CONCISE REVIEW FOR CLINICIANS

Oral Contraceptive Use and the Risk of Breast Cancer

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On completion of reading this article, you should be able to (1) differentiate between the hormonal components used in older vs newer formulations of oral contraceptives and assess their associated risks of breast cancer, (2) demonstrate an ability to make appropriate and individualized clinical decisions regarding oral contraceptive use on the basis of the risks and benefits of the various formulations available, and (3) identify the potential roles played by estrogen in breast carcinogenesis and breast cancer risk factors.

The clinical impact of the association between oral contraceptive (OC) use and breast cancer risk is important given that OCs are the most commonly prescribed contraceptive agent and that more than a quarter of a million women are diagnosed as having breast cancer in the United States annually. Substantial changes to OC formulations have been made during the past decade, and this review focuses on recent OC trends and risks and benefits. We also have a better understanding of how estrogen affects breast carcinogenesis; research on this topic is ongoing and has the goal of decreasing breast cancer incidence and mortality.


**CI = confidence interval; EE = ethinyl estradiol; HRT = hormone replacement therapy; OC = oral contraceptive; OR = odds ratio; RR = relative risk; SERM = selective estrogen receptor modulator**

**INCIDENCE AND MORTALITY**

Breast cancer is the most commonly diagnosed noncutaneous cancer in women in the United States and accounts for the second highest number of cancer deaths. In 2007, an estimated 178,000 women were diagnosed as having invasive breast cancer and another 60,000 women as having noninvasive ductal carcinoma in situ.1

The incidence of invasive breast cancer, after peaking in 2000, has been steadily decreasing, as has the mortality rate. The cause of this decrease in incidence is postulated to be multifactorial. One possible factor is the decline in the use of combined hormone replacement therapy (HRT) after the publication of the Women’s Health Initiative study in 2002.2-4 This study reported that 5 years of combined HRT (estrogen and progesterone) was associated with a 26% increased risk of invasive breast cancer in postmenopausal women.5 Another factor could be the early detection and management of noninvasive and precancerous breast lesions and the subsequent increase in the management of these lesions with selective estrogen receptor modulators (SERMs) as chemoprevention. Additionally, greater emphasis on lifestyle changes, such as increased exercise, decreased postmenopausal obesity, and altered dietary habits, could have contributed to reducing the risk of breast cancer. Finally, more recently, a reported decrease in mammographic screening could have led to a decrease in detection of breast cancer in unscreened women.6 Whether the incidence of breast cancer will continue to decrease into the next decade is unclear, emphasizing the importance of monitoring this trend over time.

The decline in breast cancer mortality is encouraging and is thought to be due to multiple factors. Improved screening that results in detection of earlier-stage cancers with better prognosis and increased detection of noninvasive cancers are contributors to this trend. Furthermore, effective adjuvant therapies using systemic and hormonal agents reduce recurrence of local or nodal disease.7

**ETIOLOGY AND RISK FACTORS**

The etiology of breast cancer is multifactorial and cannot be directly linked to any single factor, including estrogen. The epidemiological literature supports a highly complex interplay between different exposures and host characteristics and between exogenous and endogenous hormones and an individual’s genetic makeup. Clinical and laboratory evidence suggests that estrogen acts as a mammary gland carcinogen, with the strongest evidence emerging from the historical experience with SERMs (which block estrogen receptors) and aromatase inhibitors (which substantially reduce estrogen synthesis). In the adjuvant setting, SERMs and aromatase inhibitors have effectively reduced risk of recurrence by blocking estrogen’s action on the estrogen receptor and by suppressing estrogen synthesis from androgens, respectively.8

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Two major potential mechanisms have been postulated by which estrogens increase the risk of breast cancer. The first mechanism is the stimulation of estrogen receptor-mediated transcription that results in cell proliferation. The second mechanism is direct carcinogenesis via metabolic activation and direct binding of DNA. One hypothesis is that these 2 mechanisms act in an additive or even synergistic fashion to induce carcinogenesis.9,10

