

## Pregnancy-Associated Breast Cancer

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### Abstract

The frequency of pregnancy-associated breast cancer, a rare but serious occurrence, may increase in light of the secular trends for lower parity in general and for older age at first full-term delivery in particular. Data on PABC in individuals who are at high risk for breast cancer are limited. A computerized search of Pubmed showed that the reported incidence of PABC is 1:3000 pregnancies; it is often diagnosed at an advanced stage and its prognosis is inferior compared to non-PABC. Carriers of mutations in the genes BRCA1/2 may present a specific high risk group for PABC especially at younger ages. Women treated with fertility treatment drugs may be at a higher risk for PABC as well.

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Breast cancer is the most common malignancy affecting women around the world, with more than one million cases occurring worldwide annually, over half of them in developed countries [1]. Breast cancer is the most common malignancy among Israeli women, with an age-standardized rate of 96.5 per 100,000 Jewish women in 2002 [2]. Age is a major risk factor for the disease. A family history of breast cancer in a first-degree relative (a mother, a sister, a daughter) may double a woman's risk for the disease, and high risk mutations in the BRCA1 and BRCA2 genes predispose carriers to the disease [1]. Reproductive factors are associated with higher risk for breast cancer. These include early age at menarche, late age at menopause and late age at first full-term pregnancy, lower number of children or nulliparity, infertility, and no lactation [1]. Recently, some reports indicated that use of clomiphene citrate, an ovulation induction agent, may also be associated with an increased risk for the disease [3,4].

Most of the newly diagnosed cases of breast cancer are reported in postmenopausal women. In developed countries, around 35% of new breast cancer cases are diagnosed before age 55, 13% are diagnosed during the reproductive years (20–44 years) and around 2% are diagnosed before age 35 [5]. A growing number of women in their reproductive years postpone their

first pregnancy. Overall, in the United States, first births among women over 30 rose from 12.6% in 1960 to 15.7% in 1980 and to 37.1% in 2000; fertility rates (per 1000 women aged 15–44) decreased accordingly, from 118.0 in 1960 to 68.4 in 1980 and 66.4 in 2004 [6]. The trend for delayed parenthood may well increase the risk for pregnancy-associated breast cancer, since the proportion of pregnant women at an advanced age and thus at a higher risk for breast cancer is increasing. Furthermore, these women do not experience the reduction in breast cancer risk associated with young age at first full-term delivery, longer accumulative lactation period or multiparity [1].

Pregnancy-associated breast cancer is an intriguing issue; moreover, the issue of pregnancy-related breast cancer in carriers of mutations in BRCA1 and BRCA2 genes has not been sufficiently covered. The aim of the current review is to explore the characteristics of PABC, especially in high risk populations such as carriers of mutations in the genes BRCA1/2.

### Review of the available literature

We conducted a computerized search of Pubmed for papers published until 31 March 2008 to identify studies potentially eligible for this review, using the following key words: breast cancer, breast carcinoma, pregnancy, pregnancy-associated breast cancer, BRCA1, BRCA2, as well as clinical trial, cohort, case control, cross-sectional, and case series. The references of every article retrieved and those of recent reviews of pregnancy-associated breast cancer were also examined. All searches were carried out by experienced epidemiologists. The literature search was restricted by study type (excluding case reports), study subjects (humans only), subjects' gender (females only), time period (last 14 years, in light of the fact that several literature reviews have been published), and language (English). The publications retrieved were screened individually for their relevance and contribution. Included in this literature review are publications addressing epidemiology and characteristics of PABC (a brief summary), possible mechanisms for PABC, and the relationship between genetic mutations in the BRCA1 and BRCA2 genes and PABC.

### Epidemiology and characteristics of PABC

Cancer diagnosed during pregnancy is a rare event; the incidence of pregnancy-associated all-site cancer is estimated to

PABC = pregnancy-associated breast cancer

be 0.5–1.0/1000 deliveries [7,8] or 0.32–0.67/1000 pregnancies [7,9]. The most common sites are cervix, breast, thyroid, ovary, skin (malignant melanoma) and the lymph system (Hodgkin's lymphoma) [7–11], which account for around two-thirds of all pregnancy-associated cancer cases.

#### • PABC incidence

Pregnancy-associated breast cancer is commonly defined as breast cancer diagnosed during pregnancy or in the first 12 months postpartum, including any time when a woman may be lactating. The incidence of pregnancy-associated breast cancer is approximately 0.24–0.33/1000 pregnancies, and it may account for up to 6.25% of all breast cancers diagnosed in fertile women under age 45 [8,12–14]. Around two-thirds of all PABC cases are diagnosed in the postpartum period, and mostly in the first 6 months following delivery [7,8,13].

