Commentary

Intrauterine exposures, pregnancy estrogens and breast cancer risk: where do we currently stand?

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Abstract

Since 1990, when a hypothesis on intrauterine influences on breast cancer risk was published, several studies have provided supportive, indirect evidence by documenting associations of birth weight and other correlates of the prenatal environment with breast cancer risk in offspring. Recent results from a unique cohort of women with documented exposure to diethylstilbestrol *in utero* have provided direct evidence in support of a potential role of pregnancy oestrogens on breast cancer risk in offspring.

In the 1980s several investigators evaluated whether prenatal characteristics may be related to breast cancer risk in offspring [1,2]. However, it was not until 1990 that a hypothesis on roots of breast cancer in early life was articulated [3]. Trichopoulos postulated that higher concentrations of oestrogens in pregnancy increase the probability of occurrence of breast cancer in daughters. The concept was subsequently elaborated into an integrated model of the natural history of breast cancer that accommodates most established risk factors for this disease [4-6].

Until recently, the evaluation of whether exposure to pregnancy oestrogens, and conceivably other mammotropic hormones, increases breast cancer risk in offspring has relied on correlates of pregnancy oestrogens. These correlates include birth weight, which tends to increase with higher pregnancy oestrogen levels; twinning, which is characterized by higher pregnancy oestrogen levels than in singleton pregnancies; pregnancy toxaemia, in which oestrogen levels have been reported to be lower than those in normal pregnancies; and first versus higher birth orders, with first pregnancies reportedly being associated with higher levels of oestrogens. Most, although not all, studies that evaluated the association of these markers of pregnancy oestrogen levels with breast cancer risk in the offspring - including investigations into birth weight [7-9], twinning [10], pregnancy toxaemia [11] and birth order [12] - have been interpreted as suggesting that higher levels of pregnancy oestrogens may increase breast cancer risk in offspring.

However, investigations such as those cited above do not directly address the possible role played by pregnancy oestrogens. This became possible in a unique study that made the best of a tragic natural experiment [13-15]. In 1971 the daughters of mothers prescribed diethylstilbestrol (DES), a synthetic oestrogen that supposedly protects against spontaneous abortion, were found to be at a dramatically increased risk for developing clear cell carcinoma of the vagina and cervix, in a striking demonstration of transplacental carcinogenesis in humans [16]. DES had been prescribed to more than a million pregnant women in the USA from the 1940s to the 1960s.

Since 1992, all US cohorts of DES-exposed persons for whom there was an appropriate comparison group of unexposed persons and for whom there was medical record documentation of exposure (or not) to this substance are being followed in a study supported by the US National Cancer Institute. Slightly more than 4800 women exposed *in utero* to DES and approximately 2070 unexposed women are included in this cohort. Results concerning breast cancer in offspring have been reported in three reports [13-15]. The risk for developing breast cancer in the earliest report [13], when women exposed to DES *in utero* were still very young (38 years on the average), was barely 18% higher in exposed to nonexposed women. However, the increase became progressively greater with longer follow up.

In the most recent report [15], for breast cancer occurring at age 40 years or older the risk was significantly higher, by 91%, in women exposed to DES *in utero* than in those who were not exposed. For breast cancer at age 50 years or older

DES = diethylstilbestrol.

the corresponding excess was 200%, which again was significant but with a wide confidence interval. The overall pattern does not come as a surprise because breast cancer among young women is known frequently to have genetic roots [17], so an excess risk on account of intrauterine exposure to oestrogens is likely to become more evident with advancing age.

How can the evidence now be summarized? It is highly likely that intrauterine exposures are involved in breast cancer aetiology. The results of the studies conducted by Palmer and coworkers [14,15] specifically point to intrauterine exposure to oestrogens as affecting the bulk of breast cancer cases that are not genetically determined, perhaps by increasing the number of mammary gland stem cells and thus the risk for malignant transformation of one of them [4,6,18]. Nevertheless, even if further follow up of this cohort were to confirm the patterns already noted, a number of questions would remain. First, are oestrogens the only relevant hormones, or do other growth-enhancing mammotropic hormones also play a role? Second, are growth processes in the intrauterine environment of unique importance or just a phase in the growth process in childhood and adolescence, as speculated several years ago on the basis of the association of height with breast cancer risk [19]? Third, are the described phenomena unique to breast cancer, perhaps on account of the fact that human mammary gland remains inactive - and the related stem cell pool dormant - until puberty, or are they relevant to other forms of cancer [20]?

These and perhaps other questions are important and need to be addressed, but the recent report from Palmer and colleagues [15] goes a long way toward documenting that intrauterine environment is relevant to the aetiology of breast cancer and that pregnancy oestrogens are involved in this process. This is also an opportune time to express appreciation to those who had the vision to establish and pursue this important cohort.

Competing interests

The author declares that they have no competing interests.

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