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Breast Cancer in Young Women

Implications for Pregnancy, Lactation, and Fertility Preservation

Amanda N. Labora, MD, and Nimmi S. Kapoor, MD, FACS

The care of young women with breast cancer can be influenced by pregnancy and desire for future fertility. Here, we provide an overview of breast cancer management in young women with special emphasis on gestational breast cancer and postpartum breast cancer, which are now understood to be distinct clinical entities with disparate outcomes. Typically, breast cancer is detected in young women after self-identification of a breast mass. The initial workup consists of diagnostic breast ultrasonogram and mammogram. Breast cancer treatments vary by histologic subtype of cancer and stage. Chemotherapy and surgery are safe during pregnancy, and it is now known that pregnant women with breast cancer have oncologic outcomes equivalent to those of nonpregnant women when treated according to standard of care. Postpartum breast cancer, however, has higher rates of metastatic disease and mortality. In general, breastfeeding can be safely continued during treatment with appropriate counseling and guidance from a breastfeeding medicine expert. Similarly, fertility preservation and future fertility can be safely pursued with appropriate interventions in young women with breast cancer.

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Breast cancer was the leading cause of death in women aged 20–49 years in 2023 and was the most commonly diagnosed cancer in pregnancy.¹ As more women delay childbirth and pursue pregnancy at advanced ages, there has been an increase in the incidence of breast cancer during pregnancy (from 3.7 to 7.7/100,000 births) and the postpartum period (from 13.8 to 32.2/100,000 births).^{2,3} In parallel, the incidence of breast cancer in young women (age 40 years or younger) is rising.⁴ As of 2022, the incidence of breast cancer in girls and women in the United States aged 15 to 39 years is 24.6 per 100,000.⁵

Although pregnancy in general is associated with decreased breast cancer risk in the long term, a pregnancy within the past 10 years is associated with an increased short-term risk of breast cancer, an epi-

miologic phenomenon referred to as the dual effect.⁶ It is important to note that the protective effect of pregnancy is age dependent; older age at first birth both decreases the magnitude of benefit and delays the crossover effect for decades. Moreover, age at first birth more than 35 years is associated with a permanent increased risk of breast cancer.⁷ The interaction between parity and breast cancer risk and the changing epidemiology of breast cancer require women's health clinicians to be well versed in the diagnosis and management of breast cancer in pregnancy and the postpartum period. Furthermore, clinicians must be knowledgeable about the nuances of breast cancer care in young women, including how it affects lactation and future fertility.

CATEGORIES OF BREAST CANCERS AND THERAPIES

Breast cancers can be categorized according to histology (ductal or lobular), receptor profile, and more recently gene expression analysis (Table 1).⁸ The major breast cancer subtypes are luminal A, luminal B, HER2-positive, and basal-like, which is also known as triple-negative breast cancer. Luminal A breast cancer is generally the least aggressive subtype, with low-grade estrogen receptor-positive, progesterone receptor-

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Table 1. Breast Cancer Subtypes

	Luminal A	Luminal B	HER2	Basal-like
Estrogen receptor	Strong positive	Positive	Positive or negative	Negative
Progesterone receptor	Strong positive	Positive or negative	Positive or negative	Negative
HER2	Negative	Negative	Positive	Negative
Grade	Low	Intermediate/high	Intermediate/high	High

positive tumors, whereas luminal B tumors have more aggressive features and can be progesterone receptor negative. All HER2-positive cancers overexpress the HER2-neu receptor but can be hormone receptor positive or negative. Basal-like cancers are the most aggressive subtype and are more common among young women with breast cancer.⁹ Breast cancers are treated with a combination of local and systemic therapies according to stage and subtype. Advances in our understanding of breast cancer genomics have led to different treatment strategies according to subtype and increasingly personalized cancer care.

