

Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioners' oral contraception study

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ABSTRACT

Objective To examine the absolute risks or benefits on cancer associated with oral contraception, using incident data.

Design Inception cohort study.

Setting Royal College of General Practitioners' oral contraception study.

Participants Directly standardised data from the Royal College of General Practitioners' oral contraception study.

Main outcome measures Adjusted relative risks between never and ever users of oral contraceptives for different types of cancer, main gynaecological cancers combined, and any cancer. Standardisation variables were age, smoking, parity, social class, and (for the general practitioner observation dataset) hormone replacement therapy. Subgroup analyses examined whether the relative risks changed with user characteristics, duration of oral contraception usage, and time since last use of oral contraception.

Results The main dataset contained about 339 000 woman years of observation for never users and 744 000 woman years for ever users. Compared with never users ever users had statistically significant lower rates of cancers of the large bowel or rectum, uterine body, and ovaries, tumours of unknown site, and other malignancies; main gynaecological cancers combined; and any cancer. The relative risk for any cancer in the smaller general practitioner observation dataset was not significantly reduced. Statistically significant trends of increasing risk of cervical and central nervous system or pituitary cancer, and decreasing risk of uterine body and ovarian malignancies, were seen with increasing duration of oral contraceptive use. Reduced relative risk estimates were observed for ovarian and uterine body cancer many years after stopping oral contraception, although some were not statistically significant. The estimated absolute rate reduction of any cancer among ever users was 45 or 10 per 100 000 woman years, depending on whether the main or general practitioner observation dataset was used.

Conclusion In this UK cohort, oral contraception was not associated with an overall increased risk of cancer; indeed it may even produce a net public health gain. The

balance of cancer risks and benefits, however, may vary internationally, depending on patterns of oral contraception usage and the incidence of different cancers.

INTRODUCTION

Evidence suggests that current users of combined oral contraceptives have an increased risk of cancer of the breast, cervix, and liver compared with non-users¹⁻⁴ but a reduced risk of cancer of the endometrium,^{1,4} ovaries,^{1,4} and, possibly, colorectum.^{1,4,5}

We used data from the Royal College of General Practitioners' oral contraception study to test the hypothesis that, compared with never users, ever users of oral contraception have a reduced overall risk of cancer, an effect that is strongest in women aged 40-60.

METHODS

The Royal College of General Practitioners' oral contraception study began in May 1968, when 1400 UK general practitioners recruited 23 000 women who were using oral contraceptives and 23 000 women who had never used them.⁶ The doctors supplied information every six months about hormonal preparations prescribed, pregnancies, new episodes of illness (including cancer), and surgery. Women remained under follow-up until they left the practice, their doctor left the study, they obtained contraception from another source, they died, or the study stopped follow-up (end of 1996).

In the mid-1970s three quarters of the original cohort was flagged at central registries in Scotland and England so that subsequent cancers and deaths could be reported to the study; 24% of the women could not be flagged.

Two datasets were compiled. In both, women not flagged were included up until they were lost to follow-up (see bmj.com). In addition, the main dataset included information up to the date of the first relevant cancer or December 2004 (whichever came first) for flagged women still under doctors' observation when follow-up stopped in 1996, for flagged women lost to

the study before 1996 who were aged 38 or more when lost, and for flagged ever users lost to the study before 1996 who were younger than 38 when lost.

The general practitioner observation dataset included cancers, periods of observation, and other relevant information about women under observation by their doctors up to the point of their being lost to follow-up, the first relevant cancer, or December 1996 (whichever came first). This dataset had comprehensive information about type and duration of oral contraceptives used, and information on use of hormone replacement therapy.

We present cancer rates for ever and never users from both datasets; rates of any cancer in different age, parity, smoking, and social class subgroups of women in the main dataset; and cancer rates by duration and time since last use of oral contraceptives, using the general practitioner observation dataset.

The cancers were coded (see bmj.com) and grouped into three categories: individual cancers, main gynaecological cancers combined, and any cancer.