#### • PABC risk

Several studies addressed the question of excess risk for breast cancer in pregnant women by comparing the observed number of PABC to the expected number according to population rates, computing a standardized incidence ratio [10,15]. None showed an increased risk. In fact, computed SIRs were significantly lower than 1.0 [10,13,16]. However, these studies were hampered by the fact that the basis for the calculations was a linkage between a birth cohort and a cancer registry, thus including only women who gave birth to a liveborn and excluding those diagnosed in the first and second trimesters and underwent a spontaneous or induced abortion. This obstacle is reflected by a deficit of recorded breast cancer cases in early pregnancy. Still, when SIR was computed for PABC during the third trimester only, it was still significantly lower than 1.0 (SIR=0.73, 95% confidence interval 0.59–0.85) [7]. On the other hand, when only the postpartum period was considered, SIR indicated a higher risk of breast cancer in the year following delivery (SIR=1.19, 95% CI 1.04–1.34) [7]. One possible explanation for these results is that data are largely missing with regard to PABC in early pregnancy. Another reason could be selection bias, if women with early neoplastic disease also experience decreased fertility. A delay in PABC diagnosis until after delivery and/or an altered tumor progression in pregnancy could also partially explain these observations [7,10].

#### • PABC characteristics

Diagnosis of PABC is often delayed by a few weeks to a few months. Physiological changes in pregnancy and lactation may obscure physical signs of cancer that may incorrectly be attributed to the pregnancy/postpartum period. Awareness of the possibility of pregnancy-associated breast cancer may be low, and both patients and physicians may be reluctant to perform radiographs or invasive procedures during pregnancy [8,9,12,16–18]. However, different results have also been reported, where PABC cases had a shorter duration of symptoms prior to diagnosis

than non-PABC cases (mean of 5.6 vs. 9.4 months,  $P < 0.0001$ ) [19], and where no significant differences were observed [13]. The primary presenting symptoms are no different from those of non-PABC cases [12,13], and the average age at PABC diagnosis is between 30 and 38 years [5,7,9,12,13,19].

Breast abnormalities are usually examined by a diagnostic mammogram and/or breast ultrasonography [20,21] and confirmed by tissue sampling [12,13]. The rate of false negative findings on mammography is higher in pregnant women [9], calling for a higher index of suspicion and the use of different diagnostic tools. The stage at diagnosis is usually more advanced and the size of tumor larger among PABC cases compared to age-matched non-pregnant breast cancer cases [5,13,17,22–25]. These results are also reflected in the fact that the percentage of PABC cases diagnosed beyond TNM stage I is significantly higher (31.0–53.7%) compared to women diagnosed with breast cancer 9–12 months before delivery (23%) [8]. PABC is also characterized by a higher involvement of lymph nodes at diagnosis [5,11,13,17,19,24].

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*Pregnancy-associated breast cancer is an uncommon event, with a reported incidence of 1:3000 pregnancies. PABC is often diagnosed at an advanced stage and its prognosis is inferior compared to non-PABC*

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The prevalence of a positive estrogen and progesterone receptor status is usually lower in premenopausal compared to postmenopausal breast cancer patients, and in PABC patients this trend is even more pronounced [9,12,13,17,24,26].

PABC patients should be treated as early as possible and according to the latest clinical guidelines, while carefully weighing the risk to the unborn child, in the case of cancer diagnosed during pregnancy. The general rule of cancer treatment – early diagnosis followed by appropriate management – is still a key principle to improve the treatment in PABC patients [9,18,27]. Abortion is usually not recommended, unless opted for by the woman, as it was not shown to improve outcome [9], except for PABC diagnosed in the first trimester when induced abortion may avoid delayed treatment. Most patients diagnosed with PABC undergo a definitive surgical treatment. Breast conservation surgical therapy (lumpectomy), with radiation treatment given after delivery or after neoadjuvant chemotherapy, is an option for women with PABC diagnosed late in pregnancy [9]. The surgical definitive treatment is given either during pregnancy or following induced or spontaneous termination of the pregnancy, depending on the time of the diagnosis. Chemotherapy as an adjuvant or neoadjuvant therapy is potentially teratogenic in the first few weeks of pregnancy and may lead to the death of the embryo [27]. The agents usually used are 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) or epirubicin and cyclophosphamide

SIR = standardized incidence ratio  
CI = confidence interval

(EC), or 5-fluorouracil, epirubicin and cyclophosphamide (FEC). Radiotherapy is contraindicated during pregnancy because of the potential risk for the fetus. It is still a preferred adjuvant strategy following pregnancy, as is hormonal therapy if appropriate [9,12,13,19].

