ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

REVIEW
ΑΝΑΣΚΟΠΗΣΗ

ARCHIVES OF HELLENIC MEDICINE 2015, 32(5):556–565
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2015, 32(5):556–565

Pregnancy-associated breast cancer
Risk factors assessment as an important diagnostic modality

I. Kakoulidis,[1]
E. Politi[2]

[1]Postgraduate Program "Research on Female Reproduction", School of Medicine, National and Kapodistrian University of Athens, Athens
[2]Department of Cytopathology, "Aretaieion" University Hospital, Athens, Greece

Καρκίνος μαστού σχετιζόμενος με την κύηση: Η εκτίμηση των παραγόντων κινδύνου ως σημαντική διαγνωστική μέθοδος

Περίληψη στο τέλος του άρθρου

The incidence of pregnancy-associated breast cancer (PABC) is increasing, and it is becoming one of the most frequent types of cancer occurring during pregnancy. The influence of pregnancy on the risk of breast cancer is dependent on several maternal features related to reproductive, genetic and hormonal factors. In view of large-scale changes in women's life style and childbearing trends worldwide, it has become urgent for healthcare providers to reform their diagnostic management. A thorough analysis of the risk factors that contribute to the association between pregnancy and breast cancer is essential at the level of reproduction, genetics and hormonal interactions. This review covers a variety of factors related to PABC, including age at menarche and maternal age, in addition to parity, number of births, birth interval and breastfeeding, which are key factors in breast cancer risk assessment. The "menarche to first birth" time interval, along with expression of hormonal receptors and underlying compound genetic influences, are also crucial in the initiation and pathogenesis of PABC. This review aims to define the relationship and possible interactions between these factors, modifying diagnostic management and advancing the assessment of PABC risk factors as an important diagnostic modality. Search of Medline/PubMed and Google Scholar databases provided a total of 45 eligible English language articles up to November 2014. Studies focusing mainly on epidemiological, clinical, pathological and diagnostic aspects of PABC were selected, and in particular those published in recent years. The reference lists of these articles were searched for additional articles of relevance, yielding a total of 66 to be included in this review.

Key words

Diagnosis
Hormone receptors
PABC
Pregnancy associated breast cancer
Reproductive risk factors

Submitted 23.2.2015
Accepted 7.3.2015

1. INTRODUCTION

Pregnancy-associated breast cancer (PABC) is defined as any breast malignancy diagnosed during pregnancy or within the first 2 years postpartum, during lactation.[1–5] The incidence of PABC is increasing,[6] and at a reported range of 1:3,000 to 1:10,000 pregnancies[2,3,7–9] it is presently one of the most frequent types of cancer occurring during pregnancy.[5,10] The average age of women with PABC is between 32 and 38 years.[5,7,11] The diagnosis of PABC is expected to become more frequent, since the percentage of women aged 35 years and over at first birth has increased, underscoring the increasing trend for women to delay childbearing.[2,8,9,12] There is controversy about the prognosis of PABC,[9] but it is noted that breast cancer diagnosed within 5 years postpartum has a 2.8 times higher risk for metastasis and 2.7 times higher mortality risk than that in nulliparous women.[4,13] The mechanisms that make pregnancy a poor prognostic factor remain unclear but may be associated with the hormonal environment that characterizes pregnancy,[14] which possibly increases breast cancer aggressiveness.[15]

Life style has been significantly modified throughout the world, and factors associated with what is generally known as the western way of life could be implicated in the increase in incidence of breast cancer.[16] The risk of breast cancer after a pregnancy shows a pattern of initial increase, followed by decrease over time, dependent on several maternal features.[17] Earlier age at menarche, fewer pregnancies, shorter duration of breastfeeding and less women reaching full-term gestation are some of the changes that might be related to the association between pregnancy and breast cancer and which contribute to the increasing

incidence of breast cancer. In view of the considerable changes in sexual maturation and childbearing patterns that have been observed in recent years, in parallel with the rise in breast cancer incidence worldwide, definition of the relationship between reproductive history and levels of hormones is of paramount importance.[18,19] Thorough analysis of the risk factors that contribute to the association between pregnancy and breast cancer is essential. These factors should be elucidated at the level of reproduction, genetics, and hormonal interactions.

For this review, Medline/PubMed and Google Scholar databases were searched using the keywords "breast cancer in pregnancy" or "pregnancy associated breast cancer" in combination with "diagnosis", "pathology", "genetics", "risk factors". A total of 45 English language articles up to November 2014 were assembled. Studies focusing mainly on epidemiological, clinical, pathological and diagnostic aspects of PABC were chosen, and in particular those published in recent years. Reference lists of identified articles were also searched for additional articles of relevance, yielding a total of 66 to be included.

2. REPRODUCTIVE FACTORS

The frequency of reproductive-related risk factors for breast cancer has increased in recent years. Changes noted in risk factor profiles may influence the increasing incidence of hormone-sensitive tumors in younger women.[16] The association between reproductive factors and the risk of breast cancer varies according to the histological type, with significant differences in proportion in women diagnosed shortly after childbirth, indicating susceptibility to adverse effects of pregnancy-related factors.[20] Reproductive factors and their timing may influence breast cancer risk through their effects on differentiation of breast tissue and on hormonal and immunological profiles.[18] It is possible that the tissue changes related to pregnancy may make the breast more or less susceptible to carcinogenic factors, depending on the underlying genetic susceptibility to breast cancer. In this way, reproductive factors may either initiate or inhibit specific types of breast cancer with different degrees of aggressiveness.[21]

2.1. Age at menarche – Age at first full term pregnancy

Early age at menarche is associated with higher exposure to ovarian hormones throughout life and a well-established increase in breast cancer risk, regardless of cancer subtypes.[16,18,22] Late menarche, on the other hand, appears to contribute a strong protective effect.[23] It is well known that the age at menarche has decreased in most European countries,[24] but there is still debate over the significance of this phenomenon in relation to breast cancer risk.[25]

