ENDOMETRIAL CANCER AND ORAL CONTRACEPTIVES:

Individual participant meta-analysis including 27 276 women with endometrial cancer from 36 epidemiological studies

Collaborative Group on Epidemiological Studies on Endometrial Cancer

(writing group listed on next page;

collaborators listed in supplementary materials, p 2)

Correspondence to:

Secretariat

Cancer Epidemiology Unit

Richard Doll Building

Oxford OX3 7LF

United Kingdom

Tel: +44-(0)-1865-289-600

E-mail: collaborations@ceu.ox.ac.uk **Summary**

Background Oral contraceptives are known to reduce endometrial cancer risk, but it is uncertain how long this effect lasts after use ceases or whether it is modified by other factors.

Methods Individual participant data were sought from principal investigators and provided centrally on 27 276 women with endometrial cancer (cases) and 115 743 without endometrial cancer (controls) from 36 epidemiological studies. The relative risks of endometrial cancer

associated with oral contraceptive use were estimated stratifying by study, age, parity, body mass index, smoking and use of menopausal hormone replacement therapy.

Findings The median age of cases was 63 (IQR: 23-89) years and the median year of cancer diagnosis was 2001. 9459 (35%) cases and 45 625 (39%) controls had ever used oral contraceptives, for median durations of 3.0 and 4.4 years, respectively. The longer that women had used oral contraceptives, the greater the reduction in risk of endometrial cancer; every 5 years of use was associated with a relative risk (RR) of 0·76, 95% CI 0·73-0·78, p<0·0001. This reduction in risk persisted for over thirty years after oral contraceptive use had ceased, and was similar for use during the 1960s, 1970s, and 1980s, despite higher oestrogen doses in pills used in the early years. However, risk differed by tumour type, with a stronger reduction in risk associated with ever having used oral contraceptives for carcinomas (RR 0·69, 95%CI 0·66-0·71) than sarcomas (RR 0·83, 95% CI 0·67-1·04; $P_{heterogeneity}$=0·02). In high-income countries, 10 years use of oral contraceptives was estimated to reduce endometrial cancer incidence before age 75 from 1·5 to 0·7 per 100 users.

Interpretation Use of oral contraceptives confers long-term protection against endometrial cancer. These results suggest that, in developed countries, about 400 000 cases of endometrial cancer before the age of 75 years have been prevented over the past 50 years (1965–2014) by oral contraceptives, including 200 000 in the past decade (2005–14).

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Introduction

Use of oral contraceptives is known to reduce the incidence of endometrial cancer.[1] Because endometrial cancer is uncommon in young women but its incidence increases sharply with age, the public health impact of this association depends mainly on the extent to which the reduced risk of endometrial cancer persists after use ceases. To investigate the relationship between use of oral contraceptives and the subsequent risk of endometrial cancer, individual participant data from 36 epidemiological studies of endometrial cancer have been brought together, checked and analysed centrally.

Methods

Identification of studies and collection of data

This collaboration was established in 2005. Since 2012, epidemiological studies were eligible for inclusion if they collected individual data about use of hormonal contraceptives and reproductive history from at least 400 women with endometrial cancer in retrospective studies, and at least 200 women in prospective studies. Before 2012, retrospective studies with fewer than 400 cases of endometrial cancer had been eligible, and so some studies with smaller numbers of cases are included here. Eligible studies were identified from review articles, computer-aided literature searches in PubMed and MEDLINE (up to Jan 31, 2012), using combinations of the search terms 'endometrial cancer risk', 'endometrium cancer risk', 'hormon*', 'oral contraceptive', 'OC', plus the additional terms 'cohort', 'prospective', 'women' and 'cancer risk', as well as from discussions with colleagues. Efforts were made to identify all studies that included relevant information, irrespective of whether results on oral contraceptives had been published, and principal investigators from each eligible study were invited to participate.

