

Pregnancy associated breast cancer and pregnancy after breast cancer treatment

Gebelik ile ilişkili meme kanseri ve meme kanseri tedavisi sonrası gebelik

Emek Doğer¹, Eray Çalışkan¹, Peter Mallmann²

¹Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

²Department of Obstetrics and Gynecology, Universitäts-Frauenklinik, Köln, Germany

Abstract

Breast cancer is one of the most common cancers diagnosed during pregnancy and its frequency is increasing as more women postpone their pregnancies to their thirties and forties. Breast cancer diagnosis during pregnancy and lactation is difficult and complex both for the patient and doctors. Delay in diagnosis is frequent and treatment modalities are difficult to accept for the pregnant women. The common treatment approach is surgery after diagnosis, chemotherapy after the first trimester and radiotherapy after delivery. Even though early stage breast cancers have similar prognosis, advanced stage breast cancers diagnosed during pregnancy and lactation have poorer prognosis than similar stage breast cancers diagnosed in non-pregnant women. Women who desire to become pregnant after treatment of breast cancer will have many conflicts. Although the most common concern is recurrence of breast cancer due to pregnancy, the studies conducted showed that pregnancy has no negative effect on breast cancer prognosis. In this review we search for the frequency of breast cancer during pregnancy, the histopathological findings, risk factor, diagnostic and treatment modalities. We reviewed the literature for evidence based findings to help consult the patients on the outcome of breast cancer diagnosed during pregnancy and lactation, and also inform the patients who desire to become pregnant after breast cancer according to current evidences. (J Turkish-German Gynecol Assoc 2011; 12: 247-55)

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Özet

Meme kanseri, gebelik sırasında en sık tanı alan kanserlerden biridir ve daha fazla kadın gebeliklerini otuzlu, kırklı yaşlara erteledikçe sıklığı artmaktadır. Gebelik ve emzirme sürecinde meme kanseri tanısı hem hasta hem de doktoru için zor ve karmaşıktır. Tanıda gecikmeye sık rastlanır ve gebeler için tedavi yöntemlerini kabul etmek zordur. Tedavi yaklaşımı sıklıkla, tanı sonrası cerrahi, ilk trimester sonrası kemoterapi ve doğum sonrası radyoterapi şeklindedir. Erken evre meme kanserleri benzer prognoza sahip olmasına rağmen, gebelik ve emzirme sırasında ileri evrede tanı alan meme kanserleri, aynı evredeki gebe olmayan meme kanserli hastalardan daha kötü prognoza sahiptir. Meme kanseri tedavisinden sonra gebe kalmak isteyen kadınlar da pek çok çelişki ile yüzleşirler. Her ne kadar en sık endişelenilen, gebelik sırasında meme kanseri rekürrens göstermesi olsa da çalışmalar gebeliğin meme kanseri prognozu üzerine olumsuz etkisi olmadığını göstermiştir. Bu derlemede, gebelik sırasında meme kanseri sıklığını, histopatolojik bulgularını, risk faktörlerini, tanı ve tedavi yöntemlerini araştırdık. Literatürü, kanıt dayalı bulgular ile, gebelik ve emzirme sırasında tanı alan meme kanserinin seyrini ortaya koymak, ayrıca meme kanseri sonrası gebe kalmak isteyen hastaların güncel kanıtlarla uyumlu olarak bilgilendirilmesini sağlamak amacıyla derledik.

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Introduction

Among the cases with breast cancer, 0.2-3.8% are diagnosed during pregnancy and lactation (1). The frequency increases as the patients' age become younger and among women younger than 30 years of age 10-20% of the breast cancer cases are diagnosed during pregnancy or within one year after delivery (2). The breast cancer diagnosed during pregnancy or within one year after delivery is known to be pregnancy associated breast cancer (PABC) and its incidence is 1.3 in 10.000 births (3).

Breast cancer frequency is also increasing in Turkey (4). More women are postponing pregnancy to older ages as they have increasing social participation. The mean age of first pregnancy in Europe increased from 26.2 years in 1970 to 29.8 years in 2005 and approached the mean age of

breast cancer diagnosis during pregnancy, which is 33 years (Range: 22-43) (5-7). All these data point out that we will encounter more cases of PABC in the future. On the other hand, improvements in breast cancer therapy lead to more women desiring pregnancy in fertile ages after completing the cancer therapy (8). In population based studies, pregnancy after completing breast cancer therapy among women younger than 45 years of age is 3.6-5% (9, 10).