Earlier age at first birth and increased parity are factors recognized as protecting women from breast cancer. Early pregnancy is thought to produce permanent genomic changes in the breast that reduce its susceptibility to cancer and it is associated with an overall lifetime decreased breast cancer risk.[26] Less well established is the finding that pregnancy, regardless of age, is followed by a temporary increase in breast cancer risk, especially after the age of 30 years.[18,27] The estimated breast cancer risk increases by 6% per 5 years of maternal age increase, with adjustment for parity and other risk factors.[22] Conversely, in women who delivered their first baby at an age of less than 25 years, no, or only a very small, increase in breast cancer risk is observed. Accordingly, age is considered to be the main risk factor.[28] Later age at first full term pregnancy might be associated only with a specific type of hormone receptor status, however. Specifically, data show an increase in risk for estrogen receptor (ER)(+)/progesterone receptor (PR)(+) tumors but not for ER(–)/PR(–) tumors.[16,29] Although maternal age is considered to be a strong risk factor for breast cancer, increasing maternal age contributes to only 14% of the estimated increase.[8]

Studies focusing on the time between menarche and the first full term birth suggest a possible association between this interval and hormone receptor-positive breast cancer. Conversely there are indications that this interval might be inversely associated with the risk of triple-negative breast cancer. Other authors suggest that young mothers may benefit from a shorter exposure time between puberty and full term pregnancy. Given the fact that the "menarche to first birth" interval represents a period during which post-pubertal breast tissue is relatively undifferentiated and potentially more susceptible to carcinogenic factors up until the differentiation induced by pregnancy, further investigation of the association of this interval with breast cancer risk is of particular importance for PABC.[16,17,25,29]

2.2. Parity versus nulliparity

Parity has been regarded as a protective factor against breast cancer, due to the fact that the complete differentiation of mammary epithelial cells during pregnancy and lactation can inhibit the initiation of the neoplastic process.[30] Pregnancy, however, has a dual effect on breast cancer; an immediate increase in risk after childbirth is followed by long-term protection.[31] Although early age at first completed pregnancy is crucial for the establishment of

protection, the protective effect becomes noticeable only after age of 40 years.[32] Pregnancy-related clinical conditions, such as gestational hypertension, preeclampsia or eclampsia, gestational diabetes mellitus, weight gain, nausea and vomiting, may be indicative of altered hormonal and metabolic profiles which could impact breast cancer risk.[27,33] Uniparous women, however, who complete their first pregnancy before the age of 25 years, experience a transient increase in risk, but then have a lifetime risk reduction of 36% for developing breast cancer.[17] ERα(+) cell population reduction, effected by downregulated ERα expression following pregnancy in young women, may suggest a possible mechanism for the long-term protective effect of pregnancy on breast cancer risk, attributed to the reduction of estrogen reactivity and the potential development and progression of cancer.[34] There is inconsistency in the documentation of the relationship between parity and risk over different breast cancer subtypes. Parity is associated with a 30% reduction in risk of both ER(+), triple-negative breast cancer and human epidermal growth factor receptor (HER)2(–) tumors but not HER2(+) tumors. Moreover, regardless of age, parity is associated with a better clinical outcome than nulliparity in breast cancer.[21,25,33]

2.3. Number of births – Birth intervals

It has been noted that multiple births may be associated with a decrease of around 10% to 30% in breast cancer risk, while women with breast cancer have, on the average, fewer births than control subjects without cancer.[27,35] Women who were biparous, regardless of their age at the second birth, had a lower rate of transient increase in risk, peaking earlier at 3 years postpartum. This variation in risk profile is possibly due to an overlap or combination of the effects produced by the first pregnancy.[17] Increasing number of live births was shown to be associated with a reduced risk of all three breast cancer subtypes, although only statistically significant in to the case of ER(+) tumors.[21,25] Increasing parity presents a long-term risk reduction of developing breast cancer by 7% for each additional birth. Age and parity appear to act synergistically, with high parity (≥5) and younger age at the first birth (≤20 years) being associated with an ultimate reduction in lifetime breast cancer risk. This protective effect, however, is weakened among multiparous women aged over 30 years at the first birth.[17] Conversely, in some cases it has been suggested that high parity (≥5) may increase the risk of triple-negative breast cancer, which is known to have a poorer prognosis and to be more common in young women. It is therefore unclear whether the association between high parity and overall survival reflects a general decrease in female survival as a result of deaths due to parity-related diseases, such as cardiovascular disease, and postpartum related diseases, without specifically affecting the course of breast cancer.[21]

The interval between the first and second birth is also an important issue in the association of pregnancy with breast cancer risk. A second pregnancy soon after the first may decrease the risk of ductal breast cancer in young primiparas but also increase the risk in older ones, whereas interval from last birth to cancer onset may modify its behavior.[31,36] A short birth interval (<1 year) when associated with increased breast cancer risk may be related to the stimulatory effects of maternal steroid hormones produced during two close pregnancies or to defective breast maturation owing to failure in breastfeeding, especially between first and second births, because the first pregnancy plays a significant role in the maturation of the breast resistance against carcinogenic factors. It is possible that the second pregnancy continues the processes initiated by the first pregnancy and lactation.[31,36] The length of the birth interval depends on the duration of breastfeeding, which is an important determinant of breast cancer risk.[31]

Twin pregnancies differ from singleton pregnancies in both hormone levels and perinatal changes, and some, but not all, authors suggest that twin births may be associated with lower breast cancer risk; a trend towards reduced maternal risk of breast cancer is indicated by more recent data, but this was not significant.[37] The risk for breast cancer recurrence associated with subsequent pregnancies is not clear. Schnabel and colleagues reported the case of a second occurrence of PABC, indicating that pregnancy may represent a unique trigger for breast cancer in a specific type of women. Although it is generally accepted that women can bear children after breast cancer treatment without compromising their survival, the data are insufficient to assess the impact of additional pregnancies on the risk of recurrence and survival for women with PABC.[38]

