Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Contraception: reduced risk of endometrial cancer associated with combined oral contraceptives

A meta-analysis of 36 epidemiological studies that involved 143,019 cases and controls found that use of oral contraceptives (mostly combined oral contraceptives) was associated with a reduction in risk of endometrial cancer. This effect persisted for many years after the contraceptive was stopped, with longer use associated with greater reductions in risk. This reduction in risk may be considered alongside the other benefits, risks and other factors when discussing the most appropriate form of contraception. NICE guideline on medicines optimisation recommends that people should have the opportunity to be involved in making decisions about their medicines.

Overview and current advice

Endometrial cancer (uterine cancer) is the fifth most common cancer in women, with approximately 320,000 new cases diagnosed globally each year¹. The risk of developing endometrial cancer by the age of 75 is estimated to range from 0.6% in developing countries to 1.6% in developed countries¹. The Faculty of Sexual and Reproductive Healthcare (FSRH) clinical guideline on Combined Hormonal Contraception (updated 2012) advises that use of a combined oral contraceptive is associated with a reduced risk of endometrial cancer that continues for several decades after the woman stops taking it³. Endometrial cancer is predominantly a disease of post-menopausal women and most common in women over 50 years of age¹, so the clinical significance of a reduced risk depends on how long this effect lasts after the oral contraceptive is discontinued². However, there are uncertainties about exactly how long the post-exposure effect persists and whether it is modified by other factors².

The FSRH guideline gives information and advice about other non-contraceptive health benefits, risks and adverse effects associated with use of combined oral contraceptives, including other cancers, venous thromboembolism, cardiovascular disease and stroke.

New evidence

A meta-analysis of 36 epidemiological studies looked at the rates of endometrial cancer in women who had received oral contraceptives. The meta-analysis used individual person data from these epidemiological studies and included data on 27,276 women with endometrial cancer (cases) and 115,743 women without endometrial cancer (controls). Cases were defined as women with invasive cancer of any histological type of the body of the uterus who were without previous cancer (except
non-melanoma skin cancer); controls were women without previous cancer and an intact uterus. Data for numerous factors were collected, included sociodemographic information, use of hormonal therapies for the menopause, reproductive history, height, weight, consumption of alcohol and tobacco, and family history of breast and endometrial cancer. Of the 36 studies included in the meta-analysis, only 13 studies collected information on the type of hormonal contraception used; for the remaining 23 it was assumed that women were taking combined oral contraceptives because more than 95% of hormonal contraceptive users in the other 13 studies were using combined preparations. There were insufficient numbers of women with endometrial cancer who exclusively used progestin-only oral contraceptives, progestin-only injections, combined hormonal injections or sequential oral contraceptives for reliable analysis. Analysis was stratified by age, parity, BMI, smoking status and menopausal hormone therapy use. Most studies were from Europe and North America; the largest single study (contributing approximately 9000 cases and 35,000 controls) was the UK Million Women Study.

Overall, 35% (9459 out of 27,276) of women with endometrial cancer and 39% (45,625 out of 115,743) of controls had ever used oral contraceptives, with a median duration of use of 3.0 years and 4.4 years respectively. The median year of cancer diagnosis was 2001, and the median age at diagnosis was 63 years. Most women with endometrial cancer had stopped using oral contraceptives many years before diagnosis (median interval 29 years, interquartile range 22–34 years).

The risk of endometrial cancer was statistically significantly lower in women who had used oral contraceptives compared with those who had never used them (RR 0.69, 95% confidence interval [CI] 0.67 to 0.72). The longer women received oral contraceptives for, the lower their risk of endometrial cancer, with every 5 years of use associated with a RR of 0.76 (95% CI 0.73 to 0.78, \( p < 0.0001 \), based on 8873 cases and 43,783 controls). In women who had used oral contraceptives for between 10 and 15 years the risk of endometrial cancer was approximately halved (RR 0.52, 95% CI 0.48 to 0.57). The beneficial effect of oral contraceptives did not appear to be dependent on the dose of oestrogen used or factors such as parity or menopausal status and the authors conclude that the beneficial effect remained for at least 30 years after use had ceased. The risk reduction for endometrial cancer appeared to vary by histological subtype, with contraceptive use strongly associated with a reduction in type I and probably type II endometrial carcinoma, but less strongly associated with a reduction of uterine sarcoma, a rarer type of cancer.

Based on these relative risks and age-specific rates of endometrial cancer in high-income countries, the authors estimate that about 23 in every 1000 never-users would be diagnosed with endometrial cancer before the age of 75 years. The corresponding cumulative incidence among women who used oral contraceptives for 5, 10 and 15 years from age 20 years would be 17, 13 and 10 in 1000, respectively. The authors suggest that in 21 developed countries approximately 400,000 cases of endometrial cancer before the age of 75 years may have been prevented in the past 50 years by the use of oral contraceptives, including 200,000 cases in the past decade.

**Commentary**

**Commentary provided by the Medicines and Prescribing Centre, NICE**

This large, collaborative meta-analysis of epidemiological studies\(^2\) found that the risk of endometrial cancer was reduced in women who had taken oral contraceptives – assumed to be combined oral contraceptives in almost all women – that persisted for many years after the women stopped taking them, although longer duration of use was associated with greater reductions in risk. The authors of the meta-analysis suggested that combined contraceptives might protect against endometrial cancer by minimising exposure to unopposed oestradiol during the follicular phase of the menstrual cycle\(^2\).

These findings may be reassuring to women receiving or considering combined oral contraceptives, however the risk of endometrial cancer is just one of many factors that need to be considered when selecting the most appropriate form of contraception. These factors include medical history, route of administration, reversibility and side-effects. The FSRH produces the [UK Medical Eligibility Criteria and Contraceptive Use and Selected Practice Recommendations](https://fsrh.org/medications), a classification system of risk factors for all contraceptive methods\(^4\).
Many factors determine the method of contraception a person chooses to use, and to be effective, contraception must be used correctly and consistently. Effective and continued use of a contraceptive method is directly related to its acceptability to the user. Women and men should be given information on efficacy, risks and side effects, advantages and disadvantages, and non-contraceptive benefits of available methods of contraception for which they are medically eligible. This is an example of the need for shared decision-making, in which people are able to make well-informed choices that are consistent with their values and preferences. NICE guideline on medicines optimisation recommends that all people should be offered the opportunity to be involved in making decisions about their medicines.

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References


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