



# Breast Cancer and Ways to Diagnose the Risk Factors and Treat it During Pregnancy: A Narrative Review

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## Abstract

**Objectives:** Breast cancer that occurs from the beginning of pregnancy to one year after pregnancy is called pregnancy-associated breast cancer and identifying and knowing its risk factors can greatly affect the health of the mother and the baby/fetus. Therefore, the present study was conducted to investigate breast cancer during pregnancy.

**Methods:** To this end, published articles until 2019 were obtained from Persian and English databases using keywords such as “pregnancy (Mesh)” and “breast cancer (Mesh)” and included based on the inclusion and exclusion criteria.

**Results:** Epidemiological findings, pregnancy factors affecting breast cancer, and treatments were collected and presented from several articles.

**Conclusions:** In general, self-induced abortion, preeclampsia, and gestational diabetes were considered as risk factors for breast cancer. In the case of breast cancer, radiotherapy is better in the third trimester. In addition, adjusted mastectomy is preferred to other surgical and chemotherapeutic methods except for the organogenesis period, and a period of three weeks before delivery is associated with minor fetal and maternal complications.

**Keywords:** Breast Cancer, Pregnancy, Breastfeeding

## Introduction

Breast cancer is a type of cancer that starts in the breast tissue and can spread to other nearby tissues in addition to affecting the entire breast tissue (1). It is the most common cancer worldwide, causing extensive mortality and many complications (2-4). The incidence of breast cancer is globally increasing, especially in developing countries. Notably, about 6 million women with breast cancer were globally identified during 2008-2013 (5). More than 255 000 new cases of breast cancer occurred in the United States in 2017. Meanwhile, the annual incidence of breast cancer is 33 cases per 100 000 people in Iran, and the highest rate has occurred in Tehran, Isfahan, Yazd, Markazi, and Fars provinces (6).

One of the concerns associated with breast cancer is its experience during pregnancy (7). Pregnancy-associated breast cancer refers to cancer that occurs during pregnancy, breastfeeding, or one year after delivery. It is the second most common cancer in pregnancy, which rarely occurs and does not cause many deaths (8, 9). Diagnostic and therapeutic interventions during this period are implemented with special considerations. Women with breast cancer are clearly at a more advanced stage of the disease during pregnancy and usually have a poorer prognosis (10,11). One of the major challenges in diagnosis and treatment during this period is maintaining

a balance in the aggressive care of these patients and appropriate treatments to maintain the health of the fetus/baby. Given that the occurrence of this cancer during pregnancy can have adverse effects on the health of the mother, the baby, and the fetus, the current study aimed to investigate the factors affecting the incidence of this type of cancer during pregnancy.

## Materials and Methods

This review study aimed at evaluating the relationship between pregnancy-related variables and the risk of breast cancer. This article review focused on all studies performed in this field until 2019. The related studies were selected from Persian and English databases. Iranian databases included SID, Irandoc, and Magiran, and English databases included PubMed, Scopus, Science Direct, Cochrane, Google Scholar, and Embase. Keywords were based on Mesh, including breast cancer and pregnancy. The inclusion criterion was accessing the full text of the articles, and the exclusion criterion was conference papers and articles, full-text versions of which were unavailable.

## Results

In general, 161 articles were found in the first stage although they were excluded from the review process at different stages and for scientific reasons. Finally, 83

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articles were reviewed in this article (Figure 1).

### Behçet's Syndrome During Pregnancy

All cases of breast cancer diagnosed during pregnancy and up to one year after delivery or during breastfeeding are called pregnancy-associated breast cancer (12,13). Although breast cancer is rare in pregnancy (4 per 1000 people), it must be identified and treated extremely quickly, and steps must be taken extensively carefully to avoid harm to the baby/fetus (14).

### Epidemiology

The incidence of breast cancer increases with age. The epidemiological pattern of breast cancer in Iran is similar to that of the countries of the Eastern Mediterranean region and other developing countries, and its incidence has changed in recent years (15,16). According to the Center for Disease Control of the Ministry of Health, breast cancer is still in the first place among all cancers in women in Iran, and it has the highest incidence among cancers with an age-adjusted incidence of 27.15 and 6796 cases in 2007. In addition, the incidence of breast cancer in Iranian women is lower than the global average, and the age of women with this disease in Iran is at least 10 years less compared to developed countries (17,18).