Cases were defined as women with invasive cancer of the body of the uterus (including uterine sarcomas) without previous cancer (except non-melanoma skin cancer); controls were women without previous cancer who had an intact uterus. Prospective studies were incorporated using a nested case-control design, in which up to four controls were selected at random among cohort members, and matched for duration of follow-up, exact year of birth, date of recruitment (within 6 months) and, where appropriate, other specific matching criteria indicated by the principal investigators (e.g., geographical region). Individual participant data on sociodemographic and reproductive factors, use of contraceptives, use of hormonal therapies for the menopause, reproductive history, height, weight, consumption of alcohol and tobacco, and family history of breast

and endometrial cancer were sought from the principal investigators of every study. For prospective studies, reported information on the use of oral contraceptives was taken from the last record before disease onset, to calculate duration of use and time since last use (assuming no further use). Information about the use of menopausal hormonal therapy and hysterectomy was also that most recently recorded. Datasets provided by investigators were collated centrally and recoded using similar definitions, as far as possible. Apparent inconsistencies in the data were discussed with the study investigators and if they could not be rectified, decisions were made about which values to incorporate into the pooled dataset. After the records had been checked and corrected, investigators were sent summary analyses of the variables to be used for final confirmation that their data had been interpreted correctly.

44 eligible studies were identified[2–45] of which 36 are included in the current analysis.[2–37] Four groups of researchers declined to participate in this collaboration[38–41] and a further four groups agreed in principle to provide data to the collaborative group at a future date.[42-45]

Principal investigators provided individual information on whether women had ever used hormonal contraceptives (as defined by each study) and most had also collected information on total duration of use and age or calendar year at first and last use. Only 13 studies collected information on the type of hormonal contraceptives;[7,17,19,21,25–30,33,35,36] women from the remaining 23 studies were assumed to be using combined oral contraceptives (ie, those containing both oestrogen and progestin) because more than 95% of hormonal contraceptive users included in studies with such information reported using combined preparations. There were too few women with endometrial cancer who had used exclusively progestin-only oral contraceptives (56 cases), progestin-only injectable hormonal contraceptives (19 cases), combined injectable hormonal contraceptives (three cases) or sequential oral contraceptives (41 cases) for reliable analysis.

Statistical analysis and presentation of results

Statistical analyses were performed using STATA, version 13.0 (StataCorp LP, College Station, Texas). Conditional logistic regression was used to calculate relative risks (RRs) of endometrial cancer in relation to the use of oral contraceptives and their corresponding 95% confidence intervals (CIs). Where only two groups were compared, conventional CIs were used. When more than two groups were compared, variances were estimated for every group by reporting the relative risks as floating absolute risks.[47] Use of this method enables valid comparisons between

any two groups, even if neither is the baseline group, taking the variation in each group into account. This method does not alter the relative risk estimate but assigns an appropriate group-specific variance, group-specific standard error (gsSE) and hence group-specific confidence interval (gsCI) to each of the log relative risks, including that for the reference group, which appropriately reflects the group size. This method yields variances that are slightly smaller than the variances calculated using conventional methods (except for the baseline group where the relative risk is defined as 1·0).

All analyses were stratified by study, centre (for multi-centre studies), age (16-19, 20-24, and so on up to 75-79, 80-84, 85-89), parity (0, 1, 2, 3, 4, ≥5; not known), body mass index (<25, 25-30, ≥30 kg/m^2; not known), smoking (never, ever, unknown) and type of menopausal hormone replacement therapy use (never, oestrogen-only exclusively, combined exclusively, both oestrogen-only and combined, other types, or unknown use). The effect on the main findings of further stratification by ethnicity, education, age at first birth, age at menarche, age at menopause, menopausal status and family history of endometrial cancer was examined by comparing results before and after stratification for each variable separately. Women with missing information for any of these adjustment factors were assigned to a separate stratum for the relevant variable to conserve total numbers analysed; sensitivity analyses excluded these women. The RR of endometrial cancer per 5-year duration of oral contraceptive use was estimated by fitting a log-linear trend across categories of duration (never, <1, 1-<5, 5-<10, 10-<15, ≥15 years) using the median value within each category for each study separately.