Possible pregnancy outcomes in PABC patients include normal vaginal deliveries [9], as well as preterm deliveries, high proportion of cesarean deliveries [15], termination of pregnancy [19] and stillborn deliveries [8]. The proportion of congenital malformations in babies born to mothers diagnosed with PABC is apparently not higher than expected [9,19].

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Some studies suggested that the overall 5 year survival in PABC patients (40–73%) is significantly lower compared with age-matched non-PABC patients (68–77%) [5,13,17], and the same trend was also seen when metastasis-free survival was concerned [17]. Other studies, however, found no significant differences [7,9,18,19,22] when age and stage at diagnosis were adjusted for. In multivariate analyses, clinical stage, clinical tumor size, lymph node involvement and age were significantly associated with poor outcome in both PABC and non-PABC cases, while delay in diagnosis was not. However, pregnancy at diagnosis remained an independent and significant prognostic factor for poorer metastasis-free survival and overall survival [17].

### **Possible mechanisms for PABC**

One of the mechanisms suggested to account for the incidence of breast cancer in general is exposure to endogenous estradiol levels [1]. Production of endogenous estradiol is cyclic throughout the reproductive years; however, whereas estradiol peak during the follicular phase of a regular menstrual cycle reaches 400 pg/ml, exposure during pregnancy may peak as high as 6–40 ng/ml (at week 36). In fact, more estrogen is produced by the placenta during the course of a normal pregnancy than is produced by the ovaries of 200 ovulating women during the same 40 weeks [28]. Endogenous estradiol and its metabolites have genotoxic, mutagenic, transforming and carcinogenic potential, and thus could initiate or cause the progression of a carcinogenic process in humans [29,30].

The hypothesis that pregnant women exposed to high endogenous estradiol levels may transiently be at a higher risk for breast cancer is based on these facts. The hypothesis is supported by the observation that pre-eclampsia, a pathological

pregnancy condition associated with placental breakdown and decreased levels of endogenous estrogen, is closely correlated with a twofold reduction in breast cancer risk [31]. Additionally, women exposed to fertility drug treatment such as clomiphene citrate or human menopausal gonadotropins, experience, as a result, multiple folliculogenesis and, consequently, a rapid increase in estradiol production. Siegelmann-Danieli et al. [29] conducted a case-control study where 38 women exposed to fertility drug treatment and subsequently diagnosed with breast cancer were compared with 22 PABC cases and 192 non-PABC premenopausal breast cancer cases, in order to characterize each disease entity. Some significant differences were noted. Rates of BRCA1 and BRCA2 mutations were considerably lower for the PABC and the fertility drug treatment subgroups compared to the non-PABC subgroup, but this difference did not reach statistical significance. However, the PABC and fertility drug treatment cases had a more advanced disease and less favorable outcomes than did the non-PABC cases. Likewise, poorly differentiated tumors were significantly more frequent in the PABC and the fertility drug treatment cases compared to the non-PABC group, and negative ER and PR status was significantly more prevalent among the PABC and the fertility drug treatment subgroups. Although overall survival did not substantially differ between the subgroups, relapse-free survival (i.e., until first local or systemic relapse) and cancer-free survival (i.e., until evidence of a distant metastatic disease) were statistically significantly lower for the PABC and the fertility drug treatment subgroups. These results suggest a modifiable susceptibility to pregnancy-related or fertility drug treatment-related estrogenic stimuli in certain premenopausal women [29].

Studies addressing the issue of breast differentiation and involution may shed some more light on the possible mechanisms of PABC [23,25,32]. In the non-pregnant, non-lactating state, the mammary gland consists of networks of epithelial ducts and rudimentary milk-producing lobular components. During pregnancy, the breast parenchyma branches profusely, forming secretory lobular units. The full differentiated breast structure is acquired only in the last pregnancy trimester, and – if acquired through a relatively early (up to age 35) full-term pregnancy – is associated with a long-term protection against breast neoplastic transformation [23,25,32]. The remodeling of the breast following lactation is a controlled programmed process that has much in common with microenvironments occurring with inflammation and wound healing, i.e., activation of fibroblasts, endothelial cells and immune cells. The activated mesenchymal cells secrete cytokines, growth factors, tissue-remodeling enzymes and provisional extracellular matrix, all of which facilitate wound closure and remodeling of the damaged tissue. Such a microenvironment may also promote the growth and development of transformed tumor cells, if present in the tissue [23,25]. Furthermore, spread of occult breast cancer cells may also be facilitated [25]. The idea that the involuting breast may facilitate the growth of exist-

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ER = estrogen receptor

PR = progesterone receptor

ing tumor cells was supported by an *in vitro* observation [23], that extracellular matrix isolated from mammary glands of rats undergoing weaning-induced involution seemed to support ductal development in normal cells and to promote invasiveness in tumor cells, while extracellular matrix isolated from mammary glands of nulliparous rats was found to encourage ductal organization in normal MCF-12A breast cells and to suppress invasion of MDA-MB-231 breast tumor cells [23].

