Time-Dependent Effects of Oral Contraceptive Use on Breast, Ovarian, and Endometrial Cancers

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ABSTRACT

Oral contraceptive use has been suggested to influence the risk of breast, ovarian, and endometrial cancer. The purpose of this study is to clarify the time-dependent effects between long-term oral contraceptive use and cancer risk. We performed an observational study in 256,661 women from UK Biobank, born between 1939 and 1970. Information on cancer diagnoses were collected from self-reported data and from national registers until March 2019. Cumulative risk of cancer over the timespan of the study, as measured by the OR, and instantaneous risk, as measured by the HR, were assessed using Logistic and Cox regression analyses, respectively. The odds were lower among ever users, compared with never users, for ovarian cancer [OR = 0.72; 95% confidence interval (CI), 0.65–0.81] and endometrial cancer (OR = 0.68; 95% CI, 0.62–0.75), an association that was stronger with longer use ($P < 0.001$). Increased odds were seen for breast cancer in women when limiting the follow-up to 55 years of age (OR = 1.10; 95% CI, 1.03–1.17), but not for the full timespan. We only found a higher HR for breast cancer in former users immediately (≤2 years) after discontinued oral contraceptive use (HR = 1.55; 95% CI, 1.06–2.28), whereas the protective association for ovarian and endometrial cancer remained significant up to 35 years after last use of oral contraceptives. Given the body of evidence presented in our study, we argue that oral contraceptives can dramatically reduce women's risk of ovarian and endometrial cancer, whereas their effect on lifetime risk of breast cancer is limited.

Significance: These results enable women and physicians to make more informed decisions considering oral contraceptive use, thus constituting an important step toward personalized medicine.

Introduction

In the early 1960s, the first oral contraceptive pill was approved, and it is estimated that 80% of all women in Western Europe have ever used oral contraceptives (1). There have been several studies performed, trying to link oral contraceptive use to risk of breast cancer, with somewhat conflicting results (Supplementary Table S1). One of the largest studies so far suggested that women who have used oral contraceptives the previous 10 years have a slightly increased risk of breast cancer compared with never users (2). That study was based on a meta-analysis of 54 studies conducted over 25 years, which could have introduced bias due to population stratification. Similar results were obtained in a large-scale study in younger women, between 15 and 49 years of age, showing an increased risk both during and after oral contraceptive use (3). Conversely, a study performed in women from 35 to 64 years of age found no association between current or former oral contraceptive use and increased risk of breast cancer (4). Similarly, a study in women with a mean age of 29 years, that was followed up for 36 years, did not see an association between oral contraceptive use on risk of breast cancer (5). In contrast, oral contraceptive use has been associated with a lower risk for ovarian and endometrial cancer, results that are consistent across most studies (6, 7). However, the more long-term effects are not very well studied, and more detailed studies of risk during and after oral contraceptive use are needed.

The aim of this study was to determine time-dependent and long-term associations between oral contraceptive use and breast, ovarian, and endometrial cancer, in a cross-sectional cohort including over 250,000 women born between 1939 and 1970. Oral contraceptives have now been available for about 60 years, giving us the opportunity to estimate their long-term risks and benefits. A large number of women in our study, who used oral contraceptives early in their reproductive years, are now reaching the age when the risk of breast, ovarian, and endometrial cancer is peaking and our study can, therefore, give new leads on lifetime cancer risk. The large sample size of this study provides statistical power to confirm and further refine previous findings regarding oral contraceptive use, as well as to identify time-dependent and long-term associations that have not previously been reported.

Patients and Methods

Participants

The UK Biobank (UKB) is a large cross-sectional cohort, with both a pro- and retrospective study design, that was established to improve prevention, diagnosis, and treatment of a wide range of diseases. Between 2006 and 2010, the UKB recruited 502,682 individuals, including 273,404 women, born between 1939 and 1970, at 22 assessment centers across the United Kingdom. The initial invite was sent out to over nine million people (see Online Data Supplements). Participants shared extensive data regarding their lifestyle, medical history, previous exposures, and physical measures. Participants are also matched against registers for diagnoses made during hospital stay, cause of death registers and cancer registers. All UKB participants provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki. Application for using

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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UKB data for this study was approved by UKB (application no. 41143) under the ethical approval by the National Research Ethics Committee (REC reference no. 11/NW/0382).

Assessment of cancer diagnosis and covariates

Cancer incidences were assessed using data from different categories: main and secondary diagnoses made during hospital stay, medical conditions assessed both from verbal interviews and touchscreen questionnaires, as well as cause of death and cancer registers. Data from hospital stays, the cancer register, and the death register were categorized according to International Classification of Diseases, revision nine (ICD-9) and ten (ICD-10). For a detailed description of data-fields and coding used for each cancer and covariate, see Supplementary Tables S2 and S3. The largest number of cancer cases was identified from cancer registry data, but since the registry data is less complete before 1995, several additional cancer cases were identified from self-reported data (Supplementary Table S2). General characteristics (**Table 1**) and information on covariates and potential confounders (Supplementary Table S3) were assessed from data collected during the initial visit to the assessment center.

Statistical analysis

Pearson χ^2 test was used for a goodness-of-fit test for the cumulative risk of cancer over the timespan of the study and for binary covariates, whereas Wilcoxon rank sum test was used to compare continuous covariates between ever and never users, without considering any potential confounding (**Table 1**).

Uncertainties (95% confidence interval; 95% CI) in incidence rates were estimated, assuming the number of new cases and the number of person-years at risk in each age group to be independent and Poisson distributed with means (and variances) equal to the observed numbers of new cases and person-years, respectively. The distribution of the ratio of these two Poisson distributed numbers was estimated from Monte-Carlo simulations with 1,000,000 runs. Finally, CIs were given by taking the 2.5% and 97.5% quantiles of this empirical ratio distribution, and multiply by 100,000 person-years.

