GYNECOLOGY

Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study

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BACKGROUND: Oral contraceptives have been used by hundreds of millions of women around the world. Important questions remain regarding the very long-term cancer risks that are associated with oral contraception. Despite previous research, important questions remain about the safety of these contraceptives: (1) How long do endometrial, ovarian, and colorectal cancer benefits persist? (2) Does combined oral contraceptive use during the reproductive years produce new cancer risks later in life? (3) What is the overall balance of cancer among past users as they enter the later stages of their lives?

OBJECTIVES: The purpose of this study was to examine the very long-term cancer risks or benefits associated with the use of combined oral contraceptives, including the estimated overall life-time balance.

STUDY DESIGN: The 46,022 women who were recruited to the UK Royal College of General Practitioners' Oral Contraception Study in 1968 and 1969 were observed for up to 44 years. Directly standardized rates of specific and any cancer were calculated for "ever" and "never" users of combined oral contraceptives; data were standardized for age, parity, social class, and smoking. Attributable risk and preventive fraction percentages were calculated. Poisson regression that adjusted for the same variables was used to estimate incidence rate ratios between ever and never users and to examine effects by time since last oral contraceptive use.

RESULTS: There were 4661 ever users with at least 1 cancer during 884,895 woman-years of observation and 2341 never users with at least 1 cancer during 388,505 woman-years of observation. Ever use of oral contraceptives was associated with reduced colorectal (incidence rate ratio, 0.81; 99% confidence interval, 0.66—0.99), endometrial (incidence rate ratio, 0.66; 99% confidence interval, 0.48—0.89), ovarian (incidence rate ratio, 0.67; 99% confidence interval, 0.50—0.89), and lymphatic and hematopoietic cancer (incidence rate ratio, 0.74; 99% confidence interval, 0.58—0.94). An increased risk of lung cancer was seen only among ever users who smoked at recruitment. An increased risk of breast and cervical cancer that was seen in current and recent users appeared to be lost within approximately 5 years of stopping oral contraception, with no evidence of either cancer recurring at increased risk in ever users with time. There was no evidence of new cancer risks appearing later in life among women who had used oral contraceptives. Thus, the overall balance of cancer risk among past users of oral contraceptives was neutral with the increased risks counterbalanced by the endometrial, ovarian, and colorectal cancer benefits that persist at least 30 years.

CONCLUSION: Most women who choose to use oral contraceptives do not expose themselves to long-term cancer harms; instead, with some cancers, many women benefit from important reductions of risk that persist for many years after stopping.

Key words: cancer, cohort study, oral contraception

Since its introduction, first in the United States in 1960,[1] combined oral contraceptives have been used by hundreds of millions of women around the world. Today, it is estimated that 100—150 million women use this contraceptive method on a daily basis.[2] Concerns were expressed early on about the method's carcinogenic potential.[1] Cancer was of particular concern, given the likely high level of usage and the 11—22% lifetime cancer risk among women living in different parts of the world.[3] These concerns and frequent media scares have left many women wondering whether they have exposed themsleves to long-term harm by using this method of contraception.

There have been many, mostly case-control, studies that have looked at combined oral contraception and different types of cancer. Collectively, the evidence suggests that current and recent users of combined oral contraceptives have an increased risk of breast and cervical cancer and that long-term users in regions at low risk of hepatitis B virus may have an increased risk of liver cancer.[4] Conversely, users of combined oral contraceptives appear to have a reduced risk of endometrial and ovarian cancer, which is an effect that appears to persist for many years after stopping. Current users of combined oral contraceptives also appear to be protected from colorectal cancer, with uncertainty about the length of protection after stopping.

Even with this extensive body of evidence important questions remain: (1) How long do the endometrial, ovarian, and colorectal cancers benefits persist? (2) Does combined oral contraceptive use during the reproductive years produce new cancer risks that emerge later in life? (3) What is the overall balance of cancer among past users of combined oral contraceptives as they enter the later stages of their lives? These questions are best answered by large-scale, population-based studies with the prospective collection of exposure information and very long-term follow-up. We report here results from 44 years of follow up of the Royal College of General Practitioners' Oral Contraception Study, the

