**Background**

African American women experience higher rates of breast cancer mortality than white American women (DeSantis et al. 2017). This disparity is exceptionally pronounced in premenopausal women (Chollet-Hinton et al. 2017). Premenopausal women of African ancestry in America not only face higher death rates than women of European ancestry, but are also diagnosed with more lethal forms of breast cancer more often. One prognostic for lethality is the subtype of breast cancer by hormone receptivity: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). ER+, PR+, and HER2+ breast cancers are the most common diagnoses in American women. While the incidence of these subtypes of breast cancer are increasing at the population level, mortality rates have been decreasing dramatically due to improvements to screening, treatment, and prevention management. However, the improved health outcomes have not followed for non-hormone receptor positive types of breast cancer. An especially poor prognosis follows a woman with Triple Negative Breast Cancer (TNBC), a highly lethal cancer of the breast without any hormone receptivity. Regarding the black/white disparity in breast cancer, African American women between the ages of 30-50 face high significantly higher rates of TNBC than white women (Sturtz et al. 2014). It is this young group of African American women that bears the highest burden of the racial breast cancer disparity. And, while the overall disparity in breast cancer mortality can be attributed to a variety of genetic, societal, and behavioral conditions, the TNBC disparity between young black and white women is highly driven by epigenetic factors (Daly and Olopade 2015).

Considerable research has been dedicated to the epigenetic and molecular mechanisms for TNBC (Jiagge, Chitale, and Newman 2018; Davis and Newman 2018). Motivated by the evidence showing a strong relationship with a woman’s reproductive life, the following review explores the prospect of differences in patterns of breast-feeding as a determinant of TNBC disparities (Ambrosone et al. 2015; Ritte et al. 2013). But first, a brief discussion on the current research identifying racial gaps in breast feeding and an overview of existing literature on the role of breast feeding in other types of cancer. Through a mix of survey and administrative data, researchers have discovered significant differences in breast feeding patterns between black and white mothers. While 80% of white mothers initiated breast feeding, less than 60% of black women did so with their child (Jones et al. 2015). And not only were white mothers more likely to begin breast feeding, they were also more likely to continue exclusively breast feeding through six and twelve months (Ibid.). This racial disparity is further compounded by geographic and socioeconomic conditions (Anstey 2017).

The protective factors of breast feeding on both infant and maternal health have been heavily documented (Louis-Jacques et al. 2017). Breast feeding has been associated with lower rates of diabetes, hypertension, and various cancers later in life (Ibid.). Due to close connection to reproductive health, ovarian cancer has been heavily analyzed with a woman’s breast feeding history (Sung et al. 2016). Observational analyses highlight a 10-15% decline in ovarian cancer risk, controlling for parity, for women who breastfed for 6 to 12 months (Gaitskell et al. 2018). This study did not find any statistically significant differences by ovarian cancer subtype, but contributed the lack of finding to statistical power. The researchers of the Gaitskell study recommend a deeper investigation into the effect of breast feeding on more lethal subtypes of ovarian cancer. Early explanations for the lower risk of ovarian cancer in breast feeding mothers has focused on decreased inflammation due to fewer events of menstruation and ovulation (Fathalla 1971). However, more recent evidence suggests that breastfeeding alters the hormonal microenvironment (Risch 1998). Because breastfeeding (or not breast feeding) is both driven by and a driver of hormones, the causal pathway is difficult to establish. Still, the generally accepted knowledge androgen and progesterone levels are impacted by initiation and length of breastfeeding. Also generally accepted is the possibility that higher levels of androgen increase the risk, while higher levels of progesterone protect against the risk of epithelial ovarian cancer. Combining these two logic models, a noteworthy hypothesis would be to test the effect of breast feeding on ovarian cancers by measuring androgen and progesterone levels.

Breast feeding also shows protective effects against childhood leukemia (Michie 2016). The mechanistic explanation for this protective effect may rest in the content of human breast milk. Naturally occurring immunoproteins and probiotics, not found in animal milk, may provide T-cell immune protection against clonal malignancy in blood cells (McGuire and McGuire 2015). Perhaps there exists a similar benefit for mothers who maintain a milk supply with such protective immunoproteins.

Another cancer showing epidemiological associations with breastfeeding is thyroid cancer (Yi et al. 2016). Here the mechanistic effect of breast cancer remains highly speculative, due to the historical variance and controversy of the suggested claim. However, two potential avenues arise, again pointing at hormones, specifically estrogen. One possibility is that breastfeeding mothers may have regulated estrogen levels, mitigating the proliferation of malignant tumors from the thyroid (Manole et al. 2001; Rajoria et al. 2010; Glinoer et al. 1990). Conversely, women who do not establish breastfeeding may create a microenvironment with lower estrogen, promoting the migration progenitor thyroid cancer cells. Another possibility is explained, not by estrogen levels, but by heightened interaction between estrogen receptors (Lee et al. 2005; Chen et al. 2008; Bouman, Heineman, and Faas 2005). Heightened interaction between estrogen receptors decreases apoptosis in normal cells, eventually prompting tumorigenesis.