In the cumulative-risk analyses, we determined whether there was a difference in odds for breast, ovarian, or endometrial cancer diagnosis between ever and never users of oral contraceptives. For these analyses, all cases that had been reported during the visit to the assessment center or identified in any of the registers (until March 2019) were considered. Logistic regression models were then used to calculate ORs and 95% CI between ever and never users, for each cancer (**Table 2**). *P* values lower than 0.0167 (Bonferroni adjustment for three cancers tested) were considered statistically significant in these analyses. The full model (model 4), which was used for generating the main results in this article, included age, body mass index (BMI), Townsend deprivation index (TDI), year of birth (YOB), smoking status, age at menarche, hormone replacement treatment (HRT) use, number of live births, as well as menopausal and hysterectomy status as covariates (**Table 2**). Several sensitivity analyses were performed (see Online Data Supplements for more information) where: (i) covariates were investigated separately for association with cancer prevalence (Supplementary Table S3), (ii) models with different sets of covariates were constructed (**Table 2**), (iii) only cancer diagnoses before a certain age (35, 40, 45, 50, 55, 60, 65, 70, 75, and 80) were considered (**Table 3**), (iv) current users ($n = 4{,}659$) were removed from the ever users in the main analysis (model 4), in order minimize the potential effect of an induction time (i.e., the time from causal action to disease initiation) in the model (**Table 2**), and (v) only cancer diagnoses after recruitment were analyzed and current oral contraceptive users were excluded (**Table 2**).

To investigate whether the induction period (time from exposure to initiation of cancer), or latency period (initiation of cancer to

Table 1. Characteristics of ever and never oral contraceptive users in the study cohort.

	Ever users	Never users	*P*[a]
Number	210,443	46,218	—
Year of birth, median (full range)	1952 (1936–1970)	1945 (1936–1970)	<0.001
BMI[b], median (1st–3rd quartile)	25.98 (23.36–29.53)	26.5 (23.7–30.12)	<0.001
Age, median (1st–3rd quartile)	56 (49–62)	63 (57–66)	<0.001
TDI[c], median (1st–3rd quartile)	−2.27 (−3.7–0.18)	−2.2 (−3.63–0.39)	<0.001
Smoking-Current, *n* (%)	15,177 (7.21)	2,539 (5.49)	<0.001
Smoking-Never, *n* (%)	119,580 (56.82)	30,230 (65.41)	<0.001
Smoking-Occasional, *n* (%)	30,938 (14.7)	5,729 (12.4)	<0.001
Smoking-Previous, *n* (%)	44,080 (20.95)	7,527 (16.29)	<0.001
Post-menopausal-Yes, *n* (%)	123,626 (58.75)	33,838 (73.21)	<0.001
Post-menopausal-No, *n* (%)	52,835 (25.11)	5,526 (11.96)	<0.001
Post-menopausal-Not sure hysterectomy, *n* (%)	24,047 (11.43)	5,734 (12.41)	<0.001
Post-menopausal-Not sure other, *n* (%)	9,817 (4.66)	1,009 (2.18)	<0.001
Had hysterectomy, *n* (%)	37,785 (17.95)	10,642 (23.03)	<0.001
Hormone replacement therapy, *n* (%)	81,907 (38.92)	18,580 (40.2)	<0.001
Number of live births, median (1st–3rd quartile)	2 (1–2)	2 (0–3)	<0.001
Age of menarche, median (1st–3rd quartile)	13 (12–14)	13 (12–14)	0.25
Breast cancer, *n* (%)	13,937 (6.62)	3,773 (8.16)	<0.001
Ovarian cancer, *n* (%)	1,419 (0.67)	539 (1.17)	<0.001
Endometrial cancer, *n* (%)	1,633 (0.78)	827 (1.79)	<0.001

Note: Numbers are given as median (full range) for discrete data, median (1st–3rd quartile) for continuous data, and *n* (% among ever and never users, respectively) for binary data. Note that percentages do not add up to 100% exactly due to some missing data in each specific variable.
[a]Wilcoxon rank sum test for quantitative traits and Pearson χ^2 test for binary traits.
[b]Body mass index.
[c]Townsend Deprivation Index.

Table 2. Oral contraceptive use on odds of cancer.

Covariate(s)	Breast, *n* (controls/cases)	Breast OR (95% CI), *P*	Ovarian, *n* (controls/cases)	Ovarian OR (95% CI), *P*	Endometrial, *n* (controls/cases)	Endometrial OR (95% CI), *P*
Univariate (no covariates)	238,951/17,710	0.80 (0.77–0.83), <0.001	254,703/1,958	0.58 (0.52–0.64), <0.001	254,201/2,460	0.43 (0.39–0.47), <0.001
Smoking	238,156/17,644	0.79 (0.76–0.82), <0.001	253,848/1,952	0.56 (0.51–0.62), <0.001	253,353/2,447	0.43 (0.39–0.47), <0.001
Age	238,951/17,710	1.01 (0.97–1.05), 0.76	254,703/1,958	0.71 (0.64–0.79), <0.001	254,201/2,460	0.59 (0.54–0.64), <0.001
Body mass index (BMI)	237,994/17,644	0.80 (0.77–0.83), <0.001	253,689/1,949	0.58 (0.52–0.64), <0.001	253,196/2,442	0.45 (0.41–0.48), <0.001
Townsend's deprivation index (TDI)	238,669/17,693	0.80 (0.77–0.83), <0.001	254,405/1,957	0.58 (0.52–0.64), <0.001	253,906/2,456	0.43 (0.39–0.47), <0.001
Year of birth (YOB)	238,951/17,710	1.01 (0.97–1.05), 0.67	254,703/1,958	0.71 (0.64–0.79), <0.001	254,201/2,460	0.59 (0.54–0.64), <0.001
Number of live births	238,811/17,699	0.80 (0.77–0.83), <0.001	254,553/1,957	0.58 (0.52–0.64), <0.001	254,051/2,459	0.43 (0.40–0.47), <0.001
Hormone replacement treatment (HRT)	238405/17,668	0.80 (0.77–0.83), <0.001	254,118/1,955	0.58 (0.52–0.64), <0.001	253,621/2,452	0.43 (0.40–0.47), <0.001
Hysterectomy	238,792/17,701	0.80 (0.77–0.84), <0.001	254,538/1,955	0.64 (0.58–0.71), <0.001	254,033/2,460	0.47 (0.44–0.52), <0.001
Had menopause	238,736/17,696	0.88 (0.85–0.91), <0.001	254,476/1,956	0.64 (0.58–0.71), <0.001	253,973/2,459	0.48 (0.45–0.53), <0.001
Age at menarche	232,224/17,252	0.80 (0.77–0.83), <0.001	247,576/1,900	0.57 (0.52–0.64), <0.001	247,093/2,383	0.43 (0.40–0.47), <0.001
Model 1[a]	230,283/17,111	1.00 (0.96–1.04), 0.85	245,510/1,884	0.70 (0.63–0.78), <0.001	245,046/2,348	0.62 (0.56–0.68), <0.001
Model 2[a]	230,032/17,095	0.97 (0.93–1.01), 0.11	245,247/1,880	0.69 (0.62–0.77), <0.001	244,780/2,347	0.61 (0.56–0.67), <0.001
Model 3[a]	229,924/17,086	0.98 (0.95–1.02), 0.44	245,131/1,879	0.72 (0.65–0.80), <0.001	244,664/2,346	0.64 (0.58–0.70), <0.001
Model 4[a]	229,447/17,056	1.02 (0.98–1.06), 0.41	244,626/1,877	0.72 (0.65–0.81), <0.001	244,164/2,339	0.68 (0.62–0.75), <0.001
Former vs. Never users[b]	225,161/16,905	1.02 (0.98–1.06), 0.38	240,195/1,871	0.72 (0.65–0.81), <0.001	239,735/2,331	0.68 (0.62–0.75), <0.001
Incidences after recruitment[c]	225,161/6,494	0.99 (0.93–1.06), 0.85	240,195/927	0.79 (0.67–0.93), 0.004	239,735/1,070	0.71 (0.62–0.82), <0.001

