Commentary

# Intrauterine environment, mammary gland mass and breast cancer risk

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## Abstract

Two intimately linked hypotheses on breast cancer etiology are described. The main postulate of the first hypothesis is that higher levels of pregnancy estrogens and other hormones favor the generation of a higher number of susceptible stem cells with compromised genomic stability. The second hypothesis postulates that the mammary gland mass, as a correlate of the number of cells susceptible to transformation, is an important determinant of breast cancer risk. A simple integrated etiological model for breast cancer is presented and it is indicated that the model accommodates most epidemiological aspects of breast cancer occurrence and natural history.

**Keywords:** breast cancer, estrogens, intrauterine environment, mammary gland mass

## Introduction

In the early 1990s, I contributed to the development of two intimately linked hypotheses concerning breast cancer etiology in humans. The first postulated that the intrauterine environment may affect breast cancer risk in the offspring in ways over and beyond those attributed to major breast cancer genes [1]. In the second hypothesis, the argument was made that the number of mammary gland cells, particularly of those among them that are susceptible to transformation, is an important determinant of breast cancer risk [2]. In other words, intrauterine and early life events and conditions could affect the number of mammary gland cells at risk for transformation and, ultimately, breast cancer risk.

Neither of these hypotheses was developed in a vacuum. The earlier work of several authors was instrumental, and indeed critical. The striking protective effect on breast cancer risk of an early first full-term pregnancy led Cole and MacMahon to hypothesize that breast cancer risk is established, in part, early in life [3]. Loeb, as well as other investigators, argued that early phenomena, perhaps affecting mutator genes or other factors controlling genetic stability, are crucial in the process of carcinogenesis [4]. Moolgavkar *et al*. postulated that the magnitude of breast cancer risk depends on the transition rates of normal susceptible cells to intermediate cells and then to transformed cells [5]. Several authors in the late 1980s suggested that energy intake during early life may affect the number of mammary cells, mammary gland mass and, through them, breast cancer risk [6].

## Intrauterine environment and breast cancer risk

The hypothesis that breast cancer may have intrauterine component causes is based on a number of generally accepted assumptions. Mammary gland cells *in utero* are not terminally differentiated. Factors that increase the risk of cancer during adult life, as do exogenous and endogenous estrogens for breast cancer, may have similar effects when they act *in utero*. Estrogens and other hormones with growth enhancing properties are abundant during pregnancy, and adult life exposures do not fully explain the substantial variability of breast cancer occurrence between and within populations.

Simple as it may sound, this hypothesis is very difficult to directly evaluate. The scientific team in Sweden lead by

Adami and Ekbom was the first that attempted to evaluate this hypothesis using presumed positive or inverse correlates of pregnancy estrogens, including birth weight and pregnancy toxemia [7]. Pregnancy estrogens have in fact been reported as positively associated with birth weight [8] and inversely associated with pregnancy toxemia [9]. Several authors have subsequently carried out research along these lines. The results up to 1999 have been reviewed by Potischman and Troisi, who concluded that the collective evidence is consistent with the hypothesis that prenatal exposures, notably pregnancy estrogens, are associated with adult life breast cancer risk [10]. More consistent was the evidence concerning the positive association between birth weight and breast cancer risk in the offspring. Vatten *et al*. have since reported a positive association from Norway [11].

It should be noted that a link between perinatal factors and breast cancer risk in the offspring does not necessarily or exclusively incriminate pregnancy estrogens, despite the role of the latter as an important determinant of several of these factors, including birth weight. In addition to pregnancy estrogens [8], insulin-like growth factor 1 has been positively associated with birth weight [12] and there is also evidence that alpha fetoprotein may play a role [13]. Nevertheless, among all factors that are associated with birth weight and other perinatal events and conditions linked to breast cancer risk in the offspring, the inherently mammotropic pregnancy estrogens are the most likely candidates, although by no means the only ones [14]. Indeed, a cohort study comparing women exposed *in utero* to diethylstilbestrol with unexposed women reported a greater than twofold increase in breast cancer risk [15]. This is an ongoing study of a unique cohort, and the women involved have not yet reached the age of high breast cancer incidence. If the results of further followup are in line with those recently reported [15], it will be difficult to argue against the hypothesis that high *in utero* estrogenic stimulation increases breast cancer risk in the offspring.

## Mammary gland mass and breast cancer risk

With respect to mammary gland mass, as distinct from breast size, the empirical evidence linking it to breast cancer risk is very strong. Mammographic density is a powerful predictor of breast cancer risk and this density is strongly associated with mammary gland mass, although the stromal component is also likely to play an important role [16–19]. Small-breasted women who were motivated to have augmentation mammoplasty, and whose mammary gland mass had to be small, were found to have reduced breast cancer risk [20,21], although no reduction was evident in a small cohort study that included eight breast cancer cases [22]. Moreover, women who had undergone surgical reduction of their breasts subsequently had reduced breast cancer risk [23–26].

Mammary gland mass, which reflects the total number of mammary cells and can be correlated with mammary cells at risk for transformation, can also explain several of the descriptive aspects of breast cancer epidemiology. One example is breast cancer risk being higher among Caucasian women than among Asian women and being positively associated with adult height [2,23]. Large breast size mostly reflects adipose tissue but, among thin women, breast size may be a better indicator of mammary gland mass and has been positively associated with breast cancer risk [27,28].

The number of mammary gland cells at risk for transformation, and thus breast cancer risk, is reduced through the process of terminal differentiation that takes place mostly after the occurrence of the first full-term pregnancy and, to some extent, after the occurrence of subsequent pregnancies and lactation [23,29,30]. Moreover, cells at risk or at intermediate stages of transformation may be more or less responsive to the growth enhancing influences of estrogens and other mammotropic hormones, depending on the density of the respective receptors in the nonmalignant tissue. In this context, it may be of relevance that expression of estrogen receptors $\alpha$ has been found to be less common among Japanese women than among Caucasian women [31].

## Conclusion

We have tried to integrate the existing information on breast cancer epidemiology and apparent pathogenesis into an etiological model that incorporates the two presented hypotheses and the data that support them [23]. The model has four components. First, the likelihood of breast cancer occurrence depends on the number of cells at risk and, second, the number of target cells is partially determined early in life, probably even *in utero*. The third component is that, while a pregnancy stimulates the replication of already initiated cells, it conveys long-term protection through structural changes, including terminal cellular differentiation. Finally, in adult life, mammotropic hormones, in conjunction with their receptors, affect the likelihood of retention of spontaneous somatic mutations and the rate of expansion of initiated clones.

This composite, yet simple, model accommodates most, if not all, epidemiological aspects of breast cancer occurrence and natural history. These include the secular increase of breast cancer incidence during the early part of last century, the higher risk for this disease among higher socioeconomic class women in most countries of the world, as well as the gradual increase of breast cancer incidence among Asian migrants to Western countries. All these patterns reflect concomitant changes in birth size, adult birth height and breast cancer risk. The model also accommodates the effectiveness of prophylactic mastectomy among women at very

high risk on the basis of reduction of mammary gland mass [23,32].

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