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

Lisa IVERSEN, PhD, Mr Selvaraj SIVASUBRAMANIAM, MSc, Amanda J. LEE, PhD, Shona FIELDING, PhD, Philip C. HANNAFORD, MD.

Institute of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK.

Correspondence to:
Dr Lisa Iversen
Institute of Applied Health Sciences
University of Aberdeen
Polwarth Building
Foresterhill
Aberdeen
AB25 2ZD, UK
Email: l.iversen@abdn.ac.uk
Telephone: +44(0)1224 437212

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Condensation

Oral contraception users do not have an increased overall lifetime cancer risk; reductions in colorectal, endometrial and ovarian cancer persist at least 30 years.

Short title

Lifetime cancer risk and combined oral contraceptives.

Abstract

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 associated with oral contraception. Despite previous research important questions remain about the safety of these contraceptives: i) how long do endometrial, ovarian and colorectal cancer benefits persist for? ii) does combined oral contraceptive use during the reproductive years produce new cancer risks later in life? and iii) what is the overall balance of cancer among past users as they enter the later stages of their lives?

Objectives: To examine the very long-term cancer risks or benefits associated with use of combined oral contraceptives, including the estimated overall life-time balance.

Study design: 46,022 women recruited to the UK Royal College of General Practitioners' Oral Contraception Study during 1968/69 were followed-up for up to 44 years. Directly standardised rates of specific and any cancer were calculated for ever and never users of combined oral contraceptives; standardised for age, parity, social class and smoking. Attributable risk percentage and preventive fraction percentage were calculated. Poisson regression adjusting for the same variables was used to estimate incidence rate ratios (IRR) between ever and never users, and examine effects by time since last oral contraceptive use

Results: There were 4661 ever users with at least one cancer during 884,895 woman-years of observation and 2341 never users with at least one cancer during 388,505 woman-years of observation. Ever use of oral contraceptives was associated with reduced colorectal (IRR 0·81, 99% confidence interval, CI 0·66 to 0·99), endometrial (IRR 0·66, 99% CI 0·48 to 0·89), ovarian (IRR 0·67, 99% CI 0·50 to 0·89) and lymphatic and haematopoietic cancer (IRR 0·74, 99% CI 0·58 to 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 seen in current and recent users appeared to be lost within about five 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.

Conclusions: Most women who choose to use oral contraceptives do not expose themselves to long-term cancer harms; instead many benefit from important reductions in some cancers which persist for many years after stopping.

Key words: cancer, oral contraception, cohort study

Introduction

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 looking 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, an effect which 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: i) how long do the endometrial, ovarian and colorectal cancer benefits persist for? ii) does combined oral contraceptive use during the reproductive years produce new cancer risks that emerge later in life? and iii) 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 follow-up of the Royal College of General Practitioners' Oral Contraception Study, the 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 UK 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 Caucasian 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 using the Registrar General's 1966 Classification of Occupations[6]), parity and significant past medical history. Women remained under GP follow-up until: (i) they were no longer registered with the recruiting doctor (usually because the woman moved away - approximately 56% of total cohort); (ii) their doctor left the study (13%); (iii) they obtained contraceptives from another source (3%); (iv) they died (2%); or (v) GP follow-up stopped in December 1996 (26%). Whilst under GP follow-up, GPs provided on a six-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 1970's, approximately three quarters of the cohort was 'flagged' at National Health Service (NHS) central registries in Scotland and England. This enabled subsequent cancers and deaths occurring among flagged women to be reported to the study anonymously, including after women left GP follow-up. The other quarter could not be flagged because the women had already 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 recruited as takers and subsequently prescribed oral contraception (nearly always a combined oestrogen and progestogen preparation). For each calendar month that a woman used an oral contraceptive, one month was added to the period of observation (denominator) of ever users, as were periods after stopping. Women recruited as never users who were subsequently prescribed an oral contraceptive were included in the ever user group from the month of prescription. Never users lost to GP follow-up before 1996 and 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 lost to GP follow-up before 1996 and 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 so 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 one year after the last

recorded prescription. The effect of this assumption is to slightly underestimate time since stopping if a woman used oral contraception for less than 12 months after the last recorded prescription, and overestimate it if used for a longer period.