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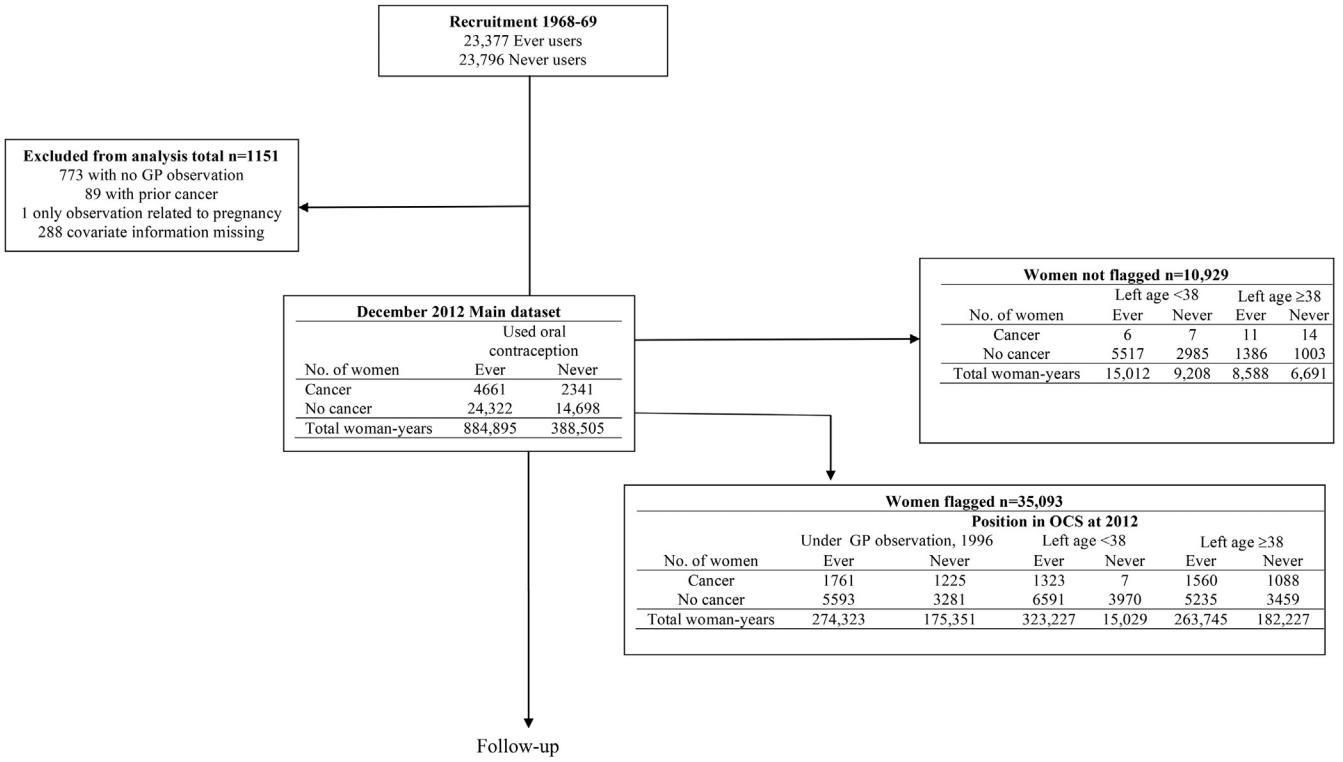
FIGURE
Flowchart of the Royal College of General Practitioners' Oral Contraception Study



The follow-up plan of the Royal College of General Practitioner's Oral Contraception Study from recruitment in 1968–1969 to December 2012 is shown.

GP, general practitioner; *OCS*, oral contraception study.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

longest running study of the health effects of oral contraception in the world.

Materials and Methods

Between May 1968 and July 1969, 1400 general practitioners (GPs) throughout the United Kingdom recruited approximately 23,000 women who were using oral contraceptives and 23,000 women who had never used this method of contraception.[5] All women were married or co-habiting; most were white, and their mean age at recruitment was 29 years. Information collected at recruitment included previous use of oral contraception, smoking habits, social class (based on partner's occupation according to the Registrar General's 1966 Classification of Occupations[6]), parity, and significant medical history. Women remained under GP follow up until (1) they were no longer registered with the recruiting doctor (usually because the woman moved away; approximately 56% of total cohort), (2) their doctor left the study (13%), (3) they obtained contraceptives from another source (3%), (4) they died (2%), or (5) GP follow up stopped in December 1996 (26%). While under GP follow up, GPs provided, on a 6-monthly report form, information about any hormonal preparations prescribed, any pregnancies, new episodes of illness or surgery, and cause of death. All GP-supplied information was coded by a team of trained clerks, with queries returned to the GPs for clarification wherever necessary.

In the mid 1970s, approximately three-quarters of the cohort was "flagged" at National Health Service central registries in Scotland and England. This enabled subsequent cancers and deaths that occurred among flagged women to be reported to the study anonymously, including after women left GP follow up. The other one-quarter could not be flagged because the women already had left the study when flagging occurred.