Until 2002, the incidence of this cancer was positively growing annually, but since then, the incidence of this cancer has slightly decreased following the discovery of the link between hormone replacement therapy and breast cancer and the lack of hormone therapy in postmenopausal women. However, the mortality rate of breast cancer remains at the same level (19). Unfortunately, the incidence of this cancer is higher in Iran in comparison

with the international statistics, and it seems that one in every 5-6 Iranian women suffers from this cancer during their lifetime (3,20). Due to the increasing incidence of this cancer with age, the association of this cancer with pregnancy and breastfeeding is low. Statistics show that 3% of breast cancers occur during pregnancy and breastfeeding although this rate is increasing due to the increasing age of marriage worldwide (21-23). Breast cancer is the most common cancer during pregnancy after cervical cancer (24).

The average age of pregnant patients is 33-34 years (25-27) and the average gestational age at the time of diagnosis is 17-25 weeks. Tumors in 80%-100% of patients are ductal invasive carcinomas, and 40%-80% of them are undifferentiated. Inflammatory tumors with a poorer prognosis are more common in pregnant women compared to non-pregnant women so that tumors in pregnant or lactating women are more advanced in comparison with non-pregnant women. In general, 54%-80% of tumors in pregnancy and lactation are estrogen receptor-negative tumors, which is higher compared to non-pregnant women and weakens the prognosis. Physiological changes in the breast and restriction in the examination of pregnant patients delay the diagnosis, and staging should be determined as soon as the disease is diagnosed in pregnant women and treatment should be chosen by considering the stage of the disease and minimizing the risks to the fetus (18, 28).

### Breast Cancer and the Contributing Factors

Several factors are involved in the development of breast cancer, which can generally be divided into three categories of nonmodifiable, modifiable, and other

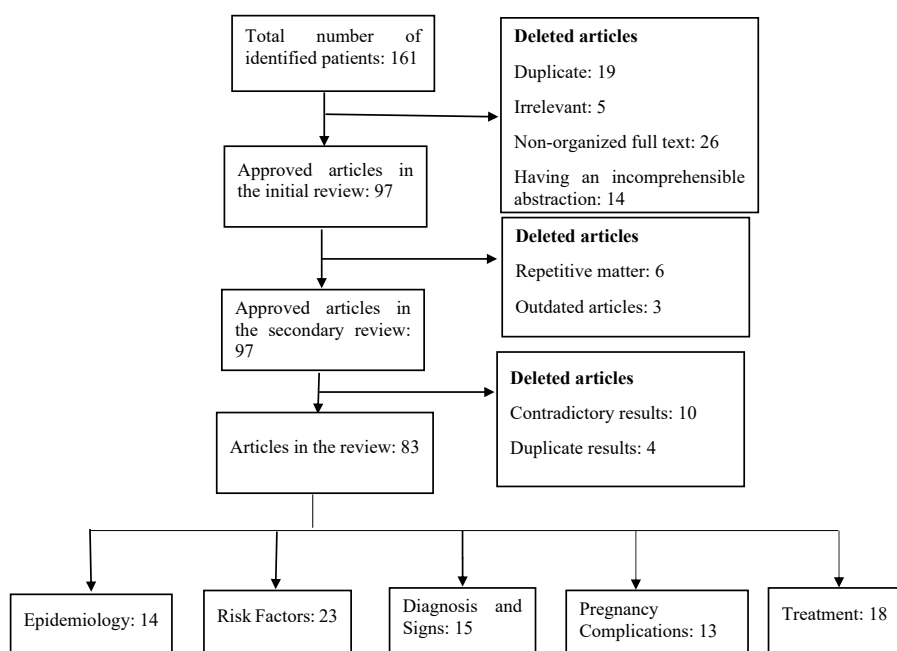


Figure 1. Flowchart Articles Login to Narrative Review.

factors. Nonmodifiable factors include age, gender, family history, premature menarche, late menopause, and genetic predisposition. Modifiable factors encompass obesity and overweight, nutrition, physical inactivity, alcohol and tobacco use, contraceptive drugs, and postmenopausal hormone use. Finally, other factors are associated with the increased risk of breast cancer, including breast density, the levels of the androgen hormones, pregnancy, breastfeeding, and bone mineral density (29-31), which are discussed as follows.

