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Breast Cancer and the Immune System

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Abstract

This article reviews the evidence that the functioning of both the innate and the adaptive immune system plays a role in preventing relapse in women with breast cancer. Lymphocytes, including T cells, T regulatory cells, and natural killer cells, and their cytokine release patterns are implicated in both primary prevention and recurrence of breast cancer. Cancer prognosis may be related to immune system functional status. The hypothesis that the immune system has a causal role in breast cancer etiology is supported by epidemiologic, preclinical, and clinical research. Empirical support for the concept that immune status and immunomodulatory therapy have important roles in comprehensive breast cancer treatment is provided.

Keywords

breast cancer; immune system

The past decade of immune system–based cancer clinical research has produced advances in breast cancer medicine in three areas: (1) growth factor therapy (granulocyte-macrophage colony-stimulating factor [GM-CSF] and granulocyte colony-stimulating factor [GCSF]) to manage and prevent chemotherapy-related leukopenia and neutropenia; (2) monoclonal antibody receptor blockade of the *HER2/neu* receptor site (trastuzumab) and the epithelial growth factor receptor site (bevacizumab); and (3) breast cancer vaccine phase I and II trials.

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Many unanswered questions remain about the role of the immune system in the pathophysiology and molecular biology of breast cancer. The full therapeutic potential of biologic and immunologic response modification has not been fully explored. The purpose of this article is to discuss how immunologic, inflammatory, and racial factors support the hypothesis that immune status is a useful marker to predict the risk of primary and recurrent or metastatic (secondary) breast cancer. This article argues that there are data to support the hypothesis that immune system status is a useful marker to predict the risk of primary, metastatic, and relapsed breast cancer. Lymphocytes, including T cells, T regulatory (T reg) cells, and natural killer (NK) cells, and their cytokine release patterns are implicated in both primary prevention and secondary prevention of breast cancer. Cancer prognosis may be related to immune system functional status, and experimental immunotherapies that modulate NK cell activity and T-cell function are currently in development.

Our breast cancer patients continue to ask what they can do to “boost” their immune system. Because of a lack of data, currently, very little can be recommended. There is no consensus that immune system status is relevant to cancer primary prevention, response to treatment, or secondary prevention. It is unclear whether white blood cell (WBC) and neutrophil status are adequate biomarkers of immune system function in regard to primary or secondary prevention. Other markers of immune system status besides total WBC and neutrophil counts exist, such as NK cell activity and cytokine levels. Naturopathic physicians who are board certified in naturopathic oncology often use these commercially available immunoassays to evaluate immune system status in breast cancer patients.

For a breast cancer immunomodulatory therapy to be useful, it must affect immune mechanisms known to play a role in pathogenesis, tumor growth rate, invasion, and metastatic spread. To take a potential synthetic, semisynthetic, or plant-based immunomodulatory therapy as a serious candidate for rigorous cancer research, the research community must be convinced that immune status has something to do with cancer biology and clinical outcomes. But is there convincing evidence that immune system status has an important role in cancer? Several key questions arise. Does immunosurveillance prevent breast cancer? Do women with immunologic disorders have a higher risk of breast cancer? Does immune system status following completion of standard therapy predict the risk of recurrence? These questions are addressed in this review article. Gaps in knowledge are defined, and support for the concept that immune system status and immunomodulatory therapy have important roles in comprehensive breast cancer treatment are provided.

Immune System Status and Breast Cancer

Immunologic Markers and Cancer: Does Immune System Function Prevent Primary or Relapsed Breast Cancer?

NK Cells—Evidence suggests that NK cells play an important role in prevention of both early and metastatic cancer.[1] Some breast cancer patients lack NK cell activity against K562 target cells.[2] NK cell activity levels are lower in women with positive nodal disease compared with node-negative women, 18% versus 31% lytic activity, respectively.[3] NK cell activity cytotoxicity was significantly lower ($p < .005$) in individuals with a high familial incidence of cancer compared with individuals with a low incidence of cancer.[4] Patients with head and neck cancers with NK cell activity less than 60 lytic units (LU) were more likely to develop distant metastatic disease than similar patients with LU > 60.[5]

Defects in NK cell-mediated cytotoxicity may play a role in the initial stages of human tumorigenesis. Significant differences were observed in several immune system parameters between healthy controls and women with advanced breast cancer prior to initiating a course of taxane-based chemotherapy, including depressed NK and lymphokine activated killer cell

toxicity, decreased levels of interleukin (IL)-2 (Il-2), GM-CSF, interferon- (IFN)γ, and increased levels of tumor necrosis factor (TNF)-α and IL-6.[6] NK cell activity was 175% lower and TNF activity was 100% higher in the breast cancer patients prior to treatment compared with healthy controls. Suppression of NK cell activity may be an important mediator of the tumor-enhancing effects of stress.7 Studies in women with breast cancer suggest that several aspects of host immunity are altered, including decrements in the number and function of NK cells.8›9 These deficits appear to be progressive and related to clinical stage.