We used the GP-supplied data to determine each woman's pill status and her contribution to the analysis. Most women in the study (91%) who used oral contraceptives did so before age 38 years. Ever users were women who were recruited as takers and subsequently prescribed oral contraception (nearly always a combined estrogen and progestogen preparation). For each calendar month that a woman used an oral contraceptive, 1 month was added to the period of observation (denominator) of ever users, as were periods after stopping. Women who were recruited as never users who subsequently were prescribed an oral contraceptive were included in the ever user group from the month of prescription. Never users who were lost to GP follow up before 1996

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and were aged <38 years when lost contributed data (as never users) up to the point of their loss before being censored because of uncertainty about whether they subsequently used oral contraceptives. Never users who were lost to GP follow up before 1996 and were aged ≥38 years when lost were likely to remain never users and so continued to make a contribution to the never user group if flagged (otherwise they were censored at this point). Never users who were still in the study when GP follow up stopped in 1996 were deemed unlikely to change pill status and remained in the analysis. For a small number of ever users (2,690/28,983; 9.3%), we did not have a stop date notified by the GP. For these women, we assumed oral contraceptive usage stopped 1 year after the last recorded prescription. The effect of this assumption was to underestimate time slightly since stopping if a woman used oral contraception for <12 months after the last recorded prescription and to overestimate it if used for a longer period.

The analysis included cancers and periods of observation up to (1) the date of first relevant cancer or the date that the women left the study for all nonflagged women and flagged never users who were lost from the study before 1996 and aged <38 years when lost and (2) the date of relevant cancer or December 31, 2012, for all flagged women still under GP observation at December 1996, for flagged never users who were lost before 1996 and aged ≥38 years when lost, and for flagged ever users who were lost from the study before 1996 (Figure 1). Most cancers were notified through flagging by the central registries (ie, 5467/7002 [78%] of all cancers).

The cancers were coded according to the International Classification of Diseases, 8th revision[7] grouped into categories: esophagus and stomach (code 150-151), colon and rectum (153-154), gallbladder and liver (155-156), pancreas (157), lung (162), skin-melanoma (172), skin-other (173), breast (174), invasive cervix (180), endometrium (182), ovary (183), bladder and kidney (188-189), central nervous system and pituitary (191 and 1943), thyroid (193), site unknown (199), lymphatic and hematopoietic (200-208), other cancers (any code between 140-209 not already mentioned); and any cancer (140-209). If a discrepancy in event type or date occurred between GP and registry notification, clarification was sought from the GP whenever possible. If this was not possible, the GP-supplied information was used, because this was likely to be most accurate because it was often based on hospital-supplied information.

Direct standardization was used to estimate the rates of cancer among ever and never users. The standardization variables for the total study population were age (<30, 30–39, 40–49, 50–59, 60–69, ≥70 years), parity (0, 1, 2, ≥3) at the time of the event, smoking (0, 1–14, ≥15 cigarettes daily), and social class (nonmanual: social classes I-IIIa [professional, managerial & technical and skilled non-manual occupations] and students; manual: social classes IIIb-V [skilled, partly-skilled manual occupations and unskilled occupations] and armed forces) at recruitment. Poisson regression was used to estimate the incidence rate ratio (IRR) and its 99% confidence interval (CI) for ever vs never users for each of the cancer types, adjusted for the same categories of age, parity, smoking, and social class as mentioned earlier. The exception was when we stratified the data by a particular variable (eg, smoking habits at recruitment), when we adjusted the IRRs for the other 3 variables. We calculated 99% CIs to allow for the large number of comparisons, which indicated statistical significance at the 1% level.

We excluded women who were known to have the cancer before recruitment and events and periods of observation related to pregnancy. Only first events in each cancer category were included;

TABLE 1
Characteristics of "ever" and "never" users of oral contraception at recruitment to the Royal College of General Practitioners' Oral Contraception Study

Characteristic	Ever users (n=22,920)	Never users (n=23,102)	All (n=46,022)
Age (y), n (%)			
<30	13,701 (59.8)	13,521 (58.5)	27,222 (59.2)
30–39	7,553 (33.0)	7,725 (33.4)	15,278 (33.2)
≥40	1,666 (7.2)	1,856 (8.1)	3,522 (7.6)
Age at recruitment, y[a]	28.5±6.7	29.0±6.5	28.8±6.6
Cigarettes smoked, n (%)			
0	11,904 (51.9)	13,569 (58.7)	25,473 (55.4)
1–14	6,261 (27.3)	5,900 (25.5)	12,161 (26.4)
≥15	4,755 (20.8)	3,633 (15.7)	8,388 (18.2)
Parity, n (%)			
0	3,401 (14.8)	4,881 (21.1)	8,282 (18.0)
1	4,520 (19.7)	6,476 (28.0)	10,996 (23.9)
2	7,543 (32.9)	7,157 (31.0)	14,700 (31.9)
≥3	7,456 (32.5)	4,588 (19.9)	12,044 (26.2)
Mean[a]	2.1 (0.9)	2.0 (0.9)	2.1 (0.9)
Social class, n (%)			
Nonmanual	8,585 (37.5)	8,417 (36.4)	17,002 (36.9)
Manual	14,335 (62.5)	14,685 (63.6)	29,020 (63.1)

[a] Data are given as mean±standard deviation.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