The association of endometrial cancer risk and duration of oral contraceptives use was analysed by cross-classifying by time since last use and by mid-calendar-year of use (grouped as 1960-69, 1970-79, and 1980-89) to assess the independent effect, if any, of these factors on risk. Although the composition of oral contraceptive pills has varied substantially over time, a strong association exists between calendar year of use and oestrogen dose in the oral contraceptives typically used.[48–50] In the USA and UK, for example, the oral contraceptives prescribed before 1970 were typically 'high dose' preparations, often containing 100µg or more of mestranol; between 1970 and 1980 prescriptions were typically for 'medium dose' preparations containing about 50µg of ethinyl-oestradiol; and by 1980 most prescriptions were for 'low dose' preparations, containing 35µg or less of ethinyl-oestradiol.[49,50] Thus, in these analyses, decade of use was taken as a proxy for oestrogen dose of oral contraceptives.

The classification system adopted in each study was used centrally to categorise tumours into three broad histological subtypes: type I (endometrioid carcinomas); type II (non- endometrioid carcinomas); and uterine sarcomas. Type I tumours, which were much the most common type, included the endometrioid tumours (International Classification of Diseases for Oncology (ICD)-O-3 morphology codes: 8380, 8381, 8382, and 8383), adenocarcinoma tubular (8210 and 8211), papillary adenocarcinoma (8260, 8262, and 8263), adenocarcinoma with squamous metaplasia (8570), mucinous adenocarcinoma (8480 and 8481), and adenocarcinoma not otherwise specified (8140). Type II tumours included serous (8441), papillary serous (8460 and 8461), squamous cell (8050, 8070, 8071, and 8072), adenosquamous (8560), small-cell carcinoma (8041), mixed-cell adenocarcinoma (8323) and clear cell carcinoma (8310), as described elsewhere.[51] Uterine sarcomas were defined as 'not otherwise specified' (8800-8806), fibrosarcoma (8810-8833), liposarcoma (8850-8858), myosarcoma (8890-8896), rhabdomyosarcoma (8900-8902, 8910–8912), endometrial stromal sarcoma (8930–8931) or cancers coded as 'sarcoma' by study investigators. Significance tests for heterogeneity of the relative risks for oral contraceptive use by tumour subtype compared cases only (case-case comparisons), because controls provide no additional information. Analyses by histological subtype were based on lower numbers than all endometrial cancers. Hence, although they were still stratified by study (centre) and age, to retain sufficient statistical information within each stratum they were adjusted rather than stratified for parity, body mass index, smoking and type of menopausal hormone replacement therapy used.

Where results are presented in the form of plots, relative risks are represented by squares and their corresponding CIs or gsCIs by horizontal lines (group-specific standard errors are also given where appropriate, to allow comparison between any two exposure groups). The position of the square indicates the point estimate of the relative risk, and the area of the square is inversely proportional to the variance of the logarithm of the relative risk, thus providing an indication of the amount of statistical information available for that particular estimate. Where summary relative risks have been calculated these are shown as open diamonds. Because of the large number of relative risk estimates presented, 99% CIs or gsCIs are generally used in the figures; however, throughout the text 95% CIs are quoted.

Cumulative incidence rates of endometrial cancer (up to the age of 75 years) associated with different durations of use of oral contraceptives were estimated by application of RR estimates for endometrial cancer from the present analyses to age-specific incidence rates for women in 21 high-income countries in western Europe, North America, and Australasia (appendix p 8).[52] Absolute

numbers of cancers prevented were estimated from birth cohort-specific prevalences of oral contraceptive use. [53]

Results

Details of the 36 participating studies are shown in table 1. The studies are listed by their design and, within each type of design, by the median year when the endometrial cancers were diagnosed in each study. Most studies were conducted in Europe or North America, with three from Asia, one from Australia, one from South Africa and one multinational study. Together, the studies included 27 276 women with endometrial cancer (cases) and 115 743 women without endometrial cancer (controls). The median year of cancer diagnosis was 2001 (interquartile range [IQR]: 1972–2011) and the median age at diagnosis was 63 (IQR: 23–89) years, with 847 (3·1%), 3743 (13·7%), 11 287 (41·4%) and 11 399 (41·8%) diagnosed aged less than 45, 45–54, 55–64 and 65 years or older, respectively.

