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# Hormonal Contraception and Birth Control

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## Abstract

The recent Danish cohort study reported a 20% l increased risk of breast cancer among current and recent hormonal contraception users. These results are largely consistent with previous studies. This study did not report on stage of disease at diagnosis and it is not clear to what extent the apparent increased risk may be due to a small advance in the timing of diagnosis. This study did not report on the risk associated with the use of a 20 mcg ethinyl estradiol pill. They did find an increasing risk in current users of longer duration and an increased risk with use of the levonorgestrel intra-uterine system – both of these potentially important findings have not been consistently found in previous studies and require further investigation. The breast cancer effects described now in multiple studies wane with time, and in the long-term HC use has been found not to be associated with any increased total cancer risk.

The recent publication by Mørch and colleagues[1] has reignited decades of controversy about the role of hormonal contraceptives (HC) in breast cancer risk. This analysis used nationwide Danish registries to identify breast cancer cases among women aged 15–49 and filled prescriptions for HC (including the levonorgestrel-intrauterine system (LNG-IUS)). The analysis included 11,517 invasive breast cancers among 1.8 million Danish women. The relative risk (RR) of breast cancer among current and recent (within 6 months) HC users was 1.20 (95% CI 1.14, 1.26), and the risk was greater among women with more than 10 years of current or recent use. The RR with combined oral contraceptive (COC) use was 1.19 and similar for the two dose levels of ethinyl estradiol (EE2) they reported on, namely, 50 mcg and 20–40 mcg. They gave no breakdown of the numbers within the 20–40 mcg dose range and they did not present the risks associated with a 20 mcg dose separately. The increased risks reported for individual COC formulations, separated by progestin type, were each compatible with the overall risk estimate.

These results largely agree with previous studies. The Collaborative Group analysis of HC and risk of breast cancer, which was published in 1996, included 53,297 cases from 54 studies combined in an individual data meta-analysis.[2,3] Nearly half of the cases were diagnosed by age 49, and the analysis had substantial data on the risks associated with COCs containing less than 50 mcg of EE2 – their under 50 mcg results were not broken down further, and are unlikely to have contained a significant amount of data on 20 mcg EE2

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COCs. Their analysis found a RR of 1.24 (95% CI 1.15, 1.33) among current or recent (within 1 year) COC users with a reduced but still elevated risk for up to 9 years in past users. Their analysis did not identify a formulation effect, or a duration effect after adjusting for recency of use. Notably, the Collaborative Group found that cases associated with COC use were more likely to have localized breast cancer; this suggests that a portion of the increased risk could be due to earlier diagnosis among the COC users. The authors wrote "It is not possible to infer … whether the patterns of risk observed are due to an earlier diagnosis of breast cancer in [COC users], the biological effects of hormonal contraceptives, or a combination of both factors. Further information is needed on whether women who have used hormonal contraceptives are more likely to have their cancers detected earlier." Twenty years later, we still need such additional information. The Danish study did not report on stage of disease.

U.S. clinicians have perhaps relied more on the apparently reassuring results from a U.S. case-control study conducted at five sites, which was published in 2002,[4] included 4575 women diagnosed with breast cancer aged 35–64. (Half of the cases were older than the cases identified in Denmark and thus unlikely to be current COC users.) That study reported no association between current or recent (within 6 months) COC use and breast cancer risk. Close reading of the paper shows unexplained differences in results by study center with reported RRs for current use from 0.4 – 1.7, which are difficult to interpret. Their results in younger women showed a small increase in risk that is compatible with the Danish and the Collaborative Group results.[5] Results from other more recent U.S. studies agree with risks reported in the Danish cohort study and the Collaborative Group's analysis including results from the Nurses' Health Study II (NHS-II) with 1344 breast cancer cases (RR for current users was 1.33, 95% CI 1.03–1.73),[6] and a nested case-control study from the Group Health Cooperative (GHC) in Washington State with 1102 cases (RR for current users was 1.5, 95% CI 1.3–1.9).[7] The NHS-II results agree with the Danish cohort results in finding an increasing risk with increasing duration of use (among current users). The GHC results were notable in finding a RR of 1.0 (95% CI 0.7, 1.8) among women using a 20 mcg EE2 COC; other studies have not reported on this EE2 dose separately.

