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Review

Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review

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ABSTRACT

The interactions between pregnancy and breast cancer (BC) are complex. Overall, parity is associated with long-term protective effects against BC, however in a small group of susceptible patients, pregnancy can lead to the development of a form of BC with a particularly poor prognosis. Pregnancy-associated breast cancer (PABC) remains an under-studied but important and growing clinical problem worldwide. Several aspects of PABC, including risk factors and mechanisms involved in its occurrence and aggressiveness, are incompletely understood. This review aims to summarize the epidemiology, biology, patho-physiology and clinical characteristics of PABC. We emphasize that age at first pregnancy, absence of breastfeeding and family history stand out as possible risk factors for developing PABC that ought to be incorporated into clinical tools for assessing a woman's risk of developing PABC. Also, improved methods for identifying women at risk of developing PABC in the general population are needed.

1. Introduction

The interactions between pregnancy and breast cancer (BC) are complex. It is well established that overall, parity is associated with a long-term protective effect against BC. Less well known is that, in a small group of presumptively susceptible patients, pregnancy leads to the development of a form of BC with particularly poor prognosis.

Pregnancy-associated breast cancer (PABC) remains an understudied but important clinical problem. Several aspects of PABC, including risk factors and mechanisms involved in its occurrence and aggressiveness, are incompletely understood. In this review, we summarize the epidemiology, patho-physiology and clinical characteristics of PABC.

2. Epidemiology and definition of PABC

Pregnancy exerts two opposing effects on a mother's subsequent risk of developing BC: a transient increase in risk in the years after pregnancy, followed by a long term protective effect [1–3]. The period of increased risk, in which parous woman in comparison to those who are nulliparous, have a higher incidence of BC, has been estimated to extend for up to 15 years [3,4]. Currently PABC is defined as a BC case which occurs during pregnancy or within 1 year following birth [5,6]. Increasingly, however, epidemiological findings and emergent biological knowledge suggest an expanded definition of PABC so that some authors consider any BC diagnosis within 15 years after childbirth as PABC [7].

PABC has been reported to affect from 1 in 10,000 to 1 in 3000 pregnancies [8–10]. Among women younger than 45 years, the rate of PABC varies from 2.6% to 6.9% of cases [11–13], which is almost 25,000 new cases per year in the world [14]. This proportion rises to 15.6% of all BC cases in women younger than 35 [15]. If the definition of PABC is expanded to diagnoses within 5 years of the most recent childbirth, its incidence increases to 29%

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among women diagnosed at ≤45 years [16]. In a large cohort study of patients aged 15–44 years of age, the incidence of PABC doubled from 16.0 to 37.4 per 100,000 childbirths during the study period (1963–2002) [11].

3. Biology and patho-physiology of the breast during pregnancy and lactation

The mammary epithelium is a bilayer, consisting of luminal cells that line the ducts, surrounded by contractile myoepithelial cells in contact with the basement membrane. With each pregnancy, the mammary gland undergoes successive cycles of proliferation, differentiation, secretion and programmed cell death leading to important remodeling of the glandular tissue architecture. In response to estrogen, ductal systems grow and branch into the fat pad throughout pregnancy. Progesterone further induces extensive side-branching and alveologenesis, and in combination with prolactin, promotes the differentiation of the alveoli into milk-secreting acini, marking the full extent of glandular differentiation. Upon weaning, the stimuli for milk production cease and the expanded epithelial compartment undergoes involution through apoptosis and extracellular matrix (ECM) remodeling to return to the resting adult mammary gland state [17]. At this point, pregnancy and lactation have generated permanent histological and molecular modifications on the breast. After full term pregnancy, the human breast is characterized by a specific genomic signature that differs from nulliparous tissues and that has been linked to the long-term protective effect of pregnancy on BC risk [18]. Up-regulated genes in the parous breast represent biological processes involving cellular differentiation and development, attachment of epithelial cells to the basement membrane and intercellular adhesion. Down-regulated genes have been linked to biological processes related to cell proliferation, regulation of insulin growth factor (IGF)-like growth factor receptor signaling, somatic stem cell maintenance, as well as downregulation of estrogen receptor (ER) α, progesterone receptor (PR) and ERBB2 (HER2) [19,20].

4. Possible mechanisms for PABC

Although the definitive mechanisms driving PABC remain unclear, several hypotheses, which are probably not mutually exclusive, have been postulated (Table 1).