Pattern of use of oral contraceptives

Table 1 presents the details of the 36 participating studies. The studies are listed by their design and, within each type of design, by the median year when the endometrial cancers were diagnosed in each study. Most studies were done in Europe or North America, with three from Asia, one from Australia, one from South Africa, and one multinational study. Together, the analyses included 27 276 women with endometrial cancer (cases) and 115 743 women without endometrial cancer (controls). The median year of cancer diagnosis was 2001 (IQR 1994–2005) and the median age at diagnosis was 63 years (IQR 57–68), with 847 (3%) of women diagnosed before 45 years of age,3743 (14%) at 45–54 years, 11 287 (41%) at 55–64 years, and 11 399 (42%) at 65 years or older.

Overall, 9459 (35%) of 27 276 women with endometrial cancer and 45 625 (39%) of 115 743 controls had ever used oral contraceptives, with a median duration of use of 3·0 years (IQR 1–7) and 4·4 years (2–9), respectively. The prevalence of ever having used oral contraceptives was substantially lower in controls from Asia (899/11 180; 8%) than in controls from Europe and North America (39 050/86 293; 45%). Figure 1 shows the study-specific and combined relative risks of endometrial cancer in ever-users compared with never-users of oral contraceptives and, in the ever-users, the RR per 5 years of use. Results are presented according to study design. Studies with a low information content (defined as 1/var[ln RR] <20) are included in the “other” category for each relevant study design. Overall, the

risk of endometrial cancer was significantly lower in women who had ever used oral contraceptives than in women who had never used them (RR 0·69, 95% CI 0·67–0·72), with no significant heterogeneity between the three types of study design (heterogeneity test; p=0·15).

The longer women had used oral contraceptives for, the lower their risk of endometrial cancer was, with each 5 years of use associated with an RR of 0·76 (95% CI 0·73–0·78, p<0 · 0001), based on 8873 cases and 43 783 controls who were ever-users (figure 1). In women who had used oral contraceptives for a duration of 10–15 years (median 11·8 years) the relative risk of endometrial cancer was 0·52 (95% CI 0·48–0·57; figure 2A). These analyses were stratified by study (centre), age, parity, BMI, smoking, and type of any menopausal hormone replacement therapy used. Similar results were obtained when the analyses were stratified by age and study alone (RR per 5 years use of oral contraceptives 0·75 [95% CI 0·73–0·77]), and further stratification for each of ethnic origin, education, age at first birth, age at last birth, age at menarche, age at menopause, menopausal status, or family history of endometrial cancer likewise changed the RR per 5 years of use by 0·01 or less (appendix p 4). The proportional reduction in risk of endometrial cancer per 5 years of oral contraceptive use varied slightly by age at diagnosis (heterogeneity test; p=0·004), with RR 0·71 (95% CI 0·67–0·75) for women diagnosed before 60 years of age and RR 0·79 (0·75–0·82) for women diagnosed at 60 years of age or older. The association did not vary by BMI, parity, use of menopausal hormone therapy, menopausal status, smoking status, age at menarche, ethnic origin, or alcohol use (figure 3). The exclusion of women with missing values for any of these stratification variables also made a negligible difference to the risk estimates (making the fully stratified RR per 5 years use of oral contraceptives 0·75, 95% CI 0·72–0·77).

