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## Commentary

## A paediatric perspective on hormonal contraception and breast cancer risk: New literature about a recurring question

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### Abstract

*The New England Journal of Medicine* recently featured an original research article, 'Contemporary Hormonal Contraception and the Risk of Breast Cancer'. (Source: Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med* 2017;377(23):2228–39). This study of 1.8 million women ages 15 to 49 years in Denmark found that women who were currently or recently using any type of hormonal contraception had an increased risk of breast cancer and this risk increased with longer duration of use. To date, the implications of this study have focused on older female populations. In this commentary, the authors summarize the key findings of the study and discuss its unique implications for adolescents. The authors emphasize that health care providers need not change their practice as a result of this 'old but new again' controversy and should continue to support the prevention of unintended pregnancy by promoting access to ALL forms of contraception.

**Keywords:** Adolescent, Birth control, Breast cancer, Contraception.

In December 2017, *The New England Journal of Medicine* featured an original research article, 'Contemporary Hormonal Contraception and the Risk of Breast Cancer' (1). This study of 1.8 million women ages 15 to 49 years in Denmark observed that women who were currently or recently using any type of hormonal contraception had a 20 per cent increased risk of breast cancer compared with women who had never used them and this risk increased with longer duration of use. Extending prior research, this study importantly included contemporary formulations of lower-dose combined oral contraceptive pills (OCPs) and levonorgestrel intrauterine systems. The study findings quickly found their way to major media outlets, such as the Washington Post that reported, 'Even low-dose contraceptives may slightly increase risk of breast cancer' (2). One hoped that readers would continue beyond this headline and understand the news report that concluded that 'while the percentage

increases look substantial, in fact they reflected a fairly small increase in actual cases' (2). As paediatricians and adolescent medicine specialists, we anticipated a resurgence of questions from patients, parents, and colleagues about the safety of hormonal contraception, as we commonly prescribe these medications for both contraceptive and noncontraceptive benefits. Many of our young patients rely on hormonal contraceptives as their main treatment for endometriosis, dysmenorrhea, menorrhagia, polycystic ovarian syndrome, acne, menstrual headaches, and premenstrual dysphoric disorder.

This large prospective study combined the data from several national registries in Denmark to produce a cohort of 1.8 million females aged 15 to 49 years followed for an average of 10.9 years. Hormonal contraceptive use was categorized as current, recent or previous use. The study also examined risk based on duration of use by comparing females with no history of use, previous use

of greater than 6 months, current or recent use (broken down into several time durations), and time since last use. Additional analyses examined the different OCP formulations categorized by their progestin ingredients, different progestin-only contraceptives, nulliparous women, and age subgroups. The main finding of this study was a relative risk (RR) of 1.20 (95% confidence interval [CI] 1.14 to 1.26) for breast cancer among current or recent users of any hormonal contraception compared to never users. The risk increased with longer duration of use but disappeared 5 years after cessation of hormonal contraception. Specifically, the duration–response association was reported as a RR of 1.09 (95% CI 0.96 to 1.23) for contraceptive use less than 1 year and a RR of 1.38 (95% CI 1.26 to 1.51) for more than 10 years of use. In women who used hormonal contraception for less than 5 years and had discontinued use, there was no increased risk. Additional subanalyses showed a statistically significant but small increase in risk of breast cancer associated with current or recent use of various formulations of combined OCPs, progestin-only pills, and the hormonal intrauterine device (IUD) but not the transdermal patch, vaginal ring, arm implant, or depot medroxyprogesterone acetate.

The subanalyses specific to adolescents focused on those who started hormonal contraception before age 20 years and found a RR of 3.03 (95% CI 1.17 to 7.86) among current or recent users of any hormonal type with duration of use greater than 10 years compared with the duration of use less than 1 year. However, shorter durations of use or prior use that was stopped more than 6 months ago showed no significant increased risk. Furthermore, for this subset of adolescents, the increased risk was found for various forms of combined hormonal contraceptive pills but no significant increases in risk were found for the arm implant, hormonal IUD, or vaginal ring, and no breast cancer events occurred in the subsets of depot medroxyprogesterone or patch users.