The Danish study reported a RR of 1.21 (95% CI 1.11, 1.33) for women who had used a LNG-IUS within 4 years prior to breast cancer diagnosis.[1] Previous studies of this association have mixed results. In the single published case-control study of 5113 German and Finnish breast cancer cases, no increased risk of breast cancer was seen with LNG-IUS use compared to copper IUD use.[8] A large cohort study in Finland comparing the breast cancer risk of LNG-IUS users to the general Finish population found an increased risk in the LNG-IUS users, but this study was unable to adjust for any breast cancer risk factors other than age.[9] A much smaller cohort study in Israel with an internal control group did not find any increased risk in LNG-IUS users, but this study also did not adjust for any breast cancer risk factor other than age.[10]

Studies of menopausal estrogen-progestin therapy (EPT)[11,12] have shown that progestins have a key role in breast cancer risk. Comparing the progestin exposure with EPT use to the exposure with the LNG-IUS is challenging due to the different progestin formulations used with different relative potencies.[13] However, using published data,[13,14,15] one can estimate

that progestin exposure at 6 months of LNG-IUS use may be roughly half of the progestin exposure with EPT (2.5 mg of medroxyprogesterone acetate), and thus it is at least plausible that LNG-IUS use could influence breast cancer risk. Since current use of the LNG-IUS in the Danish cohort did not account for previous method use, it is also plausible that the elevated risk from LNG-IUS use could relate at least in part to recent prior COC use, rather than solely to LNG-IUS use itself. The Danish cohort had too little exposure to DMPA, contraceptive implants, and most oral progestin-only pills to report precise risk estimates for those progestin-only methods, which are more widely used in the U.S.

A common reaction to these studies is to search for flaws in those studies with results that one does not prefer. None of the studies considered here was perfect, but neither were any fatally flawed. All used reliable diagnoses of invasive breast cancer; however, almost all did not report on stage of disease, and further reporting on stage may help us understand to what extent the apparent risks may be due to a small advance in the timing of diagnosis. These studies have differences in the completeness, accuracy, and classification of HC exposures. The studies also varied greatly in their ability to adjust for other breast cancer risk factors, and none of the studies adjusted for the increase in breast cancer that may last for up to 10 years after a birth.[16] Clinicians and women (and pharmaceutical companies) all hope that lower estrogen doses will yield a ‘safer’ HC; however, of all these studies only the GHC study reported on breast cancer risks with a 20 mcg EE2 COC. Despite their different methodological limitations, these studies generally agree that HC use is associated with a small increase in breast cancer risk among current and recent users. The use of HCs is concentrated among relatively young women in whom the absolute risk of breast cancer is low, and thus the consequent number of additional cases is low.

Isn’t any increase in breast cancer risk unacceptable? To address this, we must consider a larger set of health outcomes, particularly regarding cancer. The Oxford-FPA cohort study recruited over 17,000 women in 1968–1974 at 17 family planning clinics and ended in 2010 with over 600,000 woman-years of observation.[17, 18] The study used annual follow-up and cancer outcomes and vital status were identified by record linkage to Central Registries. Cancer incidence and mortality among COC users was significantly lower for endometrial and ovarian cancers (compared to non-users) with these benefits continuing for decades after COC discontinuation. Cervical cancer incidence and mortality was significantly higher among COC users. Cohort members accrued 1087 breast cancers; the incidence of and mortality from breast cancer were unrelated to COC use. Total cancer mortality was lower for COC users than non-users. The Royal College of General Practitioners (RCGP) cohort study began in 1968 with recruitment of 23,000 COC users and 23,000 non-users.[19] The RCGP study continues to follow the cohort with over 1.2 million woman-years observation, using record linkage to identify vital status and outcomes, and recently reported on long-term cancer risk; that study found significant decreases in ovarian, endometrial, colo-rectal and lymphatic/hematopoetic cancers. Current and recent (within 5 years) COC users had an increased risk of breast cancer, but this risk abated within 5–15 years of stopping. COC users had an increased risk of cervical cancer which abated within 15–25 years of stopping. The RR for ‘any cancer’ in the RCGP cohort was 0.99.

The latest results are disappointing, but generally consistent with what we already know – a relatively small and temporary increase in breast cancer during COC use. What we still need to know is whether the effect is biological or diagnostic, and further information about stage at diagnosis, and the effect of duration of use including in past users, will help to untangle this – information that many of the studies cited here could evaluate. Similarly, we still need to know more about the 20 mcg EE2 dose, which some of these studies can also further evaluate. Finally, the relationship between the LNG-IUS and breast cancer may be biological or may be due solely or in part to unmeasured confounding in any of the studies on that topic, and further work is needed before making any clinical recommendations. We can certainly tell patients that the breast cancer effects described now in multiple studies wane with time, and in the long-term HC has been found not to be associated with any increased total cancer risk.

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