Nevertheless, the role of NK cell activity in controlling breast cancer disease is still controversial. One study reported that women patients with benign breast disease showed NK cell activity that was not significantly different from NK cell activity in patients with malignancies in each of four different NK cell activity assays.[10] Sachs and colleagues reported that lymphokine-activated killer (LAK) cells, but not NK cell activity, correlated with the number of axillary nodes involved.[11] They also found that patients with estrogen receptor positive (ER^+) status had higher LAK cell activity. Additionally, this study found that breast cancer patients suffering from depression differed significantly in their LAK cell activity but not in NK cell activity. NK cell activity against K562 and MCF-7 breast carcinoma–derived cell lines has been studied using the chromium release test in 60 breast cancer patients.[12] Target cell lysis did not differentiate benign from malignant diagnoses. However, NK cell activity as measured by MCF-7 cell lysis was more related to prognostic tumor grading than NK cell activity, as defined by the lysis of leukemic K562 cells.

Although NK cell activity may be associated with factors related to cancer initiation and survival, few data address the question of whether enhancement of NK cell activity is of clinical benefit in cancer patients, let alone the question of whether modulation of NK cell activity in humans is achievable. Some tantalizing data have emerged from leukemia oncology. Remission in pediatric leukemia patients has been shown to be correlated with cytotoxic in vitro NK cell activity.[13] It is interesting to note that some integrated cancer clinics are offering NK cell therapy based on autologous ex vivo expansion with later reinfusion. Assessment of this immune therapy strategy awaits prospective outcomes and clinical trial results.

T-Cell Cytokines and Breast Cancer—Cytokines produced by T lymphocytes are critical to the efficacy of the immune system response. The view among most researchers is that solid tumors are (1) associated with a pathologic shift toward the T-helper type 2 (Th2) cytokine release pattern and (2) T-helper 1 (Th1)-induced inflammation inhibits tumor growth.[14] Clinical data present a more complicated picture.

Campbell and colleagues measured intracellular cytokine profiles of T cells in the peripheral blood of 85 women with breast cancer and correlated cytokine levels with the presence of micrometastases in lymph nodes and bone marrow.[15] Blood was drawn prior to breast cancer surgery and adjuvant therapy. The percentage of $CD4^+$ and $CD8^+$ T lymphocytes producing type 1 (IL-2, IFN-γ, or TNF-α) and type 2 (IL-4) cytokines was significantly lower in patients with breast cancer compared with healthy controls. These results indicate a general immune system dysfunction in these patients relative to a shift in the balance of type 1 and type 2 cells. The presence of micrometastatic cells in bone marrow was correlated with depressed cytokine levels. A notable association exists between immune system dysfunction as measured by IFN-γ and IL-2 and tumor cell load in the bone marrow. Breast cancer patients with larger rumors had a more depressed cytokine response. This immune system dysfunction was observed even in early-stage breast cancer patients, but there was no correlation with age, stage, or nodal status. Altered cytokine patterns may be both the cause and the result of breast tumors.

T Reg Cells and Breast Cancer—T reg cells are a defined subset of T cells that can inhibit both cell-mediated (Th1) and humoral (Th2) responses. These T reg cells are $CD4^+$ and

CD25^{hi} and express the transcription factor *Foxp3*.[16] Experiments in both mice and humans have shown that these T reg cells are critical for the maintenance of self-tolerance. In scurfy mice, mutations of *Foxp3* lead to diminished T reg populations and to the overwhelming autoimmune disease.[17] This is mirrored in humans when IPEX (immune system dysfunction, polyendocrinopathy, enteropathy, and X-linked inheritance disorder) patients have a severe polyautoimmune syndrome and mutations in *Foxp3*.

