

MINI REVIEW

Early life events and conditions and breast cancer risk: From epidemiology to etiology

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Risk factors for breast cancer—documented by intensive epidemiological investigations and viewed in the context of general principles of carcinogenesis—can be integrated to an etiologic model comprising 3 principal components: the likelihood of breast cancer occurrence depends on the number of mammary tissue-specific stem cells, which is determined in early life; all growth-enhancing mammotropic hormones affect the rate of expansion of initiated clones; and while a pregnancy stimulates the replication of already initiated cells, it conveys long-term protection through differentiation of mammary tissue-specific stem cells. This perspective accommodates much of what is known about the epidemiology and natural history of breast cancer and highlights the role of early life in the origin of this cancer.

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Breast cancer epidemiology

The incidence of breast cancer has apparently increased throughout the world during the last century, even before the widespread application of mammographic screening programs and mortality from the disease in developed countries generally exceeds that from other cancer sites.¹ Breast cancer epidemiology has been intensively studied, perhaps more than that of any other cancer.^{2–6} Table I summarizes what are generally considered as established epidemiological characteristics of breast cancer and provides an indication of the strength of the respective associations in terms of the relative risk per natural contrasts or usual increments.

Breast cancer is mostly, though not exclusively, a disease of women. The incidence of the disease increases with age, with an inflection around menopause, which is not evident for other forms of cancer. It is generally more common among urban rather than rural residents as well as among women of higher socioeconomic status. In comparison to Asian women in China or Japan, Caucasian women in the western world have a considerably higher breast cancer risk.¹

With respect to reproductive history, an earlier age at menarche and a later age at menopause are associated with increased risk whereas, for a given age at menopause, induced menopause conveys more protection than the naturally occurring one.^{6–8} The role of pregnancies is complex. Irrespective of the woman's age, a pregnancy imparts a short-term increase of breast cancer risk⁹ followed by a substantial long-term reduction of this risk, as was first documented with respect to the first pregnancy some 40 years ago in a classical international epidemiological study.¹⁰ 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, apparently because the short-term risk increase exceeds the subsequent risk reduction. Additional full-term pregnancies have similar but much weaker effects,¹¹ while spontaneous or induced

abortions do not affect breast cancer risk.¹² Prolonged lactation conveys at most modest protection, which appears to be restricted to premenopausal women.^{13,14} Current or recent use of oral contraceptives slightly increase the risk for breast cancer,¹⁵ whereas long-term use of replacement estrogens with progestins may substantially increase breast cancer risk.^{16–18}

High birth weight has been associated with increased breast cancer risk in the offspring.¹⁹ Having been breastfed as an infant has been investigated for its role in breast cancer under the assumption that it could be responsible for the transmission of an infectious agent, but the results did not support an association.²⁰ Early life growth²¹ and factors that may increase it²² have also been positively associated with breast cancer risk, as has height^{23,24} and post- (but not pre-) menopausal obesity^{8,25–27} later in life.

A high-density mammogram (75% or more of the total breast area with dense mammographic appearance) has been associated with a more than 4-fold risk in comparison to a low-density mammogram (10% or less of total breast area with dense mammographic appearance).²⁸ Atypical hyperplasia of the mammary gland has been documented as an important breast cancer risk factor.^{29,30}

Family history among first degree relatives is associated with increased breast cancer risk.³¹ BRCA1 and BRCA2, as well as some highly penetrant mutations, explain a large part of familial breast cancers, but account for a small proportion of all breast cancers.³² Many studies have examined low penetrance susceptibility polymorphisms in candidate genes, but the associations reported in some studies could not be replicated in subsequent investigations. This is an evolving field, in which large whole genome association investigations are providing new insight.³³ Breast cancer in the contralateral breast is an established risk factor for developing the disease in the other breast, but the underlying pathogenetic mechanisms are not clear.³⁴

High levels of physical activity³⁵ and high intake of vegetables, perhaps fruits³⁶ and olive oil³⁷ have been reported to be associated with reduced breast cancer risk, possibly by reducing endogenous estrogen levels.^{38,39} Nevertheless, the evidence is inconclusive and suggests, at most, weak effects. Recent evidence points to total and particularly saturated fat as been weakly, but significantly, positively associated with breast cancer risk.⁴⁰ Most studies indicate that consumption of alcoholic beverages may slightly