2.4. Breastfeeding – Lactation

In general, a long duration of lactation is associated with a small reduction in overall breast cancer risk, in addition to other health benefits for mother and child. Breastfeeding may provide greater protection against triple-negative, basal-like and *BRCA1* mutation associated breast cancer, suggesting particular protection against aggressive types of tumors.[25,39] Current data suggest that lactation decreases the lifetime risk of breast cancer by 4.3% for every 12

months of lactation and 7% for every additional birth. The risk of breast cancer within 5 years after birth is 1.24 in breastfeeding women and 1.64 in non-breastfeeding women. Although the decrease in risk in *BRCA2* mutation carriers is debated, in *BRCA1* mutation carriers breastfeeding for more than one year significantly decreases the risk compared to non-breastfeeding mothers.[17,28,35] The size of the decrease in the relative risk does not differ significantly between women in developed and developing countries and does not vary with reproductive or maternal factors.[35] Breastfeeding appears to convey a stronger effect than pregnancy alone.[23] The first pregnancy induces hormonal changes, some of which persist long-term. It is unclear how lactation affects the long-term hormonal environment over and above that of pregnancy. One theory is that the promotion of patterns of involution of terminal duct lobular units (TDLU) might be protective,[39] due to the fact that lactation participates in the differentiation of mammary epithelium in its terminal phase. Deficient breastfeeding of the first child might therefore leave the breast cells susceptible to carcinogenic influences.[31]

2.5. Nutritional status – Birth weight

There could be an association between the nutritional status of women and the risk of breast cancer, moderated by ovarian sensitivity to environmental conditions. Since ovarian function responds to nutritional status, the risk of breast cancer may be modified by changes in a woman's lifestyle. An increase in physical activity and decrease in caloric intake may lead to lower concentrations of progesterone and estrogen, resulting in a reduction in breast cancer risk.[40] Despite the fact that physical activity has been consistently associated with a lower risk of postmenopausal breast cancer, its relationship with premenopausal breast cancer is unclear. Obesity is an established risk factor for breast cancer, but in most studies an inverse relationship has been found between weight or body mass index (BMI) and breast cancer among premenopausal women. The increased incidence of breast cancer in lean young women is found to be stronger among the youngest. A high BMI is significantly associated with an increased risk of inflammatory breast cancer regardless menopausal status.[24]

Giving birth to an infant of high birth weight has also been associated with an increased breast cancer risk, related to the hormonal environment during pregnancy, independently of maternal birth weight and breast cancer risk factors.[41] In addition, Wu and colleagues showed that high birth weight may contribute to the rising breast cancer incidence in Asian-American women.[22]

2.6. Mammographic density

Mammographic breast density (MD) depicts the amount of fat, connective and epithelial tissue in the breast. The degree of density depends on the hormonal environment and the underlying compound genetics regulating epithelial proliferation.[42] MD, adjusted for age and BMI, is a strong heritable risk factor for breast cancer with odds ratios (ORs) varying from 1.8 to 6.0, and may decrease with increasing parity, which appears to be an important predictor of breast density, varying with family history.[43,44] The biological changes in breast tissue during a full-term pregnancy could explain the inverse association of parity with MD. These changes, by resulting in a permanent alteration of gene expression in the lobules, make them less susceptible to hormonal influences and carcinogenesis. It remains unclear whether MD affects the risk of PABC through biocellular interactions during early postpartum involution, or if increased MD and its associated risk in early involution reflects the increased volume of fibroglandular tissue at risk.[44]

3. GENETICS – BRCA – FAMILY HISTORY

Several studies highlight the role of DNA damage and telomere malfunction in the microenvironment of the breast. Family history, linked to genetic cancer risk modifiers, is considered to be the strongest predictor of breast cancer risk in the female population,[23,45,46] expressed in a progressive risk at 60 months of 16.5% and an annual risk of 3.3%.[46] Current data indicate that the breast tissue remodeling which occurs postpartum is associated with wound healing and the active role of the microenvironment in carcinogenesis and the aggressiveness of PABC. Breast cancer risk has a polygenetic profile, with several individual genes contributing to small cumulative positive or negative effects. Ultimately there is a genetic signature of genes related to mitosis upregulated in the malignant epithelia of PABC, where several tumor suppressor genes are downregulated.[45,47] The polygenic association with breast cancer risk might, however, be separate from established reproductive and menstrual factors.[48] Moreover, Asztalos and colleagues reported that 22% of the selected gene set analysis was differentially regulated in nulliparous than in parous breast tissues. Inflammation associated genes were significantly upregulated in parous groups, where a significant reduction in expression of ERα, ESR1, PR, and HER2 was observed, along with a 2-fold higher ERβ expression compared with nulliparous tissues.[34]

BRCA1 and *BRCA2* genes are associated with less than 20% of the inherited risk while the rest account for mod-

erate and low penetrance.[24] Family history and advancing age have a synergistic effect in increasing breast cancer risk. Women who are above 30 years of age at their first pregnancy and have a family history of breast cancer have a 2–3 fold higher incidence of breast cancer than women without a family history. Even a pregnancy at an early age does not decrease the prevalence.[28,49] Despite the potential risk for parous women with *BRCA1* or *BRCA2* mutations, it appears that they have a similar transient increase in breast cancer incidence compared to nulliparous women.[2,17] There are only indications that PABC prevalence might be higher in *BRCA1* mutation carriers than in *BRCA2* mutation.[49] *BRCA1* expression is induced during puberty, and pregnancy and is believed to promote differentiation. Loss of *BRCA1* nuclear expression is suggested to be involved in the development of breast cancer.[50] Litwiniuk and colleagues showed that *BRCA1* mutation carriers are more likely to have ERα(–) breast cancer, while the expression of Erβ protein was observed in 42% of *BRCA1*-related tumors.[51] The role of breast cancer antiestrogen resistance 4 (*BCAR4*) is an interesting example of how the genetic environment is engaged in breast cancer. *BCAR4* is a strong transforming gene causing estrogen-independent growth and antiestrogen resistance, and induces tumor formation *in vivo*. It is found in 27% of primary breast tumors and is highly expressed in human placenta and oocytes, and absent in other normal tissues. In patients treated with tamoxifen for metastasized disease, high *BCAR4* mRNA levels are associated with reduced clinical benefit and progression-free survival.[52]

