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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breastfeeding and Breast Cancer: Managing Lactation in Survivors and Women with a New Diagnosis

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ABSTRACT

Background. Supporting breastfeeding is a global health priority, yet few clinical guidelines exist to guide surgical oncologists in managing lactation during or after breast cancer treatment.

Methods. The literature was reviewed to identify evidence-based strategies for managing lactation during multidisciplinary breast cancer treatment or among breast cancer survivors.

Results. The majority of the evidence is from observational studies, with some higher levels of evidence, including systematic reviews and meta-analyses. Several significant gaps in knowledge remain.

Conclusions. This review serves as a comprehensive resource of evidence-based recommendations for managing lactation in breast cancer survivors and breastfeeding women with a new breast cancer diagnosis.

The relationship between breastfeeding and breast cancer is multifaceted. While a longer duration of breastfeeding is associated with multiple health benefits and a decreased lifetime risk of breast cancer, postpartum women are at risk for particularly aggressive breast cancers.[1–3] A growing body of evidence supports several hypotheses regarding the biologic mechanisms underlying these observations.[4] However, a paucity of literature exists to guide clinical management of lactation during or after breast cancer treatment. As national and global health initiatives improve breastfeeding rates, surgeons increasingly will be faced with managing the intersection of lactation and breast cancer treatment.[5,6]

This review will delineate evidence-based recommendations for managing lactation in breast cancer survivors and breastfeeding women with a new breast cancer diagnosis. Nearly all of the available evidence comes from observational studies (Table 1), and there are multiple gaps in knowledge. Recommendations should be utilized in the context of shared decision-making with the patient, including discussion of the limitations of the available data.

SUPPORTING LACTATION IN BREAST CANCER SURVIVORS

Due to the anatomic and physiologic impacts of their cancer treatment on lactation, breast cancer survivors who wish to breastfeed may face challenges. Support is essential, because the inability to produce sufficient breastmilk has been shown to be independently associated with significant long-term psychological stress among women diagnosed with breast cancer and other cancers during pregnancy.[7] Survivors may benefit from an antepartum visit with an International Board Certified Lactation Consultant (IBCLC) and/or breastfeeding medicine physician, as well as close postpartum support.[8,9] These women may derive significant psychosocial value from tailored peer-to-peer support groups; if none exist, they may find some overlap between their unique challenges and those of women who are breastfeeding after breast reduction surgery.[10]

Although multiple survey studies report that many breast cancer survivors fear that breastfeeding increases the risk of recurrence or a new primary breast cancer, no evidence exists to support this concern.[11–14]

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TABLE 1 Major sources, with levels of evidence, for key recommendations for lactation management strategies during multidisciplinary breast cancer care

	Recommendation	Source	Level of evidence
General considerations	Breastfeeding is protective against breast cancer, independent of the effect of parity on cancer risk	Collaborative Group on Hormonal Factors in Breast Cancer[2]	Meta-analysis
Imaging	Ultrasound should be the first-line imaging modality for lactating women with a breast mass	diFlorio-Alexander et al.[34]	Expert consensus guidelines
	Lactation-related changes on breast magnetic resonance imaging do not preclude detection of breast lesions	Espinosa et al.[39] Oh et al.[40]	Retrospective descriptive studies
Breast conservation therapy (BCT): lumpectomy and radiation	BCT impairs future lactational ability in most women, via both anatomic and histopathologic effects	Leal et al.[17]	Systematic review
Chemotherapy	Breastfeeding is contraindicated during chemotherapy, with rare exceptions	Pistilli et al.[44]	Narrative review
	It may be possible to safely breastfeed between cycles in some cases	Anderson[49]	Expert opinion
	Breastfeeding success may be diminished in women who receive chemotherapy during pregnancy	Stopenski et al.[24]	Prospective cohort study
Endocrine therapy	Aromatase inhibitors are contraindicated in lactation	The InfantRisk Center[25]	Expert opinion
	It may be safe to defer or interrupt tamoxifen therapy to complete breastfeeding	Cardoso et al.[28]	Expert consensus guidelines
		POSITIVE trial (NCT02308085) https://clinicaltrials.gov	Randomized clinical trial (in recruitment phase)
Radiation therapy (RT)	Breastfeeding during RT may increase the risk of skin toxicity	Shachar et al.[64]	Expert opinion
	Irradiated breasts may produce milk with altered biochemical composition	Green[22]	Case report
		Guix et al.[23]	Case report
Surgery	A full milk supply can be achieved and maintained by a single breast	Michaels and Wanner[15]	Observation
	Lactating women undergoing breast surgery appear to have similar risks of wound complications as non-lactating women	Dominici et al.[52]	Retrospective cohort study
	An interruption in breastfeeding of up to 24 h may be advisable after dual-tracer sentinel lymph node biopsy	The InfantRisk Center[25]	Expert opinion
		Giammarile et al.[57]	Expert consensus guidelines
	Patients may benefit from perioperative lactation support programs	Rieth et al.[62]	Retrospective descriptive study

