

Hormonal Contraception and Breast Cancer: Keeping Perspective

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In October 2006, a meta-analysis was published in the *Mayo Clinic Proceedings* on the effects of combined oral contraceptive (COC) use on premenopausal breast cancer.¹ Unlike previous attempts to examine the effects of oral contraceptives (OCs) on breast cancer, this study included only reports in which cases and controls were under 50 years of age and the diagnosis of breast cancer was made after 1980. This methodological approach was intended to give a better snapshot of the effect of modern OC usage on breast cancer in the premenopausal age group. Among 60 potential publications that were identified, 39 met these inclusion criteria. Not all of these studies could be included in all parts of the analysis because some were missing important information that was necessary for stratification of subjects.

Standard meta-analytic techniques were employed with independent extraction of data by two reviewers. In addition to ascertaining study design and details of exposure and outcome measures, the authors collected information on ever-use of OCs, ever-use in parous and nulliparous women, and use (either before or after) first full-term pregnancy (FFTP) in parous women. However, no quality assessment criteria were applied, and this may have contributed to the heterogeneity of results in regard to the effects of OCs in nulliparous women.

A decade ago, the landmark Collaborative Reanalysis examined the pooled original data from 54 epidemiological studies representing 53 297 women with breast cancer and 100 239 controls (representing 90% of the published literature on the subject at that time).² These authors reported a relative risk (RR) of breast cancer diagnosis of 1.24 (1.15–1.33) in women currently taking COCs and in the 10 years after stopping. This RR fell to 1.16 (1.08–1.23) one to four years after stopping OC use and further to 1.07 (1.02–1.13) five to nine years after stopping use. There was no increased risk observed after being off OCs for 10 years.

The absolute attributable risks calculated from these findings were low because the background rates of breast cancer in premenopausal women are so low (approximately 42 per 100 000 women per year). Estimates suggested that for women using COCs from age 16 to 19, there would be 0.5 additional breast cancers per 100 000 women during the time of use and the 10 years of follow-up (the time during which the RR remained slightly increased); for those using COCs from 20 to 24, there would be 1.5 additional cancers, and for those using COCs from 25 to 29, there would be 4.7 additional cancers.

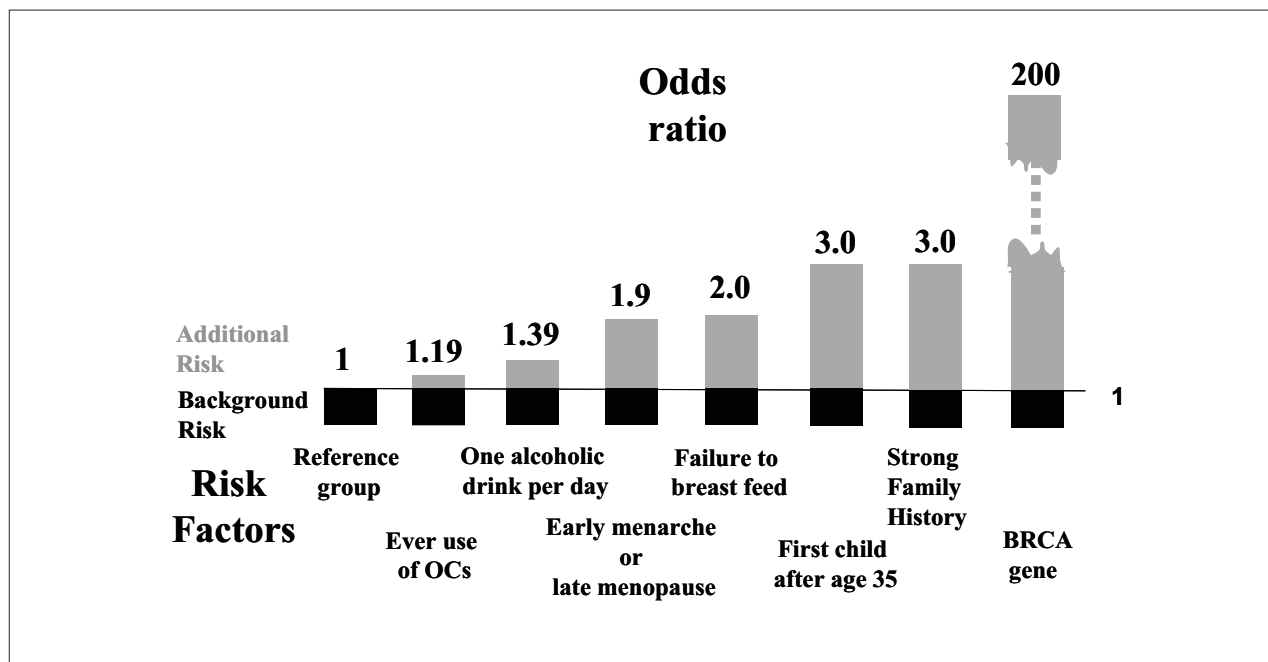
In the Collaborative Reanalysis, however, 66% of cases were in women aged 45 or older, and half the cases were diagnosed prior to 1984, suggesting that the findings reflected outcomes based on differing (older) patterns of contraceptive hormone exposure.