3.1. Stem cells

Adult stem cells of the mammary gland (MaSCs) are a highly dynamic population of cells that are responsible for ductal elongation during puberty and lobuloalveolar expansion during pregnancy. They are able to differentiate and self-renew, despite massive apoptosis after the lactation period, to drive the growth of subsequent pregnancies. In recent years significant advances have been made in understanding the association between the programmed differentiation of these cells and the hormonal microenvironment, and in particular on how changes in MaSC populations may explain both the increased risk of developing aggressive ER(–)/PR(–) breast cancer shortly after pregnancy and the long-term decreased risk of developing ER(+)/PR(+) tumors. A number of regulators and downstream targets of estrogen, progesterone and prolactin have been identified, involved in the control of growth and differentiation of MaSCs and progenitors. MaSCs lack the expression of ER, PR and HER2/Neu receptors, suggesting that they may be the "triple negative" tumor-initiating cells.[53]

4. HORMONAL RISK FACTORS – HORMONAL MILIEU

Pregnancy and breast cancer are hormone dependent entities under direct control of estrogen, progesterone and human chorionic gonadotropin (hCG).[54] Both hormonal and non-hormonal mechanisms have been suggested to explain the adverse effect of pregnancy on breast cancer risk.[20] The hormonal factors associated with pregnancy and lactation may play a complex role in PABC occurrence, together with a specific genetic background.[30] Birth characteristics, including gestational age, birth weight and birth length, are associated with maternal hormone levels, and hormonal exposure in uterus, which increases the risk of breast cancer in adulthood. This exposure has a stronger effect in early breast cancers.[24] Ovarian function plays a fundamental role in female fecundity and fertility, and ovarian hormones are major risk factors for breast cancer initiation and progression.[18] Circulating levels of estrogen and progesterone are very high during pregnancy, while the levels of prolactin, a potent mitogen for breast cancer cells, are at their peak during pregnancy and lactation. Since these hormones are powerful modulators of mammary epithelial cell proliferation, the accelerated breast tumor growth during pregnancy and lactation could be associated to differences in systemic hormone levels secreted during pregnancy, the immune suppressive effects of pregnancy and breast involution after pregnancy.[28,55]

4.1. Chorionic gonadotropin – Alpha fetoprotein – Prolactin

hCG promotes the expression of genes that are responsible for the advanced state of differentiation in the mammary gland and reduces the potential of mammary gland cells to be transformed by carcinogens.[33,54] A possible long-term protective association in breast cancer risk is related to elevated levels of circulating hCG in the early stages of pregnancy, which play an important role in the differentiation process. In rodents, pregnancy and short treatment with recombinant hCG induce a very similar genomic signature.[26,56] This ability of hCG treatment to downregulate the expression of genes involved in cancer promoting characteristics highlights its potential to reduce the effect of carcinogens and provide a protective barrier for the mammary gland.[54]

Alpha fetoprotein (AFP) has been shown to bind to estradiol and to suppress estrogen-dependent growth of breast cancer cells. A high level of AFP during pregnancy is associated with a reduced risk of breast cancer. Measurement of AFP levels during the second or third trimester

of pregnancy, when its concentrations in the maternal circulation increase substantially, may be more relevant as a determinant of breast cancer risk than checking the relatively low levels seen during early pregnancy.[56]

A long-term reduction in prolactin levels may explain the protective effect of childbirth on the risk of breast cancer.[20] Prolactin (PRL) levels were found to be associated with nulliparity in premenopausal women. PRL levels are higher among nulliparous than parous women, and they decline slightly with increasing parity. Prolactin levels are not related to ER, PR, or HER2 status.[57]

4.2. Estrogens – Progesterone

As breast cancer is hormone dependent, the effect of maternal sex-steroid hormones such as estrogen and progesterone, which are elevated during pregnancy, on cancer growth promotion could explain the transient increased risk of PABC. In general, breast carcinoma cells that express ER multiply faster in response to gestational hormones. As most PABC tumors lack ER/PR expression, estrogen or progesterone may be involved in PABC by indirect binding to related receptors expressed by breast epithelial cells.[30,32,49,58] Although the exact mechanisms remain unclear, it is estimated that direct tumor-initiating effects occur through the induction of enzymes and proteins involved in nucleic acid synthesis and through the activation of oncogenes. Indirect effects are related to the stimulation of prolactin secretion and the production of growth factors and non-growth factor peptides. The risk of breast cancer could be determined by the cumulative exposure of breast tissue to estrogen.[59] Lukanova and colleagues showed that concentrations of estrogens during the early stage of a primiparous pregnancy are associated with maternal risk of breast cancer and this effect may vary with age. Estradiol concentration was shown to be associated positively with the risk of breast cancer before age of 40 years, but inversely after that age. Conversely, estradiol concentration tended to be associated inversely with breast cancer risk in women who had their first pregnancy at the age of 30 years or older, while the opposite was observed for those under 30 years. Risk estimates for estrone matched those for estradiol but were less evident. Progesterone was not associated with risk of subsequent breast cancer.[32]

Focusing on the explanation of carcinogenesis, Wang and colleagues in their study with TA2 mice found that the concentration of estradiol and progesterone significantly increased during pregnancy and slightly increased after delivery with the increase of gravidity, and observed the same for immunosuppression. Both of these factors contribute to the presence of abnormally proliferating epithelia and the escape of tumor cells from immune surveillance.[30] Variations in tissue-specific promoters of aromatase gene expression also result in variations in estrogen production. As a result, the aromatase gene may act as an oncogene that initiates tumor formation in breast tissue.[59]