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TABLE 2
Risk of cancer among "ever" and "never" users of oral contraceptives in the Royal College of General Practitioners' Oral Contraception Study

Malignancies	International Classification of Diseases, version 8	Standardized rate, n[a]		Incidence rate ratio[b] (99% confidence interval)	Attributable risk[c]	Attributable risk, %	Preventive fraction, %
		Ever users	Never users				
Esophagus & stomach	150–151	14.51 (129)	16.59 (73)	0.87 (0.59–1.27)	−2.08		12.5
Colon & rectum	153–154	47.85 (418)	59.16 (270)	0.81 (0.66–0.99)	−11.31		19.1
Liver & gallbladder	155–156	4.65 (41)	5.72 (25)	0.87 (0.45–1.69)	−1.07		18.7
Pancreas	157	13.33 (114)	13.47 (61)	1.00 (0.66–1.52)	−0.14		1.0
Lung	162	59.16 (553)	49.19 (205)	1.17 (0.95–1.45)	9.97	16.8	
Skin							
Melanoma	172	19.76 (173)	18.34 (78)	1.12 (0.78–1.60)	1.42	7.2	
Other	173	103.04 (882)	93.73 (423)	1.11 (0.95–1.29)	9.31	9.0	
Breast	174	159.94 (1422)	155.16 (649)	1.04 (0.91–1.17)	4.78	3.0	
Invasive cervix	180	15.45 (147)	11.56 (45)	1.31 (0.84–2.04)	3.89	25.2	
Endometrium	182	19.42 (168)	29.56 (127)	0.66 (0.48–0.89)	−10.14		34.3
Ovary	183	22.10 (194)	33.27 (142)	0.67 (0.50–0.89)	−11.17		33.6
Bladder & kidney	188–189	17.64 (159)	20.25 (88)	0.87 (0.61–1.23)	−2.61		12.9
Central nervous system & pituitary	191,1943	5.73 (51)	6.95 (32)	0.76 (0.42–1.36)	−1.22		17.5
Thyroid	193	2.42 (22)	2.28 (10)	1.02 (0.37–2.74)	0.14	5.8	
Site unknown	199	23.61 (212)	28.22 (122)	0.84 (0.63–1.13)	−4.61		16.3
Lymphatic & hematopoietic	200–208	31.90 (281)	43.18 (189)	0.74 (0.58–0.94)	−11.28		26.1
Other cancers		37.25 (336)	38.95 (166)	0.96 (0.75–1.23)	1.49	4.1	
Main gynecologic	180,182,183	56.51 (503)	74.31 (312)	0.76 (0.63–0.91)	−17.80		24.0
Any cancer	140–209	542.44 (4661)	566.09 (2341)	0.96 (0.90, 1.03)	−23.65		4·2

[a] Standardized rate per 100,000 woman-years and for age, parity, smoking, and social class; [b] From Poisson regression adjusted for age, parity, smoking, and social status; [c] Per 100,000 woman-years.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

subsequent periods of observation that related to the same cancer were removed from the denominator of analyses but were included in analyses of other cancers (because the women remained at risk of having another type of cancer). The analysis of any cancer risk included only the first cancer, with subsequent observation censored. In all analyses, women were censored at death. By the end of the follow-up period, 7248 deaths occurred: 3003 deaths in never users and 4245 deaths in ever users of oral contraception.

Attributable risk was calculated by subtracting cancer incidence in never users from that in ever users. When the IRR was <1, the preventive fraction percentage was estimated (ie, the percentage of cancer reduction in ever users that might be prevented by combined oral contraception). When the IRR was >1, the attributable risk percentage was calculated (ie, the percentage of cancers in ever users that might be attributable to combined oral contraception).

For our time since last use analysis, we divided the ever users into current and <5 years since last use, 5 to <15 years since last use, 15 to <25 years since last use, 25 to <35 years since last use, and ≥35 years since last use. We undertook adjusted Poisson regression as mentioned earlier to estimate the IRR in each category that was relative to never users. Because of the strong relationship between age and time since last use of oral contraception, we did not undertake standardization to obtain adjusted rates.

The study was established before the introduction of research ethics committees in the United Kingdom. Even so, procedures were used to maintain the confidentiality of women (ie, correspondence between participating doctors and the study and between the National Health Service central registries and the study used a unique study number, the key to which only the GPs knew).

Results

The dataset contained 4661 ever users with at least 1 cancer during 884,895

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woman-years of observation and 2341 never users with at least 1 cancer during 388,505 woman-years of observation, which was an 81% increase in cancers and an 18% increase in periods of observation since our previous cancer analysis.[8] Approximately one-tenth of never users who experienced cancer (246 women; 10.5%) and a similar proportion of ever users (458 women; 9.8%) had >1 type of cancer. The mean age of women at December 2012 was 70.2 (standard deviation, 8.0) years and median cohort follow-up time was 40.7 years (interquartile range, 6.1–44.6). At recruitment, oral contraceptive users were slightly younger and more likely to smoke or be of nonmanual class than never users, but of similar parity (Table 1). The mean duration of pill use was 3.66 (standard deviation, 3.5) years.

