Review

Towards an integrated model for breast cancer etiology

The crucial role of the number of mammary tissue-specific stem cells

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Abstract

Perinatal events and conditions, notably birth weight, are associated with breast cancer risk in offspring, and correlates of mammary gland mass are predictors of breast cancer risk. These findings may be interpreted as indicating that high levels of estrogens and components of the insulin-like growth factor system during pregnancy favour the generation of mammary tissue-specific stem cells, and that the number of these cells, which is positively associated with mammary gland mass, is an important determinant of breast cancer risk. Perinatal events and conditions may also affect risk for other malignancies, but the evidence in the case of breast cancer is prominent, possibly because estrogens and the insulin-like growth factor system are both involved in breast cancer etiology and affect birth weight.

Keywords: birth weight, breast cancer, estrogens, insulin-like growth factor, perinatal, stem cells

Introduction

An etiologic model should explain as many of the epidemiologic characteristics of a disease as possible, as well as the results of analytical epidemiologic studies with specific objectives. In this regard, no issue has been studied as intensively as breast cancer etiology, and several comprehensive reviews of the epidemiology and etiology of this disease have been published.

Breast cancer epidemiology

The established epidemiologic characteristics of breast cancer are indicated below [1–4]. Breast cancer is at least 100 times more common among women than among men. The incidence of the disease has apparently increased throughout the world during the past century, even before the widespread application of mammographic screening programs, and it is generally higher among women of higher socioeconomic status and among urban rather than rural residents. Caucasian women in the western world have a considerably higher breast cancer risk than do Asian women in China or Japan. Breast cancer incidence increases with age throughout the world, but the slope of the increase decreases after the menopause. An earlier age at menarche and a later age at menopause are associated with increased risk, whereas, for a given age at menopause, bilateral oophorectomy conveys more protection than naturally occurring menopause.

In general terms, pregnancies convey protection, but in a complex way. Irrespective of the woman's age, a pregnancy imparts a short-term increase in breast cancer risk followed by a substantial long-term reduction in this risk. Hence, the earlier the age at first full-term pregnancy, the more prolonged is the subsequent long-term protection. After the age of about 35 years, a first pregnancy actually increases breast cancer risk because the short-term risk increase exceeds the subsequent risk reduction. Additional full-term pregnancies have similar but quantitatively much weaker effects, whereas spontaneous or induced abortions do not appear to affect breast cancer risk. Prolonged lactation conveys some protection

IGF = insulin-like growth factor.

but the effect is modest and may be more pronounced among premenopausal women.

Height is positively associated with breast cancer risk [5,6], whereas obesity is inversely related to this risk among premenopausal women [7] but positively among postmenopausal women [8,9]. A high-density mammogram (≥75% of total breast area with dense mammographic appearance) indicates an almost fourfold risk in comparison with a low-density mammogram (≤25% of total breast area with dense mammographic appearance) [10,11].

Several exogenous factors have been studied in relation to breast cancer, but the evidence appears adequate for only a few [3]. Ionizing radiation is an established cause of the disease but it is of limited quantitative importance, whereas most studies indicate that consumption of alcoholic beverages may slightly increase breast cancer risk. It has been reported that intake of fruits, vegetables and olive oil, as well as physical activity, may reduce breast cancer risk, but the evidence is inconclusive and points to weak effects at most. Exposure to organochlorines or electromagnetic fields has not been shown to be related to breast cancer. Current or recent use of oral contraceptives slightly increases the risk for breast cancer [12], whereas long-term use of replacement estrogens, with or without progestins, may substantially increase breast cancer risk [13–15].

Mutations in *BRCA1* and *BRCA2*, as well as highly penetrant mutations in genes such as *p53*, *CHEK2*, and *PTEN*/*MMAC1*, account for a large proportion of familial breast cancers, but they account for a small proportion of all breast cancers [16]. Among individuals with apparently sporadic breast cancers, very few carry mutations that are known to be strongly related to the disease. It has long been known that there is a familial aggregation of breast cancer [17] that cannot be fully explained in terms of the indicated major genes. Thus, it is possible that other genes associated with a more moderate influence on breast cancer risk are also involved, perhaps modifying the effects of other risk factors for breast cancer [18].