The unique hormonal milieu during pregnancy, characterized by elevated levels of circulating estrogen, progesterone and IGF1, induces breast cell proliferation and could thereby initiate tumorigenesis or stimulate the growth of cells that have already undergone malignant transformation [7,21]. Estradiol and its metabolites have been shown to have a genotoxic, mutagenic, transforming and carcinogenic potential [22] in cell cultures and xenograft models; the increased concentration of gestational hormones can increase tumoral proliferation [23]. On the other hand, the pharmacological inhibition of ER and IGF-signaling inhibits human breast tumor cell growth [24,25]. However, most PABCs do not express ER or PR. It has been shown that while lacking hormonal expression tumors arising in xenograft models of PABC require systemic estrogens for their formation, and increasing the levels of these hormones promotes the initiation and progression of ER negative cancers. These PABC xenograft tumors exhibit a highly stromalized histologic phenotype. Together with the fact that PABC cell lines do not proliferate *in vitro* (i.e. lacking their stroma) in response to estrogen, this suggests that PABC tumorigenesis may be driven by hormonal influences not on the mammary epithelial cells but on the host stroma [26].

PABC has also been linked to immune changes observed during pregnancy, consisting of a combination of cellular immunosuppression, immune tolerance, and enhanced inflammatory responses related to mammary gland involution. Prominent similarities exist between escape mechanisms used by the fetal trophoblast cells and cancer cells, including altered expression of molecules affecting local immune response and the release of various immunomodulators. Therefore, tumor cells that would normally be recognized and are immunologically destroyed may have a greater chance of proliferation and survival during pregnancy [27].

It has further been hypothesized that the development of PABC is related to breast involution. Following lactation or pregnancy - if lactation does not occur - the fully differentiated gland regresses to its pre-pregnant quiescent state. During this transformation, an innate tissue-remodeling program is initiated and is characterized by massive epithelial cell death, macrophage infiltration, collagen deposition and stromal remodeling. This physiologic process shares characteristics with wound healing and inflammatory microenvironments which have been shown to be pro-oncogenic [28–30]. The hypothesis of a causal effect of involution is supported by the fact that the human breast environment after pregnancy exhibits upregulation of inflammatory and immune-related genes [6], resulting in a tumor promotional environment [31]. In pre-clinical models, when human mammary tumor cells were injected into the mammary glands of mice 1-day post-weaning, tumor size and lung infiltration were significantly greater than when injected into nulliparous controls [32]. Preventive strategies have been tested based on these observations. In rodent models, the injection of non-steroidal anti-inflammatory drugs such as ibuprofen along with tumor cells at 1 day post-weaning reduced collagen deposition and tumor growth to levels similar to that in nulliparous controls, suggesting a role of the COX-2 pro-inflammatory pathway in the promotion of tumor aggressiveness in the involuting mammary gland [33].

5. Characteristics of PABC

PABC characteristics are shown in Table 2. The average age at PABC diagnosis is between 30 and 38 years of age [34]. Around 2/3 of PABC cases are diagnosed postpartum and 1/3 while pregnant [35]. A delay in diagnosis has often been reported, ranging from 1 to 13 months [36]. Clinical signs of PABC are often regarded as normal consequences of pregnancy and lactation. These 2 conditions increase breast density, making clinical examination and mammographic interpretation difficult [37].

As in sporadic BC, the most common histological type of PABC is invasive ductal carcinoma, representing 78–88% of cases [38,39]. Younger age is a factor that is *per se* associated with more aggressive features. When compared to non-PABC cases in age-matched studies, PABC exhibits an aggressive profile with more advanced stages at diagnosis [15,38], larger tumors [15,38–40], of higher grade [40], greater nodal involvement [9,46] and less frequent expression of ER and PR [38–40] (Table 3). It has also been reported that the proportion of inflammatory BC is significantly higher in PABC [39].

There are also differences in tumoral gene expression patterns between PABC and non-PABC, demonstrating that the two entities are different from one another and supporting the hypothesis of distinct neoplastic processes. Hsiao et al. detected through comparative genomic hybridization, that PABC epithelia exhibit a gain in copy number of DNA coding genes for morphogenesis, angiogenesis and metastases, along with a loss in copy number of DNA coding genes for tumor suppressors and cell adhesion, leading to increased invasiveness and aggressiveness [41]. Harvell et al. isolated malignant epithelia and associated stroma from PABC by