Immune Responses and Risk of Triple Negative Breast Cancer: Implications for Higher Rates among African American women

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Abstract

The etiology of triple-negative breast cancers (TNBCs) is poorly understood. As many TNBCs develop prior to the initiation of breast cancer screening or at younger ages when the sensitivity of mammography is comparatively low, understanding the etiology of TNBCs is critical for discovering novel prevention approaches for these tumors. Further, the higher incidence rate of estrogen receptor (ER)-negative breast cancers, and specifically, of triple-negative breast cancers (TNBCs), among young African American women (AAW) versus white women is a source of racial disparities in breast cancer mortality. Whereas immune responses to TNBCs have received considerable attention in relation to prognosis and treatment, the concept that dysregulated immune responses may predispose to the development of TNBCs has received limited attention. We present evidence that dysregulated immune responses are critical in the pathogenesis of TNBCs, based on the molecular biology of the cancers and the mechanisms proposed to mediate TNBC risk factors. Further, proposed risk factors for TNBC, especially childbearing without breastfeeding, high parity, and obesity, are more prevalent among AAW than white women. Limited data suggest genetic differences in immune responses by race, which favor a stronger T-helper type 2 (Th2) immune response among AAW than white women. Th2 responses contribute to wound healing processes, which are implicated in the pathogenesis of TNBCs. Accordingly, we review data on the link between immune responses and TNBC risk and consider if the prevalence of risk factors that result in dysregulated immunity is higher among AAW than white women.

Incidence of TNBC

TNBCs are clinically aggressive breast cancers that do not express estrogen receptor (ER) or progesterone receptor (PR), and do not overexpress human epidermal growth factor receptor

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2 (HER2)(1, 2), and thus do not respond to hormonal or HER2 targeted therapeutics. The incidence rate of TNBC among AAW is approximately double that among white women, with much of the disparity occurring at early ages (3, 4). Data indicate that the relative percentage of TNBCs is highest in Sub-Saharan West African countries of Ghana and Nigeria than among AAW and lower in East African countries; however, further epidemiological data are needed to confirm these results (5, 6). It has been proposed that genetic admixture between white Americans and Ghanaian/west Africans as a result of west Africa-based trans-Atlantic slave trade accounts for the intermediate prevalence of TNBC in AAW (5, 7). Improved registry infrastructure in Africa would enable estimation of age-adjusted rates, as would be needed to definitively compare rates with AAW and white women. If confirmed, the higher incidence of TNBCs among African and AAW may suggest a genetic predisposition to TNBC.

TNBC and immune responses in tissues

TNBCs are diverse with regard to clinicopathological features and prognosis (8), and immune factors figure prominently in the sub-classification of TNBCs (particularly definition of the numerically predominant subtype of TNBC, basal breast cancer). Medullary carcinoma, a morphologically distinctive form of TNBC, is defined by the presence of a prominent immune infiltrate, and more intense immune responses predict improved survival (9). Further, Casbas-Hernandez et al. (10) demonstrated that benign breast tissues adjacent to different molecular subtypes of breast cancer show different RNA expression patterns. Notably, the ontology of genes expressed in benign tissues surrounding TNBCs prominently include functions such as activation of leukocytes, proliferation of mononuclear leukocytes, cell movement of leukocytes, interferon signaling, hepatic fibrosis, T-helper cell differentiation or antigen presentation pathways. Although an effect of the tumor on its microenvironment cannot be excluded, the benign tissues analyzed in this study were grossly separated from the cancers, suggesting a possible role for immune responses in their development.

Lehmann et al. (2011) (11) initially classified TNBC into six molecular subtypes, but later revised categorization to four molecular subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR) (11). Recently, Davis et al. (2018) (12) correlated androgen receptor (AR) expression with TNBC subtypes and race, based on Lehman's initial TNBC subtyping and reported that the majority of TNBCs (75% – 90%) did not express AR (quadruple negative (QNBC)), and that the TNBCs that expressed AR had a better prognosis than QNBCs. TNBCs among AAW included a higher percentage of AR-negative BCs within each TNBC subtype. Furthermore, this study identified genes associated with immune pathways, including *E2F1, NFKBIL2, CCL2, TGFB3, CEBPB, PDK1, IL12RB2, IL2RA* and *SOS1*, which were differentially expressed in QNBC among AAW versus white women and could differentially impact immune responses in these racial groups. They concluded that these genes may represent molecular drivers within IL12, CCR5, and B-cell response pathways that reflect immunologic differences linked to racial disparities in these breast cancers. Other findings from this investigation included a higher overall frequency of AR-negative TNBCs among AAW (81%) versus white women (56%)

and upregulation of the immune checkpoint inhibitors PD-1, PD-L1, and CTLA-4 in QNBC vs non-QNBC, and in AAW with QNBC vs white women with QNBC (12).

