, the NHSII includes women born between 1947 and 1964, while the majority of the previous cohort studies on ovarian cancer and OC use were conducted among older birth cohorts, with the median birth year ranging from before 1925 to approximately 1944 (5). Importantly, mostly higher dose OCs would have been available to women in these studies, while women in the NHSII were prescribed OCs during the transition from high to low dose formulations. Only one other cohort study considered

women from a similar birth cohort as NHSII. Kumle et al. (2004) assessed OC use and ovarian cancer among women born between 1942 and 1962 (15). They observed no association with less than one year of use, but a 50% (95% CI: 0.3, 1.0) decreased risk of ovarian cancer with 10-14 years of OC use; however, they had a higher proportion of never OC users (27%) compared to our study population and the OC formulations used within their study population were not known.

Although our results may be a chance finding, there are also a few possible explanations for the differing results in our study compared to prior work. First, OC usage patterns have changed over time with more women using OCs and starting to use them at a younger age. In particular, only 17% of NHSII participants had never used OCs in 1989 and the proportion of never users decreased to 12% by the end of follow-up, a much lower proportion than prior studies. For example, as noted above, the Kumle study had 27% never users, while in the Nurses' Health Study (NHS), in which all women were born before 1947, 57% were never users (15, 38). The higher proportion of ever users is consistent with trends of OC prescriptions in the U.S. during the 1970s and 1980s, the time period in which NHSII participants were using OCs (8). As such, never users in our study may represent a highly select group of individuals who differ from never users in prior research. For example, in two cohort studies among older birth cohorts, never OC users were more likely to be parous and have ever smoked compared to NHSII never users (38, 45). As in previous cohort studies, we observed the expected decreased risk of ovarian cancer with increasing duration among ever OC users, further suggesting that NHSII never users may be a highly select group.

A potential biologic explanation for our findings, particularly among the short-term users, is that the underlying hormonal milieu of women who use OCs for a short period time may influence their ovarian cancer risk. Notably, we have a substantial number of women (7.0% of ever users at the end of follow-up) who used OCs for a very short period. In 2013, we asked NHSII participants to recall the reason(s) they had stopped using OCs. Women who had used OCs for only 6 months or less by the end of follow-up were more likely to report that they had stopped for medical reasons, e.g. cardiovascular events and negative side effects, compared to women who used OCs for longer. Longer-term OC users were more likely to report that they had stopped due to pregnancy or switching to a different contraceptive (Supplemental Table S4). Prior reports support that negative side effects are a common reason for early OC discontinuation (46-49). The most frequently reported side effects include breakthrough bleeding, nausea/vomiting, headaches, depression, weight gain, and breast tenderness (46-51). Little data are available on characteristics of women who discontinue OC use due to side effects compared to those who can tolerate and remain on OCs. These groups may respond differently to changes in hormonal levels induced by OCs or have a different underlying hormonal milieu, and such hormone differences may influence ovarian cancer risk. However, these results should be interpreted with caution as approximately 30% of ever OC users did not report the reason they had stopped using OCs. Future research should focus on differences in hormonal markers and other biologic characteristics of women who experience side effects while taking OCs compared to women who do not.

In our study, the increased risk for short-term use of OCs appeared to be driven by use of ME, an estrogen found in older formulations of OCs. The biological mechanism for this association is unclear and these results contradict the findings of older studies conducted among women who would have mostly used ME. However, one case-control study observed weaker associations with ovarian cancer for duration of 50 µg EE equivalent (HR: 0.95; 95% CI: 0.91-0.99 per year), likely to be a mixture of ME and EE OCs compared to duration of <35 µg EE equivalent (HR: 0.86; 95% CI: 0.79-0.94 per year), likely to be primarily EE OCs (13). ME is a prodrug of EE, which is more common in recent OC formulations (31). Approximately 70% of ME is converted into EE primarily by the CYP2D6 enzyme in the liver (31, 52). However, for a given ingested ME or EE dose, there is substantial inter- and intra-individual variation in bioavailable EE (25% to 65% of the ingested dose) (53). It is possible that short-term users with side effects may receive a higher bioavailable EE for a given dose than what would be expected. While it is unclear if these women would also have higher endogenous estrogen levels, the relationship between circulating estrogens and ovarian cancer risk is complex. Two small studies of postmenopausal women reported that circulating levels of estradiol or estrone were not related to ovarian cancer risk (54, 55). In one study of premenopausal, pregnant women, those in the highest tertile of estradiol levels had an almost 3-fold increased risk of endometrioid ovarian cancer compared to women in the lowest tertile (56). In the NHSII, we did not observe any significant differences by tumor histology for duration of ME or EE, although our statistical power was limited. Larger studies that can assess the premenopausal estrogenic environment with risk are needed. Additionally, future research should focus on understanding if women who experience side effects compared to women who do not are more efficient at converting their ingested EE (or ME) dose into bioavailable EE.