There exists a strong association between breast feeding and other cancers. Given that hormone levels and signaling are highly affected by breastfeeding, the exploration into the mechanistic relationship between breastfeeding inducing hormonal changes in the microenvironment causing breast cancer remains warranted. This is especially critical given the overlapping, highly variant disparity for both breastfeeding and breast cancer between black and white women.

**Epidemiology**

Before concluding this review exploring the potential epigenetic mechanisms of breastfeeding and TNBC, I delve into the epidemiological literature as a guide for identifying gaps in knowledge. Considered the bedrock of scientific knowledge, systematic reviews and meta-analyses represent established acceptance in the field. A series of such studies have been conducted to analyze the change in risk of breast cancer as determined breastfeeding. There remains a very clear, uncontroversial reduction in risk for women who exclusively breastfed for six months, and this reduction in risk continues to decline with greater length of breastfeeding ((Unar-Munguía et al. 2017); Victora et al. 2016). Notably, women who breastfeed exclusively for six months experience a 20-25% risk reduction in developing TNBC (Lambertini et al. 2016). Interestingly, the risk reduction is not lost in women with a family history of TNBC (González‐Jiménez et al. 2014). However, the protective effect of breastfeeding disappears completely in women who smoke (Ibid.).

While there may be some debate between breast feeding and parity as the primary risk reduction act for hormonal receptor positive cancers, strong evidence shows that breastfeeding is, in fact, an independent determinant of TNBC (Islami et al. 2015). In fact, the greatest gains from initiating or extending breastfeeding could be attained from young, African American women who have low baseline rates of breastfeeding and higher rates of TNBC.

**Epigenetic and Molecular Mechanisms**

The potential pathways for the risk reduction have been clearly defined by the extensive pursuit of scientific investigation (Manrique Tejedor, Figuerol Calderó, and Cuéllar De Frutos 2015). During lactation, breast cells are highly differentiated. This promotes apoptosis in healthy cells. Also, because ovulation and menstruation cycles are inhibited, the breasts experience less inflammation and hormonal signal changing. This protective effect is cumulative and lasts longer as breastfeeding continues past six months. Finally, as with the other types of cancers associated with protection from breastfeeding, estrogen has a considerable effect on breast cancer. Estrogen excretes from the breast, through the milk, during lactation. The same excretion occurs for other hormones and various carcinogens which may influence tumor development and growth. Aside from interventions to encourage breastfeeding, these pathways, however, do not provide clinical utility for preventing and treating breast cancer.

Specifically to TNBC, the field has built upon previous claims for the mechanistic effect of breastfeeding as a protective factor. Along with the limited parity and hormonal changes during lactation, the initiation of involution post-partum has been deemed as another way of promoting breast cell differentiation and apoptosis (Schedin 2006). Further, lower levels of estrogen limit hormonal receptor cells from signaling and stimulating the proliferation of HR- cells. These paracrine signals have been suspected of driving TNBC progenitor cells, but are much less frequent during lactation (Dontu, El-Ashry, and Wicha 2004). Conversely, transcription factor gene, STAT3, signaling induces involution in the breast during lacatation. Loss of STAT3 signalling could be problematic for TNBC stem cells (Faupel-Badger et al. 2013). In addition to protective factors during lactation, breastfeeding can permenantly alter the molecular environment of the breast, not only through involution but decreasing breast density (Dontu, El-Ashry, and Wicha 2004). Finally, emerging evidence exhibits possible immunoproteins which affect both proliferative cell adhesion and apoptosis (Islami et al. 2015). This is effect is not dissimilar from that of ovarian and endometrial cancers’ response to breastfeeding.

No review on the epigenetic influences on breast cancer would be complete without a brief discussion on BRCA1/2 mutations. Unsurprisingly given the publicity of these mutations, research has investigated their relationship with breastfeeding. The accepted knowledge on this topic shows that BRCA1 mutations are less frequent in women who have breastfed, but there is no association for BRCA2 (Friebel, Domchek, and Rebbeck 2014). While this is information is clinically valuable, no current hypothesis exists as to why this is the case.