The analysis included cancers and periods of observation up to: (a) the date of first relevant cancer or date left study for i) all non-flagged women, and ii) flagged never users lost from the study before 1996 and aged <38 years when lost; (b) date of relevant cancer or 31st December 2012 for: i) all flagged women still under GP observation at December 1996 ii) flagged never users lost before 1996 and aged ≥38 years when lost, and iii) flagged ever users lost from the study before 1996 (Figure 1). Most cancers were notified through flagging by the central registries (i.e. 5467/7002 (78%) of all cancers).

The cancers were coded using the International Classification of Diseases, 8th revision (ICD-8)[7] grouped into (a) individual categories: oesophagus 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 haematopoietic (200-208), other cancers (any code between 140-209 not already mentioned); (b) 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, since this was likely to be most accurate as it was often based on hospital supplied information.

Direct standardisation was used to estimate the rates of cancer amongst ever and never users. The standardisation variables using the total study population were age (<30, 30-39, 40-49, 50-59, 60-69, 70+) and parity (0, 1, 2, 3+) at time of event, and smoking (0, 1-14, 15+ cigarettes daily) and social class (non-manual: social classes I-IIIa and students, manual: social classes IIIb-V and armed forces) at recruitment. Poisson regression was used to estimate the incidence rate ratio (IRR) and its 99% confidence interval (CI) for ever versus never users for each of the cancer types, adjusted for the same categories of age, parity, smoking and social class as above. The exception was when we stratified the data by a particular variable (e.g. smoking habits at recruitment), when we adjusted the IRRs for the other three variables. We calculated 99% CIs to allow for the large number of comparisons, indicating statistical significance at the 1% level.

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

Attributable risk (AR) was calculated by subtracting cancer incidence in never users from that in ever users. When the IRR was <1 the preventive fraction percent (PF%)

was estimated, i.e. the percentage of cancer reduction in ever users that might be prevented by combined oral contraception. When the IRR was >1 the AR% was calculated, i.e. 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 less than 5 years since use, 5-<15 years since use, 15-<25 years since use, 25-<35 years and 35 years and more since last use. We undertook adjusted Poisson regression as above to estimate the IRR in each category relative to never users. Due to the strong relationship between age and time since last use of oral contraception, we did not undertake standardisation to obtain adjusted rates.

The study was established before the introduction of research ethics committees in the UK. Even so, procedures were used to maintain the confidentiality of women i.e. correspondence between participating doctors and the study, and between the NHS 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 one cancer during 884,895 woman-years of observation and 2341 never users with at least one cancer during 388,505 woman-years of observation; a 81% increase in cancers and 18% increase in periods of observation since our previous cancer analysis[8]. Approximately a tenth of never users who experienced cancer (246 women: 10.5%) and a similar proportion of ever users (458 women: 9.8%) had more than one type of cancer. The mean age of

women at December 2012 was 70.2 (standard deviation (SD) 8.0) years and median cohort follow-up 40.7 years (inter-quartile range 6.1, 44.6). At recruitment oral contraceptive users were slightly younger and more likely to smoke or be of non-manual class than never users, but of similar parity (Table 1). The mean duration of pill use was 3.66 (SD 3.5) years.

Compared to never users, ever users of oral contraception had a statistically non-significant 4% reduced risk of any cancer (Table 2: IRR 0.96, 99% CI 0.90 to 1.03). The IRR for the most common cancer, breast cancer, was close to unity (IRR 1.04, 99% CI 0.91 to 1.17). There were reductions among ever users, compared with never users, in colorectal (IRR 0.81, 99% CI 0.66 to 0.99), endometrial (IRR 0.66, 99% CI 0.48 to 0.89), ovarian (IRR 0.67, 99% CI 0.50 to 0.89), and lymphatic and haematopoietic cancer (IRR 0.74, 0.58 to 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 non-smoking ever users was 0.73 (99% CI 0.42 to 1.26) and that among smoking ever users 1.34 (99% CI 1.06 to 1.69).

In general, the IRRs resulted in modest ARs (Table 2), indicating a low absolute risk (or benefit) of any specific cancer. The PF%s suggest (assuming that the associated IRRs represent a true causal relationship) that perhaps a third of endometrial and ovarian cancers, and nearly a fifth of colorectal cancers, occurring in ever users might be prevented by combined oral contraception.