Compared with never users, ever users of oral contraception had a statistically nonsignificant 4% reduced risk of any cancer (Table 2; IRR, 0.96; 99% CI, 0.90–1.03). The IRR for the most common cancer, breast cancer, was close to unity (IRR, 1.04; 99% CI, 0.91–1.17). There were reductions among ever users, compared with never users, in colorectal (IRR, 0.81; 99% CI, 0.66–0.99), endometrial (IRR, 0.66; 99% CI, 0.48–0.89), ovarian (IRR, 0.67; 99% CI, 0.50–0.89), and lymphatic and hematopoietic cancer (IRR, 0.74; 99% CI, 0.58–0.94). An increased risk of lung cancer among all ever users was not statistically significant at the 1% level. When never and ever users were stratified by smoking habits at recruitment (Table 3), the IRR for lung cancer among nonsmoking ever users was 0.73 (99% CI, 0.42–1.26) and that among smoking ever users was 1.34 (99% CI, 1.06–1.69).

In general, the IRRs resulted in modest attributable risks (Table 2), which indicated a low absolute risk (or benefit) of any specific cancer. The preventive fraction percentages suggest (assuming that the associated IRRs represent a true causal relationship) that perhaps one-third of endometrial and ovarian cancers and nearly one-fifth of colorectal cancers that occur in ever users might be prevented by combined oral contraception.

TABLE 3
Risk of cancer among "ever" and "never" users of oral contraceptives in the Royal College of General Practitioners' Oral Contraception Study, stratified by smoking at recruitment

Malignancies	International Classification of Diseases, version 8	Ever vs never, incidence rate ratio (99% confidence interval)[a]	
		Nonsmokers	Smokers
Esophagus & stomach	150–151	0.74 (0.39– 1.39)	0.97 (0.59– 1.58)
Colon & rectum	153–154	0.82 (0.62– 1.07)	0.79 (0.57– 1.08)
Liver & gallbladder	155–156	1.05 (0.41– 2.74)	0.74 (0.29– 1.85)
Pancreas	157	0.92 (0.53– 1.59)	1.14 (0.60– 2.16)
Lung	162	0.73 (0.42– 1.26)	1.34 (1.06– 1.69)
Skin			
Melanoma	172	1.16 (0.76– 1.78)	1.03 (0.54– 1.97)
Other	173	1.14 (0.93– 1.38)	1.06 (0.82– 1.36)
Breast	174	1.00 (0.85– 1.18)	1.09 (0.90– 1.33)
Invasive cervix	180	1.67 (0.82– 3.40)	1.12 (0.64– 1.96)
Endometrium	182	0.76 (0.51– 1.13)	0.52 (0.32– 0.85)
Ovary	183	0.67 (0.46– 0.97)	0.68 (0.43– 1.07)
Bladder & kidney	188–189	1.06 (0.62– 1.80)	0.75 (0.48– 1.19)
Central nervous system & pituitary	1,911,943	0.72 (0.34– 1.52)	0.81 (0.31– 2.10)
Thyroid	193	1.92 (0.36– 10.1)	0.65 (0.18– 2.37)
Site unknown	199	0.94 (0.60– 1.51)	0.79 (0.53– 1.16)
Lymphatic & hematopoietic	200–208	0.69 (0.50– 0.95)	0.82 (0.56– 1.21)
Other cancers		1.04 (0.73– 1.48)	0.90 (0.63– 1.27)
Main gynecologic	180,182,183	0.80 (0.62– 1.03)	0.71 (0.53– 0.94)
Any cancer	140–209	0.95 (0.87– 1.04)	0.99 (0.89– 1.09)

[a] From Poisson regression adjusted for age, parity, and social class.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

In both contraceptive groups, the incidence of any cancer increased with age and smoking and was higher in the manual social class group (Table 4). Most of the IRRs in the age, smoking, social class, and parity subgroups were below unity, although none reached statistical significance.

Table 5 shows the IRRs by time since last use. Statistically significant increased IRRs were observed among current and recent (<5 years since stopping) users for breast, cervcial, and any cancer, which are associations that largely disappeared by 5 to <15 years after stopping. There was no evidence of important cancer risks that appeared many years after stopping oral contraception; indeed, the IRRs for several cancer types (colorectal, breast, ovarian, central nervous system and pituitary, lympathic and hematopoietic, other, site unknown, and any) were reduced significantly ≥35 years after stopping.