4.3 Insulin-like growth factor

Elevated serum concentrations of insulin-like growth factor (IGF-1) have been shown to be associated with increased risk of breast cancer. Toriola and colleagues found no significant association between serum IGF-1 concentrations and breast cancer risk in either their overall analysis or in analyses stratified by histological subtype, lag-time to cancer diagnosis, age at pregnancy or age at diagnosis.[60] Although the role of IGF-1 in breast cancer remains controversial, there is evidence that the adverse effect of IGF-1 on the breast is stronger before the maturation of the gland induced by the first full-term pregnancy.[24] Prebil and colleagues pointed out that characteristics of the first pregnancy may exert an influence on the degree of breast density later in life, and that this influence may vary depending on inherited IGFR1 and VEGF genotypes.[61]

4.4. Hormone receptors

Hormone-related reproductive factors are well known risk factors for breast cancer and they vary according to the expression of hormone receptors.[16] Hormone receptor status in PABC has been assessed in several studies, with contradictory results. Although current data indicate significant differential expression of ERα, ERβ, PR and HER2 receptors between nulliparous and parous women, it is still debated whether hormonal receptor status is significantly different in non-pregnant, age adjusted, breast cancer patients, since 59% to 70% of the tumors in PABC have a negative ER/PR profile, such as the triple-negative tumor with lack of estrogen receptor ER, PR, and HER2 expression. High ER-negativity, which characterizes basal-type tumors, is expressed in 70% of pregnant and lactating women compared to 39% of age-matched controls. Groenendijk and colleagues found that 2.1% of tumors with ERa(+) on mRNA analysis also demonstrate a basal-type profile.[6,47,50,62–64] ERα, PR, and HER2 receptors are downregulated and ERβ is upregulated in parous compared with nulliparous women.[34] HER2 receptor is reported to be expressed in 10 to 25% of breast carcinomas and 25 to 50% of women under 35 years of age with breast carcinomas, although documentation of HER2 expression in PABC is insufficient.[63,64] ER(–) tumors

tend to occur earlier in life. Women under 35 years who present with ER(+) tumors have worse outcomes than older women regardless of treatment.[24] The finding that expression of ERα is downregulated following pregnancy in young women suggests a possible mechanism for the long-term protective effect of pregnancy on breast cancer risk. If the ERα-positive cell population is reduced, the number of cell divisions driven by estrogen and the potential development and progression of cancer should be reduced.[34] Most hereditary breast cancers (75%) are triple-negative, but almost half (44.4%) show the expression of ERβ.[51] It thus becomes clear that further investigation is essential regarding the expression of hormone receptors in PABC.

Several studies in recent years have highlighted the role of androgen receptor (AR) as an independent prognostic factor for breast cancer, confirming their tumor suppressive effect on the ERα pathway, but the impact on outcome of AR expression in triple-negative tumors such as PABC is still unclear.[65] Niemeier and colleagues showed that 80% of consecutive invasive breast cancers were positive for AR. AR reactivity was seen in 95% of ER(+) tumors, in 10% of triple-negative tumors and in 63% of ER(–)/PR(–)/HER2(+) tumors. AR expression in ER(+) tumors was associated with smaller tumor size, lower tumor grade and less frequent tumor cell necrosis, while in ER(–) tumors AR expression was associated with lower grade and apocrine differentiation.[66]

5. CONCLUSIONS

The influence of pregnancy on the risk for breast cancer is dependent on several maternal features related to reproductive, genetic and hormonal factors. In view of the fact that PABC incidence is increasing and that large-scale changes are being observed in life style and childbearing trends in women worldwide, it has become more urgent for healthcare providers to reform their diagnostic management. A thorough analysis of the risk factors that contribute to the association between pregnancy and breast cancer is essential. Age at menarche and maternal age, in addition to parity, number of births, birth interval and breastfeeding are important key factors in PABC risk assessment. The "menarche to first birth" time interval, along with the expression of hormonal receptors and the underlying compound genetic influences are crucial in PABC initiation and pathogenesis. Definition of the relationship between reproductive history, genetic background and hormonal factors regenerates the diagnostic management plan, with PABC risk factors assessment as a prominent diagnostic modality.

ΠΕΡΙΛΗΨΗ

Καρκίνος μαστού σχετιζόμενος με την κύηση: Η εκτίμηση των παραγόντων κινδύνου ως σημαντική διαγνωστική μέθοδος

Ι. ΚΑΚΟΥΛΙΔΗΣ,[1] Α. ΠΟΛΙΤΗ[2]

[1]Μεταπτυχιακό Πρόγραμμα «Έρευνα στη Γυναικεία Αναπαραγωγή», Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα, [2]Κυτταρολογικό Εργαστήριο, Πανεπιστημιακό Νοσοκομείο Αθηνών «Αρεταίειο», Αθήνα

Αρχεία Ελληνικής Ιατρικής 2015, 32(5):556–565

Η συχνότητα εμφάνισης καρκίνου του μαστού σχετιζόμενου με την κύηση αυξάνεται, αναδεικνύοντας τον καρκίνο του μαστού σε μια από τις πλέον συχνές μορφές καρκίνου που εμφανίζονται κατά τη διάρκεια της εγκυμοσύνης. Η επίδραση της κύησης στον κίνδυνο για καρκίνο του μαστού είναι άρρηκτα συνδεδεμένη με διάφορα μητρικά χαρακτηριστικά, τα οποία σχετίζονται με την αναπαραγωγή, τη γενετική και τους ορμονικούς παράγοντες. Λαμβάνοντας υπ' όψη τη μεγάλης κλίμακας παρατηρούμενη αλλαγή στον τρόπο ζωής, στην ηλικία της μητέρας και στην τάση τεκνοποίησης στις γυναίκες παγκόσμια, καθίσταται όλο και πιο επιτακτική η ανάγκη αναπροσαρμογής της διαγνωστικής προσέγγισης. Μια διεξοδική ανάλυση των παραγόντων κινδύνου που συμβάλλουν στη συσχέτιση μεταξύ της εγκυμοσύνης και του καρκίνου του μαστού καθίσταται ιδιαίτερα σημαντική. Αυτοί οι παράγοντες κινδύνου θα πρέπει να αναζητηθούν στο επίπεδο της αναπαραγωγής, της γενετικής και των ορμονικών αλληλεπιδράσεων. Όπως επισημαίνεται στην παρούσα ανασκόπηση, η ηλικία εμμηναρχής, η ηλικία μητρότητας, η ίδια η μητρότητα ως οντότητα, καθώς και ο αριθμός των γεννήσεων, το διάστημα μεταξύ των γεννήσεων και ο μητρικός θηλασμός αποτελούν βασικούς παράγοντες για την αξιολόγηση του κινδύνου του καρκίνου του μαστού. Ακόμη, το χρονικό διάστημα από