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TABLE I—FACTORS EVALUATED IN RELATION TO BREAST CANCER RISK

Risk factor	Category/change	Strength
Gender	Women vs. men	++++
Age	Increase	++++
Ethnic group	Caucasian vs. Asian	+++
Family history	Yes vs. no	+++
Specific genes	Yes vs. no	++++
Cancer in other breast	Yes vs. no	+++
Height	Increase	++
Postmenopausal obesity	Increase	++
Birth weight	Increase	+
Having been breastfed	No vs. yes	0
Growth in early life	Increase	+
Atypical hyperplasia	Present vs. absent	+++
Mammographic density (mammary gland mass)	High vs. low density (increasing mass)	+++
Age at menarche	Earlier	++
Age at menopause	Later	++
Type of menopause	Natural vs. artificial	++
Age at 1st full term pregnancy	Later	+++
Age at other pregnancies	Later	+
Parity overall	Lower	++
Pregnancy timing	Proximal vs. distant	+
Lactation	No vs. yes	+
Abortion	No vs. yes	0
Oral contraceptive use (recent)	Increase	+
Hormone replacement	Increase	++
Plant foods and olive oil	Reduced intake	+
Saturated fat	Increased intake	+
Physical activity	Reduced	+
Ethanol intake	Increase	+
Ionizing radiation	Increased	+
Magnetic fields	Increased	0
Organochlorines	Increased	0

Association: +++++ very strong, +++ strong, ++ modest, + weak, 0 null.

increase breast cancer risk, possibly by increasing estrogen levels.⁴¹ There is no conclusive evidence for an association between tobacco smoking and the disease.^{42,43}

Ionizing radiation is an established cause of cancer of the breast as well as of several other cancers, but it is of limited quantitative importance. Exposure to organochlorines⁴⁴ or electromagnetic fields⁴⁵ has not been shown to be related to breast cancer.

It is generally believed that the association between endogenous hormones and breast cancer risk should be studied in prospective, rather than retrospective, investigations, under the undocumented assumption that disease status, even prior to treatment, may affect hormone levels. Among postmenopausal women, most hormones examined—with the notable exception of adiponectin that has been mostly evaluated through case-control designs^{46,47}—have been positively associated with breast cancer risk.^{6,48–50} The list includes total and free estradiol, estrone and estrone sulphate, androstenedione, dehydroepiandrosterone and dehydroepiandrosterone sulphate, testosterone and prolactin. Among premenopausal women, case-control studies and a few cohort investigations provide some support for a positive association between estrogens and breast cancer risk, but they also indicate that high levels of androgens could increase this risk.^{6,51} In both prospective and retrospective studies among premenopausal women, significant positive associations have been reported between blood insulin like growth factor 1 (IGF-1) and breast cancer risk.⁵²

The early life etiological model

The etiological model we have proposed for breast cancer accommodates most of what we know about the epidemiology of the disease. The model emphasizes early life events and conditions as determinants of breast cancer risk and summarizes the distinct

epidemiological characteristics of the disease on the basis of 3 major components^{5,22,53–58}:

- The likelihood of breast cancer occurrence depends on the number of mammary tissue-specific stem cells, which is determined early in life, including the intrauterine life,
- in early and later life, growth-enhancing mammatropic hormones affect the replication rate of mammary tissue specific stem cells, the likelihood of retention of cells with spontaneous somatic mutations as well as the rate of expansion of initiated clones, and
- while 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.

It should be noted that several scientists^{23,59,60} have postulated, explicitly or implicitly, that early life influences may play a role in breast cancer etiology and there have even been early studies exploring birth weight as a breast cancer risk factor.⁶¹ Moreover, the issue of pregnancy induced terminal differentiation of mammary gland has been championed by Russo and Russo.⁶²

Categorization of breast cancer risk factors according to the 3 components of the early life etiological model

An etiological model should accommodate the epidemiological profile of the disease it aims to explain. In this context, we have categorized the established breast cancer risk factors according to the 3 components of the early life etiological model, taking also into account that certain breast cancer epidemiologic characteristics reflecting general principles of carcinogenesis relevant to many cancer sites (Table II). The empirical evidence in support of the categorization has been presented in detail in earlier publications^{2,5} and is summarized below.

First component

Mammary gland mass, *as distinct from breast size*, is usually assessed through mammographic density and is an important breast cancer risk factor.²⁸ Mammary gland mass, which is likely to reflect the pool of mammary cells and be correlated with the number of mammary stem cells,^{63,64} can also accommodate several breast cancer risk factors, including the higher incidence of the disease among Caucasian compared to Asian women and women of higher rather than lower socioeconomic class as well as the preponderance of breast cancer in the slightly larger left, rather than right, breast.⁶⁵ The positive associations of breast cancer risk with birth weight, growth in early life and adult height could also be explained in terms of mammary gland mass. Finally, at the extreme, the strikingly higher breast cancer risk among women than among men, even in later life when estrogen production is not substantially different between the 2 genders, is best explained by the correspondingly higher mammary gland mass among women than among men.