Comment

Our results suggest that users of oral contraceptives are protected from colorectal, endometrial, and ovarian cancer for many years after stopping, perhaps for >35 years for colorectal and ovarian cancer. An increased breast and cervical cancer risk that is seen in current and recent users appears to be lost within

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TABLE 4
Risk of any cancer among "ever" and "never" users of different age, parity, smoking and social class in the Royal College of General Practitioners' Oral Contraception Study

Variable	Standardized rate[a] (n)		Incidence rate ratio[b] (99% confidence interval)
	Ever users	Never users	
Age, y			
<30	39.98 (25)	40.48 (12)	0.88 (0.35–2.18)
30–39	104.77 (188)	131.31 (92)	0.80 (0.57–1.11)
40–49	276.62 (585)	295.97 (260)	0.92 (0.76–1.11)
50–59	573.61 (1173)	633.75 (518)	0.91 (0.79–1.04)
60–69	1044.90 (1669)	1003.72 (707)	1.03 (0.92–1.16)
≥70	1720.88 (1021)	1795.54 (752)	0.95 (0.84–1.08)
Smoking (cigarettes daily)			
0	476.35 (2214)	505.55 (1323)	0.95 (0.87–1.04)
1–14	552.62 (1277)	565.46 (567)	0.98 (0.86–1.12)
≥15	732.67 (1170)	759.13 (451)	0.97 (0.84–1.12)
Social class			
Nonmanual	531.99 (1680)	559.74 (882)	0.97 (0.89–1.05)
Manual	546.18 (2981)	569.10 (1459)	0.96 (0.86–1.07)
Parity			
0	515.81 (252)	604.56 (201)	0.88 (0.68–1.14)
1	556.75 (603)	488.38 (332)	1.14 (0.95–1.36)
2	545.16 (1772)	573.93 (898)	0.94 (0.84–1.05)
≥3	537.61 (2034)	578.79 (910)	0.93 (0.84–1.03)

[a] Standardized rate per 100 000 woman-years and for age, parity, smoking, and social class, except where the variable itself is being examined; [b] From Poisson regression adjusted for the other 3 variables stratified by variable under examination.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

approximately 5 years of stopping oral contraception, with no evidence of either cancer recurring at increased risk in ever users with time. An increased risk of lung cancer was seen only in ever users who were smokers at recruitment. There was no evidence of new cancer risks appearing later in life among women who had used oral contraceptives. These results provide strong evidence that most women do not expose themselves to long-term cancer harm if they choose to use oral contraception; indeed, many are likely to be protected.

The large number of women recruited and the very prolonged follow-up period resulted in nearly 1.3 million women-years of observation. The near doubling of events since our last report enabled us to provide separate risk estimates for esophagus and stomach, pancreas, nonmelanoma skin, bladder and kidney, thyroid, lymphatic, and hematopoietic cancers (previously included in the "other cancer" category[8]) and more precise risk estimates for other cancers. Although some inaccuracies in cancer notifications from the registries may have occurred, systematic differences between contraceptive groups are unlikely.

The study has been prone to large losses to follow up. Previous analyses have shown that women who were lost to GP follow up in the study had similar mortality rates to those still under observation,[9] which suggests no systematic bias from loss to follow up. Mortality rates in the study have been found to be lower than the general population,[10] mainly because women with chronic disease were not recruited.[5] Age-specific rates of all cancer that was seen in our study, however, were generally only slightly lower than those for women living in the United Kingdom for 2011-2013[11] (Table 6). The observed differences would affect our estimates of absolute risk but not comparisons between contraceptive groups, unless oral contraception impacts differently on those women with underlying health conditions or risk factors for cancer. We found little evidence of this with regards to age, parity, social class, or smoking (Table 4). It is possible, however, that at least some of the lower IRRs for some types of cancer that were seen in the >35 years after stopping group may have been due to a healthy cohort effect.

The IRRs were adjusted for smoking and social class at recruitment and age and parity at time of event. Residual confounding from other personal or lifestyle factors might have affected our results. For example, we did not have information for the whole cohort about potential confounders such as body mass index, alcohol, diet, exercise, menarche, menopause, or family history. Neither did we have updated smoking information for all the women. In a separate substudy, we found that more women stopped smoking than started, but with fewer pill users stopping than never users.[12] In theory this means that a larger proportion of women in the smoking group at recruitment will have been misclassified as smokers when, in fact, they became ex-smokers during the study than those in the nonsmoker group at recruitment who subsequently started smoking. This differential misclassification could have led to an underestimation of effects of smoking in smoking-related cancers. This said, in a subgroup of the cohort who provided updated information about smoking habits in a health survey in the mid 1990s, risk estimates of myocardial infarction were virtually identical when derived with the use of updated smoking information compared with those

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TABLE 5
Risk of cancer among "ever" users of oral contraceptives in the Royal College of General Practitioners' Oral Contraception Study by time since estimated last use