Our provisional analysis of data from The Cancer Genome Atlas (TCGA) revealed that while overall mutation burden (defined by Thorsson et al. 2019(13)) did not differ significantly by race for breast cancer overall or by molecular subtype or stage (Figure 1A), the degree of microsatellite instability (defined by Bonneville et al. 2019(14)) in basal breast cancers (expressed as a continuous variable) among women ages 26–50 years was significantly higher among AAW (p<0.01) (Figure 1B). Microsatellite instability reflects a predisposition to mutation from impaired DNA mismatch repair, and accumulation of tumor cells with microsatellite instability could indicate deficiencies in tumor immunosurveillance and failure to eliminate such clones prior to cancer development (15). Consistent with this possibility, the TIL percent area, as defined by Saltz et al. 2019 and Thorsson et al. 2019 (13, 16), was significantly higher in basal breast cancer among white women than AAW (p<0.01) (Figure 1C). These results are provocative because augmentation of immune responses in tumors with microsatellite instability represents a possible new treatment approach (17); however expanded studies of basal breast cancers from AAW using state-of-the science methods are needed to more clearly define molecular features that distinguish basal breast cancers among white and AAW.

TNBC risk factors are associated with deleterious inflammation and susceptibility to DNA damage

Factors associated with increased risk of TNBC include obesity, multiparity with lack of sustained breastfeeding, and mutations in genes such as *BRCA1* and *BRCA2*, which have important functions in DNA repair (18–20). These factors may affect the immune microenvironment in the breast, leading to deleterious inflammation that can result in cancer causing mutations or failure to eliminate mutated cells (19–25).

Data for associations between obesity and TNBC risk are inconsistent, with probably the strongest support for a link found among premenopausal AAW with abdominal obesity (26, 27). A meta-analysis showed that pre-menopausal women with a BMI greater than 30 Kg/m^2 were at increased risk of TNBC versus non-obese women (odds ratio (OR): 1.43; 95% confidence interval (CI): 1.23 – 1.65)(19). A recent investigation by Schoemaker et al. (2018) (28) found that premenopausal weight gain was inversely correlated with breast cancer risk overall among women less than age 55 years, although associations with TNBC were not significant. Gaudet et al. also reported a non-significant direct association between BMI and TNBC among women ages <55 years in a pooled analysis of prospective studies (29). Obesity is associated with increased levels of serum and tissue inflammatory cytokines such as IL-6, IL-8, and TNF-α, which can activate various signaling pathways, including JAK/STAT, NF-κB, and Wnt/EZH2 that promote cell proliferation, invasion, and metastasis, which are hallmarks of aggressive cancers, including TNBC (30–33). In short, epidemiological data generally support a link between adiposity and TNBC risk, which is bolstered by mechanistic evidence implicating immune factors.

Whereas multiparity has been associated with a modest reduction in risk for ER-positive breast cancers (OR 0.92, 95% CI = 0.81 – 1.03 relative to nulliparity), parity increases the risk of TNBC (OR 1.37, 95% CI = 1.06 – 1.70) (34). Data indicate that childbirth itself is associated with a transient increase in risk of ER-positive breast cancers for over two decades and a persistent increase in ER-negative breast cancers (34, 35). Multiparity is related to increased risk of TNBC, but this effect is mitigated by breastfeeding, as originally reported in the Carolina Breast Cancer Study, and later confirmed in the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium (36, 37). We hypothesize that the impact of parity on TNBC risk and the mitigation of this risk by breastfeeding may partly reflect the effects of postpartum involution (PPI), the process that returns the breast to a baseline state after weaning (38).