Most of the signs of PABC are seen as normal consequences of pregnancy and breast feeding and usually doctors do not take the complaints into account. Due to concerns of radiation based diagnostic modalities during pregnancy, both the patients and doctors delay screening, and most patients with PABC are diagnosed in advanced stages (11). As large randomized controlled trials are lacking, an evidence based management algorithm of PABC cases is still lacking. The use and long term safety of chemotherapeutics in pregnancy

Address for Correspondence: Emek Doğer, Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Phone: +90 262 303 84 33 Fax: +90 262 303 80 03 e.mail: emekdoger@hotmail.com

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and lactation is still a matter of debate and most patients reject proper treatment because of inadequate consultation. The questions to be answered are the prognosis of PABC, the effect of pregnancy after breast cancer on recurrence and mortality rates and deciding on the appropriate time to delay a new pregnancy after PABC.

In this review we tried to summarize the findings in the literature about treatment modalities of PABC, effect of pregnancy on prognosis and provide the evidence to inform the women accordingly.

1. Pregnancy Associated Breast Cancer (PABC)

1. 1. Pathological Findings of Pregnancy Associated Breast Cancer

The most common histological type of PABC is invasive ductal carcinoma in 75-90% of the cases (12). Invasive lobular carcinoma and inflammatory carcinoma are less frequent. Most of the breast carcinoma diagnosed in pregnant women are grade 2 or 3 tumors with frequent invasion of the lymphovascular space (13).

Estrogen and progesterone receptors are found in 20-40% of the PABC cases (12-14). The estrogen and progesterone receptors are also frequently negative in non-pregnant women younger than 40 years of age and the presence of receptors is more frequent in breast cancers diagnosed after the menopause (15). Ishida and colleagues found that estrogen receptor was negative in 70% of the tumors in pregnant women while this was 39% in non-pregnant women of similar ages (16). This might be due to negative feedback of high hormone levels during pregnancy or high hormone levels might lead to false negative findings (17). In fact the presence of hormone receptors might give conflicting results with different techniques. For example, cases with a previous diagnosis of negative estrogen receptor were re-evaluated with pS2-trefoil factor 1 immunohistochemical staining and were found to have the estrogen receptors (18). It is probable that the presence of estrogen receptors is underestimated and evolving techniques might help to decide accurately on which patients would need anti-hormonal therapy.

In general, HER2/neu oncoprotein is expressed in 25-30% of the cases with breast cancer, which is present in 28-50% of pregnant women with breast cancer who are younger than 35 years of age (12, 19). Within the same age groups, some studies report higher HER2/neu expression in PABC than non-pregnant women (58% vs 16% respectively) while others report a similar expression of around 28% (12, 19).

1. 2. Pregnancy and risk of breast cancer

Age and pregnancy related risk: The cancer risk is higher within 3-15 years of term delivery (20, 21). This increased risk is specific for women whose first delivery occurred after 30 years of age. In women who delivered their first baby at ages younger than 25, none or a very small increase in breast cancer risk is observed (22). Accordingly, age is accepted as the main risk factor. A transient increase in breast cancer is seen within 10 to 15 years of delivery and after that a protective effect of delivery is seen. Among women who delivered their first baby before 25 years of age, the life time breast cancer risk is decreased by 36% after the period of transient increase (23). Among women who delivered their first baby after 30 years of age, the transient increase

in breast cancer risk is higher and may last 30-50 years whereas the protective effect after that time is low or none (24, 25). Every year of increase in the age of first delivery leads to a 3.5-5% increase in lifetime breast cancer risk (24).

Family history and parity related risk: Both the familial history and advancing age have a synergistic increase in breast cancer risk. If the age at first pregnancy is older than 30 years, women with a familial history of breast cancer have a 2-3 fold higher incidence of breast cancer risk than women without a familial history (26). Even in women who gave birth at a younger age, familial history increases the risk of breast cancer (26).

In the study of Albrektsen et al. every increase in parity was shown to decrease the total risk of breast cancer compared to nulliparous women; second birth RR=0.91, third birth RR=0.81, fourth birth RR=0.64 and fifth birth RR=0.50 (22). After the birth of the second child, the risk of breast cancer is decreased and if it develops, it occurs at later ages compared to nulliparous women (21, 27). Multiparity decreases the estrogen and progesterone receptor positive breast cancer risk if breast feeding is carried out (23). On the other hand, if breast feeding is not carried out, parity does not decrease the risk and parity does not affect the incidence of hormone receptor negative breast cancer incidence (23).