In cancer, there is evidence that T reg cells may be induced by tumors and downregulate the immune system response to tumor antigens. Akbar and colleagues showed that humans can induce T reg cells in the periphery and that T reg cells may be sensitive to apoptosis.[18] T reg cells may be dependent on constant antigenic stimulation to survive. T reg cells appear to be induced by tumors and may inhibit the normal immune system clearance of the tumor cells. Jarnicki and colleagues showed that T cells from a growing tumor in mice were suppressed by T reg cells that expressed *foxp3*, transforming growth factor β (TGF-β), and IL-10.[19] These findings suggest that tumor growth increases T reg cells, and the T reg cells can shut off the normal immune system response to the tumor. Liyanage and colleagues showed that T reg cells are increased in the peripheral blood and greatly increased in the tumor microenvironment in humans with breast adenocarcinomas.20 Knutson and colleagues extended this finding in a mouse model of breast cancer and showed that T reg cells were increased in a spontaneous mouse model of breast cancer.21 They then showed that specific depletion of the T reg cells markedly inhibited tumor growth and maintained a strong and persistent antitumor immune response. This response was specific since adoptive transfer of T reg cells into the T reg cell–depleted mice completely abrogated the immune response. In summary, T reg cells may be "turning off" the normal immune system response to tumors, and the failure of immune system–based therapies in breast and other cancers may be due to this effect. Any natural substance that can shut off or prevent the development of T reg cells in breast cancer could synergize with normal or enhanced immunity to assist in tumor killing.

Summary—Lymphocytes, including T cells, T reg cells, and NK cells, and their cytokine release patterns are implicated in both primary prevention and secondary prevention (ie, relapse or recurrence) of breast cancer. Cancer prognosis may be related to immune system functional status. Experimental immunotherapies that modulate NK cell activity and T-cell function are in development.

Contributing Immunologic Factors: Environment and Race

Environmental Factors in Breast Cancer Etiology

Pesticides: The Breast Cancer Action group reported that US breast cancer rates are highest in four coastal areas (Cape Cod, MA, Marin County, CA, Long Island, NY and The Greater Puget Sound in the Pacific Northwest). Some have hypothesized that these regions have in common a low elevation and therefore location at the bottom of water sheds. Chemicals that have already been established as being linked to increased breast cancer rates in the last 60 years include xenoestrogens (eg, bisphenol A, diethylstilbesterol, polyvinyl chloride, dieldrin), organochlorine pesticides (DDT and polychlorinated biphenyls), solvents used in many industries, aromatic amines from the plastic and chemical industries, 1,3-butadiene, polycyclic aromatic hydrocarbons, and ethyl oxide from internal combustion engines.[22] Racial disparities in breast cancer may be partially related to environmental exposures that are likely multifactorial and complex. There are too few data to even speculate on the possible links between environmental causes and racial disparities of breast cancer. Research in this area is just now beginning.

Vitamin D: Recent evidence shows that vitamin D may have a protective effect against the development of breast cancer and breast cancer progression.[23] Studies have shown that vitamin

D is able to inhibit the growth of breast cancer cells in vitro,[24–26] and epidemiologic studies in the United States have concluded that the risk of breast cancer is inversely proportional to the intensity of local sunlight.[27,28] An observational study by Palmieri and colleagues showed that serum levels of 1,25-dihydroxyvitamin D are higher in normal women than in patients with primary breast cancer and higher in women with early-stage breast cancer compared with women with locally advanced or metastatic disease.[29,30] It is unclear whether low vitamin D is causally related to more advanced cancers or is the result of changes in activities of daily living associated with a cancer diagnosis. African American women are also at risk of vitamin D deficiency because ultraviolet light from sunlight penetrates less in darker skin.

The two naturally occurring forms of vitamin D are cholecalciferol (vitamin D_3) from animal sources) and ergocalciferol (vitamin D_2, from plant sources). The predominant source of vitamin D is exposure to sunlight.28 Factors associated with low vitamin D status include aging, estrogen deficiency, liver or kidney disease, medications, diet, and limited sunlight exposure.[31] The major circulating form of vitamin D is 25-hydroxycholecalciferol [25(OH) D_3]. This form of vitamin D is activated in the liver and stored in adipose tissue and is considered to be an accurate biomarker of the body's overall vitamin D status. 25(OH)D_3 is further metabolized to 24,25-dihydroxycholecalciferol [24,25$(OH)_{2a}D_3$], which does not readily bind the vitamin D receptor (VDR) and is considered an inactive metabolite, or lα,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$], which has the ability to bind the VDR in an endocrine manner, affecting calcium homeostasis, or in an autocrine or paracrine manner, affecting cells locally in vitamin D–target tissues.[31] 1,25$(OH)_2D_3$ has been shown to possess both immunomodulatory actions and effects on cell proliferation and differentiation.