Our study had several limitations including a relatively limited number of ovarian cancer cases, reducing power in stratified analyses and to assess differences in associations by tumor histology. Like most other studies, OC use was self-reported potentially leading to misclassification; however, any misclassification should be non-differential, biasing the results towards the null, which would not explain the observed increased risk with short-term OC use. Further, potency measures were based on methods whose relevance to humans is unknown (e.g., mouse uterine weight assays), and within humans there is wide inter- and intra-individual variation in bioavailability of EE. This calls into question the relevance of potency measurements of OCs without knowledge about individual-level metabolism. Finally, the range of potency levels, particularly for progestins, was limited in our study.

Our study also has a number of strengths that should be highlighted. We had 24 years of follow-up and are one of a small number of cohort studies among younger birth cohorts with reasonable power to assess OC use and ovarian cancer risk. This enabled us to assess newer formulations. Additionally, we have detailed information on use, including brand, at each age from age 13 through baseline with updated exposure information through 2009. Finally, the NHSII is a prospective study, which allows us to assess OC use and ovarian cancer without differential misclassification due to recall bias.

Conclusion

In this study, we observed a significant increased risk of ovarian cancer with short-term OC use and a non-significant inverse association with fifteen or more years of OC use. Given the strong consistency across the previous studies there is no doubt that older OC formulations reduced the risk of ovarian cancer; however, in our study the pattern of newer formulations appears to differ from that of the older formulations. Further research into patterns of OC use in the US population during this time period, including characteristics of never users, may help clarify our results. Further, better understanding the underlying hormonal milieu among women who cannot tolerate OCs may elucidate potential mechanisms that could influence ovarian cancer development. Future research among young birth cohorts using both high and low OC formulations are needed to confirm if our results are unique to our population or reflect the association of OCs and ovarian cancer among younger birth cohorts who used newer formulations with very different use patterns than those in older studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Nurses' Health Study II participants by duration of oral contraceptive (OC) use in 1989 (n=110,929)^a

	Never (n=18,994)	6 months (n=9,770)	>6 months-1 year (n=9,065)	Duration of oral contraceptive use			15 years (n=1,417)
				>1<5 years (n=36,026)	5<10 years (n=27,800)	10<15 years (n=7,857)	
Mean (Standard deviation)							
Age (years) ^b	34.4 (4.6)	35.3 (4.6)	35.1 (4.6)	34.7 (4.8)	34.4 (4.7)	35.2 (3.9)	37.3 (3.1)
Age at menarche (years)	12.4 (1.5)	12.5 (1.5)	12.4 (1.5)	12.4 (1.4)	12.4 (1.4)	12.4 (1.4)	12.2 (1.5)
Body mass index (kg/m ²)	24.5 (5.6)	24.1 (5.1)	24.0 (5.0)	24.1 (5.0)	23.9 (4.7)	23.7 (4.6)	24.0 (4.7)
Number of pregnancies ^c	2.2 (1.0)	2.2 (1.0)	2.2 (0.9)	2.1 (0.9)	1.9 (0.8)	1.7 (0.7)	1.5 (0.6)
months ^c							
Breastfeeding (months) ^{c, d}	14.7 (13.9)	13.3 (12.6)	12.8 (12.2)	12.5 (12.1)	10.9 (10.6)	8.3 (8.2)	6.4 (5.5)
Percentage							
Ever parous	61	75	75	77	73	58	34
Infertility ^{e, f}	15	20	21	21	17	11	6
Other current contraceptive method ^g							
IUD/diaphragm	17	16	15	13	11	7	6
Male contraception	32	33	33	32	28	22	15
Other contraception	23	20	19	17	14	12	8
Ever tubal ligation	10	16	15	18	18	13	7
Endometriosis ^h	3	4	5	4	4	4	6
Ever migraines	12	16	16	16	15	15	16
Simple hysterectomy ^j	2	3	3	3	3	2	1
Family history of breast and/or ovarian cancer	8	8	7	7	7	7	11
Smoking status							
Never smoker	77	68	66	65	59	54	56
Current smoker	9	12	13	13	16	20	22
Past smoker	14	20	21	22	25	26	22
Race							

	Never (n=18,994)	6 months (n=9,770)	Duration of oral contraceptive use			10<15 years (n=7,857)	15 years (n=1,417)
			>6 months-1 year (n=9,065)	>1<5 years (n=36,026)	5<10 years (n=27,800)		
White	89	90	92	94	94	92	91
Asian	5	3	2	1	1	1	0
Other	6	7	6	5	5	7	9
Marital status ^f							
Married	68	78	79	82	80	72	56
Divorced/widowed	5	8	9	9	11	14	21
Never married	27	14	12	9	9	14	23

^a values are standardized to the age distribution of the study population.