Most women with endometrial cancer had stopped using oral contraceptives many years before their cancer diagnosis (median time since last use 29 years [IQR 22–34]). Women who had used oral contraceptives more recently had also, on average, used them for a longer duration (eg, women who had used oral contraceptives less than 15 years previously had a median duration of use of 4·7 years [IQR 1 · 3–9 · 9], whereas women who had last used oral contraceptives 30 years or more previously had a median duration of use of 3·0 years [1 · 0–5 · 3]). For a given duration of use, the reduction in risk was slightly greater in women with more recent use, although a significant protective effect remained more than 30 years after use had ceased (figure 2B and appendix p 5). In 7452 women with endometrial cancer for whom information about the timing of their oral contraceptive use was available, 3235 (43%) had a mid-year of oral contraceptive use in the 1960s and 371 (5%) had a midyear of use in the 1980s (appendix p 6). The RRs per 5 years duration of use of oral contraceptives

in the 1960s, 1970s, and 1980s did not vary significantly (heterogeneity test; p=0·15, appendix p 6). There was also no significant heterogeneity in the RR per 5 years of use by age at first use or age at last use (appendix p 7). However, there was some evidence that the RR depended on the histological subtype of endometrial cancer (table 2). Compared with women who had never used oral contraceptives, ever-users had an RR of 0·69 (95% CI 0·66‑0·71) for carcinomas, based on 26 877 cases, which was similar for type I and type II carcinomas.

Based on relatively few cases, ever-use of oral contraceptives was not significantly associated with the risk of uterine sarcoma (RR 0·83 [95% CI 0·67‑1·04], based on 399 cases; heterogeneity, from direct case-case comparison of sarcomas *vs* carcinomas p=0·02). Analyses were also done in women with information aboutduration of oral contraceptive use. For carcinoma, the RR per 5 years use of oral contraceptives was 0·75 (95% CI 0·73‑0·77, based on 8701 cases); for uterine sarcoma, the corresponding RR was 0·88 (95% CI 0·74‑1·03, based on 172 cases; heterogeneity, from direct case-case comparison of sarcomas *vs* carcinoma p=0·24).

Based on the RRs presented in figure 2 and age-specific rates of endometrial cancer for women in high-income countries, cumulative incidence rates of endometrial cancer were estimated for never-users of oral contraceptives and for women who had used them for different durations, beginning at 20 years of age. For women who never used oral contraceptives, an estimated 2·3 in every 100 would be diagnosed with endometrial cancer before the age of 75 years. The corresponding cumulative incidence rate for women who had used oral contraceptives for 5, 10, and 15 years was estimated to be 1·7, 1·3, and 1·0 per 100 users, respectively (figure 4).

The annual incidence of endometrial cancer is low in women still young enough to be using oral contraceptives, but it is much higher in those aged 60‑70 years. In this age range, the number of women who were ever-users of oral contraceptives has grown steeply over the past 50 years, from essentially zero in the 1960s to about three-quarters in high-income countries today.[53] Hence, the annual number of endometrial cancers prevented by ever-use of oral contraceptives has also increased steeply over the past 50 years. Using birth cohort-specific prevalences of oral contraceptive use in western developed countries,[53] we estimate that over the past 50 years (1965‑2014) in 21 countries in western Europe, North America, and Australasia, oral contraceptive use has prevented a total of about 400 000 endometrial cancers, including 200 000 in the past 10 years (2005‑14), at ages 30‑74 years (appendix p 8). Because these results are based on population incidence rates, they automatically allow for the different rates of hysterectomy in those populations.

Discussion

This international collaboration has brought together and re-analysed almost all of the available epidemiological evidence on the reduction in endometrial cancer incidence associated with oral contraceptive use, and includes data from 27 000 women with endometrial cancer from 36 studies. Overall, the longer women had used oral contraceptives, the greater the reduction in the risk of endometrial cancer. On average, every 5 years of oral contraceptive use was associated with a relative risk of 0.76, so about 10–15 years of use halves the risk. A protective effect persists for at least 30 years after use ceases, and does not seem to depend much on the dose of oestrogen in the contraceptive formulations or on personal characteristics such as parity, adiposity, or menopausal status.