History of Mastectomy

Due to removal of the breast parenchyma, lactation would not be expected on the affected breast after a simple, skin-sparing, or nipple-sparing mastectomy. Women who have undergone mastectomy should be counseled that unilateral breastfeeding can produce milk sufficient for not only a singleton infant, but also for twins.[15] Patients may benefit from antenatal hand expression as well as post-feed milk expression (hand expression and/or pumping) to upregulate milk production in the early postpartum period.[16] To prevent nipple trauma that could impact lactation on a single breast, optimal infant latch should be achieved.

History of Breast Conservation Therapy (BCT): Lumpectomy and Radiation Therapy

A systematic review concluded that patients who have undergone breast conservation therapy (BCT) may later produce milk, but volume is significantly reduced in the majority of cases.[17] Both surgery and radiation can impact lactational ability (Fig. 1).

Surgery involving the subareolar region may sever terminal ducts and obstruct outflow of breastmilk. Additionally, periareolar incisions may impact nipple innervation and potentially affect the milk ejection reflex and regulation of milk production.[18] Rodent models have

demonstrated recanalization of ducts, and anecdotal evidence supports both recanalization and reinnervation after nononcologic breast surgery; however, the effects of radiation likely prevent these phenomena after BCT.[19]

Histopathologically, irradiated breasts exhibit epithelial atypia in the terminal ductal-lobular units, atypical stromal fibroblasts, fibrosis with or without atrophy, and nonspecific vascular changes; these changes appear to be irreversible.[20,21] Decreased nipple-areolar complex (NAC) elasticity and radiation-induced changes in milk composition, including increased sodium levels, may result in a strong infantile preference for the unaffected breast.[17,22,23]

Chemotherapy

Chemotherapy may cause irreversible histopathologic changes that impact breastmilk production.[21] An observational cohort study reported that among women treated for cancer during pregnancy, those who received chemotherapy reported a significantly lower rate of breastfeeding success (34% vs. 91%), particularly if they underwent more cycles (5.5 vs. 3.8).[24] Women who initiated chemotherapy earlier in gestation reported significantly more difficulties, potentially suggesting a negative effect on lactogenesis I in this population.

Endocrine Therapy

After the completion of other therapies, breast cancer patients with hormone receptor-positive tumors will be prescribed endocrine therapy. Aromatase inhibitors (AIs) are contraindicated in lactation, because they readily transfer into breastmilk and can suppress estrogen formation in the infant.[25] There are no data on the transfer of tamoxifen into breastmilk. Tamoxifen is known to inhibit lactogenesis II, but its effects on established milk production are unknown.[26,27] The European Society of Breast Cancer Specialists advises that tamoxifen therapy may be interrupted for pregnancy and/or breastfeeding.[28] Results of the Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer (POSITIVE) trial will provide much-needed data on this topic.[29] This study seeks to enroll 500 women from age 18–42 years who have completed 18–30 months of endocrine therapy; it will allow for an interruption in therapy of up to 2 years for pregnancy and/or breastfeeding. Preliminary results for the primary outcome of breast cancer free interval are anticipated in June 2020.

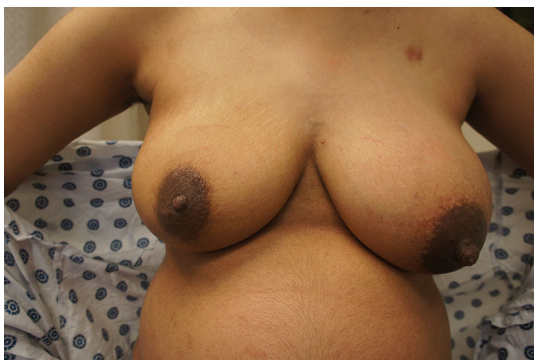

FIG. 1 Decreased lactational ability following breast conservation therapy. A 28-year-old patient status postneoadjuvant chemotherapy and breast conservation therapy for right breast triple-negative cancer diagnosed 2 years prior. At 28 weeks of pregnancy, reduced breast growth was noted on the affected side, consistent with decreased lactational ability