In 2002, a reassuring report by Marchbanks and colleagues suggested little impact of OCs on breast cancer risk in women aged 35 to 64.³ These investigators interviewed 4575 women with breast cancer and 4682 controls. They found the RR for breast cancer in women who were currently using OCs was 1.0 (0.8 to 1.3) and in those who had previously used them was 0.9 (0.8 to 1.0). The RR did not increase consistently with longer periods of use or with higher doses of estrogen. The results were similar among white and black women. Use of OCs by women with a family history of breast cancer was not associated with an increased risk of breast cancer, nor was the initiation of use at a young age.

The report from Kahlenborn et al.,¹ in addition to including only studies with more recent case accrual, included six new data sets from studies that had not been published at the time of the Collaborative Reanalysis. The common odds ratio (OR) for premenopausal breast cancer diagnosis in ever users of COCs of 1.19 (1.09–1.29) was remarkably similar to that reported in the Collaborative Reanalysis.

The findings in this study differ little from the results of the 1996 Collaborative re-analysis, but subgroup analysis of the

Comparisons of relative risks for breast cancer



impact of OC use before or after FFTP provides important new information. The evidence that the breast is more susceptible to carcinogenic insults before the differentiation that occurs during FFTP is compelling.^{4,5} Breastfeeding can further reduce breast cancer rates by as much as 50%.⁶

Given the changes in hormonal contraceptive use over the past 25 years (earlier and longer use, shortened hormone-free intervals, use of new progestins, and a variety of new delivery systems), understanding the effect of hormonal contraception during this potentially vulnerable period in breast development is important.

Among parous women, Kahlenborn et al. found that the OR for breast cancer was greater when COCs were used before FFTP (1.44 [1.28–1.62]) rather than after FFTP (1.15 [1.06–1.26]).¹ This is consistent with an adverse effect of COCs at a time when breast differentiation is incomplete. However, it is also known that a woman's risk of breast cancer is directly related to her age at the time of her first term pregnancy (i.e., the younger the mother, the lower her lifetime risk of breast cancer).⁷ Accordingly, the use of contraception to delay pregnancy could, in theory, increase the risk of breast cancer. This might account for the findings that OC use had the greatest effect in parous women when it was used to delay FFTP (OR 1.44) and that COC use in nulliparous women had a lesser effect on breast cancer risk (OR 1.29). To avoid having delay in FFTP as a confounding variable, this effect should be studied in groups of

women with a pregnancy at the same age, half of the women having used and half having never used hormonal contraception.

The nature of a meta-analysis does not allow authors to control for known breast cancer risk factors in individual women, such as age at menarche; yet women with earlier sexual maturation may just be the women who start OC use early and before FFTP. Earlier menarche is a well-recognized risk factor for breast cancer: women whose menarche is before age 12 have a 30% higher risk than women who begin menstruation after age 15.⁸

To be able to understand and interpret the significance of the ORs presented in the study of Kahlenborn et al., we must determine the absolute level of risk attributable to hormonal contraception and put this risk into perspective by comparing it with other known risks (reproductive and other). As always, the possible risks of an intervention must be balanced against potential benefits. The importance of reliable and safe contraception for younger women cannot be overstated. The considerable non-contraceptive benefits of hormonal contraception (including significant reductions in the incidence of ovarian and endometrial cancers) have been the subject of a recent review.⁹

The absolute rate of premenopausal breast cancer in North America is approximately 42 cases per 100 000 women per year.¹⁰ This information allows the calculation of the attributable risk (i.e., the number of premenopausal breast

cancers directly attributable to ever use of OCs) based on the ORs provided by Kahlenborn et al.¹ The overall risk of premenopausal breast cancer attributable to use of COCs is an additional eight breast cancers per 100 000 past users per year (or 0.8 additional cases per 10 000 women per year who used COCs). The attributable risk when used before FFTP is 1.8/10 000 users per year and after FFTP 0.6/10 000 users per year. Epidemiologist James Cerhan wrote the accompanying editorial in which he correctly concluded that the relative risk identified was “small” and that the absolute risk was “very small.”¹¹ The risk appears to be slightly greater for women using COCs before FFTP.

Finally, it is instructive to consider how the risk of breast cancer is influenced by other factors, because this is the only way to put the risks of hormonal contraception into context. Lifestyle variables such as failure to exercise, excessive ingestion of alcohol, cigarette smoking, postmenopausal obesity, and reproductive variables such as early menarche, late menopause, first full-term pregnancy after age 35 (in 2005, 25% of the North American women delayed their first pregnancy until after age 35), and reduced breastfeeding are all known to increase breast cancer risk significantly.^{12–17} Each of these factors increases the risk of breast cancer more than the risks reported for COCs by Kahlenborn et al.¹ Familial and genetic factors have the greatest effect on premenopausal breast cancer risk, with ORs ranging from 3 in those with a strong familial history to as high as 200 for those carrying BRAC gene mutations (Figure).¹⁸

In summary, the recent meta-analysis by Kahlenborn and colleagues has demonstrated a small but significant increase in the risk for premenopausal breast cancer among women who use COCs, with the risk being slightly greater for women who use COCs prior to first full-term pregnancy. The absolute risk for an individual woman is very small. According to the World Health Organization CIOMS classification of adverse events, it would be considered “rare” for most women (< 1/10 000).¹⁹

More and more women are choosing to delay first birth to advance their education and careers. Because the average age at sexual debut is lower than ever before, there are significant societal benefits when first pregnancy is delayed through the effective use of contraception. Women need to understand both the risks and benefits of hormonal contraception, and health care providers need to communicate these in a way that puts breast cancer risks into perspective by comparison with other lifestyle and reproductive factors.

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