Early-stage luminal-type cancers are typically managed with upfront surgery, either mastectomy or lumpectomy. Lumpectomy, also known as breast-conserving therapy, is paired with whole-breast radiation. Although sentinel lymph node biopsy is performed for staging purposes, axillary lymph node dissection is becoming less frequent as part of a broader trend of de-escalation stemming from the landmark ACOSOG (American College of Surgeons Oncology Group) Z0011 trial.¹⁰ Regardless of surgical approach, hormone-positive cancers are treated with adjuvant antiestrogen medications for a period of 5 to 10 years. The need for adjuvant chemotherapy is determined by genomic profiling with the OncotypeDX 21-gene recurrence score or other similar genomic tests. Cancers that also express HER2-neu are treated with either neoadjuvant or adjuvant trastuzumab, a humanized monoclonal mouse antibody that targets the HER2-neu receptor. In contrast, neoadjuvant chemotherapy is the standard of care for patients with locally advanced or inflammatory breast cancer, patients with triple-negative breast cancer, and a subset of patients with HER2-positive breast cancer. The benefits of neoadjuvant chemotherapy include downstaging breast tumor size to better facilitate breast-conserving therapy instead of mastectomy and downstaging of axillary disease to potentially allow less axillary surgery and to provide important prognostic information; residual tumor burden found at surgery is a negative prognostic indicator, whereas those who attain a pathologic complete response have better disease-free survival.¹¹ Immunotherapy with pembrolizumab

has demonstrated benefit in both early-stage and metastatic triple-negative breast cancer.¹²

Pregnancy-associated breast cancer has classically been defined as breast cancer diagnosed during pregnancy (also known as gestational breast cancer) and within the first 12 months postpartum. This classification led to conflicting epidemiologic data and obscured important differences in outcomes for patients with gestational and postpartum breast cancer.⁶ Early data suggested that gestational breast cancer was associated with worse clinical outcomes. After adjustment for age and prognostic factors, however, overall survival for pregnant women with breast cancer is comparable with that of nulliparous women.¹³ Women diagnosed with breast cancer within the first 5 years postpartum, however, exhibit a threefold increased risk of distant recurrence and death and significantly lower 5-year overall survival compared with nulliparous controls.^{6,14} As a result of these findings, there has been a push to regard gestational breast cancer and postpartum breast cancer as distinct clinical entities.^{6,15}

Although gestational breast cancer is rare, affecting 1 in 1,000 pregnancies, it is estimated that up to 35% of young women's breast cancer cases may be negatively affected by a pregnancy when cases up to 5 years postpartum are included in the definition of postpartum breast cancer.^{16,17} Here, we provide a narrative review of the diagnosis and management of breast cancer in young women with special attention to gestational breast cancer and postpartum breast cancer. It is important to note that although breast cancer more commonly affects women, not all gestating patients or patients with breast tissue identify as female.

DIAGNOSIS, MANAGEMENT, AND SPECIAL CONSIDERATIONS FOR YOUNG PATIENTS

Breast cancer in young women most commonly presents as a self-palpated mass. Initial workup includes a diagnostic mammogram and ultrasonogram followed by core needle biopsy. It is important to note that mammograms are less sensitive in young women because they tend to have more dense breast tissue, leading ultrasonography to generally be used as the



first-line imaging in this population. Although magnetic resonance imaging (MRI) is typically not indicated in the routine workup of all patients with breast cancer because of its high false-positive rate (the DENSE [Dense Tissue and Early Breast Neoplasm Screening] trial reported a false-positive rate of 79.8 in 1,000),¹⁸ it may be a useful adjunct in patients with very dense breast tissue or as part of screening protocols for women with germline mutations at high risk of breast cancer.¹⁹ All women diagnosed with breast cancer before age 65 years should undergo genetic testing; approximately 10% of young women with breast cancer have pathogenic/likely pathogenic *BRCA* mutations.^{20,21}

Among pregnant women, 80% of breast lesions are benign but should nonetheless be evaluated with ultrasonography of the breast and axilla followed by percutaneous biopsy as indicated.²² Although mammography is safe to perform with fetal shielding,²³ MRI with gadolinium contrast is relatively contraindicated given concerns about concentration of gadolinium in the fetal compartment. Evaluation for distant metastasis can be accomplished with chest radiograph, liver ultrasonogram, and noncontrast skeletal MRI. Similar to nonpregnant women diagnosed before age 35 years, women with gestational breast cancer are more likely to have hormone receptor-negative disease.²⁴ Although women with gestational breast cancer are more likely to have pathogenic germline mutations because of their young age, germline mutations do not appear to increase the risk of gestational breast cancer, and pregnancy is not associated with worse outcomes among women with *BRCA* mutations.²⁵