These observations suggest that a subset of women – i.e., those with a malignant cell transformation or a micro-invasive disease at the time of pregnancy – may have modified susceptibility to the estrogenic stimuli associated with pregnancy or the specific microenvironment associated with breast involution, and therefore may be at a high risk for tumor promotion and tumor metastasis.

### **The relationship between the mutations BRCA1 and BRCA2, and PABC**

BRCA1 and BRCA2, located on the long arms of chromosome 17 and 13, respectively, are tumor suppressor genes involved in multiple processes including DNA damage repair and recombination, cell cycle control, transcription and estrogen receptor type alpha activity. Women who carry a BRCA1 or BRCA2 mutation have a 50–80% lifetime risk of developing breast cancer and 16–65% lifetime risk of developing ovarian cancer. These risks far exceed those of breast (13%) and ovarian (1.5%) cancer in the general population [33].

Is parity a risk factor for PABC in carriers of the mutations BRCA1 and BRCA2? Most cases of breast cancer related to BRCA1 and BRCA2 are diagnosed in young women, and the probability of pregnancy in young women is high. Thus, PABC in BRCA1 and BRCA2 mutation carriers may be coincidental. But is it? Only a few studies addressed this point to date.

The study by Johannsson et al. [14] suggested that carriers of BRCA1 may be at an increased risk for PABC. The study explored the occurrence of PABC in 35 carriers of BRCA1 and 12 carriers of BRCA2 and compared it to the occurrence of PABC in 245 premenopausal Swedish women aged  $\leq 40$ . The corresponding risk estimates (odds ratios) and 95% confidence intervals for BRCA1 and BRCA2 carriers were 3.9 (1.4–10.8) and 1.9 (0.5–7.0), respectively, or 4.5 (1.9–10.2) when BRCA1 and BRCA2 carriers were combined. Whether the observed risk elevation is due to a tumor-promoting effect of pregnancy in BRCA1 carriers or to a lack of a protective effect of an intact BRCA1 protein product during pregnancy warrants further investigation. However, although based on small numbers, this study suggests that carriers of BRCA1 (and perhaps also BRCA2) may represent a high risk group for PABC, and should, therefore, be monitored carefully during pregnancy and after [14].

Parity, however, may modify PABC risk in mutant BRCA1/2 carriers. A case-control study based on BRCA1 and BRCA2 carriers from North America, Europe and Israel analyzed parity data of over 1260 pairs of carriers diagnosed with breast cancer matched with healthy control carriers by year of birth, country of residence and mutation type. Mutations in BRCA1 were preva-

lent in 74% whereas BRCA2 mutations were reported in 26% of the pairs. Parity was not associated with breast cancer risk *per se*, that is, when parous women were compared to nulliparous women, no statistically significant differences in breast cancer risk were observed (for carriers of mutant BRCA1: odds ratio 0.94, 95% CI 0.50–1.19; for carriers of mutant BRCA2: OR=1.37, 95% CI 0.93–2.03) [34]. However, when risk for breast cancer was stratified by level of parity, it seemed to be significantly reduced for BRCA1 carriers with 4 children or more (OR 0.62, 95% CI 0.41–0.94), but not for BRCA2 carriers. Likewise, when breast cancer risk in parous (compared to nulliparous) women was studied by time since last pregnancy, BRCA2 carriers were at a higher risk for breast cancer 1–2 years following their last pregnancy (the time interval that includes PABC), with borderline statistical significance: OR=1.70 (95% CI 0.97; 2.99). No excess risk was observed for BRCA1 carriers in the corresponding time window; in fact, if anything, the results could be interpreted as protective (OR 0.72, 95% CI 0.53–0.99). Thus, these results suggest that parity characteristics, if not parity *per se*, may modify PABC risk in BRCA1 carriers [34].