Statistical analyses

We calculated unadjusted and directly standardised rates of first ever diagnosis of cancer among ever and never users using Stata 9.2. Rates for the main dataset were standardised for age group and parity at the time of the event, and smoking and social class at recruitment. When analysing the general practitioner observation dataset we used the same variables (with collapsed age categories for duration and time since last use of oral contraception analyses), in addition to use of hormone replacement therapy.

We aggregated events (numerator) and periods of observation (denominator) according to each woman's status at each calendar month while under follow-up by

Risk of cancer among ever and never users of oral contraceptives in main dataset and in general practitioner observation dataset

Malignancies	ICD-8 code	Ever users		Never users		Relative risk† (95% CI)
		Observed rate (No of women)	Standardised rate	Observed rate (No of women)	Standardised rate	
Main dataset*:						
Large bowel or rectum	153, 154	24.65 (188)	26.01	38.56 (135)	36.10	0.72 (0.58 to 0.90)
Gallbladder or liver	155, 156	1.83 (14)	1.99	3.70 (13)	3.62	0.55 (0.26 to 1.17)
Lung	162	26.97 (206)	27.12	25.94 (91)	25.77	1.05 (0.82 to 1.35)
Melanoma	172	12.58 (96)	12.86	14.28 (50)	13.99	0.92 (0.65 to 1.29)
Breast	174	117.79 (891)	121.53	129.31 (448)	124.20	0.98 (0.87 to 1.10)
Invasive cervix	180	15.48 (118)	14.94	10.28 (36)	11.19	1.33 (0.92 to 1.94)
Uterine body	182	10.61 (81)	11.30	21.41 (75)	19.53	0.58 (0.42 to 0.79)
Ovary	183	12.57 (96)	13.23	26.54 (93)	24.66	0.54 (0.40 to 0.71)
Central nervous system or pituitary	191, 1943	4.45 (34)	4.79	4.27 (15)	3.56	1.34 (0.73 to 2.47)
Site unknown	199	7.20 (55)	7.22	12.54 (44)	11.34	0.64 (0.43 to 0.95)
Other cancers		113.93 (863)	119.49	145.20 (504)	135.57	0.88 (0.79 to 0.98)
Main gynaecological	180, 182, 183	38.75 (295)	39.58	58.41 (204)	55.54	0.71 (0.60 to 0.85)
Any cancer	140-209	333.68 (2485)	344.91	410.20 (1392)	390.37	0.88 (0.83 to 0.94)
General practitioner observation dataset‡:						
Large bowel or rectum	153, 154	19.63 (66)	22.07	25.85 (59)	26.11	0.85 (0.59 to 1.20)
Gallbladder or liver	155, 156	2.08 (7)	3.06	2.63 (6)	2.76	1.11 (0.37 to 3.30)
Lung	162	19.91 (67)	19.47	17.07 (39)	18.87	1.03 (0.70 to 1.53)
Melanoma	172	14.57 (49)	15.26	14.90 (34)	14.81	1.03 (0.66 to 1.60)
Breast	174	100.68 (337)	108.12	111.46 (253)	105.96	1.02 (0.87 to 1.20)
Invasive cervix	180	21.44 (72)	20.78	13.15 (30)	13.94	1.49 (0.97 to 2.28)
Uterine body	182	6.24 (21)	6.24	15.33 (35)	13.27	0.47 (0.27 to 0.81)
Ovary	183	9.81 (33)	10.25	21.90 (50)	20.28	0.51 (0.33 to 0.78)
Central nervous system or pituitary	191,1943	4.16 (14)	4.10	1.31 (3)	1.27	3.23 (0.93 to 11.24)
Site unknown	199	6.54 (22)	7.01	10.50 (24)	8.97	0.78 (0.44 to 1.39)
Other cancers		91.13 (305)	94.60	103.90 (236)	98.58	0.96 (0.81 to 1.14)
Main gynaecological	180,182,183	37.53 (126)	37.36	50.46 (115)	47.56	0.79 (0.61 to 1.01)
Any cancer	140-209	282.53 (936)	295.96	318.67 (715)	306.59	0.97 (0.88 to 1.06)

ICD-8=international classification of diseases, eighth revision.