Treatment algorithms in the pregnant patient should involve a multidisciplinary team and should be informed by tumor biology, stage, gestational age, and patient preferences about continuing the pregnancy. There are no data to suggest that pregnancy termination improves maternal outcomes, and women should be counseled that chemotherapy and surgery are safe during pregnancy.²² Generally speaking, breast surgery is safe at any gestational age, but surgical planning must account for the fact that radiation, a necessary component of breast conservation, is contraindicated in pregnancy. For example, in patients without locally advanced disease diagnosed in the first trimester, mastectomy may be preferred over breast-conserving therapy given the necessary delay in radiation administration (Fig. 1, similar to Loibl et al²⁶). Axillary staging can be safely accomplished with technetium (Tc-99m), but blue dye is contraindicated in pregnancy. Although reconstruction with tis-

sue expanders is safe and feasible, it is typically deferred until the postpartum period to decrease total surgical time.

Given the frequency of hormone receptor-negative disease in gestational breast cancer, the maternal-fetal safety profile of systemic therapy is of particular importance. Although most of the safety data on antenatal chemotherapy are limited to multicenter cohorts and case-control studies, anthracyclines, taxanes, and cyclophosphamide are considered relatively safe to administer beginning in the second trimester.^{22,26} Antenatal fetal growth monitoring is recommended because of the association of some chemotherapies with fetal growth restriction and small for gestational age.²⁷

Chemotherapy administration is not recommended after 34 weeks of gestation, and when possible, delivery should be avoided in the 3 weeks after the last cycle of chemotherapy to minimize the risk of infection attributable to maternal neutropenia.²⁸ Whenever possible, delivery should be delayed until the late-preterm or early-term period of gestation. Vaginal delivery is preferred; cesarean delivery should be considered only for routine obstetric indications.²⁹ Although chemotherapy should not be delayed after the first trimester as a result of pregnancy, diagnosis after 34 weeks of gestation should prompt multidisciplinary discussion of the risks and benefits of late-preterm compared with early-term delivery after workup and staging to facilitate initiation of treatment.

The safety data for targeted therapies are considerably more limited. After the OlympiA (Olaparib as Adjuvant Treatment in Patients With Germline *BRCA* Mutated High Risk HER2 Negative Primary Breast Cancer) trial, the use of poly(ADP-ribose) polymerase inhibitors has expanded from their use in the setting of metastatic disease to now include adjuvant therapy in early-stage breast cancers with germline *BRCA* mutations.^{30,31} As a result, more individuals with young women's breast cancer are potential candidates for poly(ADP-ribose) polymerase inhibitors. Because of the lack of clinical data in pregnant women and pre-clinical data suggesting deleterious effects on embryo fertilization and implantation, as well as fetal organogenesis, poly(ADP-ribose) polymerase inhibitors are contraindicated in pregnancy, and women of childbearing age are advised to use reliable contraception before the initiation of treatment.²¹ Trastuzumab, which targets HER2, is contraindicated in pregnancy because of its association with fetal and neonatal renal failure, oligohydramnios, and congenital pulmonary malformation.³² Endocrine therapy with tamoxifen