Breast feeding: Lactation decreases the life time risk of breast cancer. This decrease is 4.3% for every 12 months of lactation and 7% for every additional birth (28). Within five years after birth, the risk of breast cancer is 1.64 in non breast feeding women and 1.24 in breast feeding women (29). Although the decrease in risk in BRCA 2 mutation carriers is controversial, in BRCA 1 mutation carriers breast feeding for more than one year significantly decreases the risk compared to non breast feeding carriers (OR=0.55, 95% CI=0.38-0.80, p=0.001) (30). The importance of breast feeding should be stressed in women with BRCA mutations.

BRCA 1 and BRCA 2 mutations: BRCA 1 and BRCA 2 related breast cancer is diagnosed in younger women whose probability of becoming pregnant is high. In BRCA 1 mutation carriers, the OR of PABC is 3.9, in BRCA 1 carriers the odds ratio is 1.9 and when combined BRCA 1 and 2 mutation is present the odds ratio for PABC is 4.5 (31). Culliane et al. showed that the risk of breast cancer decreases significantly in BRCA 1 carriers after four or more births while parity increases the risk of breast cancer in BRCA 2 carriers which is 1.5 fold of nulliparous women after two or more births (32). In BRCA 2 mutation carriers, breast cancer risk within two years after delivery is 70% higher than for nulliparous women (32). These studies point out the importance of follow up of BRCA 2 carriers during and after breast feeding.

The cause of increased breast cancer risk after pregnancy: The probable causes of increase in breast cancer risk after pregnancy are increased malignant transformation of breast cancer cells due to estrogen, progesterone and growth hormones secreted during pregnancy, the immune suppressive effects of pregnancy and breast involution after pregnancy (24, 27, 33). Once the pregnancy reaches term, terminal differentiation of breast glands are induced and the breast becomes less vulnerable to tumorigenic effects. The shorter the time to first pregnancy after puberty the faster the induction of breast glands to terminal differentiation. On the other hand, when the first pregnancy is delayed the breast will be more vulnerable to

oncogenic effects and will have a higher risk of development of premalignant lesions. During pregnancy, very high levels of estrogen and its metabolites will have genotoxic, mutagenic and carcinogenic potential and may cause progression of premalignant lesions. The proliferation of breast cancer cells are enhanced by estrogen, progesterone and insulin like growth factor-1 (24).

Breast involution after pregnancy may also enhance tumorigenesis. In fact, breast involution resembles wound healing and is pre-tumorigenic in the presence of immune suppression. The microenvironment during involution has immune cell interaction, active trophoblasts, increased extracellular matrix deposition, increased matrix metalloproteinase levels and bioactive matrix fragments like a pretumorigenic microenvironment (33, 34).

Current studies showed that parity decreases stem cells in the breast in animals (35). Stem cells in the breast are the main targets for transformation and the decrease in their number also decreases the lifetime risk of breast cancer.

1. 3. The diagnosis of pregnancy associated breast cancer (PABC)

Breast cancer diagnosed during pregnancy and breast feeding is usually advanced in stage with a bulky tumor and a lymph node. PABC is diagnosed in stage II-III in 65-90% of cases, while these numbers are 45-66% in other breast cancers (12, 16). The average tumor diameter is 3.5 cm and lymph node metastasis is 56-89% in pregnant women, while it is 2 cm and 38-54% respectively in non-pregnant women (1, 16, 36, 37). The reasons for delayed diagnosis in PABC are increased vascularity in breast, high hormone levels and immunosuppression during pregnancy. Normal breast hyperplasia during pregnancy and lactation masks the diagnosis of palpable masses. Both the doctor and the patient detain radiographic and invasive procedures at this time, which contributes to the diagnostic delay in PABC. A one month delay in the diagnosis of primary tumor increases the axillary lymph node metastasis by 0.9%, three month delay by 2.6% and a six month delay by 5.1% (38). An average delay in definitive diagnosis after detection of a mass in pregnant women is 0.8 to 8.1 months (16, 39). In contrast, Ives et al found an average of one month (1-104 weeks) from symptom to diagnosis in pregnant breast cancer cases and Ibrahim et al found symptom to diagnosis time to be shorter in pregnant breast

cancer cases than the nonpregnant cases (5.6 months versus 9.4 months respectively) (40, 41). The summary of studies on this issue is presented in Table 1 (13, 16, 39-44).

For early diagnosis of PABC, all pregnant women should have a breast examination during the first antenatal visit. Palpable breast masses and bloody breast discharge should be evaluated carefully and it should be kept in mind that the newborn may not suck the breast with cancer. In order to prevent diagnostic delay in PABC all masses persisting for more than two weeks should be biopsied although 80% of them will be benign (1). Atypical cytological findings are common in pregnant women with normal breasts so biopsy is the preferred method rather than aspiration cytology (45). Biopsy increases the frequency of milk fistulas and infection but stopping breast feeding before biopsy, careful hemostasis and prophylactic antibiotics will decrease the risk of complications (46).