την εμμηναρχή μέχρι την πρώτη γέννηση, η ορμονική έκφραση στο επίπεδο των υποδοχέων και το υποκείμενο γενετικό υπόστρωμα διαδραματίζουν βασικό ρόλο στην έναρξη και στην παθογένεση του σχετιζόμενου με την κύηση καρκίνου του μαστού. Η επισήμανση και η ανάλυση της συσχέτισης και των πιθανών αλληλεπιδράσεων μεταξύ των εν λόγω παραγόντων ενισχύει τη διαγνωστική προσέγγιση, αναδεικνύοντας ταυτόχρονα την εκτίμηση των παραγόντων κινδύνου σε ιδιαίτερα σημαντικό διαγνωστικό εργαλείο. Με κύριο στόχο την ανάδειξη της σημασίας των παραγόντων κινδύνου στο σχετιζόμενο με την κύηση καρκίνο του μαστού, η παρούσα ανασκόπηση περιλαμβάνει την κριτική ανάλυση 66 συνολικά άρθρων μέσα από τις βάσεις δεδομένων του Medline/PubMed και Google Scholar μέχρι το Νοέμβριο του 2014. Επιλέχθηκαν όσο το δυνατόν πιο πρόσφατα δημοσιευμένα άρθρα, τα οποία επικεντρώνονται κυρίως σε επιδημιολογικές, κλινικές, παθοφυσιολογικές και διαγνωστικές πτυχές του σχετιζόμενου με την κύηση καρκίνου του μαστού.

Λέξεις ευρετηρίου: Διάγνωση, Καρκίνος μαστού, Κύηση, Ορμόνες και κύηση, Παράγοντες κινδύνου

References

1. PAVLIDIS NA. Coexistence of pregnancy and malignancy. *Oncologist* 2002, 7:279–287
2. AMANT F, LOIBL S, NEVEN P, VAN CALSTEREN K. Breast cancer in pregnancy. *Lancet* 2012, 379:570–579
3. ANDERSSON TM, JOHANSSON AL, HSIEH CC, CNATTINGIUS S, LAMBE M. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol* 2009, 114:568–572
4. JOHANSSON AL, ANDERSSON TM, HSIEH CC, JIRSTRÖM K, DICKMAN P, CNATTINGIUS S ET AL. Stage at diagnosis and mortality in women with pregnancy-associated breast cancer (PABC). *Breast Cancer Res Treat* 2013, 139:183–192
5. JACOBS IA, CHANG CK, SALTI GI. Coexistence of pregnancy and cancer. *Am Surg* 2004, 70:1025–1029
6. ASGEIRSSON KS. Pregnancy-associated breast cancer. *Acta Obstet Gynecol Scand* 2011, 90:158–166
7. BODNER-ADLER B, BODNER K, ZEISLER H. Breast cancer diagnosed during pregnancy. *Anticancer Res* 2007, 27:1705–1707
8. LEE Y, ROBERTS CL, DOBBINS T, STAVROU E, BLACK K, MORRIS J ET AL. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994–2008: A population-based linkage study. *BJOG* 2012, 119:1572–1582
9. ZAGOURI F, PSALTOPOULOU T, DIMITRAKAKIS C, BARTSCH R, DIMOPOULOS MA. Challenges in managing breast cancer during pregnancy. *J Thorac Dis* 2013, 5(Suppl 1):S62–S67
10. AMANT F, DECKERS S, VAN CALSTEREN K, LOIBL S, HALASKA M, BREPOELS L ET AL. Breast cancer in pregnancy: Recommendations of an international consensus meeting. *Eur J Cancer* 2010, 46:3158–3168
11. MOLCKOVSKY A, MADARNAS Y. Breast cancer in pregnancy: A literature review. *Breast Cancer Res Treat* 2008, 108:333–338
12. AZIM HA Jr, BOTTERI E, RENNE G, DELL'ORTO P, ROTMENSZ N, GENTILINI O ET AL. The biological features and prognosis of breast cancer diagnosed during pregnancy: A case-control study. *Acta Oncol* 2012, 51:653–661
13. CALLIHAN EB, GAO D, JINDAL S, LYONS TR, MANTHEY E, EDGERTON S ET AL. Postpartum diagnosis demonstrates a high risk for metastasis and merits an expanded definition of pregnancy-associated breast cancer. *Breast Cancer Res Treat* 2013, 138:549–559
14. DIMITRAKAKIS C, ZAGOURI F, TSIGGINOU A, MARINOPOULOS S, SERGENTANIS TN, KERAMOPOULOS A ET AL. Does pregnancy-associated breast cancer imply a worse prognosis? A matched case-case study. *Breast Care (Basel)* 2013, 8:203–207
15. MATHELIN C, ANNANE K, TREISSER A, CHENARD MP, TOMASETTO C, BELLOCQ JP ET AL. Pregnancy and post-partum breast cancer: A prospective study. *Anticancer Res* 2008, 28:2447–2452
16. CHUNG S, PARK SK, SUNG H, SONG N, HAN W, NOH DY ET AL. Association between chronological change of reproductive factors and breast cancer risk defined by hormone receptor status: Results from the Seoul Breast Cancer Study. *Breast Cancer Res Treat* 2013, 140:557–565
17. LYONS TR, SCHEDIN PJ, BORGES VF. Pregnancy and breast cancer: When they collide. *J Mammary Gland Biol Neoplasia* 2009, 14:87–98
18. IVERSEN A, THUNE I, McTIERNAN A, EMAUS A, FINSTAD SE, FLOTE V ET AL. Ovarian hormones and reproductive risk factors for breast cancer in premenopausal women: The Norwegian EBBA-I study. *Hum Reprod* 2011, 26:1519–1529
19. ZHANG Q, LIU LY, WANG F, MU K, YU ZG. The changes in female physical and childbearing characteristics in China and potential association with risk of breast cancer. *BMC Public Health* 2012, 12:368
20. ALBREKTSEN G, HEUCH I, THORESEN SØ. Histological type and grade of breast cancer tumors by parity, age at birth, and time since birth: A register-based study in Norway. *BMC Cancer* 2010, 10:226
21. LEE J, OH M; KOREAN BREAST CANCER SOCIETY. Effects of interval between age at first pregnancy and age at diagnosis on breast cancer survival according to menopausal status: A register-based study in Korea. *BMC Womens Health* 2014, 14:113
22. WU AH, McKEAN-COWDIN R, TSENG CC. Birth weight and other prenatal factors and risk of breast cancer in Asian-Americans. *Breast Cancer Res Treat* 2011, 130:917–925
23. HADJISAVVAS A, LOIZIDOU MA, MIDDLETON N, MICHAEL T, PAPACHRISTOFOROU R, KAKOURI E ET AL. An investigation of breast cancer risk factors in Cyprus: A case control study. *BMC Cancer* 2010, 10:447