		Time since last oral contraceptive use, y									
	Never user	Current and <5		5–15		15–25		25–35		≥35	
Malignancies	N	N	Incidence rate ratio (99% confidence interval)[a]	N	Incidence rate ratio (99% confidence interval)[a]	N	Incidence rate ratio (99% confidence interval)[a]	N	Incidence rate ratio (99% confidence interval)[a]	N	Incidence rate ratio (99% confidence interval)[a]
Esophagus & stomach	73	5	1.06 (0.26–4.29)	14	1.08 (0.46–2.49)	28	0.93 (0.51–1.71)	51	0.89 (0.55–1.43)	31	0.74 (0.42–1.29)
Colon & rectum	270	14	0.87 (0.39–1.96)	40	0.91 (0.56–1.47)	103	1.00 (0.73–1.37)	162	0.81 (0.63–1.05)	99	0.67 (0.49–0.91)
Liver & gallbladder	25	1	1.28 (0.07–22.4)	4	1.27 (0.26–6.18)	10	1.21 (0.43–3.44)	14	0.75 (0.31–1.78)	12	0.78 (0.31–1.94)
Pancreas	61	3	2.33 (0.43–12.6)	6	0.86 (0.26–2.82)	28	1.34 (0.71–2.51)	50	1.08 (0.66–1.78)	27	0.74 (0.41–1.35)
Lung	205	12	1.15 (0.48–2.74)	43	1.20 (0.74–1.94)	116	1.22 (0.89–1.67)	234	1.23 (0.96–1.58)	148	1.07 (0.81–1.42)
Skin											
Melanoma	78	21	1.44 (0.67. 3.10)	23	0.90 (0.46–1.75)	32	0.88 (0.50–1.54)	66	1.37 (0.88–2.14)	31	1.01 (0.57–1.80)
Other	423	28	1.16 (0.65–2.05)	83	1.17 (0.83–1.66)	179	1.10 (0.86–1.40)	349	1.13 (0.94–1.37)	243	1.07 (0.87–1.32)
Breast	649	129	1.48 (1.10–1.97)	238	1.12 (0.91–1.39)	371	1.05 (0.88–1.24)	491	1.10 (0.94–1.28)	193	0.75 (0.60–0.93)
Invasive cervix	45	50	2.32 (1.24–4.34)	42	1.52 (0.84–2.75)	27	1.05 (0.55–2.01)	22	0.98 (0.48–1.99)	6	0.51 (0.16–1.67)
Endometrium	127	5	0.61 (0.17–2.18)	13	0.44 (0.20–0.97)	46	0.70 (0.44–1.11)	56	0.58 (0.38–0.88)	48	0.83 (0.53–1.31)
Ovary	142	8	0.49 (0.18–1.36)	25	0.63 (0.35–1.15)	51	0.71 (0.46–1.10)	80	0.80 (0.55–1.15)	30	0.50 (0.29–0.84)
Bladder & kidney	88	2	0.50 (0.07–3.54)	18	1.34 (0.63–2.83)	45	1.25 (0.75–2.06)	56	0.77 (0.49–1.20)	38	0.72 (0.43–1.19)
Central nervous system & pituitary	32	5	2.20 (0.49–9.99)	8	1.16 (0.37–3.57)	13	0.84 (0.35–2.04)	21	0.84 (0.41–1.76)	4	0.25 (0.06–0.99)
Thyroid	10	2	1.45 (0.14–14.8)	7	2.29 (0.52–10.1)	4	0.79 (0.16–3.86)	4	0.56 (0.12–2.62)	5	1.10 (0.25–4.83)
Site unknown	122	6	1.53 (0.47–5.00)	18	0.92 (0.45–1.85)	50	0.93 (0.59–1.46)	99	0.99 (0.70–1.41)	39	0.56 (0.34–0.90)
Lymphatic & hematopoietic	189	25	0.92 (0.47–1.80)	28	0.63 (0.36–0.12)	68	0.87 (0.60–1.28)	108	0.81 (0.59–1.11)	52	0.55 (0.36–0.83)
Other cancers	166	21	1.20 (0.59–2.44)	43	1.07 (0.66–1.75)	77	0.99 (0.68–1.44)	140	1.11 (0.82–1.49)	55	0.65 (0.43–0.97)
Main gynecologic	312	63	1.21 (0.79–1.85)	79	0.78 (0.55–1.11)	121	0.74 (0.56–0.99)	157	0.73 (0.56–0.94)	83	0.65 (0.47–0.91)
Any cancer	2341	328	1.28 (1.08–1.54)	609	1.02 (0.90–1.16)	1125	1.01 (0.91–1.11)	1718	1.00 (0.92–1.08)	881	0.78 (0.71–0.87)

[a] From Poisson regression adjusted for age, parity, smoking, and social class.