#### Breast Density

High breast tissue density (a mammographic indicator of the ratio of the connective tissue to the adipose tissue in the breast) is a strong independent risk factor for the development of breast cancer (32,33). Factors such as age, menopausal status, consumption of certain medications (hormone therapy in menopause), pregnancy, and genetics can affect breast density (34,35). Breast density is affected by hereditary genetic factors, but it decreases with age and further decreases with pregnancy and menopause. Lower breast density is more common in women with higher body weight due to higher fat tissue ratios. A number of drugs affect breast density, including tamoxifen, which reduces density, and combination hormone therapy during menopause, which increases density. The risk of breast cancer elevates by increasing breast density. Women with extremely high breast density are 4-6 times more likely to develop breast cancer compared to those with minimal breast density (36-38).

#### Highlight

Increasing breast density increases the risk of breast cancer.

#### Androgen Hormones Levels

Postmenopausal women with high levels of androgen hormones (i.e., estrogen or testosterone naturally produced in the body) are about twice as likely to develop breast cancer as women with the lowest levels of the hormone. High levels of circulating hormones are linked to other risk factors for breast cancer, including postmenopausal obesity and alcohol consumption (39-41). Although many factors (e.g., obesity, premature menarche, infertility, and premature menopause) have been related to breast cancer during menopause, the exact effects of each factor have unfortunately remained unknown. However, the androgen receptor seems to have a larger share during menopause compared to other factors (42,43).

#### Highlight

Changes in the levels of androgen hormones during menopause increase the risk of breast cancer.

#### Pregnancy

Younger age in full-term pregnancy (less than 30 years)

and more pregnancies reduce the risk of breast cancer, but studies show a temporary increase in the risk of breast cancer following a full-term pregnancy, especially in older women at the time of the first birth (9,44). However, another study suggested that pregnancy should be done at an early age to reduce the risk of breast cancer (45).

#### Breastfeeding

Most studies indicate that breastfeeding for a year or more reduces the overall risk of breast cancer. The protective effect may be greater for basal-like breast cancer. Prolonged breastfeeding is associated with a greater risk reduction. A review of 470 studies in 30 countries showed a risk reduction of breast cancer by about 4% for every 12 months of breastfeeding. One possible explanation may be that breastfeeding inhibits menstruation and thus reduces the number of menstrual cycles. Another possible explanation is that structural changes occurring after breastfeeding can reduce breast cancer (46-48).

#### Highlight

Increasing the duration of breastfeeding can reduce the risk of breast cancer.

#### Bone Mineral Density

Many studies have reported that high bone mineral density in postmenopausal women has been associated with an increased risk of breast cancer. This risk is strongly associated with estrogen receptors. Although bone density is not an independent risk factor for breast cancer, it is an indicator of cumulative exposure to estrogen. Bone densitometry is commonly used to diagnose women at risk for osteoporosis and may also be helpful for women at risk for breast cancer (49,50).

#### Diagnosis and Staging of Breast Cancer in Pregnancy

Some of the important points in the process of diagnosis and treatment of breast cancer are as follows (51-57):

1. In a bilateral mammogram, less than 0.004 GY of radiation is received by the fetus while the risk level of radiation in the fetus is 100 mGY. Therefore, the use of abdominal lead can make this method as an efficient one with minimal risk.
2. Increased breast density makes it difficult to interpret mammography. Reports suggest that 63%-89% of mammograms change in pregnancy-associated breast cancer.
3. According to evidence, ultrasound is more sensitive in diagnosing tumors during pregnancy and lactation.
4. The risk of breast fistula, bleeding, and infection in the mother increases in any cytological examination.
5. Hyperproliferative changes in the breast tissue during pregnancy increase the possibility of misdiagnosis, thus it is recommended that an experienced cytologist perform this examination.
6. With the cessation of breastfeeding before the biopsy,

the administration of prophylactic antibiotics, and careful examination of the hematoma will reduce the risk of complications.

