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**Combined Oral Contraception and Ovarian Cancer Risk Prediction**

By

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## **Introduction:**

Ovarian cancer is the 5<sup>th</sup> leading cause of cancer-related deaths in women and the 2<sup>nd</sup> most common gynecological cancer in the United States. It is often fatal due to the predominance of high-grade disease at clinical presentation and the absence of early symptoms to forewarn of the need for prompt diagnosis and treatment in its early stages. In 2018 there will be approximately 22,240 new cases of ovarian cancer and 14,070 ovarian cancer deaths in the United States.<sup>1</sup> Incidence increases with age; it generally does not occur in young women. The general population has a 0.7% risk of developing ovarian cancer by age 70. Women with BRCA 1 and 2 mutations have a 44% and 17% -chance, respectively, of developing ovarian cancer by 80 years old.<sup>1</sup>

Ovarian cancers are histologically diverse, and include epithelial and non-epithelial (germ cell and stromal tumors) types. Epithelial ovarian tumors are the most common type and are the majority (90%) of ovarian tumors found among all racial/ethnic groups.<sup>1</sup> Epithelial types are further categorized into serous, endometrioid, mucinous, and clear cell with serous being the most common epithelial tumor. Although different types of ovarian cancers exist, they all contribute to significant morbidity and mortality. Early detection could prevent disability and premature death.

In order for prevention to occur, risk factors must be identified. Risk factors for ovarian cancer include BRCA 1 and BRCA2 gene mutations, family history of ovarian cancer, Lynch syndrome, infertility, polycystic ovarian syndrome, endometriosis, and tobacco use. Several large-scale clinical studies have not found any evidence that early detection methods, such as performing transvaginal ultrasound and testing for the tumor

marker cancer antigen 125 (CA-125), have reduced ovarian cancer mortalities. As a result, US Preventive Services Task Force continues to recommend against screening for ovarian cancer in the general population, concluding that there is adequate evidence that annual screening does not reduce ovarian cancer mortality and can lead to important harms, mainly surgical interventions in women screened for ovarian cancer.<sup>1</sup> Despite this recommendation, continued research on this topic may potentially clarify the benefits of future screening methods. In the meantime, primary prevention should be explored because effective early detection methods are lacking. Preventative measures require the identification of risk factors in order to modify them.

Fortunately, research has incidentally identified a risk reduction factor; combined oral contraceptive (COC) use is a protective factor against ovarian cancer. The incidence of ovarian cancer among women younger than age 65 has generally declined at a continuous rate since at least 1965, most likely due to increased use of oral contraceptives.<sup>1</sup> Oral contraceptives were introduced almost 60 years ago. 100,000 women use them every day worldwide.<sup>1</sup> Previous research discovered that not only did the use of oral contraceptives reduce the risk of ovarian cancer, but this protective effect also continued after the oral contraceptive use ceased. Among women who used oral contraceptives for a total of 5 to 9 years, the risk was reduced by about 35%, with the protective effect persisting with diminishing strength for at least 30 years after discontinuation.<sup>1</sup>

COCs provide both contraceptive and non-contraceptive benefits. Since many patients use COCs for either purpose, the possible additional benefits of ovarian cancer protection are worth exploring. General features of COCs would need to be considered, if they are used for ovarian cancer prevention. COCs are primarily indicated for

contraception, acne control, dysmenorrhea, polycystic ovarian syndrome, and endometriosis. Common ADRs include abnormal weight gain, headaches, amenorrhea, nausea, breast tenderness and vaginal infections. Common serious ADRs include thromboembolism, stroke, hypertension, myocardial infarction, depression, and gallbladder disease. Contraindications include hepatic disease, tobacco use older than age 35, hypercoagulopathies, history of stroke, current breast cancer, uncontrolled hypertension, and coronary artery disease. Within the past decade, the decrease in both estrogen and progestin content of newer formulations has resulted in a decrease in side effects and cardiovascular complications.

This paper specifically examines whether women ages 25-50 who have taken oral contraceptives for at least 5 years are at a reduced risk for developing ovarian cancer over their lifetime compared to women ages 25-50 who have never used oral contraceptives. The answer to this question is particularly important in clinical practice in order to implement risk prediction and preventative counseling strategies, particularly for women with BRCA mutations, a strong family history of ovarian cancer, or personal history of breast cancer.

### **Discussion**

An extensive literature search of PubMed, Medline, Embase, Science Direct, Scopus, and Web of Science, and U.S. National Library of Medicine databases was performed using the following search terms: “ovarian neoplasms”, “oral contraception,” “risk factors,” “histotype,” or “protective effects”. Articles were screened for relevance and eligibility criteria. Studies were selected which compared incidences of ovarian cancer among women who have a history of oral contraceptive, compared to non-users. Inclusion

criteria included women between the ages of 20 and 75, parous women, non-parous women, postmenopausal women, and pre-menopausal women. Exclusion criteria included non-human subjects, non-English language studies, and studies published prior to the year 2000. An assessment of quality was performed using article critiques and a table of evidence.

The initial result of the search yielded over 50 articles for review. After screening relevant articles for human studies and primary data, 25 were found that met the inclusion criteria. Out of the 25 articles, four were selected for this discussion based on the most recent publication dates, and most novel contributions to the already well-established facts on this topic.