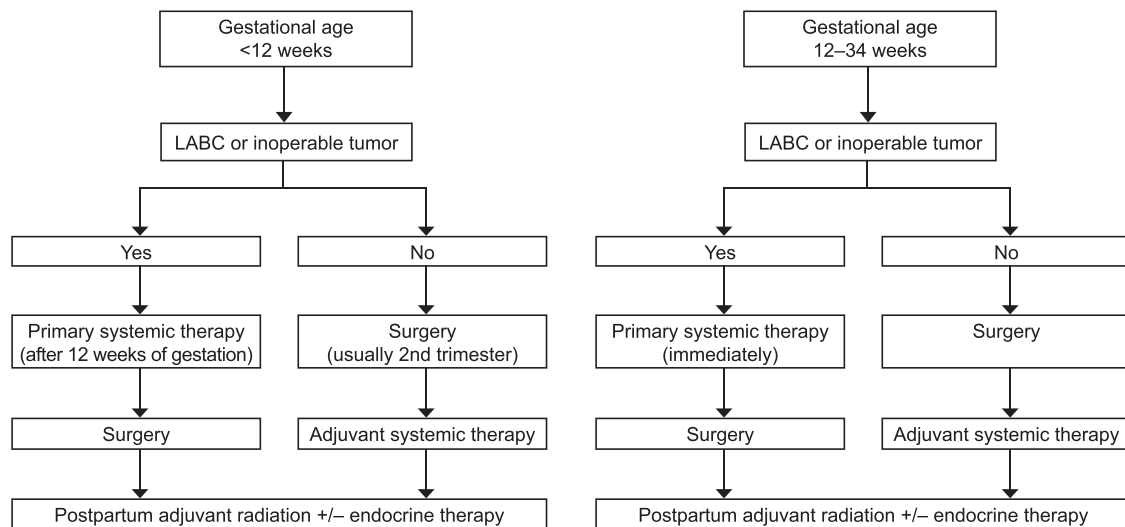


Fig. 1. Treatment algorithm for gestational breast cancer. LABC, locally advanced breast cancer. Data from Loibl et al.²⁶ *Labora. Breast Cancer Care for Women of Childbearing Age. Obstet Gynecol* 2026.

is also contraindicated in pregnancy as a result of its association with congenital anomalies and spontaneous abortion.²⁶

Postpartum Breast Cancer

Multiple studies, including two large meta-analyses, have demonstrated that women diagnosed with postpartum breast cancer have an increased risk of mortality compared with women with gestational breast cancer and nulliparous controls.^{6,7,33,34} Both Hartman et al³⁴ and Callihan et al⁶ found that the highest risk occurs within the first 5 years postpartum. Callihan et al additionally reported a threefold increased risk of distant recurrence in postpartum breast cancer cases, which may explain the higher risk of death. This finding was later replicated by Goddard et al,³³ who found that the risk of distant metastatic disease persists for up to 10 years. Given the overlap between younger age and pregnancy, it has been hypothesized that the worse outcomes in postpartum patients is attributable to the more aggressive tumor biology seen in young women, in particular triple-negative disease. However, Surveillance, Epidemiology, and End Results data demonstrate that the 1.62-fold increase in young women's breast cancer cases since 2000 can be attributed exclusively to estrogen receptor-positive disease.⁴ Taken together, these epidemiologic data implicate factors unique to the postpartum breast microenvironment.⁷

Work by Jindal et al³⁵ demonstrated that estrogen receptor-positive postpartum breast cancer has a distinct molecular profile associated with decreased 15-year overall survival in a young women's breast can-

cer cohort compiled from gene expression data from seven previously published studies. This postpartum breast cancer signature was found to be distinct from nulliparous breast cancer and associated with T-cell exhaustion, reduced TP53 activity, and reduced estrogen receptor signaling despite strongly positive immunohistochemical staining.³⁵ They hypothesized that T-cell exhaustion and reduced TP53 activity may reflect normal mammary gland involution biology, a developmentally regulated period of apoptosis and tissue remodeling after cessation of lactation that resembles wound healing.³⁵ The hypothesis that mammary gland involution generates a proinflammatory microenvironment was corroborated by Schedin et al.^{17,36,37}

Although there are no validated tools to identify women at high risk of developing postpartum breast cancer, advances have been made in the detection of postpartum breast cancer through breast milk.³⁸ Saura et al³⁸ demonstrated that cell-free tumor DNA can be detected in the breast milk of patients with early-stage breast cancer and that this cell-free tumor DNA recapitulates tumor variants with a sensitivity of 71.4% and specificity of 100%. Remarkably, in two cases, cell-free tumor DNA was detectable before radiologic evidence of disease. These data raise the exciting possibility of a noninvasive screening method for breast cancer in the high-risk postpartum period.

Lactation and Breast Cancer

The current evidence that postlactation weaning results in a protumorigenic and prometastatic microenvironment adds complexity to the question of how

lactation modifies breast cancer risk. Although high-quality epidemiologic data demonstrated that the relative risk of breast cancer was significantly reduced by breastfeeding,³⁹ postpartum breast involution appears to confer increased risk for a brief period of time. It may be that, like pregnancy, lactation has a dual effect. The benefits of breastfeeding are time dependent; for every 12 months of breastfeeding, the relative risk of breast cancer decreases by 4.3%. Although the American Association of Pediatrics recommends exclusive breastfeeding for the first 6 months of life because of the well-substantiated infant health benefits,⁴⁰ only approximately 50% of women in the United States report breastfeeding at 6 months. As a result, a minority of American women breastfeed long enough to benefit from the cancer risk reduction associated with breastfeeding.⁴¹ It is unknown how duration of breastfeeding or duration of weaning, whether gradual or sudden, affects the breast involution microenvironment or augments breast cancer risk.