Combining results from many studies has the obvious advantage of yielding a large sample size, which reduces random errors, and it also avoids the biases that could be produced by undue emphasis on particular studies with extreme results. Only a third of the eligible studies have published on oral contraceptives and endometrial cancer,[4,7,8,10,17,18,21,24,29–31,33,35] so a review based solely on these studies could be affected by publication bias. Despite extensive eff orts to identify all studies with unpublished results, it is impossible to guarantee that others do not exist; furthermore, it is not possible to have completely up-to-date information from the continuing prospective studies. However, the eight eligible studies that were identified but did not contribute data to this collaboration together contain only about 12% as many women with endometrial cancer as the included studies. Hence, failure to include these studies probably had no material effect on the main findings. Only one of these eight studies has published results on oral contraceptives and endometrial cancer, and its reported findings are broadly similar to ours.[39] The 36 included studies were of varied variation in the duration of use and time since last use of oral contraceptives. However, the effects of a given duration of use did not vary significantly between women with different characteristics or between studies with different designs.

The main analyses were stratified simultaneously by study, centre within study, age at diagnosis, parity, BMI, smoking, and use of menopausal hormone therapy. This fine stratification was feasible because of the large sample size. It meant that the analyses of the association between oral contraceptive use and risk of endometrial cancer are based on comparisons between women in the same study who were of the same age and who had a similar history of other risk factors for endometrial cancer.

Although few studies provided information about hormonal constituents of the preparations used, the oral contraceptives of the 1960s would generally have contained much higher doses of oestrogen than those of the 1980s. Overall, however, there was no apparent decrease between use in the 1960s and 1980s in the relative risk associated with a given duration of use. These results show that the amount of oestrogen in the lower-dose pills is still sufficient to reduce the incidence of endometrial cancer, which is consistent with findings from two studies that have assessed individual dosages of the hormonal constituents.[41,54] The numbers of women who reported using anything other than combined oral contraceptives (eg, sequential oral or progestin-only oral contraceptives and/or injectable hormonal contraceptives) were too small for reliable analysis.

The decline in endometrial cancer risk with increasing duration of use does not seem to vary substantially with parity, BMI, use of menopausal hormone therapy, menopausal status, smoking status, age at menarche, ethnic origin, or alcohol intake. The reduction in risk associated with 5 years use of oral contraceptives was slightly greater in women diagnosed before 60 years of age than in women diagnosed at an older age, but given the number of significance tests done, this could be due to chance. The reduction in endometrial cancer risk with increasing duration of use does not seem to vary much with factors related to the timing of use, such as age of first or last use, time since last use, or calendar period of use.

The effect of oral contraceptives does, however, seem to vary by histological subtype, with ever-use strongly associated with a reduced risk of type I and probably of type II endometrial carcinoma, but somewhat less strongly associated with a reduced risk of uterine sarcoma—a much rarer type of cancer. Another pooled analysis that included 15 studies, most of which contributed to the current analysis, also reported a similar reduction in risk of both type I and type II endometrial carcinoma for ever use of oral contraceptives[51] but no significant association with uterine sarcoma.[55]

Taken together, it is reasonable to infer that the associations recorded here are causal (ie, that current or past oral contraceptive use reduces the incidence of endometrial cancer in otherwise similar women). Almost all of the hormonal contraceptive use in these studies is likely to involve combined oral contraceptives, which contain oestrogen plus progestin. These contraceptives might protect against endometrial cancer by minimising exposure to unopposed oestrogen during the follicular phase of the menstrual cycle, thereby inhibiting oestrogen-induced cell proliferation;[56,57]

moreover, the addition of a progestin to menopausal hormone therapy has been shown to reduce the adverse effects of oestrogen on the risk of endometrial cancer in postmenopausal women.[53,58–60] However, the exact mechanisms by which oral contraceptives cause substantial protection against endometrial cancer many years after cessation of use are still unclear.