Most prospective studies on endogenous hormones in relation to breast cancer risk have been undertaken among postmenopausal women because of difficulties relating to menstrual timing of sampling among premenopausal women, the relative frequency of postmenopausal and premenopausal breast cancer, and the age spectrum of most established cohorts. Among postmenopausal women, virtually every hormone examined – with the notable exception of adiponectin, which has only been evaluated through case–control designs [19,20] – is positively associated with breast cancer risk [3,21,22]. The list includes total and free estradiol, estrone and estrone sulphate, androstenedione, dehydroepiandrosterone and dehydroepiandrosterone sulphate, testosterone, and prolactin. Most reported studies conducted in premenopausal women have been of the case–control design and tend to support a positive association between estrogens and breast cancer risk [3,23,24]. In both prospective and retrospective studies conducted in premenopausal women, significant associations have been found between blood insulin-like growth factor (IGF)-1 and breast cancer risk [25].

The etiologic model

Our views on the etiology of breast cancer were presented in several reports [1,26–32] and the main points are as follows. First, the likelihood of breast cancer occurrence depends on the number of mammary tissue-specific stem cells, which is determined early in life, notably *in utero* or during immediate postnatal life. Second, in adult life all growth-enhancing mammotropic hormones, in conjunction with their receptors, affect the likelihood of retention of cells with spontaneous somatic mutations, as well as the rate of expansion of initiated clones. Finally, although a pregnancy stimulates the replication of already initiated cells, it conveys long-term protection through differentiation of a large fraction of the mammary tissue-specific stem cells.

Breast cancer epidemiology under the early life modulation of mammary stem cells model

In this part of the review we examine the extent to which the etiological model we present accommodates the epidemiology of breast cancer. Parts of this discussion are based on an earlier report [1], in which many of these issues were considered in detail.

First postulate

The evidence linking mammary gland mass, as distinct from breast size, to breast cancer risk is strong. Mammographic density is a powerful predictor of breast cancer risk, and this density is strongly associated with mammary gland mass [10,11]. Small breasted women who were motivated to undergo augmentation mammoplasty, and whose mammary gland mass had to be small, were found in most studies to have reduced breast cancer risk [33,34]. Mammary gland mass, which is likely to reflect the total number of mammary cells and be correlated with the number of mammary stem cells, can also accommodate several breast cancer risk factors, including the following: breast cancer risk is higher among Caucasian than among Asian women; it is higher in women of higher than in those of lower socioeconomic status; and it is higher in women residing in urban than in women residing in rural areas (in each of these comparison sets, the women in the first group are generally taller and bigger, independently of obesity) [1].

The postulate is also in accordance with the positive association between adult height and breast cancer risk, an association that has long been known but generally underappreciated [1,5,6,28], as well as the repeatedly supported association between birth size and breast cancer risk [35–37]. This postulate may also underlie the secular increase in breast cancer incidence in many populations during the past century (a period during which growth accelerated and attained height increased in these populations) [31], the higher breast cancer risk among leaner premenopausal women (who are known to have higher density mammographic pattern) [10], and the apparent protective effect of anorexia nervosa against breast cancer [38]. Last, but by no means least, the strikingly higher breast cancer risk among women than among men even in later life is best explained by the correspondingly higher mammary gland mass among women than among men, because estrogen production in later life is not substantially different between the two sexes [28].

Second postulate

The traditional view on breast cancer implicates estrogens in general, or specific categories of estrogens, or progesterone, prolactin, or other hormones, including IGF, as central to the etiology of the disease. The second postulate of the etiological model we propose deviates slightly from the traditional view in that it accepts that all growth enhancing and mammotropic hormones are involved in one or more stages in the long process that leads to clinical breast cancer. An important implication of this postulate is that, in studies evaluating several of these hormones, it would be worth considering assessing their additive consequences for breast cancer risk (e.g. by expressing each of these hormones in terms of the corresponding standard deviates). It is not necessary for each hormone to have a quantitatively similar breast cancer risk implication per standard deviate, and the proposed model's third postulate accommodates any role that may be played by differential hormone receptor expression [39,40].

This postulate accommodates several breast cancer risk factors: the inflection of breast cancer incidence after menopause; the increased risk for this disease with earlier menarche and later menopause; the protective effect of a surgical menopause with oophorectomy; the transient increase in risk following a pregnancy; the increased risk among overweight postmenopausal women and the positive association with breast cancer risk of alcohol drinking (which tends to increase estrogen levels); hormone replacement therapy; and – however weakly – oral contraceptives.