24. POLLÁN M. Epidemiology of breast cancer in young women. *Breast Cancer Res Treat* 2010, 123(Suppl 1):3–6
25. LI CI, BEABER EF, TANG MT, PORTER PL, DALING JR, MALONE KE. Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20–44 years of age. *Breast Cancer Res Treat* 2013, 137:579–587
26. RUSSO J, BALOGH G, RUSSO IH. Breast cancer prevention. *Climacteric* 2007, 10(2 Suppl 2):47–53
27. NECHUTA S, PANETH N, VELIE EM. Pregnancy characteristics and maternal breast cancer risk: A review of the epidemiologic literature. *Cancer Causes Control* 2010, 21:967–989
28. DOĞER E, CALIŞKAN E, MALLMANN P. Pregnancy associated breast cancer and pregnancy after breast cancer treatment. *J Turk Ger Gynecol Assoc* 2011, 12:247–255
29. RITTE R, TIKK K, LUKANOVA A, TJØNNELAND A, OLSEN A, OVERVAD K ET AL. Reproductive factors and risk of hormone receptor positive and negative breast cancer: A cohort study. *BMC Cancer* 2013, 13:584
30. WANG X, HUANG C, SUN B, GU Y, CUI Y, ZHAO X ET AL. The effect of high gravidity on the carcinogenesis of mammary gland in TA2 mice. *Am J Reprod Immunol* 2010, 63:396–409
31. KAUPPILA A, KYYRÖNEN P, HINKULA M, PUKKALA E. Birth intervals and breast cancer risk. *Br J Cancer* 2009, 101:1213–1217
32. LUKANOVA A, SURCEL HM, LUNDIN E, KAASILA M, LAKSO HA, SCHOCK H ET AL. Circulating estrogens and progesterone during primiparous pregnancies and risk of maternal breast cancer. *Int J Cancer* 2012, 130:910–920
33. BRASKY TM, LI Y, JAWOROWICZ DJ Jr, POTISCHMAN N, AMBROSONE CB, HUTSON AD ET AL. Pregnancy-related characteristics and breast cancer risk. *Cancer Causes Control* 2013, 24:1675–1685
34. ASZTALOS S, GANN PH, HAYES MK, NONN L, BEAM CA, DAI Y ET AL. Gene expression patterns in the human breast after pregnancy. *Cancer Prev Res (Phila)* 2010, 3:301–311
35. COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER. Breast cancer and breastfeeding: Collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002, 360:187–195
36. KAUPPILA A, KYYRÖNEN P, LEHTINEN M, PUKKALA E. Dual effect of short interval between first and second birth on ductal breast cancer risk in Finland. *Cancer Causes Control* 2012, 23:187–193
37. KIM HS, WOO OH, PARK KH, WOO SU, YANG DS, KIM AR ET AL. The relationship between twin births and maternal risk of breast cancer: A meta-analysis. *Breast Cancer Res Treat* 2012, 131:671–677
38. SCHNABEL F, BILLIG J, CIMENO A, CHUN J. Pregnancy-associated breast cancer and increased risk of pregnancy-associated recurrence: A case report. *J Med Case Rep* 2012, 6:144
39. FAUPEL-BADGER JM, ARCARO KF, BALKAM J, ELIASSEN HA, HASSIOTOU F, LEBRILLA CB ET AL. Postpartum remodeling, lactation, and breast cancer risk: Summary of a National Cancer Institute-sponsored workshop. *J Natl Cancer Inst* 2013, 105:166–174
40. JASIEŃSKA G, THUNE I. Lifestyle, hormones, and risk of breast cancer. *Br Med J* 2001, 322:586–587
41. BUKOWSKI R, CHLEBOWSKI RT, THUNE I, FURBERG AS, HANKINS GD, MALONE FD ET AL. Birth weight, breast cancer and the potential mediating hormonal environment. *PLoS One* 2012, 7:e40199
42. WARREN R. Hormones and mammographic breast density. *Maturitas* 2004, 49:67–78
43. YAGHJYAN L, MAHONEY MC, SUCCOP P, WONES R, BUCKHOLZ J, PINNEY SM. Relationship between breast cancer risk factors and mammographic breast density in the Fernald Community Cohort. *Br J Cancer* 2012, 106:996–1003
44. CHEW GL, HUANG D, HUO CW, BLICK T, HILL P, CAWSON J ET AL. Dynamic changes in high and low mammographic density human breast tissues maintained in murine tissue engineering chambers during various murine peripartum states and over time. *Breast Cancer Res Treat* 2013, 140:285–297
45. XU L, WANG SS, HEALEY MA, FAUPEL-BADGER JM, WILKEN JA, BATTAGLIA T ET AL. The Ninth Annual American Association of cancer research international conference on frontiers in cancer prevention research. *Cancer Prev Res (Phila)* 2011, 4:616–621
46. THIS P, DE LA ROCHEFORDIÈRE A, SAVIGNONI A, FALCOU MC, TARDIVON A, THIBAULT F ET AL. Breast and ovarian cancer risk management in a French cohort of 158 women carrying a *BRCA1* or *BRCA2* germline mutation: Patient choices and outcome. *Fam Cancer* 2012, 11:473–482
47. HARVELL DM, KIM J, O'BRIEN J, TAN AC, BORGES VF, SCHEDIN P ET AL. Genomic signatures of pregnancy-associated breast cancer epithelia and stroma and their regulation by estrogens and progesterone. *Horm Canc* 2013, 4:140–153
48. WARREN ANDERSEN S, TRENTHAM-DIETZ A, GANGNON RE, HAMPTON JM, FIGUEROA JD, SKINNER HG ET AL. The associations between a polygenic score, reproductive and menstrual risk factors and breast cancer risk. *Breast Cancer Res Treat* 2013, 140:427–434
49. YU JH, KIM MJ, CHO H, LIU HJ, HAN SJ, AHN TG. Breast diseases during pregnancy and lactation. *Obstet Gynecol Sci* 2013, 56:143–159
50. REED W, SANDSTAD B, HOLM R, NESLAND JM. The prognostic impact of hormone receptors and *c-erbB-2* in pregnancy-associated breast cancer and their correlation with *BRCA1* and cell cycle modulators. *Int J Surg Pathol* 2003, 11:65–74
51. LITWINIUK MM, ROZNOWSKI K, FILAS V, GODLEWSKI DD, STAWICKA M, KALETA R ET AL. Expression of estrogen receptor beta in the breast carcinoma of *BRCA1* mutation carriers. *BMC Cancer* 2008, 8:100
52. GODINHO M, MEIJER D, SETYONO-HAN B, DORSSERS LC, VAN AGTHOVEN T. Characterization of *BCAR4*, a novel oncogene causing endocrine resistance in human breast cancer cells. *J Cell Physiol* 2011, 226:1741–1749
53. TIEDE B, KANG Y. From milk to malignancy: The role of mammary stem cells in development, pregnancy and breast cancer. *Cell Res* 2011, 21:245–257
54. SANTUCCI-PEREIRA J, GEORGE C, ARMISS D, RUSSO IH, VANEGAS JE, SHERIFF F ET AL. Mimicking pregnancy as a strategy for breast cancer prevention. *Breast Cancer Manag* 2013, 2:283–294
55. McCREADY J, ARENDT LM, GLOVER E, IYER V, BRIENDEL JL, LYLE SR ET AL. Pregnancy-associated breast cancers are driven by differences in adipose stromal cells present during lactation. *Breast Cancer Res* 2014, 16:R2
56. LUKANOVA A, ANDERSSON R, WULFF M, ZELENIUCH-JACQUOTTE