Note: Different sets of covariates included in the model. The covariate-specific models include the specified covariate, apart from the oral contraceptive use. The association is expressed as ORs and 95% CIs.
Abbreviation: *n*, number of controls/cases for each cancer.

[a]Model 1: Age, YOB, smoke, BMI, TDI, age at menarche. Model 2: Age, YOB, smoke, BMI, TDI, age at menarche, had menopause, had hysterectomy. Model 3: Age, YOB, smoke, BMI, TDI, age at menarche, had menopause, had hysterectomy, number of live births. Model 4: (full model): Age, YOB, smoke, BMI, TDI, age at menarche, had menopause, had hysterectomy, number of live births, hormone replacement therapy.

[b]Same as model 4, but current oral contraceptive users were excluded.

[c]Same as model 4, but all participants with a cancer prior to recruitment as well as current oral contraceptive users excluded.

Table 3. Oral contraceptive use on odds of breast, ovarian, and endometrial cancer for different follow-up ages.

Follow-up age	Current users (%)[a]	Breast cancer			Ovarian cancer			Endometrial cancer		
		Never users[b] (cont./cases)	Ever users[b] (cont./cases)	OR (95% CI), *P*	Never users[b] (cont./cases)	Ever users[b] (cont./cases)	OR (95% CI), *P*	Never users[b] (cont./cases)	Ever users[b] (cont./cases)	OR (95% CI), *P*
35	36.6%	48,203/33	179,359/238	1.53 (1.05–2.23), 0.026	48,205/31	179,498/99	0.65 (0.42–0.99), 0.046	48,206/30	179,493/104	1.16 (0.75–1.77), 0.505
40	19.5%	45,762/119	181,598/690	1.13 (0.92–1.38), 0.235	45,834/47	182,133/155	0.62 (0.44–0.88), 0.007	45,821/60	182,133/155	0.74 (0.54–1.02), 0.065
45	8.8%	44,830/307	181,576/1,739	1.10 (0.97–1.24), 0.155	45,065/72	183,078/237	0.61 (0.46–0.80), <0.001	45,053/84	183,092/223	0.72 (0.55–0.94), 0.015
50	3.1%	44,171/710	179,966/3,785	1.09 (1.01–1.19), 0.038	44,768/113	183,380/371	0.62 (0.50–0.78), <0.001	44,752/129	183,420/331	0.65 (0.52–0.81), <0.001
55	0.6%	43,506/1,321	177,528/6,392	1.10 (1.03–1.17), 0.004	44,643/184	183,370/550	0.61 (0.51–0.73), <0.001	44,609/218	183,383/537	0.63 (0.53–0.75), <0.001
60	0%	42,833/1,992	175,478/8,448	1.06 (1.01–1.12), 0.018	44,577/248	183,193/733	0.66 (0.57–0.77), <0.001	44,467/358	183,092/834	0.66 (0.58–0.75), <0.001
65	0%	42,149/2,676	173,654/10,272	1.05 (1.00–1.10), 0.039	44,508/317	182,976/950	0.75 (0.66–0.86), <0.001	44,304/521	182,842/1,084	0.64 (0.57–0.71), <0.001
70	0%	41,545/3,280	172,309/11,620	1.04 (1.00–1.09), 0.056	44,405/420	182,810/1,119	0.74 (0.66–0.83), <0.001	44,157/668	182,641/1,288	0.64 (0.58–0.71), <0.001
75	0%	41,222/3,603	171,844/12,086	1.02 (0.98–1.06), 0.347	44,323/502	182,721/1,209	0.72 (0.64–0.80), <0.001	44,059/766	182,553/1,377	0.63 (0.57–0.70), <0.001
80	0%	41,145/3,680	171,788/12,142	1.01 (0.97–1.05), 0.647	44,306/519	182,711/1,219	0.71 (0.64–0.79) <0.001	44,037/788	182,543/1,387	0.63 (0.57–0.69), <0.001

Note: Different follow-up ages were considered. For example, for a follow up age of 35 years, cases were defined as participants diagnosed with cancer at an age of 35 or before, while remaining participants were set as controls. Age, year of birth, smoking status, BMI, Townsend deprivation index, age at menarche were included as covariates in the models, which equals model 1 in the cumulative-risk analyses (see **Table 1**). The association is expressed as OR and 95% confidence interval (CI).

[a]Denotes the fraction of ever oral contraceptive users who still were using oral contraceptives at the specific follow-up age.

[b]Number of controls/cases for each cancer among never or ever users, respectively.

detection), could influence our results, we performed additional sensitivity analyses. For a cancer to develop, a number of mutations are normally required, and while some could have occurred during oral contraceptive use, others could have occurred after discontinuation. Also, we have no possibility to separate the induction and latency periods and we are therefore focusing on the empirical induction period (time from first exposure to diagnosis). In this analysis, we included women who had no prior diagnosis of the cancer under investigation at age of starting oral contraceptive use. Never users were assigned starting ages and age at discontinuation, by resampling (100 replicates) from the distribution of ages among ever users. Users and never users were then followed from starting oral contraceptive use to discontinuation and the cumulative incidence of the three cancers were compared between users and never users by logistic regression. The individuals were then followed an additional number of years after discontinuation, to allow for an extended empirical induction period, and the cumulative incidence of the three cancers were reestimated for each year of extension. In this analysis, year of birth, smoking status, age at menarche, TDI and number of live births were included as covariates.