Given the health benefits to women and infants, it is important to address how lactation is affected by a new breast cancer diagnosis and a history of breast cancer treatment. Palpable breast masses in lactating women should be evaluated initially with ultrasonography, and core needle biopsy should be performed as indicated given the exceedingly low risk of milk fistula.⁴² In terms of diagnostic imaging, mammography, MRI with gadolinium, computed tomography with intravenous contrast, and nuclear medicine studies are safe to perform during lactation, although the last may require brief separation of mother and infant because of organ radioactivity.⁴² Lactating women diagnosed with breast cancer will need support from a lactation expert such as an international board-certified lactation consultant or breastfeeding medicine physician whether they intend to continue breastfeeding or plan to wean. Women who plan to wean should taper the frequency of milk expression to reduce complications such as mastitis and may benefit from pharmacologic interventions to assist with weaning.⁴² Given that undesired weaning can have negative effects on mental health, they should also be offered psychosocial support.⁴³

Women who desire to continue breastfeeding during or after treatment can do so with appropriate counseling and support. Weaning is not necessary before surgical resection, but for women who desire continuous breastfeeding, it is recommended to avoid a periareolar incision if appropriate from an oncologic perspective because damage to the subareolar region can sever terminal ducts, cause milk outflow obstruc-

tion, and potentially impair the milk ejection reflex.⁴² Ideally, the incision should also be placed where it will not come into contact with a breast pump flange. Women should be informed that breastfeeding can be continued regardless of surgical approach by nursing from the unaffected breast⁴⁴ and that it is possible to produce enough milk to exclusively breastfeed from one breast.⁴⁵ Similarly, breastfeeding from the unaffected breast can continue during radiation therapy, but future lactation from the treated breast can be significantly impaired by radiation therapy.⁴⁵ Although lactation is contraindicated during chemotherapy administration, women who desire to continue breastfeeding can work with a lactation expert and continue expressing and discarding milk to maintain supply, but they should be counseled about the potential risk of mastitis in the setting of neutropenia and the possibility that chemotherapy administration may impair lactation.⁴²

Fertility Considerations

The question of how a breast cancer diagnosis and subsequent treatment will influence fertility is of great concern to many individuals with young women's breast cancer.⁴⁶ The American Society of Clinical Oncology guidelines recommend that all women be offered counseling about fertility preservation at the time of diagnosis and as part of survivorship care, but despite significant patient interest, only a minority of patients with young women's breast cancer choose to access fertility preservation services at the time of a new diagnosis.^{47,48} An important part of that counseling is to inform women that cytotoxic chemotherapy, in particular alkylating agents, is associated with risk of infertility and premature ovarian insufficiency.⁴⁸ The effects of targeted therapies on fertility are less well understood. No trials investigating CDK4/6 inhibitors, poly(ADP-ribose) polymerase inhibitors or immunotherapy have prescribed ovarian function end points.²¹ Preclinical data on poly(ADP-ribose) polymerase inhibitors suggest that they are toxic to primordial follicle oocytes, reduce in vitro fertilization rates, and accelerate age-related oocyte decline in *BRCA* mutation carriers.²¹ The potential adverse effects of poly(ADP-ribose) polymerase inhibitors in *BRCA* mutation carriers are of particular interest given their expanded use in early-stage breast cancer in this population and the reported effect of deficient *BRCA* function on ovarian reserve.⁴⁹ Biomarker analysis of women younger than age 45 years from the NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial suggested a possible short-term gonadal effect of anti-HER2

therapy as measured by anti-müllerian hormone levels, but little is known about their effect on ovarian reserve.⁵⁰