Of multiple risk factors for the development of breast cancer, many are directly or indirectly related to endogenous or exogenous estrogen exposure.11 Relative risk (RR) is used to compare the magnitude of risk among risk factors. A woman’s age is the strongest risk factor for breast cancer, and older women have an RR greater than 10 compared with younger women. Women with a family history of breast cancer in a first-degree relative, particularly in one younger than 50 years, have a higher risk (RR, >2). Reproductive risk factors associated with risk of breast cancer include menarche before age 11 years (RR, 2), menopause after age 54 years (RR, 3), and age greater than 40 years at first full-term pregnancy (RR, 3). Exogenous hormone use is a modifiable risk factor; use of HRT for more than 10 years (RR, 1.35) and current or recent use of oral contraceptives (OCs) (RR, 1.24) are both associated with higher risk. Although caution must be used in directly comparing RRs, current knowledge suggests that OC use is one of the weakest risk factors for breast cancer.

**ORAL CONTRACEPTIVES**

**Use and Effectiveness**

More than 100 million women worldwide use OCs. According to a 2005 *Morbidity and Mortality Weekly Report,*12 OCs are the most commonly used contraceptive method for US women. Health care professionals prescribe OCs because they are safe, effective, and well tolerated. Women take them for the same reasons, as well as for convenience.

The effectiveness of OCs and of the other combination hormonal contraceptives including the patch and ring is 99.7% if used exactly as directed and only slightly lower at 92% if the dose is occasionally taken late or not taken. The effectiveness of other contraceptives ranges from approximately 85% for barrier methods, such as condom, sponge, and diaphragm, to upward of 99% for intrauterine devices, subdermal implants, progesterone injection, and sterilization (in both men and women).13,14

**Estrogen and Progestin Components**

Since the introduction of OCs 40 years ago, the progestin and estrogen components have been modified substantially to improve the adverse-effect profile and decrease hormone-associated risks. Desogestrel, norgestimate, and dros-
users. In both groups, the median time to conception was 3 months, and the 1-year pregnancy rate was 80%. This trend was noted in short- and long-term OC users, a finding that should allay the fear that these options have a deleterious effect on future fertility. Currently, it is safe for a woman not to experience a monthly menstrual cycle.

**Benefits**

Oral contraceptives offer many noncontraceptive health benefits, including a decreased risk of bone loss, benign breast disease, pelvic inflammatory disease, ectopic pregnancy, and rheumatoid arthritis. They have been found to be helpful during the perimenopausal years in regulating menses and treating vasomotor symptoms. Patients with acne, hirsutism, premenstrual syndrome, and endometriosis symptoms have benefited from treatment with OCs.¹⁹⁻²¹

**Risks and Contraindications**

Although many of the traditional risks and adverse effects of OCs have been minimized with the newer formulations, some absolute and relative contraindications still exist. Women who have a history of venous thromboembolism or who are at risk for these complications, such as pregnant and newly postpartum patients and those immobilized after surgery, are generally not candidates for combination OCs. Women with history of or at risk for coronary artery disease, such as those with uncontrolled hypertension and current smokers older than 35 years, should consider other contraceptive options. Oral contraceptives are relatively contraindicated in patients with a history of migraines including focal auras. In these patients, ischemic stroke risk increases from an odds ratio (OR) of 6.2 to 13.9 with OC use, although the absolute risk remains very low at 19 of 100,000 women per year.²² Breast and other estrogen-dependent cancers as well as liver disease preclude the use of OCs.²³

It is important to emphasize the risk of unintended pregnancy when effective contraception is not used. In 2003, mortality associated with pregnancy was 12.1 deaths per 100,000 live births; in 2001, mortality associated with termination was 11 deaths per 850,000 legal abortions. In addition, financial and psychosocial implications should be included in patient counseling.²⁴

**OCs VS HRT HORMONES: WHAT ARE THE DIFFERENCES?**

In the wake of the Women’s Health Initiative, it is important to remember that all estrogens are not alike and that estrogen doses, although numerically similar between OCs and HRT, are not biologically comparable. Most OCs available today contain EE. Compared to estradiol, the ethinyl group increases the estrogen’s potency 4- to 18-fold and prolongs its half-life.²⁵ Hormone replacement therapy contains either a mix of conjugated estrogens or 17-β-estradiol. Thus, adverse effects attributable to OCs might not always occur with HRT and vice versa.