All cancers were also analyzed by stratifying for duration of oral contraceptive use into six different intervals (<2, ≥2–<5, ≥5–<10, ≥10–<15, ≥15–<20, ≥20 years) and compared with never users (**Table 4**). *P* values lower than 0.00278 (0.05/3 cancers/6 duration intervals) were considered significant when analyzing the duration of oral contraceptive use intervals. Furthermore, to test for a trend in duration of oral contraceptive use, we estimated the linear association between years of duration and risk of developing cancer, by including "duration of use", in years, as a quantitative explanatory variable to the full model. Never users were excluded from this analysis. The *P* value for the estimate was taken as the P_{trend}.

In the instantaneous-risk analyses, we investigated cancer incidence, both during oral contraceptive use (during use) and after discontinuation of oral contraceptive use (after use), by Cox regression. Two different analyses were performed; one where time-independent HRs were estimated (proportional hazards modeling) and one where time dependence was explored by splitting the follow-up time in a number of time strata and the HR was estimated in each stratum (see Online Data Supplements). The same covariates were used in the survival analysis as in the logistic regression modeling (model 4), except for number of live births, which was excluded from the main survival analyses. This covariate was instead accounted for in one of the sensitivity analyses (see Online Data Supplements, Supplementary Fig. S1A–S1F). In all survival analyses, smoking, menopause, hysterectomy, and hormone replacement therapy were modeled as time-varying covariates (Online Data Supplements).

In the analyses for instantaneous risk during oral contraceptive use, age at entry was defined as age at first use of oral contraceptives. Follow-up time was used as primary time scale and was defined as the time between age at entry (first use) and age at last use, or age at the initial visit to the assessment center, whichever came first. In the analysis of cancer incidence after use, age at entry was instead defined as age when oral contraceptive use was discontinued (last use) and follow-up time was defined as the time between last use and age at initial visit to the assessment center. In these analyses, we only used self-reported age of first cancer diagnosis since the registry data is less complete before 1995, and most women in UKB started oral contraceptive use before that year. Ages of first cancer diagnosis are given as interpolated ages in data-field 20007. These data were accurate and nearly in parity with registry data, with an absolute median difference less than 0.05 years and an interquartile range of the difference of

Table 4. Duration of oral contraceptive use on odds of having been diagnosed with cancer.

Duration of use (N[a])	Breast cancer N (controls/cases)	Breast cancer OR (95% CI), P[b]	Ovarian cancer N (controls/cases)	Ovarian cancer OR (95% CI), P[b]	Endometrial cancer N (controls/cases)	Endometrial cancer OR (95% CI), P[b]
<2 year (N = 19,891)	60,184/5,158	1.01 (0.95–1.08), 0.70	64,634/708	0.84 (0.70–1.00), 0.055	64,289/1,053	0.80 (0.69–0.93), 0.0037
≥2-<5 years (N = 27,907)	67,654/5,704	1.07 (1.00–1.13), 0.037	72,586/772	0.89 (0.75–1.04), 0.15	72,265/1,093	**0.74 (0.64–0.86), <0.001**
≥5-<10 years (N = 46,049)	84,755/6,745	1.01 (0.96–1.07), 0.69	90,631/869	**0.79 (0.68–0.92), 0.0018**	90,294/1,206	**0.71 (0.62–0.81), <0.001**
≥10-<15 years (N = 39,615)	78,778/6,288	1.03 (0.97–1.09), 0.29	84,309/757	**0.63 (0.53–0.75), <0.001**	83,989/1,077	**0.59 (0.51–0.69), <0.001**
≥ 15-<20 years (N = 23,571)	63,813/5,209	1.03 (0.96–1.11), 0.35	68,372/650	**0.55 (0.44–0.68), <0.001**	68,080/942	**0.52 (0.42–0.63), <0.001**
≥20 years (N = 28,077)	68,153/5,375	1.04 (0.97–1.12), 0.27	72,866/662	**0.60 (0.48–0.75), <0.001**	72,616/912	**0.36 (0.28–0.45), <0.001**

Note: The table shows the ORs, and 95% CIs, and for subgroups of ever users with different years of duration of use, compared with never users (N = 45,451) using the full model (model 4). The odds of duration (in years) were also estimated for all 185 510 ever users, using the same covariates as in the full model (model 4) on breast cancer: OR = 1.000 (95% CI = 0.998–1.002), P = 0.96, ovarian cancer: OR = 0.979 (95% CI = 0.971–0.987), P < 0.001, and endometrial cancer: OR = 0.971 (95% CI = 0. 963–0.978), P < 0.001.

[a]N denotes the number of users within the specific duration-of-use interval who were included in the analyses (had all covariate data available). The never users (N = 45,451 with covariate data available) were the same in all comparisons.

[b]P values in bold are significant after adjusting for multiple testing using Bonferroni method (3 diseases × 6 tests; P < 0.0028).

0.6 years for all three cancers (Supplementary Fig. S2A–S2C). The interpolated ages at diagnosis were rounded off downwards to enable comparison with, for example, age at entry (age of first/last use). In the during-use analyses, participants who reported that they were diagnosed with the cancer under investigation before age at first oral contraceptive use, were excluded from the analyses, while diagnoses between, and including age of first use and age of last use were considered as events. In the after-use analyses, however, cancer cases were only counted as events when occurred between one year after discontinuing oral contraceptive use and the assessment when entering UKB, to minimize the risk of reversed causation. Participants who did not develop cancer during the follow-up time were censored. All statistical tests were two-sided.

Power calculations for the OR were performed using the normal approximation, where the power is given by

$$1-\beta=\Phi\left(z-\Phi^{-1}(1-\alpha/2)\right)+\Phi\left(-z-\Phi^{-1}(1-\alpha/2)\right).$$

Here, $\Phi(.)$ denotes the standard normal cumulative distribution function, $\Phi^{-1}(.)$ denotes its inverse, and $\alpha = 0.05$ is the significance level. The z-statistic is given by

$$z=\frac{\log(\mathrm{OR})\sqrt{n_{\mathrm{never}}}}{\sqrt{\frac{1}{\kappa p_{\mathrm{ever}}(1-p_{\mathrm{ever}})}+\frac{1}{p_{\mathrm{never}}(1-p_{\mathrm{ever}})}}},$$

where p_{never} and p_{ever} are the fractions of cases in never and ever users, respectively, n_{never} is the number of never users, and κ is the ratio of the number of ever to never users. In the generic calculations (Supplementary Fig. S3), we simply assumed a fixed number of controls, with the number of controls for ever users being 200,000 and the number of controls for never users being 50,000.

