Oral contraceptives and the risk of breast cancer

Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med* 2002;346(26):2025-32.

Background: The putative association between oral contraceptive (OC) use and breast cancer has long been a source of uncertainty and controversy. Although the Cancer and Steroid Hormone (CASH) case–control study,[1] published in 1986, showed no such association (relative risk 1.0, 95% confidence interval [CI] 0.9–1.1), a 1996 systematic overview,[2] which pooled the results of 54 epidemiological studies, showed a modest increase in the risk of breast cancer in current OC users (relative risk 1.24, 95% CI 1.15–1.33). This meta-analysis also demonstrated that the relative risk declined progressively after termination of OC use.

Question: Is there an association between current or former OC use and the development of invasive breast cancer in women between the ages of 35 and 64 years?

Design: The Women's Contraceptive and Reproductive Experiences (Women's CARE) Study was a population-based case–control study conducted in 5 US sites that involved over 9000 participants. Case subjects were women between the ages of 35 and 64 in whom invasive breast cancer developed between 1994 and 1998. Control subjects were selected at random, and in a 1:1 ratio, from a sample of eligible subjects without breast cancer (stratified according to age, race and study site), identified through random digit dialing.

Structured, standardized face-to-face interviews were conducted to ascertain the following information from all participants: date of diagnosis (or, in control subjects, date of telephone screening), use of OC and other hormonal therapies, history of reproductive and general health, and family history of breast cancer. Data were analyzed using conditional logistic regression to develop odds ratios as an expression of relative risk. Confounding variables considered included number of term pregnancies, body mass index, menopausal status, family history of breast cancer, education level, income level, level of physical exercise, number of breast biopsies, breast-feeding, smoking status, alcohol consumption, tubal ligation, mammography, comorbid illnesses, use of contraceptive injections or implants, and age at menarche, first term pregnancy and menopause.

Results: The mean age of the participants was 49.6 years, and 65% were white. Current or former OC use was documented in 77% of the 4575 case subjects and in 79% of the 4682 controls. Compared with the control subjects, the case subjects had significantly fewer term pregnancies (2.1 v. 2.3, $p < 0.01$), were older at the first term pregnancy (23.1 v. 22.9 years, $p = 0.02$) and were more likely to report a family history of breast cancer (17.0% v. 9.7%, $p < 0.01$). Among the postmenopausal women, age at menopause was significantly higher among the case subjects than among the control subjects (47.0 v. 45.2, $p < 0.01$). Current or former use of hormone replacement therapy was reported more often by control than by case subjects (41.3% v. 38.0%, $p < 0.01$).

No significant association between OC use and breast cancer was found. The relative risk of breast cancer was 1.0 (95% CI 0.8–1.3) among current OC users and 0.9 (95% CI 0.8–1.0) among former OC users. Subgroup analysis of various aspects of OC use, including estrogen dose, duration of use, age at first use and interval since last use, failed to demonstrate any association with breast cancer. The results of the analysis for younger subjects (aged 35–44 years) were similar to those for older subjects (aged 45–64). Similarly, race was not found to have any significant influence on relative risk.

Commentary: Case–control methodology is useful in evaluating the association between alleged risk factors (e.g., oral contraceptives) and infrequent outcomes (e.g., breast cancer), especially when it is either impractical or unethical to undertake randomized controlled trials. Recall bias, which can threaten the validity of case–control studies, was minimized in the Women's CARE Study through the use of such visual aids as photographs of hormonal medications and a life-events calendar. Taking measures to enhance recall is particularly important when the latent period between putative exposure and the outcome of interest is long, as it was in this study (time since last OC use was 20 years for 3702 participants).

Practice implications: The Women's CARE Study — conducted 30 years after the widespread introduction of oral contraception — confirms the results of the 1986 CASH study. Practitioners prescribing oral contraceptives can reassure their patients that there is no significant association between OC use and subsequent breast cancer.

Donald Farquhar
Division of Internal Medicine
Queen's University
Kingston, Ont.

References

1. Oral-contraceptive use and the risk of breast cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *N Engl J Med* 1986;315:405-11.
2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713-27.