A, GRANKVIST K, DOSSUS L ET AL. Human chorionic gonadotropin and alpha-fetoprotein concentrations in pregnancy and maternal risk of breast cancer: A nested case-control study. *Am J Epidemiol* 2008, 168:1284–1291
57. FAUPEL-BADGER JM, SHERMAN ME, GARCIA-CLOSAS M, GAUDET MM, FALK RT, ANDAYA A ET AL. Prolactin serum levels and breast cancer: Relationships with risk factors and tumour characteristics among pre- and postmenopausal women in a population-based case-control study from Poland. *Br J Cancer* 2010, 103:1097–1102
58. McCREADY J, ARENDT LM, RUDNICK JA, KUPERWASSER C. The contribution of dynamic stromal remodeling during mammary development to breast carcinogenesis. *Breast Cancer Res* 2010, 12:205
59. CLEMONS M, GOSS P. Estrogen and the risk of breast cancer. *N Engl J Med* 2001, 344:276–285
60. TORIOLA AT, LUNDIN E, SCHOCK H, GRANKVIST K, PUKKALA E, CHEN T ET AL. Circulating insulin-like growth factor-I in pregnancy and maternal risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2011, 20:1798–1801
61. PREBIL LA, EREMAN RR, POWELL MJ, JAMSHIDIAN F, KERLIKOWSKE K, SHEPHERD JA ET AL. First pregnancy events and future breast density: Modification by age at first pregnancy and specific *VEGF* and *IGF1R* gene variants. *Cancer Causes Control* 2014, 25:859–868
62. GROENENDIJK FH, ZWART W, FLOORE A, AKBARI S, BERNARDS R. Estrogen receptor splice variants as a potential source of false-positive estrogen receptor status in breast cancer diagnostics. *Breast Cancer Res Treat* 2013, 140:475–484
63. HALASKA MJ, PENTHEROUDAKIS G, STRNAD P, STANKUSOVA H, CHOD J, ROBOVA H ET AL. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: A matched controlled study. *Breast J* 2009, 15:461–467
64. NAVROZOGLOU I, VREKOUSSIS T, KONTOSTOLIS E, DOUSIAS V, ZERVOUDIS S, STATHOPOULOS EN ET AL. Breast cancer during pregnancy: A mini-review. *Eur J Surg Oncol* 2008, 34:837–843
65. PISTELLI M, CARAMANTI M, BISCOTTI T, SANTINELLI A, PAGLIACCI A, DE LISA M ET AL. Androgen receptor expression in early triple-negative breast cancer: Clinical significance and prognostic associations. *Cancers (Basel)* 2014, 6:1351–1362
66. NIEMEIER LA, DABBS DJ, BERIWAL S, STRIEBEL JM, BHARGAVA R. Androgen receptor in breast cancer: Expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. *Mod Pathol* 2010, 23:205–212

Corresponding author:

I. Kakoulidis, 12 Telesiou street, GR-111 43 Athens, Greece
e-mail: i_kakoulidis@yahoo.gr