Results

A total of 256,661 women were included in this study. Of these, 210,443 (82%) had used or were still using oral contraceptives and were designated as ever users, while 46,218 (18%) had never used oral contraceptives and were designated as never users. Among ever users, 4,659 women reported to be current users. Compared with never users, ever users were younger, more frequently smokers, had a lower BMI, as well as lower TDI (higher socioeconomic status), and were less likely to have gone through menopause (**Table 1**). The only variable tested that did not differ between ever and never users was age at menarche. Most women were postmenopausal, but a significant fraction was unsure about their menopausal status. However, a comparison between the age distribution at recruitment for women being unsure about menopausal status and the age distribution of last menstrual period for postmenopausal women (Supplementary Fig. S4), suggests that women unsure about their status were likely to be close to enter menopause at recruitment.

The total number of cancer cases identified in the study was 17,739 (6.9%), 1,966 (0.76%), and 2,462 (0.96%) for breast, ovarian and endometrial cancer, respectively. With these numbers, we should have 80% power to detect an effect of OR = 1.06, 1.18, and 1.16 for the three cancers, respectively. The number of cases is significantly higher among never oral contraceptive users, as compared with ever users, which can predominantly be explained by never users having a higher median age (**Table 1**). The cancer incidences in the UKB females included in this study were similar to the incidence in UK women in general (**Fig. 1A–C**). Most women started oral contraceptive use at young age (1st–3rd quartile = 18–24; **Fig. 1D**), and year at first use primarily occurred

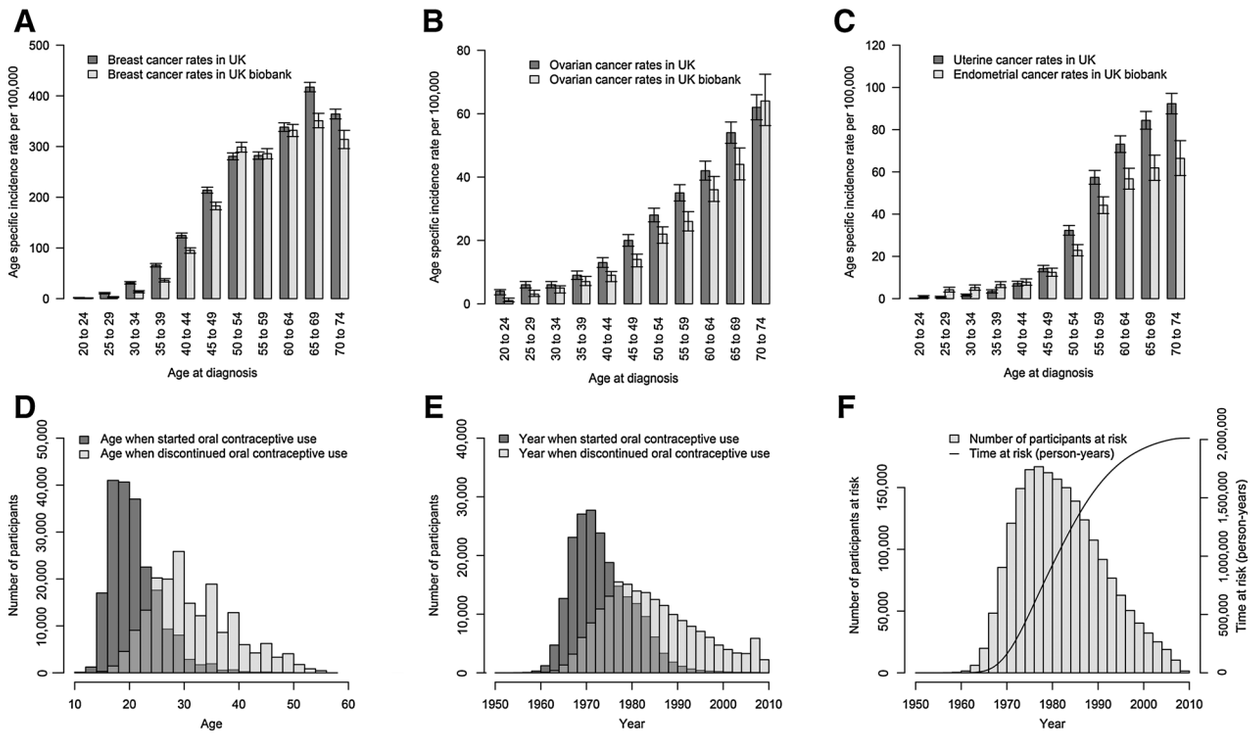

Figure 1.

Incidence rates of cancers and the pattern of oral contraceptive use in UKB. Age specific incidence rates for breast (**A**), ovarian (**B**), and endometrial cancer (**C**) in the UKB females (light gray), as compared with all women in UK (dark gray). UKB female incidence rate is estimated from females in UKB who were diagnosed (first diagnosis) within a certain age interval. UKB diagnoses are based on self-reported information as well as cancer/cause of death/in hospital registry data (ICD-9/10). UK female rates are statistics for all women in UK who were first diagnosed between 2015–2017 according to Cancer Research UK (https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk, accessed April 2020), which is based on cancer registry data (ICD-10). Endometrial cancer (ICD-10 C541) in UKB is compared with a somewhat broader definition of uterine cancer among all UK women (ICD-10 C54/C55). The 95% CIs for the incidence rates were estimated from an empirical Poisson ratio distribution, based on 1,000,000 simulations. The pattern of oral contraceptive use in UKB shows: the distribution of start and stop ages (**D**), the distribution of start and stop calendar years (**E**), and the total number of person-years of oral contraceptive use per year (bars) and the cumulative number of person-years (**F**), that is, the total time of exposure to oral contraceptives (time at risk) up to a given calendar year (line). The total time at risk is 2.01 million person-years for oral contraceptive users in the UKB. For **D**–**F**, CIs were too narrow to be clearly visible, and were omitted.

between 1969 and 1978 (1st–3rd quartile; **Fig. 1E**). The distributions of age/year when stopping were broader and last use of oral contraceptives occurred on average 10.7 years after first use. Already in 1982, more than 50% of the total person-time of exposure to oral contraceptives was reached in the UKB (**Fig. 1F**).