7. Ionizing radiation at 3-8 days of gestational age causes the death of the fetus and increases the risk of intrauterine growth retardation, microcephaly, and mental retardation until the eighth week. In general, the chances of infertility and future cancers in pregnant mothers' offsprings demonstrate an increase.
8. A chest X-ray can be done because of the low dose of radiation in pregnancy.
9. It is best to avoid computed tomography (CT) scans to determine the grade of the disease.
10. Magnetic resonance imaging (MRI) test and ultrasound are good alternatives to CT scans in the study of metastases. However, it is best not to perform MRI in the first trimester until further investigation of the effects of magnetic waves on the fetus.
11. The contrast agent (i.e., gadolinium) crosses the placenta, and therefore, it is better to avoid MRI with contrast during pregnancy.
12. After diagnosis and staging, medical treatments should begin immediately after consultation with a group of clinicians.

#### *Highlight*

In pregnancy, it is best to use an ultrasound or MRI (to look at the age of the fetus) to diagnose breast cancer.

#### **Early Diagnosis of BS**

The World Health Organization and the American Cancer Society consider early diagnosis as the best way to control breast cancer. Considering that this disease goes through a long, hidden stage (8-10 years), the patient's life can be saved from premature death by identifying and diagnosing the mass in the early stages. Given that breast cancer patients are diagnosed in 50% of the cases in the advanced stages of the disease in Iran, the early diagnosis of the disease is important. Therefore, it is strongly recommended to counsel women regarding encouraging them to perform routine screening tests for the early detection of breast cancer (58, 59).

#### **Complications of Pregnancy Affecting Breast Cancer**

##### **Abortion**

Abortion refers to the loss of a pregnancy before 20 weeks of gestation, the global prevalence of which is 25%, and it is most common in East Asia. During pregnancy, the breast tissue undergoes changes, and after a full pregnancy, a differentiation of the breast is made, which has a protective effect against breast cancer. When an abortion occurs, the pregnancy is incomplete, and the differentiation of the breast tissue is not complete, which increases the risk of breast cancer. Some studies have reported a history of abortion as a risk factor for breast cancer. Studies

investigating self-induced and spontaneous abortions separately have found that only self-induced abortions are associated with the risk of breast cancer. A number of studies have also reported the risk of breast cancer only in people who have had more than one abortion (60, 61). Nonetheless, abortion can clearly increase the risk of breast cancer (62).

##### **Preeclampsia**

Preeclampsia is defined as systolic blood pressure of above 140 and diastolic blood pressure of above 90 after the twentieth week of pregnancy, which is usually associated with proteinuria. Approximately 6.4% of pregnancies worldwide lead to preeclampsia. The prevalence of this complication in Iran has been announced as 0.007, and this rate is increasing. Women suffering from this complication have hormonal changes (63,64). The maternal estrogen level decreases during this complication. The decreased estrogen level supports the biological hypothesis of the protective effect of preeclampsia against breast cancer. It also increases the levels of progesterone, androgens, and the human chorionic gonadotropin (hCG), all of which have anti-estrogenic effects. On the other hand, a decrease in the insulin-like growth factor in this complication may also play a role in this hypothesis. A number of studies have confirmed the link between breast cancer and preeclampsia (65-67).

##### **Gestational Diabetes**

Gestational diabetes is a disorder of glucose tolerance that first begins or is diagnosed during pregnancy. The global prevalence of gestational diabetes is estimated at 17%, which is higher in South and East Asian women. The prevalence of gestational diabetes in Iran is about 3.5%. Hyperinsulinemia and hyperglycemia are disorders that occur in gestational diabetes. Studies have shown that insulin and glucose are associated with an increased risk of breast cancer while constant hyperglycemia, hyperinsulinemia, and insulin resistance increase the insulin-like growth factor, which is associated with an increased risk of breast cancer onset and its progression. On the other hand, an increase in blood insulin reduces the production of sex hormone-binding globulin, resulting in an increase in the amount of active estradiol. Some studies have identified gestational diabetes as a risk factor for breast cancer while some others reported no link between breast cancer and gestational diabetes (68-70).