1. 4. Imaging in pregnant women with breast cancer

Many imaging modalities expose the fetus to ionizing radiation. If the fetus is exposed to radiation within two weeks after conception, it results in the loss of pregnancy, while developing organ systems are affected 8 weeks following this period. If the radiation dose is more than 0.05 Gy during organogenesis it results in major malformations and if the radiation dose is more than 0.28 Gy it might result in mental retardation (47, 48). In pregnant women if the abdomen is protected, thoracic radiation exposes the fetus to less than 0.0001 Gy radiation and this dose is considered to be safe (49). In suspected cases, mammography can be performed but its sensitivity is 63-78% during pregnancy (16, 42). Besides these limitations, mammography is useful for detecting microcalcifications. Fetal radiation dose due to mammography is 0.01-0.004 Gy (11, 50). Upper abdominal or thoracic computed tomography delivers 0.0036 Gy radiation and is considered to be safe for the fetus, while lower abdominal tomography scan delivers a unwanted amount of 0.089 Gy radiation (49).

Breast ultrasonography can be used to diagnose breast cancer cases with high sensitivity and specificity. In their study on 20 preoperative breast cancer cases, Yang et al. found that a cancer lesion was detected in 18 cases using mammography compared to 20 detected cases with ultrasonography and furthermore ultrasonography detected axillary lymph node metastasis in 15 out of 18 cases (50). Although some concerns about

Table 1. The time interval from the initial symptoms to the diagnosis among the patients with the diagnosis of pregnancy associated breast cancer and other breast cancer patients

	Year	PABC (month)	(case)	(month)	Non-pregnancy (control)	Assoc.	Difference
Applewhite et al. ^a	1973	13.2	(48)	5.1	(2689)		8.1
King et al.	1985	1.4	(63)	-			-
Tretli et al. ^a	1988	2.5/6 ^b	(20/35 ^b)	-		-	
Ishida et al. ^a	1992	6.2	(72/120 ^c)	5.4	(191)		0.8
Libermann et al.	1994	8.2	(12/19 ^b)	1.9	(11)		6.3
Bonnier et al. ^a	1997	2.2	(154)	1.2	(308)		1
Ibrahim et al.	2001	5.6	(72)	9.4	(216)		3.8

^aInclude postpartum patient, ^blactation group ^cinclude first 2 years of postpartum period, PABC: Pregnancy associated breast cancer

magnetic resonance imaging were mentioned, it can be used to detect breast cancer and its metastasis to liver, bone and brain (51). Gadolinium contrast is not used in pregnant women as it was shown to pass the placenta and cause malformations in mice (52). As in non-pregnant women, screening the bones is not necessary in stage I and II tumors (37).

1. 5. Surgical treatment modalities in pregnant breast cancer patients

An individualized approach should be planned for every case to provide the most appropriate treatment and protect the ongoing pregnancy. Surgery should be scheduled in every case without considering the trimester. Usually, modified radical mastectomy or breast sparing surgeries with axillary lymph node dissections are performed. In the case of stage I and II tumors, total survival and disease free survival is similar between breast sparing surgery and modified radical mastectomy (53). Although survival is similar, radiotherapy is not necessary after mastectomy for early stage breast cancer, whereas after breast sparing surgery radiotherapy should be applied after delivery to avoid local recurrences (54). Although radiotherapy can be postponed after delivery in cases with breast cancer diagnosed at the second or third trimester, if the patient is far from term, starting chemotherapy after surgery and postponing radiotherapy until after delivery is advised (55). Sentinel lymph node biopsies are found to be safe and sufficient but it is not part of the routine surgery during pregnancy (56). Isosulfane mapping during sentinel lymph node biopsy carries a risk of anaphylaxis and its possible effects on the fetus are yet to be determined. There is also no data regarding the safety of radioactive probes on the fetus.

After surgery, if the pregnancy is in its first trimester, chemotherapy should be postponed until the second trimester and if the woman is in the second or third trimester, chemotherapy is started immediately after surgery, if indicated. If surgery was performed near term chemotherapy can also be postponed until after delivery. On the other hand, if indicated neoadjuvant chemotherapy can be given in the second and third trimester and surgery can be performed after (57). General anesthesia has little risk for the pregnant women and the fetus, also complication rates after breast and axillary surgery are not increased in pregnant women. On the other hand, the rate of low birth weight, premature delivery and intrauterine growth restriction is increased in breast cancer cases (58).