Elegant preclinical studies by Lyons et al. and others (39–42) have demonstrated that breast re-modeling after weaning results in an immune suppressed microenvironment resembling wound healing, characterized by immune cells expressing PD1/PD-L1 and increases in M2 macrophages, T regulatory cells, cyclooxygenase-2 expression and collagen synthesis. While PPI is a physiological process required to return the lactating breast to a baseline state (38), PPI may provide a favorable microenvironment for progression of mutated cells. Thus, MCF10 DCIS cells placed into the fat pad of dams that have been weaned develop rapidly growing metastatic TNBCs; treatment of such mice with non-steroidal anti-inflammatory agents (NSAIDs) inhibits TNBC development (39). Parity appears to expand breast lobules from which breast cancers arise (43), and we hypothesize that PPI may produce DNA damage, especially in the absence of breastfeeding.

Given the limited availability of benign post-partum human breast tissues, studies have analyzed breastmilk to understand PPI among women. Murphy et al. (44) analyzed convenience samples of breastmilk from 130 AAW and 162 white women for 15 analytes to compare the breast immune milieu by race. In multivariable analyses, samples donated by AAW demonstrated higher levels of IL-1β and leptin, whereas samples from obese women showed elevated levels of IL-1β, BFGF, EGF, leptin and FASL. Factor analysis identified two main discriminating factors related to: 1) angiogenesis and apoptosis and 2) inflammation. The level of the inflammation factor was higher among AAW than white women and declined with duration of breastfeeding (44). In another analysis, measurement of 80 cytokines in breastmilk donated by 15 women at 1, 4, 5 and 12 weeks post-partum revealed that levels of 9 inflammatory cytokines decreased with time since childbirth (45). These preliminary data suggest that the post-partum milieu of AAW and obese women may be more inflammatory than that of white and lean women, respectively, and that sustained breastfeeding may be associated with reduced inflammation in the breast.

Molecular alterations occur frequently in normal breast epithelium and breast cancer precursors (reviewed by Danforth (46, 47)); however, intrinsic cellular mechanisms (e.g. senescence, DNA repair) and extrinsic immune responses prevent most such changes from progressing to breast cancer. Deleterious inflammation may produce DNA damage, but the impact of this effect is mitigated by competent DNA repair. Homologous recombination repair deficiencies associated with germline *BRCA1* or *BRCA 2* mutations are associated with approximately 20% of TNBCs and somatic alterations that reduce function of these

genes occurs in about 40% of TNBCs (18). Mutations in other genes with DNA repair functions, including *BARD1*, *PALB2* and *RAD51D* are also associated with increased risk of TNBC (48), irrespective of race (49). TNBCs are associated with mutations in *TP53* and DNA repair genes, a high mutational burden and a high neoantigen load, which would be anticipated to evoke robust immune responses (50, 51). Subsets of TNBCs are associated with abundant tumor infiltrating lymphocytes (TILs) (21, 52–56). However, studies of normal breast epithelium that interrelate DNA damage, neoantigen production and immune responses are technically challenging to perform and have not been conducted. Nonetheless, limited data evaluating immune responses in benign breast biopsies in relation to breast cancer risk (overall) have identified that decreased B cells in normal lobules are related to increased risk (57).

Prevalence of risk factors for TNBC among AAW

Several TNBC risk factors are higher for AAW. These include higher birth rates: in 2018, birth rates for AAW were 13.6/1,000 for non-Hispanic AAW versus 10.0/1,000 for non-Hispanic white women(58). Multiparity is also higher among AAW versus white women (59). The prevalence of obesity among AAW is approximately 58% versus 38% among white women in the U.S (60, 61), and 64.9% of AAW were overweight or obese at time of giving birth as compared with 51.1% of white women. These factors are linked, as multiparity is associated with an increased prevalence of obesity among parous women (62). Data from the National Longitudinal Survey of Youth Cohort showed that the 5-year incidence rate of obesity was 11.3/100 parous women versus 4.5/100 among nulliparous women; among parous women, the incidence of obesity was 15.1/100 in AAW versus 9.1/100 among white women (63). AAW also have higher pre-pregnancy BMI than white women and are more likely to retain weight post-delivery (62), and AAW participate less in breastfeeding than white women (31% vs 58%) (20). A study by McKinney et al. reported that analysis of data from the Community and Child Health Network study (N=1636) revealed that African American mothers were less likely to initiate breastfeeding compared to white mothers (61% vs 78%), and had lower intention to breastfeed (57% vs 77%) (23). Thus, obesity, weight gain after childbirth and limited breastfeeding are more prevalent among AAW than white women, and may significantly contribute to increased inflammation and high TNBC incidence in AAW.