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Parity impact on breast cancer risk (but not necessarily PABC risk) in BRCA1/2 carriers was addressed in several other studies, with inconclusive results. One study, a matched case-control study, indicated that parous BRCA1 or BRCA2 mutation carriers were significantly more likely than nulliparous carriers to develop breast cancer by the age of 40. This excess risk of early-onset breast cancer was evident in association with *any* previous pregnancy, not only those that occurred in the previous year (PABC) [35]. Two other studies, however, suggested that in the long run, parity may have a protective effect regarding breast cancer risk in BRCA1/2 carriers [36,37]. The study by Narod and colleagues [37] suggested that pregnancy in BRCA1 and BRCA2 carriers (compared to nulliparity) was actually associated with delayed onset of the disease [37]. Similar results were also reported by Andrieu and co-authors [36], who found that each additional pregnancy in both BRCA1 and BRCA2 carriers who are over 40 years of age reduced breast cancer risk by 14% (95% CI 6%–22%) [36].

Histological findings, based on two PABC case series, give rise to the hypothesis that loss of heterozygosity and deletions in the BRCA2 gene in PABC cases may present an early genetic event that might eventually lead to the occurrence of PABC. Shen and team [38] reported in 1999 on a case series of 12 PABC



patients and 15 cases of sporadic breast cancer, whose pathologic samples were retrospectively analyzed for loss of heterozygosity at multiple chromosomal loci, including those of BRCA1 and BRCA2. A high frequency (88%) of allelic deletions at the BRCA2 locus in this series of PABC cases was reported, whereas the rate of BRCA2 deletion in sporadic breast cancer cases was around 20%. The authors concluded that BRCA2 deletion may represent a relatively early genetic event in the development of PABC. Furthermore, loss of heterozygosity with BRCA2 markers was also observed in lactational hyperplasia in 4 out of 9 PABC cases. The authors commented that although lactational change is generally a physiological phenomenon, it may still bear genetic alterations long before a carcinoma is developed in these PABC cases [38]. This hypothesis was supported by the findings of a Norwegian population-based PABC case series from 2003, where BRCA1 expression was reported to be reduced in 33% of the 122 cases [26].

The picture so far is inconclusive. Because of the general lack of data no firm conclusions can yet be drawn. However, in light of the histological and clinical findings so far, carriers of mutations in the BRCA1 and BRCA2 genes, which constitute a high risk population for breast (and ovarian) cancer, may also form a high risk group for PABC. This possibility should be pursued further. The role of parity in this regard should be better assessed as well, since this may provide caregivers and BRCA1/2 carriers with a potentially risk-modifying strategy.

## Conclusions

This review explored the characteristics of PABC, especially in high risk populations. Carriers of mutations in the genes BRCA1 and BRCA2 may present a specific high risk group for PABC especially at younger ages, even if multiparity may prove to be protective against breast cancer in the long run. Hormonal factors associated with pregnancy and lactation may play a role in PABC occurrence, together with a specific genetic background. The contribution of the unique involution process in the breast following weaning to PABC susceptibility warrants further investigation.

In light of the potential etiological role played by hormonal factors associated with pregnancy and lactation, the case of pregnancy following breast cancer should also be mentioned. It involves women diagnosed with early-onset breast cancer during their reproductive years who undergo a full-term pregnancy following their diagnosis. One may assume that the mechanisms contributing to the promotion and progression of the primary tumor may be reactivated once such women are exposed to the changing hormonal environment associated with pregnancy, lactation and the postpartum period, thus putting them at a higher risk for recurrence of the disease. Surprisingly, several studies indicated that pregnancy subsequent to breast cancer diagnosis did not adversely affect the prognosis of the patients; quite the opposite, in fact [26,39,40]. Though subjective to potential selection bias, these findings may contradict a preferential occurrence of breast cancer during pregnancy, and should also be kept in mind.

The incidence of breast cancer in Israel is high, and as in

other developed countries, an older age at first full-term pregnancy is also common. Still, local cultural and social values place a strong emphasis on multiparity. Taking into account that free fertility treatments are offered by the Israeli National Health Insurance Law up to age 45 and up to a second child, we may be facing a higher than expected rate of PABC in the future, even if breast cancer diagnosis during pregnancy may be basically coincidental.

In conclusion, PABC – a rare event – is often diagnosed at an advanced stage either because of delayed diagnosis, despite ample opportunity for a physical breast examination during pregnancy follow-up, or because of specific tumor characteristics. A high index of suspicion, both by the physician and the patient, and better use of appropriate diagnostic tools may contribute to early detection and treatment and subsequently affect survival rates considerably. Special attention – by clinicians and researchers alike – should be given to groups that may be at a higher risk for PABC, such as carriers of BRCA1 and BRCA2 mutations and women undergoing fertility treatments. The information gaps with regard to these specific subgroups should be bridged.

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