1. 6. Radiotherapy in pregnant women with breast cancer

Although radiation has dose and gestational week dependent effects on the fetus, radiotherapy can be applied during pregnancy after a careful dose adjustment and if not targeting the pelvis or abdomen (59). Breast, chest wall and lymph nodes should be the primary targets at radiotherapy. Radiotherapy is relatively safer during the first and second trimester when the fetus is far from the targeted area, but during the third trimester the fetus comes closer to the radiotherapy area and can receive a dangerous amount of radiotherapy (60). Radiation can cause intrauterine growth restriction, mental retardation and childhood cancers (47, 48). As this age group, of women have poorer prognosis, their management should include chemotherapy after surgery and radiotherapy postponed until after delivery.

1. 7. Systemic chemotherapy in pregnant women with breast cancer

The standard approach is applying chemotherapy to all breast cancer cases if the tumor size is larger than one centimeter or if there is lymph node metastasis. When planning chemotherapy to pregnant women with breast cancer, increased plasma volume, increased glomerular filtration rate, liver metabolism, and changes in plasma protein concentrations should be kept in focus, whereas body mass index is the only important parameter in non-pregnant breast cancer cases (61). Also the placental transfer and fetal effects of the chemotherapeutics should be considered.

Cyclophosphamide, adriamycin and fluorouracil combination is frequently used during pregnancy and is well tolerated. Anthracycline based chemotherapy can be used in pregnant women after the first trimester (62). Current evidence showed that taxanes do not pose any risk to the fetus beyond the first trimester (63). Taxanes can also be appropriate for neoadjuvant chemotherapy before surgery or as a second line drug for anthracycline resistant cases. Alkylating agents and methotrexate are not used during pregnancy (62). HER2/neu is synthesized from many embryonic tissues during pregnancy. In a limited series of case reports Trastuzumab, a monoclonal antibody that interferes with the HER2/neu receptor, was shown to reverse anhydramnios, fetal renal and heart failure and in one case had no effect on the fetus (64, 65). In the presence of limited data anti-HER2 therapies are not recommended during pregnancy and if there is medical necessity for their use, a close follow up of the amniotic fluid is mandatory. Selective estrogen receptor modulator tamoxifen used in cases of hormone receptor positive breast cancers is teratogenic and may cause craniofacial malformations and ambiguous genitalia (66). Aromatase inhibitors were reported to be teratogenic in animals but there is insufficient data in humans (67).

The possible harmful effects of chemotherapeutics on the fetus largely rely on the week of gestation. If used during the first trimester chemotherapeutics cause abortion and malformation at a rate greater than 17%, on the other hand during the second and third trimester pregnancy loss and malformation is seen in 1.3% of the cases while preterm delivery, intrauterine growth restriction, neurologic developmental delay, cardiotoxicity and carcinogenesis are more commonly encountered (57). Whether these complications result from breast cancer, chemotherapy or surgery is yet to be determined. In their study, Berry et al found that in 24 women receiving cyclophosphamide, adriamycin and 5-fluorouracil, no malformation was seen but three preterm births, two transient tachypnea, one low birth weight occurred with hyaline membrane disease and transient leucopenia (68). In their study of locally invasive breast cancer during the second and third trimester of pregnancy, Hahn et al applied adjuvant chemotherapy to 32 cases and neoadjuvant chemotherapy to 25 cases, with a mean of four cycles of 5-FU, doxorubicin and cyclophosphamide combination (69). The patients delivered at a median gestational age of 37 weeks with one maternal death due to pulmonary embolism after cesarean delivery but no intrauterine or perinatal fetal death, only 10% need for ventilation and one fetus with neutropenia, thrombocytopenia and subarachnoid bleeding (69). In the light of the literature, chemotherapy can be applied safely after the first trimester of pregnancy. If indicated, chemotherapy should not

be postponed in the second and third trimesters of pregnancy. Also inducing the pregnancy early to apply chemotherapy is not right, as prematurity related problems will cause more problems than the chemotherapy itself (60). However, if the pregnant woman refuses to receive chemotherapy, labor can be induced at 32-34 weeks of gestation. After chemotherapy myelosuppression may increase the risk of sepsis and postpartum hemorrhage, while low blood counts can also be seen in the newborn (70). In order to avoid myelosuppression during delivery, it is better to discontinue chemotherapy after 34th week of gestation, three weeks earlier from delivery. Vaginal birth is the preferred method rather than cesarean section as maternal morbidity is lower.