Data for the prevalence of pathogenic mutations in DNA repair genes by race are limited. Several studies show that *BRCA1/2* mutation prevalence is highest among the Ashkenazi Jews, while not significantly different in other ethnic groups (64–66). John et al. (2007) found that the prevalence of *BRCA1* mutations was highest among African-Americans younger than 35 years of age (16.7 %) as compared with other racial/ethnic groups (67) in Northern California, although these data may not be representative of the broader United States. A larger study conducted by Hall MJ et al. (2009) found that the risk of *BRCA1/2* mutations in breast cancer patients was similar across diverse racial/ethnic groups (68). Limited available data suggest that approximately 50% of *BRCA1/2* pathogenic variants are likely or possibly of African origin, with many suggesting distinctive functions versus those detected among white women, suggesting the need for further studies among AAW (49)

Variation in genetic markers and circulating cytokine levels by race in relation to breast cancer risk

The principal arms of adaptive immunity designated as type 1 and type 2 T-helper (T_h1 and T_h2) each play distinctive but pivotal roles in anti-tumor responses, with potential implications for breast cancer development and progression. However, more complex differentiation states among macrophages and CD4+ T-helper cells are now acknowledged, and it is unclear how these differentiation states might impact immunity (69). T_h1 immune response is operationalized through IL2, TNFα, IFNγ, M1-polarized macrophages, and natural killer (NK) cells, and results in activation of CD8 positive cytotoxic T cells that can potentially eliminate breast cancer cells. T_h2 immunity is characterized by production of IL-4, IL-5, IL-9, IL-10, IL-13, with concomitant suppression of cytotoxic T cell function, resulting in a microenvironment that is proposed to be more conducive to breast cancer development. Studies suggest that distinctive evolutionary pressures contributed to genetically determined differences in immune responses by race, with heightened T_h2 responses among AAW (70, 71). T_H2 responses are tumor suppressive, suggesting that the breast immune microenvironment of AAW may contribute to increased incidence of TNBC.

The AMBER consortium identified single nucleotide polymorphisms (SNPs) in *IL2RB, TLR6, and IL8* to be associated with the risk of ER-negative breast cancer among premenopausal AAW (72). In another study, Quan L et al. (2014) (73) in The Women's Circle of Health Study (WCHS) tested the association between breast cancer risk and 47 SNPs in 26 cytokine related genes of the adaptive immune system using a two-stage approach. The first stage included 650 white women and 864 AAW, followed by a confirmatory study including 1307 white women, and 1365 AAW. Multivariable logistic regression analyses identified genetic variants in the adaptive immune response pathway associated with breast cancer risk, which differed by ancestry groups, menopausal status, and estrogen receptor (ER) status (73). This study identified five SNPs in genes important for T helper (T_h) immunity: *IFNGR2* rs1059293, *IL15RA* rs2296135, *LTA* rs1041981, *IL4R* rs1801275 for T_h2 immunity, and *TGFB1* rs1800469 for T regulatory cell-mediated immunosuppression, which were associated with breast cancer risk among AAW, and related to a statistically significant aggregate effect among AAW (p-trend=0.0005). However, the effects were not significant after adjustment for multiple comparisons. A notable finding from the same study was that the SNP rs746868 in the *LTA* gene, which was associated with increased risk for ER-positive BC among white women, conferred increased risk for ER-negative breast cancer among AAW. Of the 47 SNPs in 26 genes tested in this study, the genotype frequencies of 41 SNPs (87%) differed significantly between AAW and white women who were controls. This study had multiple strengths, which included racial comparisons, relatively large sample size, and in-person interviews; nonetheless, larger validation studies are needed. Numerous other studies have also reported racial differences in SNP variants with immune response regulatory functions (see table 1) (73–84). These differences in immune response genes are potential sources of differences in breast cancer incidence and mortality, leading to breast cancer disparity.