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 since last use. Statistically significant increased IRRs were observed among current and recent (<5 years since stopping) users for breast, cervcial and any cancer, associations which largely disappeared by 5-<15 years after stopping. There was no evidence of important cancer risks appearing many years after stopping oral contraception; indeed the IRRs for several cancer types (colorectal, breast, ovarian, CNS and pituitary, lympathic and haematopoietic, other, site unknown, and any) were significantly reduced 35 or more 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 more than 35 years for colorectal and ovarian cancer. An increased breast and cervical cancer risk seen in current and recent users appears to be lost within about 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 very prolonged follow-up, 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 oesophagus and stomach, pancreas, non-melanoma skin, bladder and kidney, thyroid, and lymphatic and haematopoietic cancer (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 lost to GP follow-up in the study had similar mortality to those still under observation,[9] suggesting 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 seen in our study, however, were generally only slightly lower than those for women living in the UK for 2011-13[11] (Table 6) The observed differences would affect our estimates of absolute risk but not comparisons between contraceptive groups unless oral contraception impacts differently upon those 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 incidence rate ratios for some types of cancer seen in the more than 35 years after stopping group may have been due to a healthy cohort effect.

The incidence rate ratios 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 sub-study 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 non-smoker 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 sub-group 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 using updated smoking information compared to those produced using smoking information at recruitment.[12]

In this paper we could not adjust for hormone replacement therapy (HRT) use since we did not know about such use after women left GP observation although we did collect information about such usage whilst under GP follow-up. Oral contraceptive users in our study who did not have a hysterectomy were more likely to subsequently use HRT than similar never users[13]. In a previous paper in which we examined cancer risk among women whilst 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, even though 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, suggesting 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 developing 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 (10.0%) of all women with one cancer had at least another type of cancer, suggesting 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 more than one preparation, making 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 used in our study contained 50µg of oestrogen combined with an older progestogen, 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 non-oral 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 empirical evidence becomes available, users of non-oral 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. Meta-analyses of breast cancer and oral contraception show a modest elevated risk among ever users[25, 26], reflecting the temporary increased risk in current and recent users. The absence of long-term breast cancer risk in our study is reassuring, supporting findings from two other cohort studies: the Oxford-Family Planning Association (FPA) study[27] and the Nurses' Health Study.[28] The Oxford-FPA study found an elevated risk of cervical cancer among ever users of oral contraceptives.[27] This observation was contrary to our findings, and a re-analysis of global data which suggests that the elevated cervical cancer risk in current and recent users disappears within about 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 more than 35 years after stopping.

Widespread implementation of effective cervical cancer prevention measures such as HPV vaccination or cervical cancer screening should result in reduced cervical cancer incidence over time; resulting in an even more favourable overall balance of main gynaecological cancer in ever users.

The IARC 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 tumours of the central nervous system[4]. Our findings do not suggest a need to review this conclusion.

In many part of the world, such as the Americas, Europe and 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 AR of smoking ≥ 15 cigarettes a day at recruitment was approximately 250 per 100,000 woman-years; 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 contractive users living in other global regions. It is reassuring, however, to find in one of the regions of the world with high cancer incidence among women, no indication of substantial lifetime cancer risk among ever users, more than 35 years after stopping this popular method of contraception.

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Table 1. Characteristics of ever and never users or oral contraception at recruitment to the Royal College of General Practitioners' Oral Contraception Study, number (%)

Characteristic	Ever Users (N=22920)	Never Users (N=23102)	All (N=46022)
Age (years)	n (%)	n (%)	n (%)
<30	13701 (59.8)	13521 (58.5)	27222 (59.2)
30 – 39	7553 (33.0)	7725 (33.4)	15278 (33.2)
40 +	1666 (7.2)	1856 (8.1)	3522 (7.6)
Mean age at recruitment (SD)*	28.5 (6.7)	29.0 (6.5)	28.8 (6.6)
Number cigarettes smoked			
0	11904 (51.9)	13569 (58.7)	25473 (55.4)
1 – 14	6261 (27.3)	5900 (25.5)	12161 (26.4)
15+	4755 (20.8)	3633 (15.7)	8388 (18.2)
Parity			
0	3401 (14.8)	4881 (21.1)	8282 (18.0)
1	4520 (19.7)	6476 (28.0)	10996 (23.9)
2	7543 (32.9)	7157 (31.0)	14700 (31.9)
3	7456 (32.5)	4588 (19.9)	12044 (26.2)
Mean (SD)	2.1 (0.9)	2.0 (0.9)	2.1 (0.9)
Social class			
Non-manual	8585 (37.5)	8417 (36.4)	17002 (36.9)
Manual	14335 (62.5)	14685 (63.6)	29020 (63.1)