Long term effect of chemotherapy is still a matter of debate. In a large study, 82 fetuses subjected to chemotherapy during maternal treatment of hematological malignancies were followed up until a mean of 18.7 years of age: no malignancies were encountered and normal physical, neurological and psychological development was observed (71).

Breast feeding is not recommended in mothers receiving chemotherapy, biological therapy, endocrine therapy or radiotherapy (25). Almost all therapeutics are secreted in the milk, and breast feeding should start four weeks after the last cure.

1. 8. Prognosis

The prognosis of pregnancy associated breast cancer is similar to breast cancers unrelated to pregnancy when matched according to age and stage of the disease (13, 33, 72-74). On the other hand, several existing data indicate that advanced stage cancer prognosis is worst in the pregnancy associated

group when compared to stage matched cases unrelated to pregnancy (13, 16, 75, 76). In fact, the diagnosis in PABC cases is almost always delayed (13, 16, 39, 76). PABC also have unfavorable biological features related to poor prognostic outcome such as high grade tumor, low hormone receptors, increased HER2/neu expression and high ki-67 nuclear antigen (12, 24, 77). The risk of being in an advanced stage at the time of diagnosis is 2.5 times higher in PABC compared to other cases (24). Overall survival rate in PABC is 40-73% compared to 48-97% in other breast cancer cases. Five years and 10 years survival rates among pregnancy associated breast cancer and other breast cancer patients is presented in Table 2 (13, 16, 18, 43, 53, 63, 73, 74, 76, 78-84).

Petek et al. showed that the five year survival rate is 82% in cases of PABC and other cases if lymph node metastasis is not present (79). On the other hand, they also showed that if lymph node metastasis is present the five year survival rate in PABC cases is 47% which is lower than the 59% in pregnancy unrelated breast cancer cases (79). Similar findings have also been confirmed by other studies showing the worst prognosis of PABC in stage II-IIIa cases (13, 16, 76).

Poor prognosis was reported in breast cancer cases diagnosed in the postpartum period which was independent of age, stage and additional biological features of the tumor (80, 81). In a study focusing on the cases of postpartum diagnosed breast cancer, Whiteman et al. showed that the poorest survival rate of 38% was seen in cases diagnosed within 12 months after delivery, which was 51% in cases diagnosed at 13-48 months postpartum, and 60% in cases diagnosed after 48 months postpartum compared to the 65% survival among age matched

Table 2. Five year and 10 year survival rates among pregnancy associated breast cancer and other breast cancer patients

	Year	Number of Patient Cases/Control (n)	PABC Survival Rate		Other breast cancer Survival Rate	
			5 years (%)	10 years (%)	5 years (%)	10 years (%)
Nugent ve O'Connel	1985	19/157	56	-	56	-
King et al.	1985	63	75 ^b /33 ^c	-	-	-
Pertek et al.	1991	63	61	45	73	62
Ishida et al. ^a	1992	192/191	-	55	-	7
Zemlickis et al.	1992	118/269	-	40	-	48
Chang et al.	1994	21/199	57	-	70	-
Guinee et al. ^a	1994	66	40	-	70	-
Anderson et al.	1996	22/205	-	73 ^d /17 ^e	-	74 ^d /47 ^e
Bonnier et al. ^a	1997	114/280	61	-	75	-
Kuerer et al.	1996	26	60 ^b /45 ^c	-	-	-
Bladström et al. ^a	2003	94/7799	52	44	80	69
Whiteman et al.	2004	60	-	38 ^f	-	65 ^f
Mathelin et al. ^a	2008	40/61	-	72 ^g /63 ^h	-	97
Beadle et al.	2009	104/668	-	63 ^g /65 ^h	-	65
Stensheim et al.	2009	105	-	56 ⁱ	-	69 ⁱ
Cardonick et al.	2010	130	100/86 ^j /0 ⁱ	-	-	-

^aStatistically significant survival difference (p<0.01), ^blymph node involvement negative, ^clymph node involvement positive, ^dStage I-IIa, ^eStage IIb-III, ^f15 years survival, ^gGroup includes only pregnant patients, ^hGroup includes only postpartum patients, ⁱSurvival rate of 60th years. ^jAfter 3.14±2.5 years follow up survival rate according to stage, ^kStage I, ^lStage II ve III, ^mStage IV, PABC: Pregnancy associated breast cancer

nulliparous women (80). Steinsheim et al also showed that the highest breast cancer related death rate of 67% was seen in breast cancer cases diagnosed within six months after delivery and the overall death rate was 44% in pregnant group compared to 31% in the control group (81).