T_h2-associated cytokines have also been shown to activate innate immune cells leading to chronic inflammation and diminished anti-tumor responses (85). The variations in cytokine expression have been observed in different populations, races and ethnic groups (see table 2) (44, 86–89). In a study of 914 AAW and 855 white women, Yao et al. (2014) (89) examined plasma levels of 14 cytokines involved in innate and adaptive immunity, including those implicated in chronic inflammation. After adjusting for age, obesity, smoking, and other potential confounding factors, they found that the cytokines CCL11, CCL2, IL-10, IL-4, IFNG, and IL-1B were significantly higher in white women, while IFNα2, IL-1RA, CX3CL1, IL-5, TNFα, and CXCL10 were significantly higher in AAW (89). The data from Multi-Ethnic Study of Atherosclerosis (MESA) support the proposal that circulating biomarkers might provide insights into racial disparities in risks of chronic diseases among AAW versus white women (90). Unpublished data from MESA suggest that soluble IL-2R (sIL-2R) levels are significantly higher in white women as compared with AAW, which is of interest because of the protean role of this cytokine on immune functions (Suzette Bielinski, personal communication). The contribution of these potential differences to racial disparities in immune responses and disparities in breast cancer incidence and mortality remain undefined, and require further investigation.

Proposed Model of the Immune Pathogenesis of TNBC

We propose a life course model to describe the manner in which immune dysregulation may increase TNBC risk, especially among AAW (Figure 2). Bagby et al. (91) summarized evidence that genetic factors and deleterious exposures at young ages (e.g. psychosocial stress, toxins and poor nutrition) may increase cortisol levels, alter macrophage and T cell cytokine secretion and cause metabolic dysregulation, among other mechanisms, resulting in a "disease-susceptible phenotype". Repeated exposures to adverse events pose greatest disease risks (i.e. high allostatic load) (91). Further, adverse early life events and African American race are associated with earlier onset of puberty, obesity and metabolic dysregulation, which may increase breast cancer risk (92). After puberty, lobules undergo proliferation (and differentiation) with each menstrual cycle, which favors the accumulation of mutations. Pregnancy is associated with proliferation of breast epithelium and differentiation (43, 93); during nursing, immune cells increase in milk in response to infections among mothers or infants (94). At weaning, the breast undergoes PPI, which re-establishes the baseline state of the breast (38–40). During PPI, best studied in animal models, activation of inducible COX-2 leads to up-regulation of inflammatory and cell survival pathways with deposition of fibrillar collagen and increases in M2 macrophages, creating an immune suppressed wound healing microenvironment that drives the progression of mutated cells to aggressive breast cancer, including TNBCs, and can be inhibited with anti-inflammatory agents (39–42). Limited data from women suggest that immune cell populations in the postpartum breast return to baseline within months to a few years of weaning (42); however, benign tissues of parous women show durable alterations in gene expression, including up-regulation of immune and inflammatory pathways (95). We hypothesize that dysregulated immune function could lead to intense or prolonged PPI related inflammation, increasing TNBC risk among women. Normal breast tissues and breast cancer precursors may contain a range of mutations (46) and the frequent presence

of mutations in TP53 or DNA repair genes, as in TNBC mutations, favors persistence and progression of mutated cells. The growth promoting effects of pregnancy and the tumor-promoting effects of PPI may increase risk particularly among individuals with a large burden of occult mutated cells. These effects may be opposed by neoantigen expression on precancerous cells, which may evoke protective immune responses that result in "elimination" of mutated cells; however, if unrecognized by the immune system or situated within cancer promoting microenvironments, such cells may remain dormant and then escape.

Outstanding questions and future directions for research

Large definitive studies using optimal analytical methods are needed to determine TNBC subtypes by race, and the associations of these subtypes with exposures, genetic variants, and mutations that may be related to immunity. Determining attributable fractions of potentially modifiable TNBC risk factors, such as obesity, weight gain and failure to breastfeed could have potential to drive public health interventions to improve "immune health" and lower rates of TNBC among young mothers. Identifying features of pregnancies that link dysregulated PPI to increased TNBC risk could point to early detection strategies, increase understanding of mechanisms that mediate TNBC risk and evaluation of short-term low risk interventions, such as use of anti-inflammatory agents, as suggested by elegant preclinical studies by Lyons et al. (39) and subsequent research (96, 97). Efforts to improve health messaging about breastfeeding and healthy weight maintenance among young AAW are important, especially with digital health strategies and online support groups. Studies to characterize and compare immune responses among women by race in relation to risk of TNBC and other cancers and chronic diseases with suggested immunologic etiologies could suggest public health efforts to improve immune health in African American communities.