Given that oocyte and embryo preservation entails ovarian stimulation, the oncologic safety of assistive reproductive technology (ART) in the setting of breast cancer is of particular concern. A meta-analysis of 11 studies found that neither ovarian stimulation for cryopreservation before treatment nor ART after treatment was associated with increased risk of recurrence, even among women with hormone-positive breast cancers.⁵¹ For women with hormone receptor–positive breast cancers, the addition of letrozole to ovarian stimulation protocols has been proposed as a protective intervention to avoid the substantial estrogen spike associated with conventional protocols. A multicenter retrospective study of two oncofertility centers in Europe compared letrozole-associated ovarian stimulation with conventional ovarian stimulation protocols and reported no differences in disease-free survival or total number of mature oocytes obtained during the 2-year follow-up period.⁵² The letrozole-associated ovarian stimulation protocol was associated with significantly higher rates of oocyte maturation, but the clinical relevance of this finding is unclear because live birth rates were not reported.⁵²

A 2025 Cochrane review seeking to determine the safety and effectiveness of the two main fertility preservation strategies in premenopausal women with breast cancer undergoing chemotherapy—ovarian stimulation with gonadotropins plus a protective agent (letrozole vs tamoxifen) and ovarian suppression during chemotherapy with gonadotropin-releasing hormone (GnRH) agonists—evaluated 23 randomized controlled trials (2,647 women) and rated the certainty of evidence to be very low to moderate. The authors found that ovarian suppression with GnRH agonists may result in a large reduction of ovarian insufficiency but rated the effect on live birth rates as “very uncertain.”⁵³

More recently, prospective data from the POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer) trial showed that women with hormone-positive cancers who underwent fertility preservation at the time of diagnosis did not have higher recurrence rates compared with women who did not undergo ovarian stimulation with a median follow-up period of 41 months.⁵⁴ Concurrent GnRH antagonist administration during chemotherapy was not reported to influence pregnancy rates in the POSITIVE trial.^{54–56} For patients desiring fertility preser-

vation who are unable or unwilling to delay chemotherapy, a fertility preservation cycle can be performed between chemotherapy cycles to limit the cumulative effects of chemotherapy on ovarian reserve. However, the fertility potential of oocytes recently exposed to chemotherapy and the health implications for future offspring are unknown.⁴⁸

After surgery and radiation treatment, women with hormone-positive breast cancers are recommended to take endocrine therapy for 5 to 10 years. Endocrine therapy is contraindicated during pregnancy, and these years often correspond to peak fertile years in individuals with young women's breast cancer. Therefore, it is important that women of childbearing age undergoing breast cancer treatment receive counseling on reliable contraception. Recent data from the POSITIVE trial demonstrated that after the first 18 to 30 months of endocrine therapy, it is safe to interrupt endocrine therapy in women with hormone-positive breast cancer for up to 2 years to pursue pregnancy.⁵⁷ The trial additionally found that pregnancy rates were highest in younger women (younger than age 35 years) and among women who used previously cryopreserved embryos.⁵⁴ That being said, pregnancies were observed among older women (cumulative incidence of 37.7% at 1 year among women aged 40–42 years), and the overall pregnancy rate with in vitro fertilization was 68%.⁵⁴ Of the 507 pregnancies that occurred in the POSITIVE trial, there were 350 live births (69.0%), including 323 full-term pregnancies (63.7%) and 27 preterm live births (5.3%). Fortunately, the safety of pregnancy after a cancer diagnosis has also been reported in patients with germline *BRCA* mutations and in patients with pregnancy-associated breast cancer.^{58,59}

CONCLUSION

Breast cancer in young women raises unique considerations for both patients and clinicians. As women continue to delay childbearing, the incidence of these cancers during pregnancy and the postpartum period will continue to rise. Fortunately, our understanding of these subtypes of breast cancer has advanced significantly. It is now known that chemotherapy and surgery are safe during pregnancy and that pregnant women with breast cancer have oncologic outcomes equivalent to those of nonpregnant women when they are treated according to standard of care. Furthermore, breastfeeding can be safely continued during treatment with appropriate counseling and guidance from a breastfeeding medicine expert. Postpartum breast cancer, on the other hand, has higher rates of metastatic disease and mortality because of its

unique pathogenesis rooted in mammary involution. For individuals with young women's breast cancer who desire future fertility, ovarian stimulation is safe both before and after treatment. Furthermore, as a result of the POSITIVE trial, there are more data to guide women who desire to interrupt endocrine therapy to conceive after treatment. Despite these advances, there are considerable knowledge gaps. Given the apparent dual effect of lactation on breast cancer risk, future research is needed to identify the patients at highest risk and possible modifiable risk factors, including length of breast feeding and duration of weaning.

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