There is no evidence that termination of pregnancy favorably affects the prognosis (85). On the other hand, if stage II or IV disease was diagnosed during the first trimester, if there is an aggressive primary tumor and if the expected survival is shorter than the duration of pregnancy, then pregnancy termination can be an option (11).

Despite these findings, there is still uncertainty if the pregnancy or postpartum period is an independent prognostic factor on breast cancer. In most studies, case and control groups are extracted from national registries which causes methodological problems in comparisons due to age and stage matching, inadequate data on biological features of the tumor, different treatment modalities and postponing of chemotherapy to the postpartum period by many patients.

2. Pregnancy After Breast Cancer Treatment

Fertility history of the women is a well known risk factor for breast cancer and estrogen is a known growth factor for breast cancer (24, 27, 33, 86, 87). It was hypothesized that the induction of tumor growth was caused by the hormonal changes of pregnancy which results in the poor prognosis of advanced stage breast cancer diagnosed during pregnancy or the postpartum period. It is not clear whether a similar relationship exists in pregnancies occurring after breast cancer treatment. The possibility that high hormonal levels during pregnancy might induce dormant micrometastases is the main source of anxiety for the patient and her doctor.

2. 1. The effect of pregnancy after breast cancer treatment on survival, recurrence and distant metastases

Studies targeting the effect of pregnancy after breast cancer treatment on the survival of the patients generally agreed that it has no adverse effect on the prognosis of the disease and survival rate. The first population based studies showed that the relative risk of pregnancy after breast cancer on survival and distant metastases is 0.2 and 0.4 respectively (88, 89). The subgroup analysis of term deliveries, preterm deliveries and abortions after breast cancer treatment showed that none worsens the prognosis even after considering age at diagnosis, tumor size, lymph node metastasis, time from prior pregnancy to breast cancer diagnosis and time from breast cancer diagnosis to last pregnancy (9, 86). These studies statistically lower breast cancer related death risk (RR=0.73) if a term delivery is present in low risk tumors (86). Mueller et al. found that pregnancy after breast cancer treatment lowers the death risk (RR=0.54) which was statistically lower in cases younger than 35 years, white ethnicity, tumor size larger than 2 cm (90). In another study, age and stage adjusted analysis revealed a lower relative risk for death (0.8) in cases who became pregnant after breast cancer treatment in which the survival in cases and controls were similar according to tumor size, the extent of surgery, need for chemotherapy or radiotherapy (91). Blakely et al. showed that, in 370 breast cancer cases younger than 35 years of age, 47 became pregnant after adjuvant chemotherapy and pregnancy

did not increase the recurrence or death risk (92). Ives et al. also found that pregnancy after breast cancer treatment did not adversely effect survival, but better survival rates were found in cases delaying pregnancy for 24 months or more after the end of breast cancer treatment (10). Table 3 summarizes the case control and population based studies calculating survival rate considering whether the patient got pregnant after breast cancer treatment (9, 10, 86, 88-93, 95).

In most case control studies, providing a multivariate analysis including presence of estrogen receptor, age at diagnosis, tumor size, histological grade, pregnancy after breast cancer treatment has a favourable effect on 5 to 10 years of survival (88, 93-95). This favourable effect of pregnancy on survival after breast cancer treatment was explained with the `healthy mother effect` which was first proposed by Sankila et al stating that women who can plan pregnancy are more likely to have local disease without recurrence during follow up and who are in a good general health (88). It is obvious that women with advanced tumor, early recurrence and poor general health will not consider pregnancy as an option. Comparison of these women with poorer prognosis to women who feel healthy enough to plan a pregnancy may cause a selection bias.

Besides the `healthy mother effect` theory, immune mediated `fetal antigen hypothesis` is also worth attention. Fetal antigen hypothesis is based on the assumption that fetal and maternal tissues share common antigens and isoimmunisation during pregnancy might be protective against breast cancer (96). According to the fetal antigen hypothesis, pregnancy after breast cancer treatment provokes an immune memory against fetal antigens which keeps subclinical metastases under control through humoral and specific cellular immune system (97). Also, it was shown that pregnancy after breast cancers creates high estrogen and progesterone values together with hCG which induce apoptosis in breast cancer cells with receptors for these hormones (98). The presence of estrogen receptor on breast cancer cells is mainly seen in postmenopausal women and premenopausal women becoming pregnant after breast cancer treatment have 23-34% estrogen receptor (9, 10, 92). However, the estrogen receptor status was not proven to have any effect