Similarly, most progestins currently used in OCs are not the same as those contained in HRT combinations, and thus their potencies and potential risks cannot be readily compared. The exception is drospirenone, a novel antiandrogenic progestin, which has been used in OCs for approximately 5 years and was recently introduced in a postmenopausal combination HRT.

**WHAT IS THE LINK BETWEEN OCs AND BREAST CANCER AND OTHER MALIGNANCIES?**

In 2005, the International Agency for Research in Cancer classified estrogen-progestogen OCs as a group 1 carcinogen, the highest rating, indicating that there is sufficient evidence that these agents are carcinogenic to humans.²⁶⁻²⁷ This evaluation was based on increased risks of breast and cervical cancer, as well as of liver cancer in populations with a low prevalence of hepatitis B infection. This classification is higher than that reported in the 1999 evaluation.²⁸ The report further concluded that there is convincing evidence in humans that these agents confer a protective effect against cancer in the endometrium and ovaries and suggestive evidence for a protective effect against colorectal cancer.

The Oxford pooled analysis, published in 1996, contains the most comprehensive data that addressed the issue of OC use and breast cancer risk. It is based on pooling of original data from 54 epidemiological studies enrolling more than 50,000 women with breast cancer and 100,000 controls.²⁹ Key findings from that analysis included a 24% increased risk of breast cancer in current OC users (RR, 1.24; 95% confidence interval [CI], 1.15-1.33), a weaker but still elevated risk in recent OC users (1-9 years after discontinuation), but no increased risk 10 or more years after discontinuation of OCs (RR, 1.01; 95% CI, 0.96-1.05). The risk was also greater in women who began taking OCs before age 20 years and in women who used OCs before the birth of their first child, a time when breast tissue is thought to be more susceptible to carcinogens. This effect was also reported in a more recent meta-analysis by Kahlenborn et al.³⁰

Although the aforementioned studies strongly support an association between OCs and breast cancer risk, the RR is small, and the absolute risk (excess breast cancer cases due to OC exposure) is very small. For example, only a small number of additional cases of breast cancer were noted among 10,000 European or North American women.
in the 10 years after discontinuation of OCs: 0.5 cases, for OC use from age 16 to 19 years; 1.5 cases, for OC use from age 20 to 24 years; and 4.7 cases, for OC use from age 25 to 29 years. This very small excess risk must be put into perspective when counseling women and weighing the overall risks vs benefits of OC use.

Furthermore, these studies29,30 are based on older data with higher-dose estrogen and older progestin OC formulations. The largest modern study, published in 2002, enrolled more than 4500 patients with breast cancer and 4500 controls aged 35 to 64 years from the United States from 1994 to 1998.31 Key findings included no breast cancer risk among current (OR, 1.0; 95% CI, 0.8-1.3) or former (OR, 0.9; 95% CI, 0.8-1.0) OC users and no risk associated with duration of use or dose of estrogen. Moreover, a recent study of OC use in more than 4200 patients with breast cancer found no association between breast cancer mortality and OC use when duration of OC use, time since first use, age at first use, and use of specific formulations were examined.32 Breast cancer risks with the newest formulations of OCs are still unknown but are predicted to show no association with the dose and composition of the estrogens and progestins being used. However, future studies will need to evaluate this empirically.