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

TABLE 6
Comparison of age-specific incidence rate of all cancer in 2011–2013 in the UK and the Royal College of General Practitioners' Oral Contraception Study for women aged 30–75 years

	United Kingdom 2011–2013[a]		Royal College of General Practitioners' Oral Contraception Study 1968–2013	
Age, y	Average no. per year	Incidence rate per 100,000 women	N	Incidence rate per 100,000 women
30–34	2,239	105.2	106	94.9
35–39	3,239	159.0	174	127.2
40–44	5,833	252.7	301	202.5
45–49	9,617	406.1	544	362.1
50–54	12,188	570.3	706	480.5
55–59	13,552	726.1	985	701.5
60–64	18,577	997.3	1227	937.0
65–69	21,713	1278.6	1149	1159.6
70–74	19,901	1516.1	906	1518.5

[a] Source: Cancer Research UK.[11]

Iversen et al. Lifetime cancer risk and combined oral contraceptives. Am J Obstet Gynecol 2017.

produced with the use of smoking information at recruitment.[12]

In this article, we could not adjust for hormone replacement therapy (HRT) use because we did not know about such use after women left GP observation; we did collect information about such usage while under GP follow up. Oral contraceptive users in our study who did not have a hysterectomy were more likely to use HRT subsequently than similar never users.[13] In a previous paper in which we examined cancer risk among women while under GP observation, adjustment for HRT made little difference to the unadjusted results.[8] HRT use, however, is associated with an increased risk of breast and ovarian cancer in current and recent users.[14,15] It is noteworthy therefore that we found no overall increased risk of breast cancer among oral contraceptive ever users, although many will have also used HRT. Similarly noteworthy is the continued observation of a significant reduction overall in ovarian cancer risk among ever users of oral contraception, which suggests a powerful counterbalance to any harmful ovarian effects of subsequent HRT use.

We censored women from analyses of the same cancer but not from analyses of other cancers because women remained at risk of the development of another type of cancer. It is possible that treatments for a first cancer may affect the risk of another cancer. For example, tamoxifen treatment for breast cancer may increase the risk of endometrial cancer.[16] Overall, 704 of all the women (10.0%) with 1 cancer had at least another type of cancer, which suggests minimal problems from such concerns.

We did not conduct analyses by the hormonal content of the pill, principally because most women in the study used >1 preparation, which made it impossible to know whether any cancer associations are due to the effects of the last preparation used or lingering effects from previously used products. Most oral contraceptives that were used in our study contained 50μg of estrogen combined with an older progestogen, which was used mostly by women who had completed their families. Our findings therefore may not reflect the experience of today's user, although limited evidence suggests similar effects from currently available products.[17-23] Very few studies have reported cancer associations with nonoral combined hormonal contraception. Limited evidence related to deep venous thrombosis suggests that such preparations have a similar or slightly higher risk than oral products.[24] Thus, until empiric evidence becomes available, users of nonoral combined hormonal contraceptives should assume that they have a similar pattern of cancer risk as oral preparations.

Few studies have assessed the very long-term cancer risk among women who have used oral contraceptives. Metaanalyses of breast cancer and oral contraception show a modest elevated risk among ever users,[25,26] which reflects the temporary increased risk in current and recent users. The absence of long-term breast cancer risk in our study is reassuring and supports findings from 2 other cohort studies: the Oxford-Family Planning Association study[27] and the Nurses' Health Study.[28] The Oxford-Family Planning Association study found an elevated risk of cervical cancer among ever users of oral contraceptives.[27] This observation was contrary to our findings, and a reanalysis of global data that suggests that the elevated cervical cancer risk in current and recent users disappears within approximately 10 years of stopping oral contraception.[29] The reduced risk of ovarian and endometrial cancer in our study is consistent with the global evidence that oral contraception provides prolonged protection.[20,21] Colorectal cancer was also reduced in ever users in our study, including those >35 years after stopping.

Widespread implementation of effective cervical cancer prevention measures such as human papillomavirus vaccination or cervical cancer screening should result in reduced cervical cancer incidence over time and result in an even more favorable overall balance of main gynecologic cancer in ever users.

The International Agency for Research on Cancer Working Group concluded that oral contraception is unlikely to alter the risk of thyroid, lung, stomach, urinary tract, gallbladder, pancreas cancer, or the risk of lymphoma, cutaneous melanoma, and tumors of the central nervous system.[4] Our

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findings do not suggest a need to review this conclusion.

In many parts of the world, such as the Americas, Europe, and the Western Pacific, lung cancer is common or becoming so.[3] Most lung cancers occur in people who have smoked or been exposed to smoking. In our study, the attributable risk of smoking ≥15 cigarettes each day at recruitment was approximately 250 per 100,000 woman-years, which is a powerful reminder of the need for strong policies to dissuade women from smoking.

Patterns of cancer vary widely around the world.[3] Our results therefore may not reflect the experience of oral contraceptive users who live in other global regions. It is reassuring, however, to find that, in 1 of the regions of the world with high cancer incidence among women, there is no indication of substantial lifetime cancer risk among ever users >35 years after stopping this popular method of contraception. ■

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