Third postulate

The number of mammary gland cells at risk for transformation, and, thus, that confer 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 [41]. When the first full-term pregnancy occurs at an early age, malignant transformation is likely to have already been initiated in only few mammary cells, which could be boosted by the many fold increases in mammotropic and growth enhancing hormones that accompany a pregnancy. The later the age at first full-term pregnancy, the higher the number of already initiated cells and the more limited the protection. Beyond the age of 35 years or so, the transient increase in breast cancer risk that accompanies a pregnancy overshadows the protection conveyed by the terminal differentiation of immature mammary cells. In addition to the substantial protection conveyed by an early full-term pregnancy, the more limited protection conveyed by subsequent pregnancies and by lactation, and the crossover in the effect of a first pregnancy around the age of 35 years, the third postulate also accommodates what was largely thought to be an enigma, namely that breast cancer risk is higher among parous than among nulliparous women of premenopausal age.

The three postulates: general comments

It should be noted that this model relying on the three indicated postulates is not refuted by the fact that populations at low risk for breast cancer (e.g. native Chinese populations) have higher levels of most pregnancy – or even adult life – hormones [42]. It is plausible that, in striking ecologic contrasts (e.g. between native Chinese and Caucasian populations), pregnancy growth hormones tend to increase in order to compensate for physically constrained fetal growth [31], and the perinataly programmed higher levels of these hormones could track throughout adult life. Also, the model is not refuted by the absence of association of breast cancer with induced abortions and exposure to organochlorines or magnetic fields, because none of these exposures has been documented to affect the factors and processes that are involved in the three postulates [43]. The possible, but undocumented, effects of diet and physical activity on breast cancer risk could be explained in terms of the first or the second postulate, although there is inadequate evidence as to whether these two variables affect either the number of mammary cells at risk or the levels of circulating mammotropic and growth hormones. Finally, the general positive association between age and breast cancer risk, and the established role of ionizing radiation and some major genes in the causation of a small fraction of breast cancer cases can be explained in terms of general carcinogenesis theory.

The model, the evidence, and the predictions

The model we outline above goes beyond being a simple hypothesis. It has evolved during the past 15 years to

accommodate most of the existing and emerging empirical evidence. Also, the proposed model is not a collation of three independent postulates that happen to cover different aspects of the epidemiology of breast cancer. The three postulates represent stages in a single biologic process that points to the number of mammary tissue-specific stem cells as the core determinant of breast cancer risk. The first postulate focuses on the perinatal period, when stem cells in general, and tissue-specific stem cells in particular, are generated. The second postulate concentrates on pre-initiation and post-initiation growth factors that modulate the number of mammary stem cells at risk and the growth of the initiated clones. The third postulate explains how cells at risk are removed through terminal differentiation or related processes. The whole model is in agreement with the results of theoretical exercises and speculations undertaken long ago by several authors, including Moolgavkar and colleagues [44].

Two important questions emerge from what has been presented above. How can this model be further evaluated, and is this suggested process specific for breast cancer or does it concern human carcinogenesis in general? The most critical evaluation may rely on a design proposed by Hsieh and coworkers [45], who are evaluating whether mammotropic and growth hormones are associated with cord blood stem cells. Another approach was taken by Ekbom and colleagues (personal communication), who are evaluating whether immediate postnatal growth, a period during which the number of stem cells is likely to be modulated, is associated with breast cancer risk in offspring. Useful results may also emerge from a unique follow-up study of women born to mothers who had taken diethylstilbestrol during their pregnancies [46]. It would also be useful to confirm the findings of a study [47] that reported that perinatal characteristics indicative of high breast cancer risk predict mammographic patterns that are associated with high breast cancer risk in adult life.

It is not implausible that a process similar to that outlined in the proposed model may also apply to other forms of human cancer [30], and, indeed, there have been reports that birth weight may have associations with other types of childhood and adult onset cancer [48,49]. It may be that the positive association between birth weight and cancer risk is stronger for the mammary gland than for other organs, because hormones critical for breast cancer risk, including estrogens and IGF-1, are also critical determinants of birth weight. Alternatively, it may be that the number of tissue-specific stem cells is more intimately linked to cancer in the mammary gland than to cancer in other organs, because mammary gland is exceptional in that it is not fully developed at birth [50] and is regularly stimulated by hormones during the menstrual cycle.

This article is the second in a review series titled *Towards an integrated model for breast cancer etiology*, edited by Hans-Olov Adami.

Other articles in the series can be found at http://breast-cancer-research.com/articles/review-series.asp?series=bcr_Towards

Conclusion

High levels of pregnancy estrogens and components of the IGF system during the perinatal period favor the generation of mammary tissue-specific stem cells, and the number of these cells, which is positively associated with mammary gland mass, is an important determinant of breast cancer risk. A proposed three-tier model accommodates essentially all of the known risk factors for breast cancer and provides a plausible biologic mechanism for human breast carcinogenesis.

Competing interests

The author(s) declare that they have no competing interests.

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