MANAGING LACTATION IN BREASTFEEDING WOMEN WITH A NEW BREAST CANCER DIAGNOSIS

Lactating women diagnosed with breast cancer will require support whether they continue to breastfeed during treatment or actively wean. Therefore, the multidisciplinary treatment team should include a lactation expert, such as an IBCLC and/or a breastfeeding medicine physician. In many cases, the patient must wean earlier than she and her child(ren) desire. Because undesired weaning can significantly impact the mother's mental health, psychosocial support is essential.[30] To minimize the risks of plugged ducts and mastitis, women should taper the frequency of breastfeeding and/or milk expression. They may require herbal and/or pharmacologic interventions to promote weaning, such as sage, peppermint oil, pseudoephedrine, or cabergoline.[31]

Radiologic Evaluation

Radiologic studies and interventions necessary at time of diagnosis are not contraindicated with breastfeeding. Milk fistula resulting from core-needle biopsy is rare and described on a case-report level.[32,33] The American College of Radiology recommends ultrasonography as the first-line diagnostic imaging modality in breastfeeding women with a palpable mass, and digital breast tomosynthesis is the preferred adjunct.[34] Mammography (Fig. 2) and breast magnetic resonance imaging (MRI) with intravenous gadolinium contrast (Fig. 3) are safe in lactation.[35,36] The sensitivity of mammography is decreased due to increased parenchymal density of lactating breasts, which can be partially ameliorated by breastfeeding or pumping immediately before the exam.[37] On MRI, lactating breasts demonstrate increased background parenchymal enhancement due to physiologic hypervascularity and diffusely increased T2 signal from

milk.[38] Despite these limitations, multiple reports document the diagnostic accuracy of MRI in the setting of lactation.[39,40]

Nuclear medicine staging studies, such as bone scintigraphy and positron emission tomography (PET), utilize radioisotopes that are not excreted in breastmilk. However, radioactivity of organs may require brief separation of the mother and child; providers should consult their local nuclear medicine department as well as refer to International Commission on Radiological Protection (ICRP) guidelines related to specific studies and isotopes.[41,42] It should be noted that due to the hypermetabolic nature of the lactating breast, additional areas of enhancement demonstrated on PET may require further workup and biopsy (Fig. 4). Computed tomography with intravenous iodinated contrast is safe in lactation and does not require interruption of breastfeeding.[43]

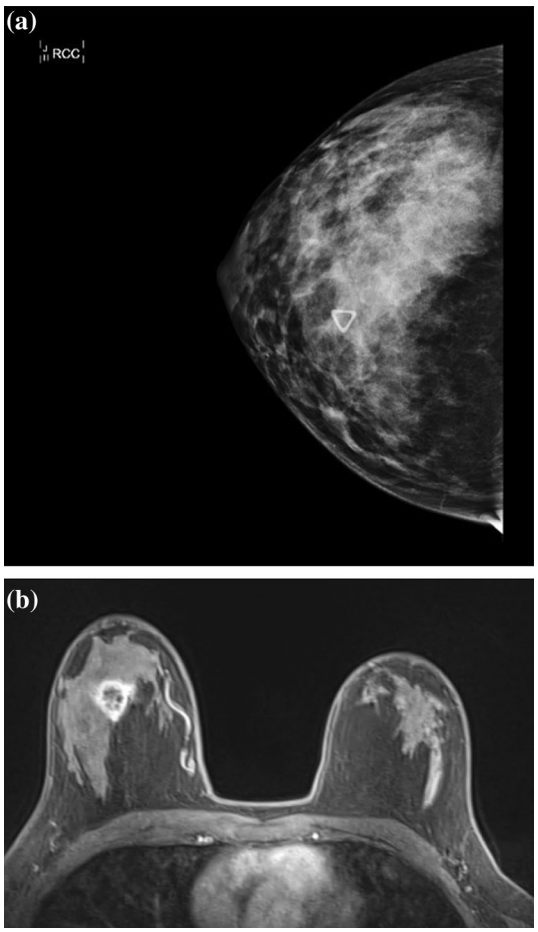

FIG. 2 a Extremely dense lactating breast tissue may obscure mammographic detection of a mass. Right mammogram of a 38-year-old patient with right breast cancer and deleterious BRCA mutation diagnosed at 7 months postpartum. **b** Supplemental imaging modalities may facilitate identification of postpartum breast cancers. Breast magnetic resonance imaging of the same patient demonstrating the right breast mass

