Are combination estrogen-progestin oral contraceptives associated with an increased risk of cancer?

Combination estrogen-progestin oral contraceptive (COC) use is associated with a decreased risk of ovarian and endometrial cancer, and the risk reduction persists after discontinuing the COC. In some studies, current use of COCs is associated with a small increased risk of breast cancer. Prolonged COC use is associated with an increased risk of cervical cancer, but confounding factors, including sexual exposures, may account for the association. Following discontinuation of oral contraceptives the increased risk for breast and cervical cancer diminishes.

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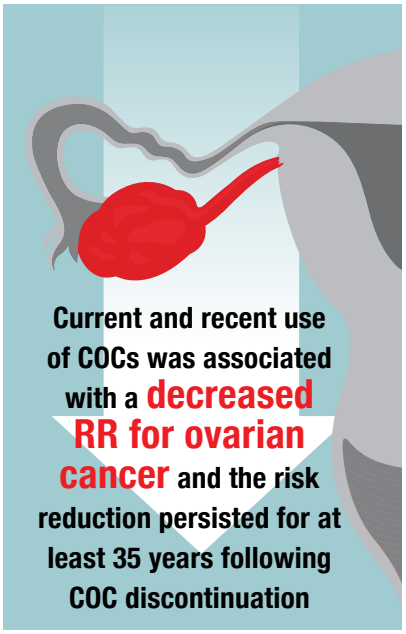
There are no large randomized clinical trials exploring the relationship between COCs and the risk of developing cancer. Many epidemiological studies, however, have investigated the possible association between COC use and the risk of cancer. Such prospective and retrospective studies consistently report that the use of COCs significantly decreases the risk of ovarian and endometrial cancer. The epidemiological data are less consistent concerning the possible association between COC use and the risk of breast cancer. Meta-analyses conclude that current use of COCs may be associated with a small increase in breast cancer risk. In addition, prolonged use of COCs may be associated with an increased risk of cervical cancer.

Ovarian cancer

COC use is associated with reduced risk of ovarian cancer, and the risk reduction persists after discontinuing COC use. In an individual data meta-analysis of 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 women without it, COC use was associated with a relative risk (RR) of 0.73 for ovarian cancer. The magnitude of risk reduction increased with increasing duration of COC use. The RR and 99% confidence interval (CI) for ovarian cancer and mean duration of use was[1]:

- 0.78 (0.73–0.83) for 2.4 years
- 0.64 (0.59–0.69) for 6.8 years
- 0.56 (0.50–0.62) for 11.6 years
- 0.42 (0.36–0.49) for 18.3 years.

In the Royal College of General Practitioners Oral Contraceptive (RCGPOC) study, about 23,000 women who did not use COCs and 23,000 current users of COCs were



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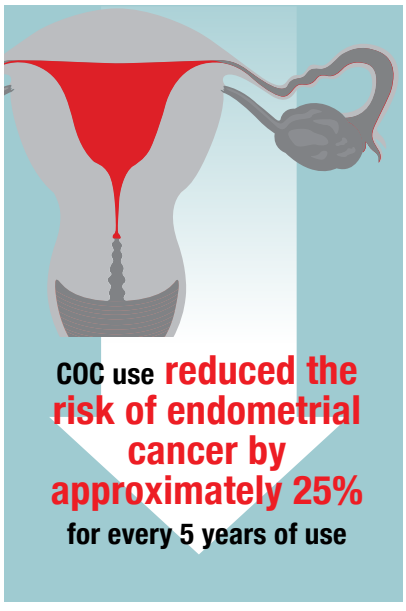
recruited around 1968 and followed for a median of 41 years. In this study, current and recent use of COCs was associated with a decreased RR for ovarian cancer (0.49) and the risk reduction persisted for at least 35 years following COC discontinuation (RR, 0.50; 99% CI, 0.29–0.84).[2]

In the prospective Nurses' Health Study (NHS) I, 121,700 nurses were recruited in 1976 and followed for more than 30 years.[3] For nurses who reported using COCs for more than 5 years, the rate ratio for ovarian cancer at 20 years or less and greater than 20 years since last use was 0.58 (95% CI, 0.61–0.87) and 0.92 (95% CI, 0.61–1.39), respectively. These studies show that the association between COC use and a decreased risk of ovarian cancer persists for many years after discontinuing COCs.