Assessing cumulative risk

Each cancer was influenced by a number of covariates (Supplementary Table S3), which we adjusted for in our analyses (**Table 2**). The full model (model 4), showed that the odds for developing ovarian and endometrial cancer (OR = 0.72; 95% CI, 0.65–0.81 and OR = 0.68; 95% CI, 0.62–0.75, respectively), were lower among ever compared with never users. However, we did not see a significant association between oral contraceptive use and breast cancer (OR = 1.02; 95% CI, 0.98–1.06). In the sensitivity analysis, in which only cases diagnosed after recruitment were included (**Table 2**), the results were very similar, even if the negative association to ovarian cancer was slightly weaker (OR = 0.81; 95% CI, 0.69–0.97). When considering different follow-up ages (**Table 3**), the ORs for endometrial and ovarian cancer were quite similar to the main logistic analyses. For breast cancer, however, the OR was significantly greater than one for several follow-up ages, for example, OR = 1.10 (95% CI, 1.03–1.17) with a follow-up until 55 years of age.

Duration of oral contraceptive use

A total of 187,057 ever users had reported both a start and stop date for oral contraceptive use, of which 185,110 also had covariate data available and were included when analyzing duration of oral contraceptive use. Among these, the duration of use was on average 10.7 years (median: 9 years, and ranging from 1 to 48 years). ORs were estimated for participants in a number of duration-of-use intervals in relation to never users (**Fig. 2**; **Table 4**). Long-term oral contraceptive use was associated with substantially lower odds of ovarian and endometrial cancers, with ORs of 0.60 (95% CI, 0.48–0.75) and 0.36 (95% CI, 0.28–0.45), respectively, in women who had been using oral contraceptives for at least 20 years. A significant trend ($P < 0.001$) with duration of use was also found, for both ovarian and endometrial cancer (**Fig. 2**; **Table 4**). In contrast, no significant trend with duration of use was observed for breast cancer. Duration was estimated as the number of years between first and last use of oral contraceptives. Especially, women that have given birth are likely to have had an interruption in their oral contraceptive use. We therefore

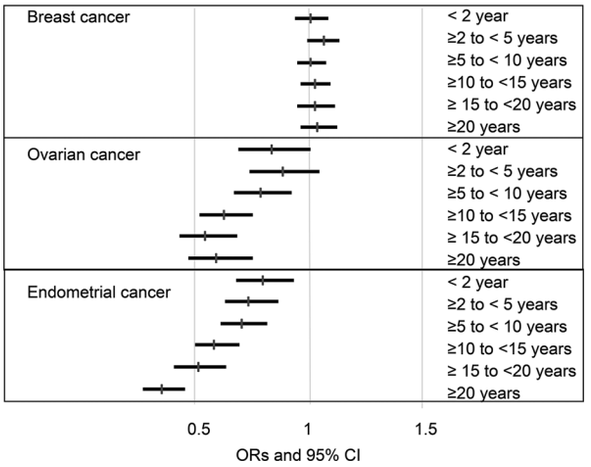

Figure 2.

ORs and 95% CIs for duration of oral contraceptive use subgroups compared with never users. All estimates are adjusted for covariates included in the full model (model 4): age, year of birth, smoking, BMI, and TDI, number of live births, age at menarche, hormone replacement therapy, as well as menopausal and hysterectomy status. Each extra year of oral contraceptive use decreased the odds of ovarian and endometrial cancer, such that OR = 0.98 (95% CI, 0.97–0.99), and OR = 0.97 (95% CI, 0.96–0.98), respectively.

also estimated the odds of the length of duration in women that had no live births, with slightly larger odds for ovarian (OR = 0.961; 0.945- 0.977) and endometrial cancer (OR = 0.967; 95% CI, 0.951–0.982) per year of oral contraceptive use, but with similar results for breast cancer.

Empirical induction period

We investigated the cumulative cancer incidence during oral contraceptive use when an additional follow-up time was added after the oral contraceptive discontinuation. There was a tendency (Supplementary Fig. S5) of an increased odds for all cancers, during the second additional years of follow-up, after discontinuation. For breast cancer, no significant difference in odds was observed between never users and users when followed to age of discontinuation. However, by including an additional year of follow-up to the model, the OR increased to 1.30 (95% CI, 1.04–1.61). The higher odds for breast cancer among current and recent users did not start to decrease until eight years after discontinuation. This could agree with an average empirical induction period of up to eight years for breast cancer. For ovarian, but even more pronounced for endometrial cancer, the OR appeared to decrease for more than 20 years after discontinuation, which would suggest long empirical induction periods for ovarian and endometrial cancer.

Assessing instantaneous risk

Since logistic regression analysis is a cumulative assessment of risk and does not separate between events occurring during or after discontinued use, we also performed a number of analyses using Cox regression modeling assessing instantaneous risk. During use, both ovarian and endometrial cancer showed a negative association in most time strata (**Fig. 3C** and **E**), which agrees with our cumulative-risk analyses. The time-independent HR during use (Supplementary Table S4) was lower for ovarian cancer (HR = 0.46; 95% CI, 0.26–0.85) than for endometrial cancer (HR = 0.74; 95% CI, 0.45–1.23), results that were consistent in all sensitivity analyses (Supplementary Fig. S1C and S1E; Supplementary Table S5). However, it should be highlighted that the majority of cancer incidences occur later in life (**Fig. 1A–C**), and, therefore, the number of events during oral contraceptive use was small for ovarian ($N = 68$) and endometrial cancer ($N = 102$), which limits the power in these analyses (Supplementary Fig. S3). In the time-dependent analyses, there was a tendency of lower hazard rate among oral contraceptive users, also for breast cancer (**Fig. 3A**). This effect was found to be strongest directly after initiating oral contraceptive use, but appeared to weaken after many years of use (**Fig. 3A**; Supplementary Table S6).

After discontinuation of use, we identified a HR significantly below one in the time-independent analyses, for both ovarian (HR = 0.62; 95% CI, 0.52–0.75) and endometrial cancer (HR = 0.61; 95% CI, 0.52–0.71), but not for breast cancer (**Fig. 3B**, **D**, and **F**; Supplementary Table S4). In a sensitivity analysis, we found no evidence of any modifications due to age (Supplementary Table S5). This suggests that the linear adjustment for age at entry is adequate in our analyses. Immediately after discontinuation of oral contraceptive use, the time-dependent HR was above one for all cancers (Supplementary Table S7), although only significantly larger than one for breast (**Fig. 3B**) cancer (time-dependent HR = 1.55; 95% CI, 1.06–2.28). For ovarian (**Fig. 3D**) and endometrial (**Fig. 3F**) cancer, the HR decreased to reach values significantly below one, already 5–10 years after discontinuation of use. This negative association was statistically significant in most time strata up to 30 and 35 years after last use, in ovarian and endometrial cancer, respectively (Supplementary Table S7). HR also decreased with time for breast cancer, and five years after discontinuation of use, there was no sign of an increase in hazard rate for previous oral contraceptive users (Supplementary Table S7; **Fig. 3B**). None of these results changed notably in any of the sensitivity analyses (Supplementary Fig. S1A–S1F).