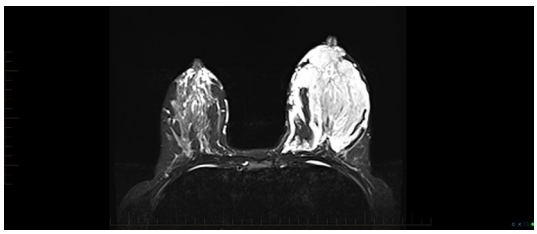

FIG. 3 Lactating breasts have high background enhancement on breast magnetic resonance imaging. Breast MRI obtained for extent of disease in a patient with new diagnosis of left breast cancer in an actively lactating breast. The patient had weaned on her right breast due to recurrent mastitis, demonstrating the difference in background enhancement of a lactating versus nonlactating breast

Chemotherapy

Because postpartum breast cancers demonstrate increased virulence and propensity for metastatic spread and may present at a locally advanced stage, many cases will benefit from neoadjuvant chemotherapy.[3]

Breastfeeding while receiving cytotoxic chemotherapy for breast cancer is contraindicated. A 2013 review details the level of evidence for each of the major classes of chemotherapeutic agents and describes a long half-life and a high rate of transfer from plasma to breastmilk of several agents commonly administered to breast cancer patients, including doxorubicin and cisplatin.[44] Carboplatin and paclitaxel readily pass into breastmilk and are associated with significant relative infant doses of these medications.[45] Infantile neutropenia was demonstrated several days after breastfeeding with maternal receipt of cyclophosphamide.[46,47] No human data exist on anti-HER2 targeted agents during lactation. Despite the likelihood that a monoclonal antibody will have minimal excretion into breastmilk, trastuzumab and pertuzumab are nearly always administered in combination with other agents that are

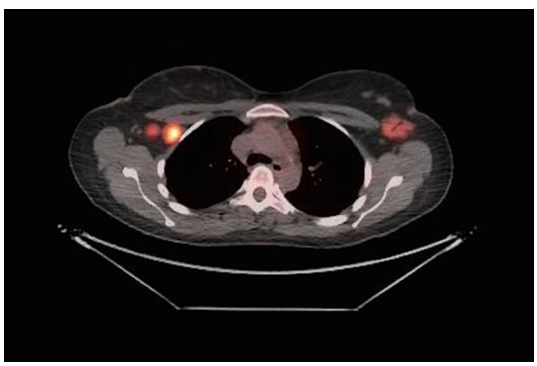

FIG. 4 Hypermetabolic activity from lactating breasts on positron emission tomography (PET) may prompt additional evaluation. PET CT performed on a lactating patient with a right breast cancer with hypermetabolic activity in the left axillary tail, with biopsy showing lactational change and resolution on follow-up surveillance imaging

considered unsafe in lactation.[25] As breast oncologic care continues to evolve and new agents are introduced, physicians may refer to the National Institute of Health's LactMed® database, a continually updated online resource addressing the safety of pharmaceuticals in lactation.[48]

Patients who indicate interest in maintaining milk production during chemotherapy via expressing and discarding milk should be counseled about the risks of mastitis and other complications in the setting of neutropenia and also be advised that chemotherapy likely impairs lactation, as discussed above. It may be possible for some women to breastfeed safely between chemotherapy cycles; a waiting period of five serum half-lives of the agent or metabolite with the longest half-life is advised.[49] However, this practice may result in alterations of both the microbiome and metabolome of breast milk.[50]

Surgery

General Considerations Theoretical risks exist regarding increased wound complications in the lactating breast, including bleeding related to hypervascular parenchyma, wound infections due to the presence of microbes in breastmilk, and milk fistulae. No data support additional antibiotic prophylaxis above current practice; in fact, the antimicrobial components of breastmilk may confer natural protection against wound infections.[51] A cohort study of patients diagnosed with breast cancer during pregnancy showed an overall wound complication rate of 9%, consistent with rates observed in the general population of breast cancer surgery patients.[52] None of the patients developed a milk fistula. Antepartum versus postpartum surgical treatment and total versus partial mastectomy had no impact on complication rates.

No consensus exists regarding optimal timing of surgery following weaning. While post-lactational involution has been well-studied in murine models, it is unknown whether the same events occur similarly in humans. Although many women report minimal milk production and high levels of epithelial apoptosis are observed 6 weeks after weaning, limited evidence suggests that human mammary involution is not complete until 12–18 months after the cessation of lactation.[53] Overall, the weaning process should not delay oncologic surgery.