Endometrial cancer

COC use is associated with decreased risk of endometrial cancer, and the risk reduction persists for many years after discontinuing COC use. In an individual data meta-analysis of 36 studies that included 27,276 women with endometrial cancer and 115,743 women without it, COC use reduced the risk of endometrial cancer by approximately 25% for every 5 years of use. With 10 years of COC use the absolute risk of endometrial cancer before age 75 was 2.3 and 1.3 per 1,000 women for never and ever users of COC. Risk reduction varied slightly by histopathology, with risk reduction being greatest for type I endometrial cancer (RR, 0.68), slightly less for type II endometrial cancer (RR, 0.75), and lowest for endometrial sarcoma (RR, 0.83).[4]

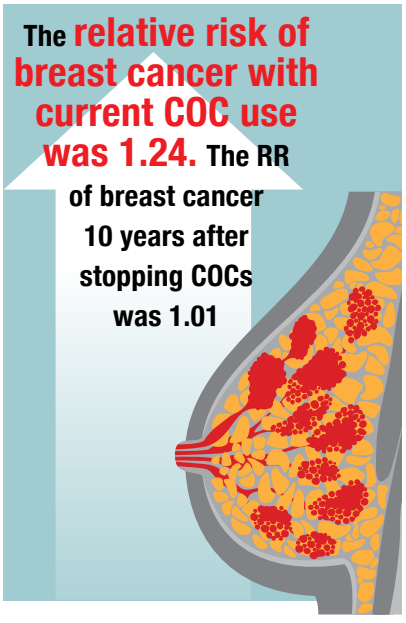


In the RCGPOC study of 46,000 women, the RR of endometrial cancer among current and recent users of COCs was 0.61, and the reduced risk (0.83) persisted for more than 35 years after discontinuing the COC.[2]

It is thought that the progestin in the COC provides most of the beneficial effect. Progestin-only contraceptives, such as depotmedroxyprogesterone acetate, progestin implants, and levonorgestrel-releasing intrauterine devices (LNG-IUDs) are also thought to reduce endometrial cancer risk. For instance, in a study of 93,842 Finnish women who used the LNG-IUD, the standardized incidence ratio for endometrial cancer was 0.50 among LNG-IUD users compared with the general population.[5]

Breast cancer

The relationship between COC use and breast cancer is controversial. However, **most oncologists believe that current use of COCs may be associated with a small increase in the risk of breast cancer diagnosis. The risk is attenuated after discontinuing COC use.** In an individual data meta-analysis of 54 epidemiological studies including 53,297 women with breast cancer and 100,239 without it, the RR of breast cancer with current COC use was 1.24 (95% CI, 1.15–1.33; *P*<.0001). The RR of breast cancer 10 years after stopping COCs was 1.01 (95% CI, 0.96–1.05; NS).[6]



In the prospective NHS study of 116,608 nurses with 1,246,967 years of follow-up, the multivariate relative risk (mRR) of breast cancer with current COC use was 1.33 (95% CI, 1.03–1.73). Past use of COCs was not associated with a significantly increased risk of breast cancer (mRR, 1.12; 95% CI, 0.95–1.33; NS).[7]

In the RCGPOC study (approximately 46,000 women), current use of COCs was associated with an increased risk of breast cancer (incidence rate ratio [IRR], 1.48; 95% CI, 1.10–1.97). Five to 15 years after stopping COCs, there was no significant association between prior COC use and breast cancer (IRR, 1.12; 99% CI, 0.91–1.39; NS).[2]

It is important to note that it is not possible to conclude from these data whether the reported association between current use of COCs

and breast cancer is due to early and accelerated diagnosis of breast cancer, the biological effects of hormones contained in COCs on breast tissue and nascent tumors, or both. In addition, formulations of COCs prescribed in the 1960s and 1970s contained higher doses of estrogen, raising the possibility that the association between COCs and breast cancer is due to COC formulations that are no longer prescribed. However, in animal models and postmenopausal women certain combinations of estrogen plus progestin clearly influence breast cancer biology and cancer risk.[8,9]

Cervical cancer

Prolonged COC use is associated with an increased risk of cervical cancer. The risk is no longer observed 10 years after stopping COC use. In an individual data meta-analysis of 24 epidemiological studies including 16,573 women with cervical cancer and 35,509 women without it, the relative risk of cervical cancer with less than 5 years or 5 or more years of COC use was 1.09 and 1.90, respectively. Analyses of potential confounding exposures, including age at first sexual intercourse, condom use, cigarette smoking, and number of sexual partners, did not significantly weaken the observed association between cervical cancer and COC use of 5 or more years.[10] In a study of women who were positive for HPV DNA, the odds ratio for cervical cancer among women who had used COCs[11]:

- less than 5 years, 0.73 (95% CI, 0.52–1.03)
- 5 to 9 years, 2.82 (95% CI, 1.46–5.42)
- ≥10 years, 4.03 (95% CI, 2.09–8.02).