*SD= Standard deviation

Table 2. Risk of cancer among ever and never users of oral contraceptives in the RCGP Oral Contraception Study.

		Standardised Rate[†] (n)					
Malignancies	ICD-8[*]	Ever Users	Never Users	IRR[‡] (99% CI)	AR[§]	AR%[‖]	PF%[¶]
Oesophagus & 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	
Skin: 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
CNS & 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 & haematopoietic	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 gynaecological	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

[*]ICD-8: International Classification of Diseases, version 8

[†]Standardised rate per 100 000 woman-years, standardised for age, parity, smoking and social status

[‡] IRR incidence rate ratio and 99% confidence interval from Poisson regression adjusted for age, parity, smoking and social status

[§]AR: Attributable risk per 100,000 woman-years; [‖]AR%: Attributable risk percentage; [¶]PF%: Preventive fraction percentage

Table 3. Risk of cancer among ever and never users of oral contraceptives in the RCGP Oral Contraception Study, stratified by smoking at recruitment.

		Ever versus Never	
		Non-smokers	Smokers
Malignancies	ICD-8*	IRR† (99% CI)	IRR† (99% CI)
Oesophagus & 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)
Skin: 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)
CNS & 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 & haematopoietic	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 gynaecological	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)

*ICD-8: International Classification of Diseases, version 8

†IRR incidence rate ratio and 99% confidence interval from Poisson regression adjusted for age, parity and social status

Table 4. Risk of any cancer among ever and never users of different age, parity, smoking and social class in the RCGP Oral Contraception Study.

	Standardised Rate* (n)		
	Ever users	Never users	IRR† (99% CI)
Age (years)			
< 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			
Non-manual	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)

*Standardised rate per 100 000 woman-years, standardised for age, parity, smoking, and social status, except where the variable itself is being examined.
†IRR incidence rate ratio and 99% Confidence interval from Poisson regression adjusted for the other three variables stratified by variable under examination

Table 5. Risk of cancer among ever users of oral contraceptives in the RCGP Oral Contraception Study by time since estimated last use.

		Time since last oral contraceptive use (years)									
	Never user	Current and <5		5-15		15-25		25-35		35+	
Malignancies	n	n	IRR* (99% CI)	n	IRR* (99% CI)	n	IRR* (99% CI)	n	IRR* (99% CI)	n	IRR* (99% CI)
Oesophagus & 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)
Skin: 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)
CNS & 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 & haematopoietic	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 gynaecological	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)

* IRR incidence rate ratio and 99% confidence interval from Poisson regression adjusted for age, parity, smoking and social status

Table 6. Comparison of age-specific incidence rate of all cancer in 2011-2013 in the UK and the RCGP Oral Contraception Study, for women aged 30-75 years.

	UK 2011-2013*		RCGP study 1968-2013	
Age (years)	Average number per year	Incidence rate per 100,000 women	Number	Incidence rate per 100,000 women
30-34	2239	105.2	106	94.9
35-39	3239	159.0	174	127.2
40-44	5833	252.7	301	202.5
45-49	9617	406.1	544	362.1
50-54	12188	570.3	706	480.5
55-59	13552	726.1	985	701.5
60-64	18577	997.3	1227	937.0
65-69	21713	1278.6	1149	1159.6
70-74	19901	1516.1	906	1518.5

*Source: Cancer Research UK. Female age-specific incidence rates of all cancers excluding non-melanoma skin cancer (C00-97 Excl. C44): 2011-2013. http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero accessed 3.8.16.

Figure title:

Figure 1. Flow chart of the Royal College of General Practitioner's Oral Contraception Study

Legend:
The figure shows the follow-up of the Royal College of General Practitioner's Oral Contraception Study from recruitment in 1968-69 to December 2012