#### *Highlight*

Complications of pregnancy (i.e., abortion, gestational diabetes, and preeclampsia) can increase the risk of breast cancer.

#### **Multiple Pregnancies**

Twin pregnancies are the result of fertilizing two separate eggs or dividing a fertile egg. There have been 314 twinning

cases per 10 000 pregnancies, and the rate is rising. The elevated levels of estradiol, testosterone, progesterone, hCG, and alpha-fetoprotein have been shown in multiple pregnancies. In multiple pregnancies, an increase in hCG, progesterone, and alpha-fetoprotein appears to have long-term protective effects against breast cancer due to its anti-estrogenic effect on the breast tissue. Some studies have reported the protective effects of multiple pregnancies on breast cancer (18,71).

### Signs and Symptoms of Breast Cancer

The tumor does not typically cause any symptoms when it is small, thus it is important for women to consider screening guidelines for the early diagnosis of breast cancer (72, 73). The most common sign is a painless mass, which occurs when breast cancer has progressed. Cancer can occasionally spread to the axillary lymph nodes and cause a bulge. Less common signs and symptoms include breast pain or heaviness, nipple abnormalities in the form of spontaneous discharge, itching and scaling of the nipple, breast tenderness, peau d'orange, and any new appearance changes such as sores, redness, prominent veins, dimples, and stretch marks on the skin or nipples. Therefore, in any case of such masses, follow-ups should be done regardless of pregnancy. Another symptom of this disease is the baby's refusal to breastfeed while the baby has previously been well-nourished (74-77).

### Breast Cancer Treatment During Pregnancy

#### Surgery

General anesthesia in pregnant women is associated with conditions such as increased blood volume, coagulopathy, decreased lung capacity, slow gastric emptying, and postural hypotension (78-80). The results of a study of 5405 pregnant women with breast cancer undergoing surgery and comparing it to 720 000 healthy pregnant women showed an increase in low birth weight due to prematurity, intrauterine growth restriction, and neonatal mortality without an increase in congenital abnormalities or stillbirth. The second trimester of pregnancy is the best time for surgery. Placing the patient in the left lateral position is one of the most important measures during surgery. The common surgical method during pregnancy is modified radical mastectomy, which is the standard treatment for stages 1 and 2 breast cancer and can be performed under general anesthesia. Surgical interventions after the 12th week of pregnancy are associated with the least risk to the fetus. Modified radical mastectomy is also a standard treatment throughout pregnancy. Palliative care is recommended for younger women, but the side effects of radiotherapy during pregnancy should be considered as well (81,82).

#### Radiotherapy

Radiotherapy is contraindicated with an increased risk of mutations and fetal death in pregnancy. In standard

radiotherapy, 50 000 cGY of radiation is irradiated to the patient. Early in pregnancy, the fetus receives only about 10 cGY of this radiation when it is in the pelvis although this amount will increase to 200 cGY by the end of the pregnancy, and this is why radiotherapy is delayed until after delivery if the cancer is diagnosed early in the third trimester. The greatest fetal risk of radiotherapy is in the first trimester of pregnancy, and more specifically before the organogenesis stage while the lowest risk is in the third trimester. The risks of radiation include the following issues (83-85):

- Teratogenesis;
- Increased risk of abortion;
- Development of cancers in advanced ages.

#### Chemotherapy

Chemotherapy is recommended in metastasis to the lymph nodes or large tumors without the involvement of lymph nodes. Numerous studies have been conducted on the effects of chemotherapy on fetal health. The highlights of these studies as follows (86-89):

- In the organogenesis stage, the potential impact of drug teratogenicity is greater than other stages of pregnancy, thus if chemotherapy is needed, the benefits of treatment should be carefully compared with the danger of teratogenicity and selected accordingly.
- In stages other than organogenesis, treatment with cyclophosphamide and doxorubicin is relatively safe.
- Methotrexate is contraindicated due to the high risk of teratogenicity in pregnancy.
- Laboratory studies show that only small amounts of Epirubicin cross the placenta.
- Taxanes safety requires further studies.