It is not possible to conclude from these data whether the association between COC use and cervical cancer is due to the biological effects of hormones on the initiation and progression of HPV disease or confounding factors that have yet to be identified. It is known that estrogens and progestins influence the immune defense system of the lower genital tract, and this may be a pathway that influences the acquisition and progression of viral disease.[12] From a clinical perspective, cervical cancer is largely preventable with HPV vaccination and screening. Therefore, the risk between COC use and cervical cancer is likely limited to women who have not been

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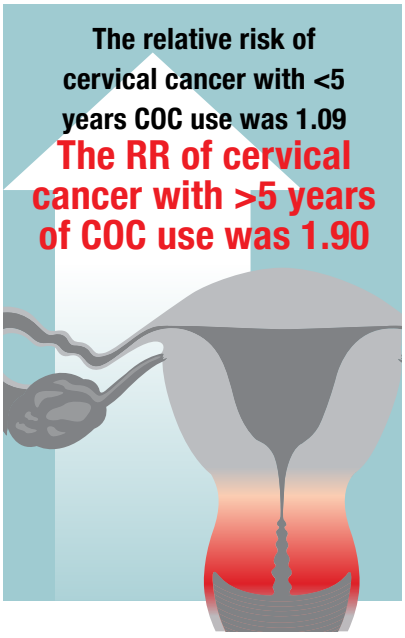

COC use among *BRCA1* and *BRCA2* carriers

Women carrying *BRCA1* and *BRCA2* mutations, which increase the risk of ovarian and breast cancer, are often counseled to consider bilateral salpingectomy between age 35 and 40 years to reduce the risk of developing ovarian cancer. An important clinical question is what is the impact of combination estrogen-progestin oral contraceptives (COC) use on ovarian and breast cancer risk among these women?

Meta-analyses of the association between COC use and ovarian cancer consistently report that COC use reduces the risk of ovarian cancer in women with clinically important *BRCA1* and *BRCA2* mutations.[1,2] For example, a meta-analysis of 6 studies reported that women with *BRCA1* and *BRCA2* mutations who used COCs had a significantly decreased risk of ovarian cancer (odds ratio [OR], 0.58; 95% CI, 0.46–0.73).[1]

The association between COC use and breast cancer risk is not clear. One meta-analysis reported no significant association between COC use and breast cancer risk among *BRCA* mutation carriers (OR, 1.21; 95% CI, 0.93–1.58).[1] Another meta-analysis reported a significant association between COC use before 1975 and breast cancer risk (RR, 1.47; 95% CI, 1.06–2.04) but not with recent low-estrogen formulations of COC (RR, 1.17; 95% CI, 0.74–1.86).[2]

Based on the available data, the Society of Gynecologic Oncologists recommends that women with clinically significant *BRCA1* and *BRCA2* mutations be offered chemoprevention with COCs because the benefit of ovarian cancer risk reduction outweighs the possible impact on breast cancer risk.[3] A contrarian viewpoint espoused by some oncologists is that since women with *BRCA* mutations should have their ovaries removed prior to getting ovarian cancer, the clinical utility of recommending COC chemoprevention of ovarian cancer is largely irrelevant.

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vaccinated and who are not actively participating in cervical cancer screening.

The bottom line

COC use markedly reduces the risk of ovarian and endometrial cancers, and slightly increases the risk of breast cancer. Prolonged COC use may be associated with an increased risk of cervical cancer. Using available epidemiological data, investigators attempted to project the impact of these competing risks on the approximate 12,300,000 females who live in Australia. Based on the pattern of COC use and the cancer incidence in Australia in 2010, the investigators calculated that COC use would cause about 105 breast and 52 cervical cancers and prevent 1,032 endometrial and 308 ovarian cancers.[13] This analysis indicates that the balance of risks and benefits related to COC use and cancer generally favors COC use.

Prevention of unintended pregnancy is a major public health goal. Many women choose COCs as their preferred approach to preventing unintended pregnancy. Evaluated from a whole-life perspective the health benefits of COCs are substantial and represent a great advance in women's health.

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