Conclusion

Data suggest that racial differences in immune health may contribute to increased risks of TNBC among AAW. We propose that increased understanding of the immunologic mechanisms that define high-risk AAW represent important steps towards early detection and prevention of these aggressive breast cancers.

Acknowledgments

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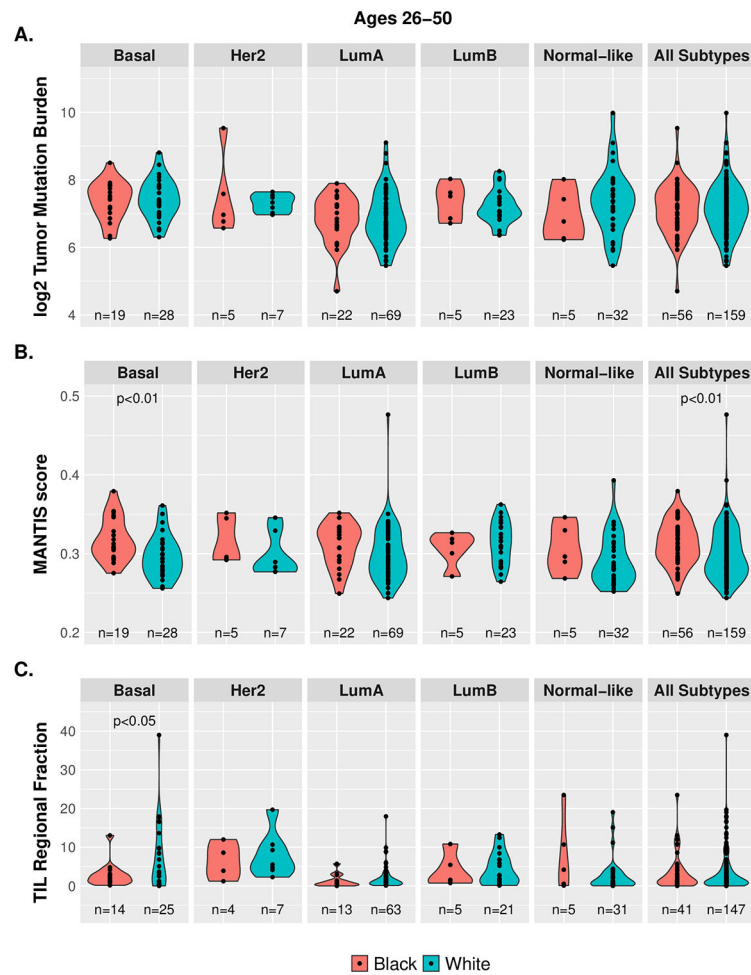
Figure 1.
Racial and molecular subtype differences in tumor mutational burden, microsatellite instability, and TIL regional fraction in breast cancer. TCGA data does not show significant racial differences in mutation burden (1A), whereas microsatellite instability levels (continuous) are suggestively higher among AAW ages 26–50 years with basal breast cancer (1B), and TIL regional fraction is higher in basal breast cancer among white women (1C). TIL: tumor infiltrating lymphocyte; TCGA: the cancer genome atlas.