†Never users as baseline.

*Main dataset: standardised rate per 100 000 woman years, adjusted for age, parity, smoking, and social status.

‡General practitioner observation dataset: standardised rate per 100 000 woman years, adjusted for age, parity, smoking, social status and ever use of hormone replacement therapy

The total population available in each dataset was used as the standard in each analysis. This, as well as allowing for different variables in each dataset, means that the results from the two datasets should not be compared directly.

her doctor, or that pertaining when she left follow-up (except for age). Women recruited as never users who subsequently started oral contraception were included in the ever user group from the date of starting. Only the first event in each cancer category was counted; we removed subsequent periods of observation for that woman from the denominator of analyses relating to the same cancer category but included them in analyses of other cancer groups. When analysing the risk of any cancer we counted only the first cancer (and censored subsequent periods of observation). Women therefore could have contributed data to more than one category. When calculating 95% confidence intervals we assumed approximate normality for the log of estimated relative risks.⁷ We tested trends for duration and time since last use of oral contraception using the log-linear trend test, by including them as metric explanatory variables with even spaced levels.⁷ For clarity of presentation we give only the standardised rates for the subgroup analyses of duration and time since last use of oral contraception.

RESULTS

The main dataset contained about 744 000 woman years of observation for ever users of oral contraception and 339 000 woman years for never users. The corresponding values for the general practitioner observation dataset were 331 000 and 224 000. Compared with never users ever users tended to be younger, smokers, of high parity and manual social class at recruitment, and to have used hormone replacement therapy (see *bmj.com*).

Using the main dataset ever users compared with never users had a statistically significant 12% reduction in the risk of any cancer (adjusted relative risk 0.88, 95% confidence interval 0.83 to 0.94, table). Statistically significant reductions were found in rates of cancer of the large bowel or rectum, uterine body and ovaries, as well as those of site unknown and "other." Small, non-significant increases were found in the risk of cancers of the lung, cervix, and central nervous system or pituitary. No material difference was found between groups for breast cancer. Taken together there was a 29% reduced risk of the main gynaecological cancers combined.

The risk estimates in the smaller general practitioner observation dataset were less precise, with many of the relative risks losing significance, including that of any cancer (adjusted relative risk 0.97, 0.88 to 1.06, table). The reduced risk of cancer of the uterine body and ovaries among ever users, however, remained significant, with main gynaecological cancers combined of borderline significance.

In both ever and never users the rate of any cancer increased with age and smoking (see *bmj.com*). In all age groups except the youngest, ever users had a lower risk of any cancer than never users, with significant lower risks in women aged 30-39 and 50-59. Among all smoking and social class, and most parity,

subgroups ever users had a reduced risk of any cancer compared with never users; in many cases the differences were significant.

The median duration of oral contraceptive use was 44 months (range 1 to 344 months). When cancers were considered together, women who used oral contraceptives for more than eight years had a significant increased risk of any cancer (adjusted relative risk 1.22, 1.07 to 1.39, see *bmj.com*). Significant increased risks among longer term (≥ 8 years) users were observed for cancers of the cervix (adjusted relative risk 2.73, 1.61 to 4.61) and central nervous system or pituitary (5.51, 1.38 to 22.05). Conversely, prolonged use of oral contraception was associated with a significant reduced risk of ovarian cancer (0.38, 0.16 to 0.88). The trends of increasing rates of cervical and central nervous system or pituitary cancer, and decreasing risk of uterine body and ovarian malignancy, with longer durations of oral contraceptive use were all significant.