Second component

Most investigators agree that oestrogens in general, or specific categories of oestrogens, or prolactin, or other hormones, including IGF, are important in the etiology of breast cancer. Our view is that all growth enhancing and mammatropic hormones are involved in one or more stages in the long process leading to clinical breast cancer. An important issue that has not been sufficiently explored in empirical research is the way these hormones interact in the causation of the disease. A small study presented evidence that mammatropic hormones may act as permissive factors for breast cancer occurrence and that values of any one of these above a certain level may suffice for sustaining growth of a developing tumor⁶⁶—the finding is intriguing but requires confirmation in larger datasets. The second component of the etiological model accommodates our knowledge about the role of reproductive factors in the etiology of the disease

TABLE II – GROUPING OF BREAST CANCER RISK FACTORS ACCORDING TO THE GENERAL PRINCIPLES OF CARCINOGENESIS AND THE POSTULATED PATHOGENIC PROCESS

General principles of carcinogenesis	Number of mammary tissue specific stem cells	Growth enhancing mammatropic hormones	Terminal differentiation
Age Ionizing radiation Family history Specific genes	Mammographic density (gland mass) Atypical hyperplasia Gender Birth weight Growth in early life Height Ethnic group	Gender Age incidence pattern Age at menarche Age at menopause Type of menopause Oral contraceptives Hormone replacement Pregnancy timing Postmenopausal obesity Ethanol intake Physical activity Adult life diet	Age at 1st full term pregnancy Age at other pregnancies Parity overall Lactation

as well as that of alcohol drinking (which tends to increase oestrogen levels), physical activity and adult life diet.^{2,5}

Third component

Terminal differentiation of the mammary gland takes place mostly after the occurrence of the first full-term pregnancy, and to a lesser extent, after the occurrence of subsequent pregnancies and lactation.⁶⁷ The later the age at first full term pregnancy, the higher the number of already initiated cells and the more limited the protection conveyed by pregnancy. Beyond the age of 35 or so, the transient increase of breast cancer risk that accompanies a pregnancy (due to the effect on already initiated clones of the many-fold increases of mammatropic and growth enhancing hormones) overshadows the protection conveyed by the terminal differentiation of immature mammary cells. The 3rd component of the etiologic model also accommodates what was largely thought to be an enigma, namely why breast cancer risk is higher among parous than among nulliparous women of premenopausal age.

The ecological challenges

One of the most challenging characteristics in breast cancer epidemiology is the sharp ecological contrast in breast cancer incidence between women in western Europe and North America and women in China and Japan,¹ which fades in Asian women migrating to the west after 2 or more generations. Neither reproductive nor dietary factors in adult life can explain the 4-fold difference in incidence observed in these populations,^{8,68} nor can they explain the subsequent incidence assimilation. On the contrary, diet in early life could provide an explanation for the ecological contrast in the context of the early life etiologic model: reduced energy intake in early life is associated with smaller body size in adult life and smaller body size constrains birth weight and subsequent development of offspring. Increased energy intake, on the other hand, facilitates growth and removes constrains on birth weight and eventual body size. This cycle tends to repeat over consecutive generations of Asian migrants in western countries and is associated with a gradual increase in body size and breast cancer incidence among them.^{22,57}

The early life etiologic model is not refuted by the fact that populations at low risk for breast cancer have higher levels of most pregnancy—or possibly adult life—hormones.⁶⁹ It is plausible that in striking ecological contrasts (*e.g.* between native Chi-

nese and Caucasian populations), pregnancy growth hormones tend to increase in order to compensate for physically constrained fetal growth^{58,70} and the perinatally programmed higher levels of these hormones could track through adult life.

Avenues of future research

Future research assessing the early life aspects of the etiology of breast cancer could follow many directions and some of them are outlined here. Hsieh and coworkers^{65,71,72} are evaluating how pregnancy mammatropic and growth hormones affect cord blood stem cell populations. In their recent work, they reported that cord blood plasma levels of IGF-1 were strongly correlated with all the hematopoietic stem and progenitor concentrations examined, whereas estradiol and insulin-like growth factor binding protein-3 levels were positively and significantly correlated with some of these cell populations. Hilakivi-Clarke and her coworkers have used rodent models to explore the ways through which diet and otherwise induced epigenetic changes in target genes might lead to strategies to prevent breast cancer.^{73,74} Critically important results may also emerge from a unique follow-up of women born to mothers who have taken diethylstilbestrol (DES) during their pregnancies. Two recent publications indicated that in utero DES exposure may substantially increase breast cancer risk in the offspring.^{75,76} Moreover, it would be important to firmly document what has already been reported in previous publications, that is, that perinatal characteristics predictive of high breast cancer risk in adult life are also predictive of high breast cancer risk mammographic patterns.^{77,78}

Conclusion

The early life etiologic model we have outlined accommodates the existing epidemiological evidence. Its 3 components refer to stages of a single biological process that points to the number of mammary tissue-specific stem cells as a core determinant of breast cancer risk. The first component focuses on the perinatal period, when stem cells are generated. The second component concentrates on preinitiation and postinitiation 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.

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