^b Value is not age adjusted

^c Among parous women

^d Missing breastfeeding duration among parous women (n=13,845)

^e Infertility defined as trying to get pregnant for more than 1 year

^f Missing infertility (n=142)

^g IUD=Intrauterine device, male contraception includes vasectomy and male condoms, other contraception includes sponge, foam, rhythm method, and other contraception

^h Laparoscopically-confirmed endometriosis

ⁱ Missing simple hysterectomy status (n=918)

^j Missing marital status (n=257)

Oral contraceptive characteristics among ever OC users in the Nurses' Health Study II by total duration of OC use in 1989 (n=91,935)^a

Table 2

Mean (Standard deviation)	6 months OC use (n=9,770)	>6 months to 1 year OC use (n=9,065)	>1-5 years OC use (n=36,026)	5-<10 years OC use (n=27,800)	10-<15 years OC use (n=7,857)	15 years OC use (n=1,417)
Estrogen^{b,c}						
Cumulative dose	6,330 (2,969)	13,340 (5,419)	38,829 (20,063)	91,526 (37,426)	150,888 (52,505)	215,019 (68,410)
Cumulative potency	4,692 (2,625)	9,735 (4,020)	28,499 (13,649)	67,112 (24,124)	111,095 (33,502)	158,237 (51,250)
Average dose	1,135 (468)	1,135 (450)	1,127 (424)	1,127 (401)	1,096 (355)	1,091 (312)
Average potency	840 (416)	829 (331)	825 (283)	825 (244)	808 (223)	805 (239)
Progestin^{d,e}						
Cumulative dose	125 (158)	256 (278)	716 (721)	1,651 (1,337)	2,716 (1,711)	3,796 (2,443)
Cumulative potency	146 (143)	305 (247)	879 (652)	2,045 (1,166)	3,411 (1,461)	4,922 (1,960)
Average dose	22 (27)	22 (23)	21 (20)	20 (16)	20 (13)	19 (12)
Average potency	26 (25)	26 (21)	26 (17)	25 (14)	25 (11)	25 (9)
Percentages						
Current OC use	4	5	10	18	35	57
Ever estrogen type use^f						
Mestranol	31	36	41	49	55	54
Ethinyl estradiol	49	56	64	71	78	84
Missing type	20	14	11	7	7	8
Ever progestin type use^f						
First generation ^g	58	65	71	76	80	76
Second generation ^h	23	28	36	42	46	54
Missing type	20	14	11	7	7	8
Number of OC brands used						
1 brand	80	68	52	37	23	13
2 brands	1	17	27	33	33	30
3 brands	0	0	7	13	20	22
4 or more brands	0	0	2	5	12	19

	6 months OC use (n=9,770)	>6 months to 1 year OC use (n=9,065)	>1-<5 years OC use (n=36,026)	5-<10 years OC use (n=27,800)	10-<15 years OC use (n=7,857)	15 years OC use (n=1,417)
Unknown ⁱ	20	14	13	12	13	15

^aValues are standardized to the age distribution of the study population

^bN=9750 women missing cumulative and average estrogen dose and N=16,014 women missing cumulative and average estrogen potency

^cUnits are as follows: cumulative estrogen dose: µg; cumulative estrogen potency: µg ethinyl estradiol equivalents; average estrogen dose: µg per month; average estrogen potency: µg ethinyl estradiol equivalents per month

^dN=9750 women missing cumulative and average progestin dose and N=16,013 women missing cumulative and average progestin potency

^eUnits are as follows: cumulative progestin dose: mg; cumulative progestin potency: mg norethindrone equivalents; average progestin dose: mg per month; average progestin potency: mg norethindrone equivalents per month

^fPercentages can sum to more than 100% as women could have used both estrogen or progestin types

^gFirst generation progestin includes norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, medroxyprogesterone acetate, and chlormadinone acetate

^hSecond generation progestin includes levonorgestrel and norgestrel

ⁱWomen were included in the unknown number of brands category if they reported an 'unknown OC brand' at least once on the baseline questionnaire

Table 3

Association between duration of OC use and ovarian cancer risk among Nurses' Health Study II participants (1989–2013)