HIGH-RISK WOMEN AND OC USE

The risk of breast cancer has been reported to be particularly high among OC users with a family history of breast cancer in first-degree relatives compared with women with no such history, but this was noted only for OC use before 1975, when estrogen doses were much higher.33 The Oxford pooled analysis29 and the large US study31 found no difference in the association between breast cancer and OC use by family history. Similarly, the association between OC use and breast cancer risk does not appear to be modified for women who have BRCA1 and BRCA2 mutations, although data are more limited.34-36

COUNSELING WOMEN REGARDING OC USE

In counseling a woman regarding OC use, physicians should (1) discuss the relative and absolute risks (including those associated with unintended pregnancy), benefits, and alternatives in a thorough and individualized manner; (2) present all available and appropriate options clearly, accurately, and without bias; if the data are unclear, the patient should be apprised of this fact; (3) consider the patient’s value system and explore her anxiety and fears to help her make an informed choice; and (4) reassess the patient’s choice periodically as new information becomes available and as her medical or life situation changes.

CONCLUSION

Oral contraceptives are a highly effective, safe, well-tolerated, and convenient contraceptive method for a substantial number of women in the United States. They are contraindicated in certain groups of patients. Given the variety of formulations currently available, therapy can and should be individualized to the patient’s needs. Although epidemiological studies have documented a small increased risk of breast cancer associated with use of older OC formulations, recent studies that included newer formulations have not detected an increased risk. Even with the older formulations, the absolute (or excess) risk of breast cancer is minimal. Thus, current evidence suggests that OCs do not play a clinically important role in the risk of breast cancer. This evidence must also be weighed against the effect on other health outcomes and the risks associated with other contraceptive methods and with unintended pregnancy.

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CME Questions About OC Use and Risk of Breast Cancer

1. Which one of the following statements about OCs is true?
   a. The estrogen compounds in OCs and in HRT are not comparable
   b. The biological activity of the estrogen components of HRT and OCs is comparable
   c. Postmenopausal women should not take OCs
   d. Oral contraceptives have lower doses of estrogens than HRT
   e. The biological activity of the estrogens in OCs is different in premenopausal vs. postmenopausal women

2. A 20-year-old nulliparous woman presents to discuss birth control and is interested in taking OCs. She is otherwise healthy and does not smoke. Which one of the following is true?
   a. Because of her family history, she is at increased risk of breast cancer, and therefore OC use is not recommended
   b. She should try alternative birth control options because they are more effective
   c. She should be informed of the risks and benefits of OC and then a prescription should be written
   d. The baseline risk of breast cancer is unacceptably high in this patient’s age group.
   e. Screening mammography should be performed before OC use can be recommended

3. A 38-year-old single woman in a new relationship presents to discuss birth control. Her mother was diagnosed as having breast cancer at age 45 years. The patient is otherwise healthy and quit smoking 2 years ago. Which one of the following is the best answer regarding OC use?
   a. Oral contraceptives are contraindicated in women older than 35 years
   b. Oral contraceptive use is associated with a significant reduction in both endometrial and ovarian cancer risk
   c. There is strong evidence of continued increased breast cancer risk after discontinuation of OC use
   d. Because the patient was a smoker, health risks for using OCs are unacceptably high
   e. Because the patient is at risk for sexually transmitted diseases, her best contraceptive option is condoms
4. A 48-year-old woman presents with bothersome hot flashes and irregular menstrual bleeding of 6 months’ duration. She has a history of endometriosis but is otherwise healthy and a nonsmoker; her mother has osteoporosis. Which one of the following is the best answer regarding OC use during the perimenopausal years?
   a. Oral contraceptives are effective in the management of dysfunctional uterine bleeding
   b. Hormone replacement therapy is the best option for this woman
   c. Oral contraceptives should be prescribed at the lowest dose for the shortest period because of hormonal exposure and the associated increased risk of breast cancer
   d. Unfortunately, OCs will not help decrease hot flashes
   e. Irregular bleeding due to endometrial hyperplasia could be masked by OCs

5. Which one of the following best describes the contribution of estrogens in the development of breast cancer based on experimental and epidemiological data?
   a. Short-term exposure to estradiol
   b. Rate of cell proliferation increased by stimulating estrogen receptor–mediated transcription resulting in errors in DNA replication
   c. Menarche onset after age 11 years
   d. Early menopause before age 54 years
   e. Exogenous estrogen secondary to OC use

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