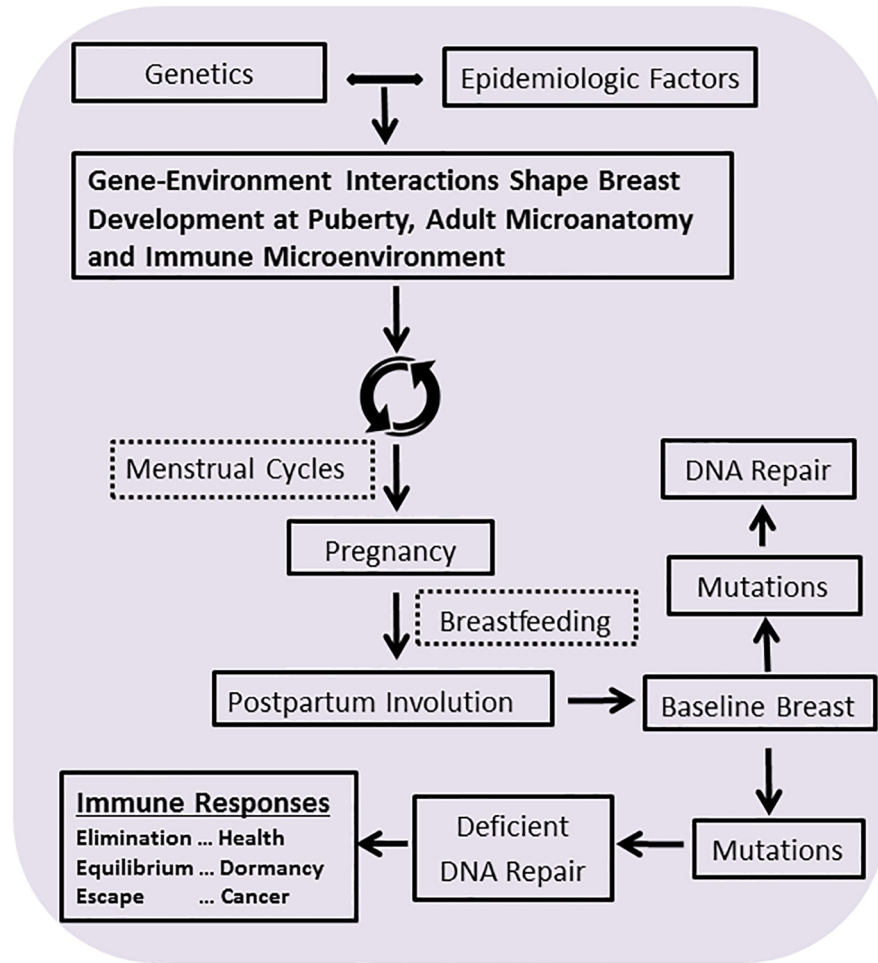
Figure 2.
Gene environment interactions influence the microanatomy of the pre-pubescent and pubertal breast, both with regard to lobular architecture and the immune microenvironment. After puberty, menstrual cycles and other breast cancer risk factors alter this baseline state; however, the most dramatic changes occur with pregnancy and then postpartum involution, two factors that dramatically impact breast anatomy and cancer risk. Breastfeeding impacts the immune component of the breast, protecting the breast from infection, contributing to the developing immune system of the infant, and influencing breast cancer risk. Postpartum involution restores the baseline state of the beast after weaning and may contribute importantly to breast cancer risk or health.