	Cases	Person-yrs	Model 1 ^a		Model 2 ^b		Model 3 ^c	
			HR	95% CI	HR	95% CI	HR	95% CI
			Duration of OC use					
Never	36	321,519	1.00	(Ref.)	1.00	(Ref.)	1.00	(Ref.)
6 months	33	165,347	1.65	(1.02, 2.64)	1.78	(1.10, 2.85)	1.82	(1.13, 2.93)
6 months – 1 year	25	159,328	1.36	(0.82, 2.27)	1.46	(0.87, 2.44)	1.51	(0.90, 2.53)
>1-<5 years	96	679,339	1.19	(0.81, 1.75)	1.29	(0.88, 1.90)	1.33	(0.90, 1.97)
5-<10 years	59	551,456	0.95	(0.63, 1.44)	0.98	(0.65, 1.49)	1.03	(0.67, 1.56)
10-<15 years	26	207,436	1.10	(0.66, 1.83)	1.06	(0.63, 1.76)	1.11	(0.66, 1.84)
15 years	6	94,253	0.47	(0.20, 1.11)	0.40	(0.17, 0.96)	0.43	(0.18, 1.04)
<i>p</i> -trend ^d				0.02		0.003		0.006
<i>p</i> -trend ^e				0.003		0.0003		0.0005

^a Adjusted for age (years) and calendar time

^b Adjusted for Model 1 variables + tubal ligation (yes/no), parity (number of pregnancies), breastfeeding duration (months), and missing breastfeeding duration, laparoscopically-confirmed endometriosis (ever/never)

^c Adjusted for Model 2 variables + body mass index (kg/m²)

^d *p*-trend is calculated including the never OC users

^e *p*-trend is calculated among ever OC users

Table 4

Associations between duration of OC use by estrogen and progestin type and ovarian cancer risk in the Nurses' Health Study II (1989-2013)^a

	Cases	Person-yr	Multivariate-adjusted model ^b	
			HR	95% CI
Never OC users	36	321,519	1.00	(Ref.)
Duration of mestranol use ^{c,d}				
1 year	42	203,173	1.83	(1.16, 2.88)
>1-<5 years	44	330,914	1.09	(0.70, 1.71)
5-<10 years	25	181,313	1.04	(0.62, 1.75)
10 years	5	37,056	0.90	(0.35, 2.32)
Duration of ethinyl estradiol use ^{c,e}				
1 year	31	245,293	1.22	(0.75, 1.98)
>1-<5 years	58	466,580	1.25	(0.82, 1.92)
5-<10 years	27	327,298	0.82	(0.49, 1.36)
10 years	16	147,750	0.90	(0.49, 1.64)
Duration of 1 st generation progestin use ^{f,g}				
1 year	51	279,314	1.72	(1.11, 2.65)
>1-<5 years	67	510,199	1.21	(0.80, 1.82)
5-<10 years	31	342,785	0.82	(0.50, 1.33)
10 years	17	131,927	1.02	(0.57, 1.83)
Duration of 2 nd generation progestin use ^{h,i}				
1 year	22	183,337	1.22	(0.71, 2.10)
>1-<5 years	37	294,897	1.24	(0.77, 1.98)
5-<10 years	16	156,456	0.97	(0.53, 1.77)
10 years	5	48,872	0.78	(0.30, 2.02)

^aDuration of OC use by type of estrogen and progestin is non-exclusive use, e.g. women with ethinyl estradiol use and mestranol use are included in both variables.

^bAdjusted for age (years), calendar time, parity (number of pregnancies), tubal ligation (yes/no), breastfeeding duration (months), missing breastfeeding duration (yes/no), laparoscopically-confirmed endometriosis (ever/never), body mass index (kg/m²)

^cExcludes women who used progestin-only pills exclusively

^dExcludes women who exclusively used ethinyl estradiol

^eExcludes women who exclusively used mestranol

^fFirst generation progestins include norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, medroxyprogesterone acetate, and chlormadinone acetate

^gExcludes women who exclusively used 2nd generation progestins

^hSecond generation progestins included levonorgestrel and norgestrel

ⁱExcludes women who exclusively used 1st generation progestins

Association between cumulative average estrogen and progestin dose/potency and ovarian cancer risk adjusting for duration of OC use among ever OC users (1989-2013)

Table 5

Multivariate-adjusted models ^a					
Cases	HR	95% CI	Cases	HR	95% CI
Cumulative average estrogen dose ^b					
< Median			Median		
Average progestin dose					
< Median	48	1.00 (Ref.)	31	1.24	(0.77, 2.00)
Median	20	0.91 (0.54, 1.52)	92	1.34	(0.92, 1.95)
Cumulative average estrogen potency					
< Median			Median		
Average progestin potency ⁴					
< Median	34	1.00 (Ref.)	19	0.99	(0.56, 1.74)
Median	55	1.16 (0.75, 1.80)	76	1.13	(0.74, 1.75)

^aAdjusted for age (months), calendar time, parity (number of pregnancies), tubal ligation (yes/no), breastfeeding duration (months), missing breastfeeding (yes/no), body mass index (kg/m²), duration of OC use (months)

^bMedian values were updated at each follow-up cycle