Since the introduction of oral contraception in the early 1960s, about 400 million women have used it in high income countries alone,[61] often for prolonged periods during early adulthood.53 Medium-to-long-term use of oral contraceptives (eg, for 5 years or longer) results in a substantial proportional reduction in the incidence of endometrial cancer, the magnitude of which is similar to that seen for ovarian cancer.[53] Because this reduction in risk persists more than 30 years after use has ceased, and the incidence of endometrial cancer increases steeply with age, the public health effect of oral contraceptive use on endometrial cancer is most apparent many years after use has stopped. The present results, taken together with what is known about past patterns of use, suggest that in high-income countries oral contraceptives have, over the past 50 years (1965–2014), already prevented a total of about 400 000 endometrial cancers before the age of 75 years, including 200 000 in the past decade (2005–14).

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The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to publish. The writing committee had full access to all the data and had final responsibility for the decision to submit for publication.

Analysis and writing committee: N Allen, V Beral, SW Kan, G Reeves, S Sweetland, R Stevens, R Peto, TO Yang

Affiliations of writing committee:

N Allen, R Peto: Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK
V Beral, SW Kan, G Reeves, S Sweetland, TO Yang: Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
R Stevens: Department of Primary Care Health Sciences, University of Oxford, Oxford UK.

Contributions of the analysis and writing committee:

N Allen, V Beral, SW Kan, R Stevens, S Sweetland, TO Yang identified studies, received and checked data, conducted analyses, and had full access to all materials and results.
N Allen, V Beral, G Reeves, S Sweetland and R Peto drafted the report and all writing committee members helped revise it before and after circulation to collaborators.

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Table 1: **Details of studies and women included**