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Table 1.

Differences in genetic variants of SNPs in genes related to cytokines by race

Study first author, year	Number of subjects	Study design	Gene – SNP variants that differ by race	Main findings
Cox ED et al., 2001 (74)	CA (n = 102) AA (n = 43)	Prospective cohort	*IL6*-174G *IL2*-330T	• *IL-6* and *IFN-γ* genotypic distribution differ by race among AA and white women
Lazarus R et al., 2002 (75)	CA (n = 23) AA (n = 24) HA (n = 24)	Retrospective cohort	*IL10*-1117	• Higher number of population-specific polymorphisms found in AA compared to white women and Hispanic women
Hoffmann SC et al., 2002 (76)	CA (n = 216) AA (n = 58)	Prospective cohort	*IL2*-2330G *IL6*-174G *IL10*-1084G	• Statistically significant variations in *IL-2* allele and genotype distributions between Blacks and Whites, with Blacks having no homozygous (G/G) individuals who are high *IL-2* producing. *IL-2* promotes the development of self-tolerance
Martin AM et al., 2003 (77)	CA (n = 74) AA (n = 84)	Prospective cohort	*TNFaR*-28T→C *TNFaR*-36G→A *TNFaR*-7979C→T *IL-1a*-2121C→T *IL-1β*-3406C→T	• 7/12 novel SNPs identified in the study were exclusively seen in AA populations
Hassan MI et al., 2003 (78)	CAW (n = 81) AAW (n = 42)	Prospective cohort	*IL6–174C/G* *IFNγ-873T/A*	• AAW had higher frequency of high *IL-6* producing SNP • White women had a higher frequency of high *IFNγ* producing SNP
Ness RB et al., 2004 (79)	CAW (n = 396) AAW (n = 179)	Prospective cohort	*IL1A*-4845G/G *IL1A*-889T/T *IL1B*-3957C/C *IL1B*-511A/A *IL6*-174G/G *IL10*-819T/T *IL10*-1082A/A	• AAW were significantly more likely to carry allelic variants known to upregulate proinflammatory cytokines
Rady PL et al., 2004 (80)	CA (n = 91) AA (n = 97)	Retrospective cohort	*IL10*-1082 A	• AA had a lower rate of high producing SNPs and a higher rate of low *IL-10* producing SNPs compared to white women
Zabaleta J et al., 2008 (81)	CA (n = 299) AA (n = 294)	Retrospective cohort	*IL1B*-511T *IL1B*-31C *IL10*-1082A *IL10*-592A *TNF*-308A *IL1R*2	• Higher allelic variants conferring increased cancer risk in AA
Van Dyke AL et al., 2009 (82)	CAW (n = 380) AAW (n = 103)	Prospective cohort	*IL1B* rs16944 *IL2* rs2069763 *IL8* rs4073 *IL15* rs1057972 *IL15RA rs2228059* *IFNGR2* rs1059293	• 52 out of 70 investigated SNPs that met criteria for analysis differed by race in genotypic, haplotypic, and allelic frequencies
Gong Z et al., 2013 (83)	CAW (n = 650) AAW (n = 864)	Case - Control	*TNFA*-rs1799724	• Variants in genes involved in innate immune pathways differ by race in AAW and white women
Murray JL et al., 2013 (84)	CAW (n = 739) AAW (n = 141)	Retrospective cohort	*NFKB1* rs230532 *IL13* rs1800925 *NFKB1* rs3774932 *IL4R* rs3024543	• SNPs that predicted time-to-recurrence (TTR) different in AAW and CAW • *NFKB1* rs230532 and *IL13* rs1800925 SNPs were independent predictors of a shorter TTR in white BC patients,

Study first author, year	Number of subjects	Study design	Gene – SNP variants that differ by race	Main findings
				while *NFKB1* rs774932 and *IL4R* rs3024543 SNPs were predictive of shorter TTR in AA
Quan L et al., 2014 (73)	CAW (n = 1307) AAW (n = 1365)	Case - Control	*IFNGR2* rs1059293 *IL15RA* rs2296135 *LTA* rs1041981 *IL4R* rs1801275 *TGFB1* rs180469	• Cytokine and cytokine receptor SNPs in the adaptive immune response pathways associated with breast cancer risk differed by race, menopausal, and ER status

Table 2.

Differences in measured circulating levels of cytokines by race

Study first author, year	Number of subjects studied	Study design	Differentially expressed cytokines	Main findings	
Negi SI et al., 2012(86)	CA (n = 596) AA (n = 488)	Nested case-cohort	IL-18 - higher in white women	•	IL-18 is higher in CAW, and is associated with incident diabetes in white, but not AA populations
Deshmukh SK et al., 2015(87)	CA (n = 5) AA (n = 5)	Retrospective cohort	IL-6 - higher in AAW	•	IL-6 highly differentially expressed among AA and CA breast cancer patients. High expression of IL-6 in AA associated with increased breast cancer risk
Gillespie SL et al. 2016(88)	CAW (n = 43) AAW (n = 41)	Prospective cohort	IL-6 – higher in AAW IL-1β – higher in white women	•	IL-6, IL-1β, and TNF-α levels change significantly during pregnancy. Cytokine production was highly similar among AAW and CAW
Yao S et al., 2018(89)	CAW (n = 855) AAW (n = 914)	Case-Control	CCL2, CCL11, IL4, IL10 – higher in white women IL1RA, IFN-α2 – higher in AAW	•	Levels of proinflammatory chemokines CCL2 and CCL11 strongly correlated with percent of African ancestry among AA
Murphy J et al., 2018(44)	CAW (n = 162) AAW (n = 130)	Prospective cohort	IL1-β - higher in white women	•	Higher levels of proinflammatory cytokine IL-1β in AAW compared to CAW

CA; Caucasian American, CAW; Cucasian American women, AA; African American, AAW; African-American women