#### Hormonal Therapy

Since most pregnancy tumors lack estrogen receptors, this drug is not usually used during pregnancy (90, 91).

#### Bisphosphonate

In rare cases of metastatic breast cancer, bisphosphonate is prescribed for mothers. Careful monitoring of the baby's calcium should be done since babies of such mothers are more prone to hypocalcemia. Nonetheless, no information is available on the long-term effects of these drugs (92,93).

### Pregnancy in Women With Breast Cancer

The prognosis of women who become pregnant after treatment is not different from that of non-pregnant women. However, it is recommended that they do not become pregnant for two to three years after treatment due to the possibility of recurrence in the first two years of treatment (94).

#### Breastfeeding

Breastfeeding is not prohibited in women whose disease is



diagnosed early and treatment is complete. Breastfeeding is prohibited in women undergoing chemotherapy or radiotherapy (95).

### Conclusions

Breast cancer is a multifactorial disease that has been shown to play a role in many risk factors. According to studies, these risk factors include family history, advanced age, age of menarche under 12 years, menopausal age after 54 years, age of first delivery after 30 years, no history of delivery, high density on mammography, and high levels of sex hormones. Contact with ionizing radiation in childhood, race, economic status, body mass, and lifestyle in terms of nutrition, physical activity, smoking, and alcohol consumption (29,77,96).

Breast cancer is linked to female hormones, and any factor that alters the levels of hormones in a woman's body may increase the risk of breast cancer. In other words, changes in the normal amount of female hormones are a risk factor for breast cancer. Factors that can alter the levels of female hormones, especially estrogen, in the body include premature or under 11 years of age and late menopause, or after 53 years, factors that increase the duration of breast tissue contact with ovarian hormones. These factors increase the risk of breast cancer (97-100).

Breastfeeding is one of the effective factors in preventing breast cancer. Research shows that after childbirth and breastfeeding, cancer cells fall asleep and do not grow as before pregnancy (31). In addition, the growth rate of cancer cells in the breasts of women who are breastfeeding their babies reduces by more than 50% and stops occasionally. The risk of breast cancer in women with a breast cancer gene significantly reduces in women who have been breastfed for at least 12 months. The protective effect of breastfeeding seems to be extensively higher in people with this gene compared to women. Further, people with cancer are significantly less likely to breastfeed, and women with a breast cancer gene who have been breastfed for more than a year are extremely less likely to develop breast cancer compared to women who have not been breastfed at all (18).

Since women are the axis of the health of the family and given the widespread role of women in the socio-economic change of the country and the goal of sustainable health development with a focus on women, the need for early detection and prevention of breast cancer due to high prevalence is important all over the world as one of the best approaches for controlling this disease. Therefore, early prevention in the form of lifestyle changes, avoiding risk factors, and extensive education and awareness raising, especially through mass media such as radio and television for raising people's awareness of breast cancer screening methods, become essential and are recommended accordingly. Secondary prevention also includes the early detection of cancer or precancerous lesions with effective and efficient screening methods.

Currently, mammography (as the most effective method in breast cancer) can play an important role in reducing the incidence and mortality due to breast cancer.

The early diagnosis and determination of the tumor growth stage and the uninterrupted initiation of treatment are the most important strategies for disease management. In addition, the self-examination and periodic examinations of health staff and the use of appropriate diagnostic methods with regard to pregnancy are important. Apart from the organogenesis period and three weeks before delivery, chemotherapy is associated with minor fetal and maternal complications. The greatest fetal risk in radiotherapy is in the first trimester, especially before organogenesis whereas the lowest risk is observed in the third trimester. The standard surgical treatment throughout the pregnancy is a modified radical mastectomy and the best time for surgery is the second trimester of pregnancy.

### Authors' Contribution

NG participated in preparation of the manuscript. LG helped in design of the study and contributed to the literature review. TH checked all articles and deleted unrelated articles. FM finalized the study and participated in the design of the study.

### Conflict of Interests

Authors declare that they have no conflict of interests.

### Ethical Issues

The research project was approved by the Ethics Committee (The ethics number IR.TBZMED.REC.1398.009).

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