**Implications**

The implications for a better understanding of breastfeeding’s mechanism for protection against lethal breast cancer cannot be understated. Governments have conducted national analyses to assess the financial and livelihood cost from low rates of breastfeeding, suggesting that policy-makers are willing to pay for proven methods of confronting this seemingly preventable disease (Unar-Munguía et al. 2017; Deloitte 2016) Areas of opportunity include detection and TNBC prediction through greater understanding of breastfeeding processes, ultimately leading to improved precision screening techniques. The molecular environment alterations from breastfeeding highlight potential clinical and translational value for TNBC treatment. Finally, more than simply promoting breastfeeding in African American women, perhaps TNBC could be prevented altogether by translating the mechanistic framework of breastfeeding protection to all African American women.

This report concludes with a discussion on opportunities for scientific, clinical, and translational utility of breastfeeding mechanisms as protection against TNBC.

**Discussion**

The use of predictive, machine learning models could be combined precision, cohort genetic testing in different populations before and after pregnancy. A novel research study could provide free genetic tests to women planning to have a child, along with a brief survey on lifestyle factors and family history of breast cancer. The value of a genetic test to the participants would be to immediately learn about risks to their unborn child, as well as potential cancer risks. Hopefully this information would incentivize participation in the study. Following the mother through three, six, and twelve months of new genetic tests could shed light onto epigenetic environmental changes associated with breastfeeding. Researchers could then identify potential genes as suspects for driving or suppressing tumorigenesis. Potential targets could include FOX1A, p53, Inv5, ki-67, and BLC2 (Bambhroliya et al. 2018; Espinal et al. 2017; Gonzalez-Sistal et al. 2016). To date, the best genomic and lifestyle studies for breast cancer have only assessed study participants at one time interval, missing the possibility of changes due to breastfeeding (Makama et al. 2017).

This type of study could investigate questions related to the effect of breastfeeding for women with a family history of TNBC. Does breastfeeding negate the hereditary effect or is the effect of breastfeeding mechanisms stronger than that of possible hereditary mutations, ex-post? Another logic model could help understand the effect of breastfeeding on BRCA1/2 for both breast and ovarian cancers. Finally, additional attention should be paid to smokers, both before, during, and after breastfeeding. This would help explain why breastfeeding protection dispears for women with a history of smoking, but more importantly identify critical oncogenic events for tumorigenesis, proliferation, and metastasis in TNBC.

While hormonal therapy is widely driving the improved outcomes for HR+ survivors, the same treatment would not likely affect TNBC patients. However, there is reason to believe that pre-treatment of hormonal therapy, regulating estrogen, androgen, and progesterone levels could have clinical value, especially in women of high risk for TNBC. Another possible treatment lies in the realm of immunotherapy. The evidence of TNBC, as well as thyroid and ovarian cancer, support the role of immunoproteins as mitigators and suppressors of tumor development. Recently, a study showed that a cell with immune subversion properties, HLG-A is over expressed in breastfeeding women (Zidi et al. 2016). Pre-clinical trials advancing immunotherapies become warranted based on the knowledge of other enhanced or overexpressed molecules typically found in breastfeeding women.

Finally, actual human breast milk itself may be the key to solving current disparities in TNBC. One recent study tested the hypothesis that the link between early-onset TNBC and late-first pregnancy are driven, not by less parity, but variance in proteins expressed in breast milk (Qin et al. 2012). This study provides clinical value, as some proteins which cause methylation, KLK and others suppression tumorigenesis, TGFB, were found depending on the age of first birth (Qin et al. 2012). The findings of this study were enhanced by reviewing the expression of milk after stratifying women by family history of breast cancer, affirming the previous studies conclusions (Qin et al. 2013). Further building on this foundation, studies have since explored multiplicative effects of other proteins and calcium levels on the onset of early TNBC after pregnancy (Bayram et al. 2016; Qin et al. 2016).

Many hospitals and birth centers across the world have returned to emphasize breastfeeding. Perhaps in conjunction with nurses assisting with breastfeeding initiation, genetic counselors could express and test early breast milk. This test could provide new mothers with information about their breastmilk content, as well as potential breast cancer risk, but also begin a “milk bank” for scientific exploration. Such studies are not farfetched. Look at the recent “Parent Science Gang” collaboration with King’s College where mothers from across the UK donated and stored breast milk as a citizen-driven research study (London et al. n.d.). Not only does this grassroots research project show the potential for “breast milk databanks”, but also begins a long-term study on the heterogeneity of human breast milk across the lactation life cycle.

**Conclusion**

Just as with breast cancer, there exists significant heterogeneity in both the contents of breast milk, as well as potential mechanisms for protecting against tumor development. The scientific community has heavily explored the epidemiology and pathology of Triple Negative Breast Cancer and its relationship to breast feeding. Despite the gains in knowledge, disparities persist. The time has come for genomic analyses at the population level, as well as novel pre-clinical trials utilizing the evidence from breastfeeding studies. The dire prognosis of TNBC and proven protection of breastfeeding against cancer warrant expedited precision screening, treatment, and prevention protocols as determined by the positive effects of breastfeeding.

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