PHARMACY REVIEW

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Hormonal Contraception and Breast Cancer Risk

Abstract: *Contemporary hormonal contraception formulations contain lower doses of estrogen, have new synthetic progestin components, and provide novel methods of delivery that have not been studied extensively in relation to breast cancer risk. Given that hormonal contraception is the leading method of birth control in the United States, it is important to reevaluate risk using current formulations. Recent studies including contemporary hormonal contraception formulations will be described.*

Keywords: breast cancer; birth control; estrogen; hormones; contraception

The relationship between the use of oral contraceptives and breast cancer has been broadly studied. In 1996, a pooled analysis of more than 150 000 women from 54 studies worldwide analyzed the relationship between breast cancer and use of hormonal contraceptives.[1] The evaluation revealed an increased risk (relative risk [RR] = 1.24; 95% confidence interval [CI] = 1.15-1.33) of breast cancer in current or recent (within the last 12 months) users of oral contraceptives. This increased risk was no longer evident 10 years after cessation of hormonal therapy, and other variables, including duration of use, age of initiation, and pharmacotherapeutic formulation, had little additional effect on risk.

This study included approximately 90% of the epidemiologic information on the topic at the time of publication and thus seemed to provide a strong level of evidence supporting the association between hormonal contraception and breast cancer. However, there are limitations and additional gaps in knowledge regarding the relationship between hormonal contraception and breast cancer risk. The majority of breast cancer cases from the aforementioned study were diagnosed in the 1980s and included only oral contraceptive pills. Contemporary hormonal contraception formulations contain lower doses of estrogen, have new synthetic progestin components, and provide novel methods of delivery including intrauterine devices, patches, vaginal rings, implants, and injections as well as extended cycle formulations. Given that hormonal contraception is the leading method of birth control in the United States, utilized by 9.7 million women, it is important to reevaluate risk using updated data which includes these changes.[2,3] Below a summary of recent studies evaluating contemporary hormonal contraception will be discussed.

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Contemporary Hormonal Contraception and Breast Cancer Risk

Mørch et al

One of the largest studies, published in December of 2017 in the *New England Journal of Medicine*, evaluates data from a Danish sex hormone registry.[4] The study included 1.8 million women aged 15 to 49 years between January 1, 1995, and December 31, 2012. The mean follow-up for the study was approximately 11 years, and 11 517 breast cancer cases were identified. Hormonal contraceptive use was categorized as current or recent use (within the last 6 months) or previous use (discontinuation more than 6 months previously).

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The study found that compared with women who had never used hormonal contraception, the relative risk of breast cancer in current or recent users was increased (RR = 1.20; 95% CI = 1.14-1.26). Interestingly, the study also found that risk of breast cancer increased with duration of use and that women who used hormonal contraception for more than 5 years had increased risk for at least 5 years following discontinuation of therapy. The study included various contemporary formulations of hormonal contraceptives (low-dose estrogen, new progestins, non–oral delivery systems). A subgroup analysis of the various oral progestin components suggested no difference in breast cancer risk across products. Levonorgestrel-only oral and intrauterine device formulations were also associated with increased risk of breast cancer (RR = 1.93, 95% CI = 1.18-3.16, and RR = 1.21, 95% CI = 1.11-1.33, respectively). There were limited breast cancer cases among users of non–oral combined hormonal contraception delivered by patch or ring and progestin-only implant or injection formulations and thus insufficient evidence to identify a statistically significant increased risk of breast cancer in these groups.

Beaber et al

Beaber et al conducted a nested case-control study among women aged 20t o49 years from 1989 to2009 utilizing pharmacy dispensing data and health data from the Cancer Surveillance System registry.[5] In total, 1102 breast cancer cases and 21 952 matched controls were included in the final analysis. Only combined oral hormonal contraceptives were included (progestin-only and non–oral formulations were excluded).

The study found that recent (within the last 12 months) combined oral contraceptive use was associated with a 50% increased risk (odds ratio [OR] 1.5; 95% CI = 1.3-1.9) for breast cancer compared with never or former use (discontinuation at least 12 months prior). The study also found that recent use of high-dose estrogen (OR = 2.7; 95% CI = 1.1-6.2), ethynodiol diacetate (OR = 2.6; 95% CI = 1.4-4.7), or triphasic dosing with an average of 0.75 mg of norethidrone (OR = 3.1; 95% CI = 1.9-5.1) was associated with a particularly high risk (OR >2) compared with other formulations.

Lovet et al

In the United States, women today are, on average, younger at menarche, older at first full-term pregnancy, have fewer live births and experience lactational amenorrhea for shorter durations than women in natural fertility populations.[6] The availability of oral contraceptives certainly plays a role in the current pattern of frequent menses and associated increased hormonal exposure, but what is unknown is whether oral contraceptives further increase or possibly decrease hormonal exposure over the course of a menstrual cycles. Lovet et al compared the pharmacokinetics of 7 of the most commonly used oral contraceptives to endogenous hormone levels over one menstrual cycle in women aged 19 to 40 years. The study found no difference in exogenous versus endogenous estrogen exposure, regardless of formulation, but did identify 4 formulations that increased levels of progesterone exposure compared with endogenous exposure from ovulatory menstrual cycles.[1] Specifically, formulations that contained levonorgestrel, norethindrone, or drospirenone more than quadrupled progestin exposure compared to endogenous levels. The authors hypothesized the increased progestin exposure may play a role in breast cancer risk; however, further research is needed to confirm.

Discussion and Conclusions

Evaluations of contemporary hormonal contraceptive formulations support previous findings of an approximately 20% increased risk of breast cancer for women who are using or have recently used hormonal contraception. Literature also indicates that this risk may increase with duration of use and that risk may persist for up to 5 years in women who have used hormonal contraception for at least 5 years. This finding is further supported by a recent evaluation of lifetime cancer risk in which women who utilized oral hormonal contraceptives had similar breast cancer risk to never users within 5 years of discontinuing therapy.[7] Women in the lifetime cancer risk study were followed for up to 44 years. Importantly, the authors note that because of the lengthy follow-up most of the hormonal contraceptives used were high-dose estrogen combined oral contraceptives and cautioned findings from their study "may not reflect the experience of today's user," The lifetime cancer risk study also found that compared with nonusers, women who used oral hormonal contraceptives had reduced risks of colorectal, endometrial, ovarian, lymphatic, and hematopoietic cancers and these benefits persisted for many years following pharmacologic cessation. Although the long-term cancer benefits of contemporary hormonal contraceptives have not been studied, the cancer risks of hormonal contraception should be balanced with the potential cancer reduction benefits later in life.

In sum, there appears to be an increased risk of breast cancer in women using combined oral contraceptives, regardless of progestin component or monophasic versus extended cycle administration. An increased risk was also identified in levonorgestrel-only oral and nonoral products. However, most women who choose to use these methods of contraception do not expose themselves to long-term breast cancer risk and may benefit from reduction of other types of cancer later in life. Further research is needed to determine the breast cancer risk of nonoral combined contraceptives and non-levonorgestrel progestin-only formulations. Furthermore, recent studies suggest there could be a difference in progestin exposure and breast cancer risk across available synthetic preparations, and additional research should focus on the comparative risks associated with different formulations.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

Not applicable, because this article does not contain any clinical trials. AJLM

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