Analysis of the data by time since last use of oral contraception suggests that the protective effect of oral contraception for ovarian cancer lasts for at least 15 years after stopping, with reduced (non-significant) relative risks still seen after longer time intervals (see *bmj.com*). All of the risk estimates for uterine body cancer were also below unity, although only that for current and recent use (< 5 years after stopping) was significant. The trends for other cancers were less consistent. None of the tests for trend for individual cancers with time since last use were significant. A borderline statistical trend was seen of declining risk of main gynaecological cancers combined with longer time since last use ($P=0.041$), as the initially increased risk of cervical cancer among current and recent users of oral contraception disappeared with time.

DISCUSSION

In this UK cohort, oral contraception was not associated with an overall increased risk of cancer. Depending on which dataset was examined, our analyses suggest either a significant 12% reduced risk of any cancer (main dataset) or a more modest, non-significant, 3% reduction (general practitioner observation dataset). In either case we found no evidence of a substantial increased risk of cancer overall.

A major strength of the study was the inclusion of more than a million woman years of observation, accumulated over 36 years. Most of the women are now post-menopausal, of an age when many cancers become common. This provided a large number of events for analysis. Although a small proportion of cancers are likely to have been missing or wrong,⁸ there is no reason to suspect that systematic differences occurred between oral contraceptive groups.

We were able to adjust for the potential confounders of age, smoking, social class, parity, and (for the general practitioner dataset) use of hormone replacement therapy. In general this made little difference to the unadjusted rates. Although the smoking data used

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral contraceptives are associated with an increased risk of some cancers and a decreased risk of others

The absolute overall balance of incident cancer associated with oral contraception is unknown

WHAT THIS STUDY ADDS

Oral contraception is not associated with an overall increased risk of cancer

Oral contraception may produce a net benefit, with absolute risk reduction estimated at 10 or 45 per 100 000 woman years of use, depending on the dataset used

were those collected at recruitment, any bias would tend to underestimate the effects of smoking. We did not adjust for differences in lifestyle or familial variables. Residual confounding therefore could explain our findings.

The study has had large losses to follow-up. Our main dataset contained only 67% of the potential 1 656 000 woman years of observation. We have previously shown that women lost to general practitioner follow-up had similar mortality risks as those still under observation,⁹ suggesting no major systematic bias from loss to follow-up. In case our main dataset results were affected by the censoring of flagged never users younger than 38 when lost to general practitioner follow-up before 1996, we carried out an analysis in which both flagged ever users and never users satisfying these criteria were excluded. The adjusted relative risk for any cancer was 0.95 (95% confidence interval 0.88 to 1.02). The main dataset analyses may have been prone to misclassification of exposure as we assumed that never users older than 38 when they left the study did not subsequently start oral contraception. The level of misclassification is likely to have been small and its effect will have been to underestimate pill related cancer risks. Depending on which dataset was examined, our results suggest either a 12% or 3% reduction in overall cancer risk from oral contraception.

The reduced risk of main gynaecological cancers among ever users was almost identical to that observed by the Oxford/Family Planning Association contraceptive study¹⁰ and contrasts with an earlier report from our study.¹¹ In that publication, a large proportion of the ever user experience related to current rather than past oral contraceptive use, and many women were just entering the age when the incidence of uterine body and ovarian cancer rises. In this paper much more of the data on oral contraception related to past use, and the cohort was older.

Our findings might not reflect the experience of women using oral contraceptives today, if preparations have a different risk to earlier products, or if differences in usage materially affect cancer risk. Although relatively limited, current evidence suggests that lower oestrogen formulations provide similar protection from uterine body and ovarian cancer as older, higher dose preparations.^{12 13}

In our study oral contraception was not associated with a significantly increased risk of any cancer. Indeed in the main dataset the estimated overall absolute reduction in risk of any cancer among ever users of combined oral contraceptives was 45 per 100 000 woman years, with greater benefits in older rather than younger women. In the smaller general practitioner observation dataset the estimated absolute risk reduction was 10 per 100 000 woman years. These results suggest that, at least in this relatively healthy UK cohort, the cancer benefits associated with oral contraception outweigh the risks.

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Competing interests: None declared.

Ethical approval: 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. 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 general practitioners knew.

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