Discussion

We have performed one of the most comprehensive studies, so far, investigating the short- and long-term associations between oral contraceptive use and breast, ovarian, and endometrial cancer. While some of our results support earlier findings, parts of our results are novel with regards to what have been reported previously. Notably, we have a much longer follow up compared with most previous studies, clearly indicating that oral contraceptive use gives a protective effect against ovarian and endometrial cancers up to 30–35 years after discontinuation. We have also shown that the association between oral contraceptive use and breast cancer is time and age dependent, which can explain inconsistencies in the previously reported results for breast cancer, when different study designs have been used.

Oral contraceptive use was associated with lower odds of ovarian and endometrial cancer, which is consistent with previous findings (6). It is also evident with longer duration of use, the odds decreased, especially for endometrial cancer. Thanks to the retrospective study design, we could identify a large number of women with over 20 years of use, and in this group the OR for endometrial cancer was as low as 0.36 compared with never users, which indicates a stronger protective effect compared to what has been indicated in previous studies (8). The lower incidence rate for endometrial cancer among oral contraceptive users, appears to be constant during the period of use, which results in a very strong cumulative odds of cancer with a long duration of use. In contrast, the lower incidence rate for ovarian cancer appears to be more pronounced in the beginning of the use, and extrapolating from

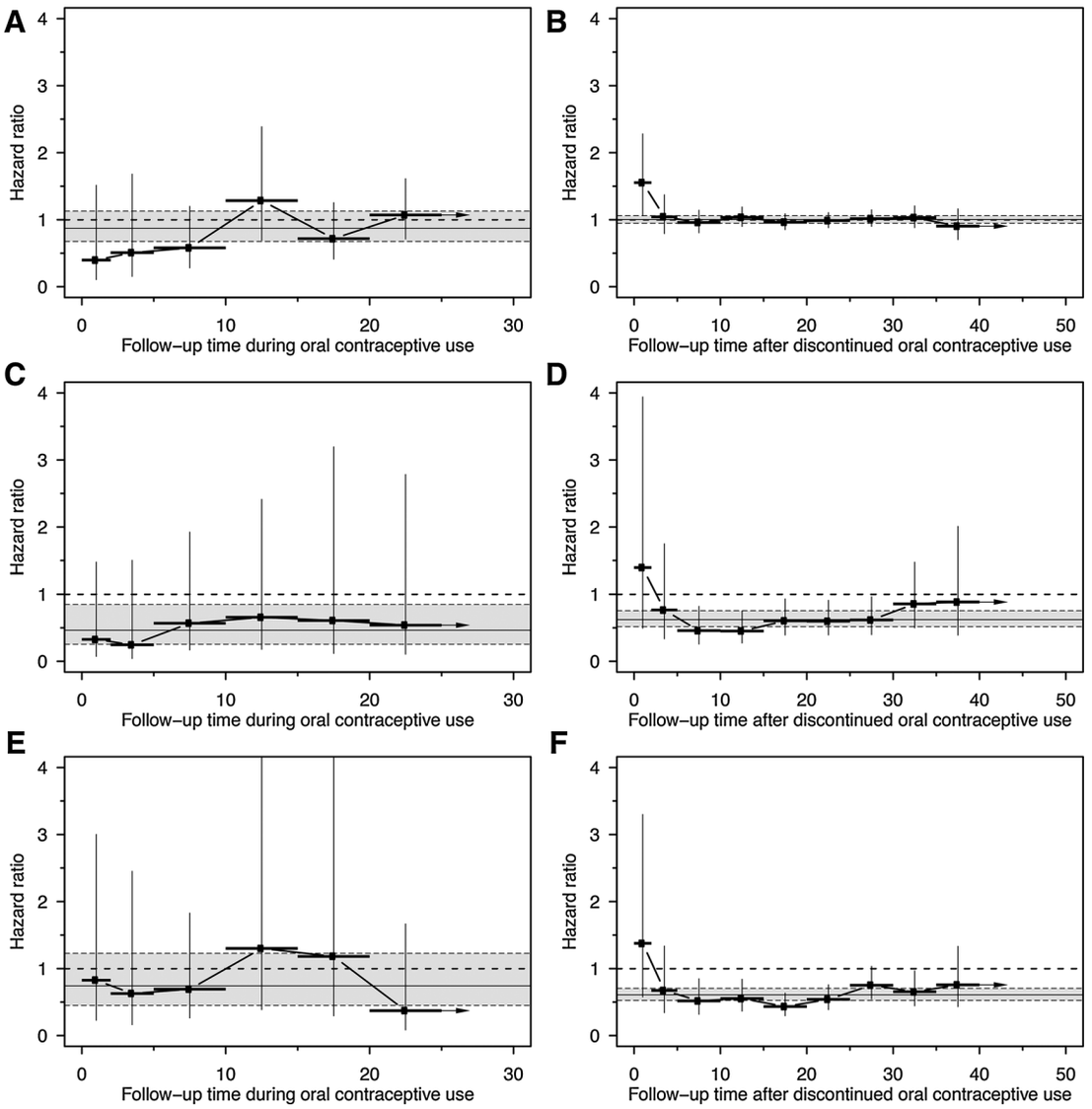

Figure 3.

Time-dependent HR of oral contraceptives during use (**A, C,** and **E**) and after discontinued use (**B, D** and **E**) for breast cancer (**A** and **B**), ovarian cancer (**C** and **D**), and endometrial cancer (**E** and **F**). The solid, black line, and gray area indicates the time-independent HR with its 95% CI, respectively. The points are the time-dependent HR with its 95% CI as vertical lines. The thick horizontal bars represent the time strata that are contributing to each point. For example, the HR in the first time point in **A** is estimated from all participants who developed breast cancer (events) within two years after first use of oral contraceptives, as indicated by the thick horizontal bar ranging from 0 to 2 years.

the data, one could speculate that after 30 years of oral contraceptive use, one more year does not add more protection against ovarian cancer. This agrees with the duration of interval analyses, where the lower odds among ever users are of similar magnitude in all groups of users with a duration of more than 10 years. Previous studies have estimated the empirical induction period for ovarian cancer to be more than 15–20 years (9) and for endometrial cancer to be on average 14 years (9). However, our results rather suggest a longer empirical induction period for endometrial cancer. It has been suggested that the higher cancer incidence rate in older women, might dilute an estimated risk ratio (2). There is a clear difference in age-specific incidence rate between ovarian and endometrial cancer, where the risk for endometrial cancer increases very dramatically between age of 45 to 65 years, while the risk for ovarian cancer appears to increase more rapidly at a higher age. Therefore, it is possible that we do not capture the long-term effects of oral contraceptive use on ovarian cancer to the same degree as for endometrial cancer.