Breast Surgery Some women diagnosed with breast cancer during lactation will require a mastectomy. Women who present with early-stage disease and some who demonstrate excellent clinical response to neoadjuvant chemotherapy may be candidates for breast conservation therapy (BCT). Regardless of surgical approach, unilateral breastfeeding from the unaffected breast will not interfere with breast cancer treatment. Women should be counseled to increase the frequency and duration of breastfeeding on the unaffected breast while gradually decreasing the frequency and completeness of emptying the affected breast. If the patient desires uninterrupted breastfeeding or milk expression on the affected breast, we recommend avoiding a periareolar incision and ensuring the incision will not contact breast pump flanges.

Axillary Staging There are no data on the transfer of vital dyes such as methylene blue or isosulfan blue into breastmilk, nor on their oral bioavailability. Some sources advise a 24-h interruption in breastfeeding after intravenous administration of methylene blue, but no recommendations for intradermal administration exist.[25] Although specific doses of intravenous methylene blue can be safely administered to infants to treat acquired methemoglobinemia, several case reports document life-threatening neonatal toxicity from enteral administration.[54–56] While no data on the lactational safety of intradermal injection of radiotracers for sentinel lymph node biopsy exist, some societies suggest a 24-h interruption in breastfeeding.[57] A 0–12 h interruption is recommended after *intravenous* administration of technetium-99-labeled radiotracers, supporting that a 24-h interruption after intradermal injection fits well within the recommended safety range for this clinical scenario.[42]

Contralateral Surgery The National Comprehensive Cancer Network (NCCN) recommends contralateral prophylactic mastectomy (CPM) versus high risk imaging surveillance for some high-risk patients, including those with deleterious BRCA mutations.[58] Therefore, an aggressive surveillance regimen may be utilized and risk-reduction surgery delayed until after child bearing is complete. Patients without an oncologic indication for risk-reduction surgery who express interest in a CPM should be counseled that while CPM decreases the incidence of breast cancer, a Cochrane review concluded that insufficient evidence exists to determine whether this translates to a survival benefit.[59] In addition, CPM has been well documented to increase the risk of surgical complications.[60,61] Furthermore, the relative reduction in breast cancer risk conferred by prophylactic mastectomy versus breastfeeding and chemoprevention remains unknown.

Perioperative Considerations Women undergoing breast cancer surgery will derive significant benefit from a comprehensive perioperative lactation support program.[62] The Academy of Breastfeeding Medicine outlines recommendations for individualized perioperative lactation plans.[63] Appropriate medication selection, judicious fluid management, and allowing for direct

breastfeeding or milk expression in the recovery room can minimize the risk of mastitis and unnecessary interruptions in lactation.

Adjuvant Therapy: Radiation and Endocrine Therapy

Women electing to continue lactation and who require adjuvant radiation therapy likely will be breastfeeding solely from the unaffected breast at the time of radiotherapy. As external beam radiation fields are restricted to the affected breast and/or ipsilateral regional lymph node basins, no impact on the contralateral lactating breast is expected. Patients who desire to breastfeed from the affected breast during radiation therapy should be advised that radiation-induced histopathologic changes described above may increase the risk of complications, such as mastitis, which may interrupt and delay completion of therapy.[20,21] One consensus panel advises against breastfeeding during radiation treatment due to concerns about increased risk of skin toxicity.[64] Additionally, skin and NAC changes may make infant latch and milk expression difficult, potentially predisposing the mother to skin breakdown and infection. While a postpartum breast cancer patient likely would not qualify for partial breast radiation, we recommend careful multidisciplinary management if this approach is considered and continued breastfeeding is desired.

If a woman has continued lactation throughout breast cancer treatment and meets criteria for adjuvant endocrine therapy, a nuanced discussion with the patient is indicated, with consideration given to issues discussed above.

CONCLUSIONS

Lactating women diagnosed with breast cancer and breast cancer survivors who wish to breastfeed constitute a vulnerable population that requires unique clinical support from oncologic multidisciplinary teams as well as lactation experts. While the body of literature on the intersection of breastfeeding and breast cancer has grown in recent years, much remains to be determined. In addition to the areas that warrant additional study described above, a particularly intriguing topic is the suitability of breastmilk as a biospecimen. Because epithelial cells, including those from the terminal lobular-ductal unit, are shed into breastmilk, analysis of breastmilk may facilitate an improved understanding of carcinogenesis.[65] As suggested by Murphy and colleagues, a breastmilk repository would enable more robust research that may translate into meaningful clinical impacts.

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