Of the four studies that investigated the relationship between oral contraceptives and ovarian cancer risk, the findings were fairly consistent among them and with many other studies that examined this risk relationship. Despite age differences among the test subjects, those women having a history of oral contraceptive use clearly had a decreased risk of developing ovarian cancer. All four of these studies had findings that were remarkably similar to results from other studies done in the past; ever users of oral contraceptives had a reduced risk of ovarian cancer compared to non-users, increased duration of use had an increased protective effect, risk reduction in previous users diminished with time. Furthermore, no differences of risk estimates across histological types of epithelial ovarian cancers were found. This consistency in research findings implies that an inverse relationship exists between oral contraceptive use and ovarian cancer risk, with protective effects that lasting beyond the cessation of this form of contraception.

The Beral et al study was a collaborative meta-analysis, which assessed how long the protection from ovarian cancer lasted after oral contraceptive was stopped. It also sought to reinforce the fact that the risk of ovarian cancer decreased with longer durations of use. Data from this study combined 45 epidemiological studies, which included a total of 23,257 women with ovarian cancer (cases) and 23,257 women without ovarian cancer (controls) from 21 different countries. The findings in this meta-analysis revealed that the longer the duration of use, the greater the reduction in ovarian cancer risks. For every 5 years of use an overall 20% risk reduction was achieved. The risk reduction persisted for greater than 30 years, but attenuated over time (29% risk reduction for less than 10 years cessation, 19% risk reduction for use ceased 10-19 years, and 15% risk reduction for use ceased 20-29 years).<sup>2</sup> Once duration of use and time since last use of oral contraceptives were taken into account, no other index of the timing of use had any effect (such as timing in relation to parity).

Taking investigation on risk reduction a step further, the Cook et al study examined the risk of oral contraceptive use before the FFTP (first full term pregnancy). This Canadian case-control study was the first study to explore oral contraceptive use exclusively before and after the first full-term pregnancy and to evaluate the timing of COC use with pregnancy. Contrary to Beral et al, the results revealed that COC use before the first full-term pregnancy was associated with a 40% risk reduction, even with short-term use.<sup>1</sup> Use exclusively after the first birth was associated with a smaller reduction in EOC (epithelial ovarian cancer) risk, with no correlation with increasing duration of COC use.<sup>1</sup> Consistent with other literature, COC use was associated with a risk reduction. Among COC users,

the risk was strongly related to longer durations of use overall, shorter interval since last use, and younger ages at first use.

Iversen et al had findings similar to those found in the Beral et al study, except Iversen et al included subjects who were younger women (age 15-49) and subjects who used contemporary formulations, including progestin-only forms. This large Denmark cohort study included 1,879,227 women. In this study, progestin-only formulations had an insignificant effect on risk reduction. Also, due to the younger ages of women (less than 50 years of age) in this sample, few had used hormone replacement therapy, which has been known to increase ovarian cancer risk. The Beral et al study showed that the only significant exceptions in ovarian cancer risk reduction associated with longer duration of use were related to the age at diagnosis and the menopausal status. The Iversen et al study did not provide information on COC risk in older women, thus could not validate the Beral et al findings. However, older age was taken into account in other studies, such as McGuire V et al.

McGuire V et al investigated whether prior oral contraceptive use and parity have a continued risk reduction as a woman ages (>age 65). Three large US cohort studies were used, with a target population of white women over the age of 50 who developed subsequent invasive epithelial ovarian cancer. The results showed statistically significant risk reduction among COC users compared to non-users. Increasing duration of COC use was also associated with decreasing risk. In addition, patterns of decreasing EOC risk with increasing parity were found in women age < 75. Statistically significant risk reductions were also found for full term pregnancy, 12% per full term pregnancy among women aged

<65 years and 8% per full term pregnancy among women age 65-74 years.<sup>2</sup> In contrast, the lower EOC risk associated with duration of COC use did not vary with attained age.<sup>2</sup>

### **Conclusion:**

The studies evaluated in this paper confirm the protective effects of oral contraceptives against ovarian cancer development. According to the evidence, oral contraceptive use reduces the risk of ovarian cancer, and provides long-term protection. The longer the duration of use, the greater the risk reduction of ovarian cancer. Risk reduction attenuates over time after cessation of use. These studies also revealed that risk reduction does not vary significantly between histological types of epithelial ovarian cancer. Furthermore, implications derived from two of the studies suggested that the risk for ovarian cancer is reduced with increasing parity. This finding suggests that fewer ovulation cycles, whether by use of oral contraceptives or by increased parity, would result in a decreased risk of ovarian cancer by reducing the burden of epithelial cells at risk of conversion to malignancy.

The protective effect of COCs against ovarian cancer as an additional benefit of COC use was established by this evidence. Furthermore, this evidence suggests that COC use for ovarian cancer prevention may be justified as an additional independent indication for COCs. Nonetheless, COCs are not without potential harms. Before prescribing, their contraindications and potential adverse reactions would need to be considered. In particular, when recommending COC's for ovarian cancer prevention (in addition to other indications), a patient's risk for breast cancer would need to be assessed.

Although patients may be counseled based on the evidence in these studies, several new questions emerge. All these studies included women who developed ovarian cancer prior to age 75. Research is needed to assess the development of ovarian cancer in women above this age. In addition, assessment of the protective effects, if any, of progesterone-only products would determine their role in ovarian cancer prevention as well as reveal possible mechanisms of hormonal preventive effects. Lastly, trials to assess the risk of ovarian cancer based on the timing of oral contraceptive use before and after the first full-term pregnancy may uncover underlying biological mechanisms that are unrelated to ovulation. Results from such research could suggest prevention strategies other than ovulation prevention. Overall, findings obtained from future research could further refine means for implementing ovarian cancer risk reduction in high-risk women, especially the use of chemopreventive strategies.

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