Table 3. RR ratios for survival if the patient became pregnant after breast cancer treatment

	Year	n (case)	RR
Population based trials			
Sankila et al.	1994	91	0.20
Von Schoultz.	1995	50	0.42-0.48 ^a
Kroman et al.	1997	173	0.55
Ives et al.	2007	123	0.59
Kroman et al.	2008	371	0.73
Cohort based trials			
Malamos et al.	1996	21	0.48
Velentgas et al.	1999	53	0.80
Gelber et al.	2001	94	0.44
Müller et al.	2003	438	0.54
Blakely et al.	2004	47	0.70
^a RR for distant metastasis after adjustment to lymph node status			

on the prognosis of breast cancer if the women become pregnant (9, 10, 92).

The effect of pregnancy after breast cancer treatment is still an open question because the studies conducted on the subject are mostly retrospective case control studies depending on hospital records or patient responses. Also the unknown spontaneous or induced abortion rate after breast cancer renders exact comparisons impossible.

2. 2. The effect of abortion after breast cancer treatment on the prognosis

The pregnancies after breast cancer treatment have a 70% higher rate of both spontaneous and induced abortions compared to the general population (91). In the study of Kroman et al, among 465 pregnancies after breast cancer treatment, 41% ended with induced abortion and 7.7% ended with spontaneous abortion (9). The overall abortion rate was found to be 24-29% in several studies (91, 92). Abortion rate is higher if the women become pregnant within two years of therapy and is especially high in the first six months after therapy. Although chemotherapy triggered hormonal changes might be a reason, the main determinant of decision on abortion is the doctors' and patients' negative attitude to the pregnancy. Gelber et al showed that two thirds of induced abortions were done according to the doctors' advice (95). It is possible that in a few studies, women whose pregnancies end with abortion have a poorer prognosis than women carrying the fetus to term (86, 91). Selection bias is possible as doctors advise abortion to women with poorer prognosis more commonly. Most of the studies show no negative effect of abortion on the prognosis of breast cancer cases (9, 10, 86, 91, 92, 97). It was concluded that it is not necessary to advise abortion to breast cancers cases becoming pregnant after therapy unless there is lymph node involvement.

2. 3. What is the optimum time for pregnancy after breast cancer therapy?

As recurrences after breast cancer therapy are mostly seen in the first two years and pregnancy may interrupt the therapy, it is generally advised that patients should wait for two years to become pregnant (98, 99). In addition, due to the poorer prognosis, higher recurrence rate in young women, those younger than 35 years of age were advised to wait for three years and women with lymph node involvement were advised to wait for five years before becoming pregnant (97). In their study, Clark and Chua showed that women who became pregnant within the first six months of therapy have a 59% survival rate compared to the 92% survival rate in women who become pregnant between 6 to 24 months (100). This was not confirmed in other studies (10, 101).

Breast cancer cases who would consider pregnancy are usually at the end of their thirties or at the beginning of their forties. Chemotherapy may further decrease their ovarian reserve so cases who desire a baby but have advanced disease or critical ovarian reserve might consider surrogate motherhood as an option.

In conclusion, women experience a transient increase in breast cancer risk after pregnancy. This risk is more evident in women with a familial history of breast cancer, mutation in BRCA genes and who have their first pregnancy after 30 years of

age. Pregnancy associated breast cancers might have a poorer prognosis in advanced stages compared to other advanced cases unrelated to pregnancy. Also, breast cancers which were diagnosed in the postpartum period have a poorer prognosis. If breast cancer is suspected in pregnant women, the diagnostic work-up should be similar to non-pregnant women as diagnostic delays are unacceptable costs. Surgery is acceptable in pregnant women but radiotherapy and hormonal therapy should not be used. Chemotherapy is an acceptable alternative after the first trimester but longterm effects are still obscure. Terminating the pregnancy has no favorable effect on survival. In the light of current literature, pregnancy after stage I or II breast cancer therapy has no negative effect on the overall or five year survival rate. Also considering pregnancies after breast cancer therapy the time elapsing until pregnancy, number of pregnancies, spontaneous abortions, induced abortions, and term pregnancies have no negative effect on survival rates. Although recurrent stage I and II breast cancer cases and women with advanced stage tumor were not advised to become pregnant or to postpone their pregnancy there is scarce data in the literature to support these.

A multidisciplinary approach to pregnancy associated breast cancer is important and all decisions should include the opinion of the patient. A patient tailored approach should be designed considering disease status, desire for pregnancy, ovarian reserve and survival.

Conflict of interest

No conflict of interest was declared by the authors.

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