Study	Country	Number of cases/controls analysed	Median year of diagnosis	Median age (IQR) of cases (years)	Numbers (%) ever users of oral contraceptives in cases/controls
15 Prospective studies					
BCDDP[2]	USA	583/2337	1990	65 (59–60)	116 (20)/598 (26)
Netherlands Cohort[3]	Netherlands	344/1784	1992	68 (65–72)	36 (11)/435 (24)
NHS[4]	USA	643/1633	1993	68 (65–72)	259 (40)/729 (45)
CNBSS[5]	Canada	781/3008	1993	60 (55–65)	376 (48)/1697 (56)
IWHS[6]	USA	585/2315	1995	72 (67–77)	78 (13)/415 (18)
Shanghai BSE[7]	China	191/752	1995	60 (53–65)	14 (7)/97 (13)
MEC[8]	USA	482/1830	1999	68 (62–74)	148 (31)/666 (36)
NIH-AARP[9]	USA	1354/5431	2000	66 (62–70)	406 (30)/2008 (37)
EPIC[10]	Europe	925/3622	2000	60 (55–65)	386 (42)/1842 (51)
Women's Health Study [11]	USA	263/1012	2000	62 (57–67)	144 (55)/639 (63)
PLCO[12]	USA	640/2438	2002	68 (63–72)	282 (44)/1291 (53)
MISS[13]	Sweden	239/950	2002	64 (58–70)	96 (40)/447 (47)
SWLHC[14]	Sweden	142/555	2003	55 (50–58)	100 (70)/440 (79)
Swedish mammography[15]	Sweden	324/1279	2003	70 (62–77)	152 (47)/682 (83)
Million Women Study[16]	UK	8848/34 590	2006	64 (60–68)	4018 (45)/19 881 (58)
Sub-total		**16 344/63 536**	**2002**	64 (59–69)	**6611 (40)/31 867 (50)**
11 Retrospective studies with population controls					
CASH[17]	USA	408/3177	1981	49 (44–52)	150 (37)/1968 (62)
Brinton[18]	USA	408/486	1988	61 (52–66)	111 (27)/215 (44)
Pike[19]	USA	767/749	1989	64 (59–67)	166 (22)/189 (25)
Newcomb[20]	USA	685/2288	1992	64 (56–71)	207 (30)/709 (31)
Weiderpass 1[21]	Sweden	762/3402	1994	63 (57–68)	184 (24)/1162 (34)
Weiderpass 2[22]	Sweden	144/184	1996	65·5 (59–71)	26 (18)/51 (28)
Rebbeck[23]	USA	485/1396	2000	62 (56–69)	208 (43)/798 (57)
Shu[24]	China	1179/1211	2001	54 (49–62)	214 (18)/302 (25)
Brinton/Lissowska[25]	Poland	548/1904	2002	62 (55–68)	28 (5)/201 (11)
Friedenreich[26]	Canada	534/1016	2004	58·5 (53–65)	390 (73)/797 (78)
ANECS[27]	Australia	1252/670	2006	61 (55–67)	844 (67)/559 (83)
Sub-total		**7172/16 483**	**2000**	60 (53–67)	**2528 (35)/6951 (42)**
10 Retrospective studies with hospital controls					
Antunes[28]	USA	372/818	1975	61 (55–69)	6 (2)/22 (3)
Rosenberg[29]	USA	766/2267	1981	59 (53–64)	61 (8)/285 (13)
WHO[30]	Worldwide	263/16 498	1983	47 (43–52)	43 (16)/4961 (30)
La Vecchia[31]	Italy	527/2394	1985	61 (55–68)	14 (3)/ 230 (10)
Moysich[32]	USA	520/1729	1988	63 (55–70)	77 (15)/401 (23)
Levi[33]	Switzerland	240/568	1990	64·5 (59–70)	31 (13)/125 (22)
Negri[34]	Italy	223/224	1990	60 (54–66)	17 (8)/10 (5)
Dal Maso[35]	Italy	454/907	2000	61 (54–67)	46 (10)/117 (13)
Urban[36]	South Africa	166/1102	2002	64 (57–71)	17 (10)/156 (14)
Aichi[37]	Japan	229/9217	2003	55 (47–62)	8 (3)/500 (5)
Sub-total		**3760/35 724**	**1987**	59 (52–66)	**320 (9)/6807 (19)**
Total		**27 276/115 743**	**2001**	**63 (57–68)**	**9459 (35)/45 625 (39)**

Table 2: **Relative risk of endometrial cancer in ever versus never users of oral contraceptives by histological subtype***

Histological subtype	Ever use		Never use		Relative risk (95% CI) for ever vs. never use of oral contraceptives
	Cases	**Controls**	**Cases**	**Controls**	
Carcinoma	9280	45 625	17 597	70 118	0·69 (0·66-0·71)
Type I	6096	39 191	9921	56,365	0·68 (0·65-0·71)
Type II	488	39 191	850	56,365	0·75 (0·66-0·85)
Sarcoma	179	40 024	220	57 788	0·83 (0·67-1·04)

In a case-case comparison of sarcoma *vs* carcinoma, p=0·02.* Stratified by study (centre) and age; adjusted for parity, smoking, body mass index, and type of menopausal hormone replacement therapy use. Information on histological subtype (type I, type II or uterine sarcoma) was available for 17 754 cases (65%); the remaining cases were classified as carcinoma, unspecified.

FIGURE LEGENDS

Figure 1: Relative risk of cancer of the endometrium by use of oral contraceptives in each of the contributing studies

Figure 2: Relative risk of endometrial cancer in users of oral contraceptives compared to never users, by (A) duration, and (B) time since last use of oral contraceptives

Figure 3: Relative risk (99% CI) of endometrial cancer associated with 5 years use of oral contraceptives by various lifestyle and reproductive characteristics.

Figure 4: Absolute risk of endometrial cancer incidence per 100 women up to age 75 years in high income countries by duration of use of oral contraceptives population-weighted rates, 2003–07, for 21 countries in Western Europe, North America, and Australasia) Endometrial cancer incidence rates are extremely low before the age of 35 years.