So, how do we as paediatric health care providers apply this study to our practices when we have adolescent and young adult patients who are considering hormonal contraception? In the larger picture, clinicians who care for youth understand very well that prevention of teen pregnancy is a common public health goal and that pregnancy and parenting in adolescence is not without substantial risks. Furthermore, when it comes to contraceptive management, clinicians are continually balancing the benefits and risks of each method. The myriad of considerations includes contraceptive effectiveness, menstrual effects, side-effect profiles, practicality of use, need for confidentiality, accessibility, and personal preferences of the individual, partners, peers, and family members—factors that patients prioritize differently at different stages of life. If we consider the potential for increased risk of breast cancer, the literature to date does not provide a clear answer to this question. As discussed in the accompanying editorial in the same *NEJM* issue, the main

findings are consistent with the collection of mixed results from prior large studies, where some have reported similar significant but small relative risks and others have reported no significant increased risk (3).

The current study does not provide further substantial clarity on this issue, given the methodological limitations, some of which have been highlighted in letters to the editor, as well as the small magnitude of RRs found (4,5). First, as noted by the authors and others, the dataset used in this study did not include information on age of menarche, age at first birth, breastfeeding, alcohol use, physical activity, or body mass index in nulliparous women which are potential cofounders, or on nonhormonal copper IUD users as a comparison group (1,5). Second, we note that the numerous comparisons made raises concern for spurious associations as the authors corrected for multiple comparisons in the analyses comparing different hormonal formulations but did not correct for multiple comparisons in the other subanalyses. Third, it is important to remember that observational studies using large administrative databases such as this have inherent limitations and potential for bias (4). As Grimes and Schulz point out, “observational studies are not able to evaluate weak associations defined as RRs in cohort studies less than 2 to 3 as selection bias and residual confounding factors may lead to these weak associations without any causal association being present” (4), as it is difficult for a national registry to address all the factors impacting breast cancer risk on the individual level.

The data on the initiation of hormonal contraception use in adolescence (<20 years of age) also has limitations to consider. These subanalyses found a less precise RR of 3.03 with a wide 95% CI of 1.17 to 7.86 among those who currently or recently used hormonal contraception for more than 10 years, compared with those who used for less than 1 year. However, the lack of even a nonsignificant trend in dose response among the categories of shorter duration of use (1 to <5 years, 5 to 10 years) raises caution in our interpretation of the RR of 3.30 for the >10 years group and whether adolescents who proceed to use hormonal contraception for many years are truly at increased risk for breast cancer. For adolescents, it is also important to note that there no significant increases in risk for the arm implant, hormonal IUD, or vaginal ring, and there were zero breast cancer events among depot medroxyprogesterone or patch users. This is reassuring given that hormonal IUDs are a recommended first line method of contraception for adolescents (6) given their superior typical-use effectiveness.

With all of this in mind, as paediatric health care providers we assert that this study’s findings contribute to an interesting discussion but do not alter our current prescribing practices. In summary, there are several limitations to the study and the main finding was only a weak association between hormonal contraception and the risk of breast cancer where causality cannot

be inferred. Furthermore, in light of the very low incidence of breast cancer in younger women, the reported risk difference equates to two additional cases of breast cancer per 100,000 women under 35 years old taking hormonal contraception for 1 year, highlighting the important distinction between *statistical* significance and *clinical* significance, and that a higher *relative* risk does not imply a high *absolute* risk. For reference, in the full cohort of women 15 to 49 years old, the risk difference equated to one additional case of breast cancer per 7,690 women taking hormonal contraception for 1 year. To further emphasize the complexity of the risk to benefit ratio, this study of breast cancer risk must not be viewed in isolation of evidence that hormonal contraception provides protection against endometrial, ovarian epithelial, and colorectal cancers (7). Finally, while diagnosis of breast cancer may increase slightly, hormonal contraception users are by definition engaged in health care, and the study was not able to report on whether breast cancer mortality increased or perhaps decreased due to participation in health care (5).

### TAKE HOME POINTS

This study contributes to our informed discussions with patients, but we emphasize that these findings should not change our practice in supporting the prevention of unintended pregnancy among adolescents by promoting access to ALL forms of contraception. As clinicians, we have the responsibility to provide accurate information to our adolescent patients and help them to consider all of the benefits and risks of hormonal

contraception as they determine their own individualized contraceptive goals.

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