In our primary cumulative-risk analyses, we did not observe an association of oral contraceptive use on breast cancer, despite over 17,000 breast cancer cases in our study, which should provide adequate power to detect an OR of 1.06. However, most previous studies have concluded that users of oral contraceptives have an increased risk for breast cancer, both during use and shortly after discontinuation (2, 3). One of the largest studies performed to date on oral contraceptive use

and breast cancer risk, with over 13,000 cancer incidences, was performed in a Danish cohort where almost 2 million women, 15–49 years of age, were followed over 10 years on average (3). The study found an increased risk of breast cancer in both current and in previous oral contraceptive users, compared with never users. When women were followed until 50 years of age in our study, we obtained an OR of 1.09, which better agrees with an increased cumulative risk. This suggests that lifetime risk of breast cancer might not differ between ever and never users, even if there is an increased short-term risk. This also agrees with two previous studies where women were followed-up to a higher age (5, 10), and where no increased risk associated with oral contraceptive use was seen. UKB participants included in our study, predominantly started to use oral contraceptives between the late 60s and the late 70s compared with, for example, the Danish study that started in 1995 (3). Oral contraceptives include both estrogen and progestin and are roughly divided into four generations based on their type of progesterone. Until the 70s, only the first generation of progestins (Norethisterone) was available. The second-generation progestin Levonorgestrel was introduced in 1970 (11), first with higher estradiol levels, but in 1974 (12) with the lower dose that is more commonly used today. In the Danish study, women were using oral contraceptives, mainly based on the second and third generation of progestins in combination with a lower estradiol dose (3). However, oral contraceptives containing only Norethisterone, or Norethisterone in combination with high estradiol levels (50 μg), did not show an increased risk for breast cancer in the Danish study. Hence, the difference in results between studies can partly also be attributed to the frequency of different types of oral contraceptives. In addition, the patterns of oral contraceptive use have changed since the 1970s and 1980s, such that the age at which women start has decreased, and consequently the number of years of use before the first pregnancy has increased. Such differences in the pattern of use may also have an impact on the risk of cancer.

It has been suggested that a decreased risk for ovarian and endometrial cancer is most probably due to the ovulations being prevented in oral contraceptive users. This effect would be achieved by contraceptives inhibiting gonadotropin secretion both at the level of the pituitary gland and the hypothalamus (13). Follicle stimulating hormone, which is a type of gonadotropin, is directly inhibited by the estrogen component in oral contraceptives, limiting the development of the follicles. The progestin component of oral contraceptive pills prevents the rise in luteinizing hormone, another gonadotropin, which normally triggers ovulation (14). Hormone levels increase dramatically during ovulation, including the levels of estrogen and progesterone. These hormones also regulate growth and differentiation of many tissues (15), and it is therefore likely that the increase in hormones during ovulation triggers cancer development. However, a protective effect, as a result of fewer ovulations, does not rule out additional modifying effects by the exogenous hormones from the pills. It is possible that the endogenous hormones also directly influence tumor development (13). Therefore, the protective effect of fewer ovulations caused by oral contraceptives might be weakened by its hormone content. For example, about 80% of all breast cancers are hormone dependent (16), where cells grow in response to estrogen or progesterone. Thereby, oral contraceptive use could also shorten the latency period, at least for breast cancer, which has been suggested in previous studies (7). In our study, we did see an increased hazard of breast cancer, primarily after oral contraceptive discontinuation, an association that rapidly declined toward null, and no difference in cumulative breast cancer risk was seen when participants were followed up to 2019. This agrees with that our results reflect a shorter latency period for breast cancer in oral contraceptive users, rather than a larger lifetime risk, compared with never users.

There are some possible limitations of our study design. Most importantly, only 6% of participants who were invited to UKB volunteered to participate in the study. This might lead to participation bias within the cohort, toward a healthier cohort, not representative of the underlying population. However, a recent study (17) that compared risk factor-disease estimations in UKB with those from 18 nationally representative studies with conventional response rates showed that there were more favorable levels of baseline characteristics and disease specific mortality in UKB, but that etiologic findings from UKB are generalizable to England and Scotland. We also showed a comparable incidence rate between cancers in UBK compared with UK in general. In addition, our sensitivity analyses only including cancer incidences after recruitment, showed highly similar result to the primary analyses, indicating that selection bias is not a major problem in our analyses. It is also important to consider that oral contraceptives have changed over the years. Today, most oral contraceptive users take lower doses of estrogen and other types of progesterone, as compared with formulas in the preparations commonly used in the 1960s and 70s, when many of the participants in the UKB started using oral contraceptives. Our results may therefore not directly be applicable to the oral contraceptives that are commonly used today, but should be important for future drug development of cancer prevention and of new types of contraceptives.

In summary, we identified associations between oral contraceptive use and breast, ovarian, and endometrial cancer and found that these effects are both age, and time dependent. Among oral contraceptive users, the odds were lower for both ovarian and endometrial cancer, compared with never users, an effect that extended for decades after discontinuation of use. The association with lower risk was particularly prolonged for endometrial cancer, which is consistent with this cancer type being associated with number of ovulations (18). In contrast, the highest odds for breast cancer appeared to occur in association with discontinuation of oral contraceptive use, which could possibly be explained by a shorter empirical induction period in oral contraceptive users. Given the large number of women currently using oral contraceptives, it is essential to understand both short, and long-term effects of exposure to exogenous hormones. A deeper knowledge will enable both women and physicians to make more informed decisions with regards to oral contraceptive use. Decisions may also be based on a woman's individual risk factors or on family and previous history of cancers, and thus constitute an important step toward personalized medicine.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

T. Karlsson: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **T. Johansson:** Data curation, formal analysis, writing-original draft, writing-review and editing. **J. Höglund:** Formal analysis, supervision, writing-review and editing. **W.E. Ek:** Conceptualization, formal analysis, supervision, funding acquisition, investigation, methodology, writing-original draft, writing-review and editing. **Å. Johansson:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing.

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