The detection of vitamin D receptors in human peripheral blood mononuclear cells led to the idea that vitamin D may possess immunomodulatory properties.[32,33] Vitamin D deficiency has now been linked to the development of various autoimmune diseases and is implicated in the pathogenesis and progression of various cancers. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], inhibits development of some but not all autoimmune diseases. Moreover, it has not been effective in improving immunity to infectious organisms. The effects of vitamin D on the immune system appear to be related to the nature of the immune system response. The VDR, in addition to vitamin D, plays a role in immune system status, and deficiencies in vitamin D or the VDR have been shown to worsen inflammatory bowel disease (IBD) status but do not appear to affect the severity of experimental asthma.[34]

1,25$(OH)_2D_3$ has a direct effect, on Th1 and Th2 function. Mahon and colleagues showed that activation of $CD4^+$ T cells increased expression of VDR fivefold.[35] Th cells treated with 1,25 $(OH)_2D_3$ resulted in decreased proliferation and decreased cytokine production. In VDR-deficient mice, 1,25$(OH)_2D_3$ was shown to increase IFN-γ production and decrease the production of IL-2- and Th2-associated cytokines, perhaps pointing to a stronger Th1 response in vitamin D-deficient environments and subsequent increased risk for autoimmune dysfunction and carcinogenesis. In a murine model, exposure to T cells preferentially expressing Th1 cytokines led to the development of IBD-like symptoms.36,[37] Concurrent vitamin D deficiency accelerated the development of these symptoms in IL-10 knockout (KO) mice.[37] IL-10 KO vitamin D–deficient mice succumbed to IBD-like disease beginning at 6 weeks of age, whereas IL-10 KO vitamin D–replete mice remained symptom free until 12 weeks of age.34

Vitamin D compounds have the ability to regulate growth factor and cytokine signaling specifically in breast cancer cells.[38] Insulin-like growth factor 1 (IGF-1) is a potent mitogen and may interfere with apoptosis.[39–4l] IGF-1 receptors are overexpressed in many breast cancer cell lines.28 Vitamin D analogs inhibit mitogenic activity of IGF-1 in breast cancer cell lines by increasing the expression of IGF-1 binding proteins, which serve to decrease the levels

of free cytokine available to interact with the IGF receptor.[38,42] Vitamin D may also diminish the antiapoptotic effects of IGF-1, although the mechanism is unclear.

The effects of TNF-α on MCF-7 cells are potentiated by pretreatment with vitamin D analogues,[43] which serves to enhance phospholipase A_2 and nuclear factor κB activation and increase expression of TNF receptor 1 and cathepsin D,[38,44] Breast cancer cells treated with vitamin D in vitro demonstrated increased production of TGF-β, an inhibitory growth regulator, measured in the culture medium, and upregulation of TGF-β receptors.[28,45–48]

A Th1 immune system response is prominent in vitamin D and VDR-deficient environments, which, in combination with Th2 suppression, may predispose the host to the development of autoimmune disease and increased cancer risk. It appears that vitamin D exerts its protective effects through the regulation of growth factor and cytokine signaling and by altering the balance between Th1 and Th2, allowing for improvement in the body's ability to mount a defense against tumors and other intracellular pathogens.

The Inflammatory Hypothesis—In the last 15 years, cancer biology research has led to the hypothesis that chronic inflammation involving T lymphocytes is a possible pathophysiologic pathway to breast adenocarcinoma.[49–54] Exposure to proinflammatory endogenous molecules and exogenous gene-modifying toxins is also thought to lead to damaged genome involving "tumor suppressor" genes, such as *P53*. IFN-related pathways may be particularly important. Using a bioinformatics approach with genetic data from leukemia patients, Einav and colleagues reported that there is a group of 30 genes related to the IFN response pathway.[55] In their study, 40% of the breast cancer samples expressed an IFN-related pathway, thus relating breast cancer to an inflammatory etiology.

Several environmental and lifestyle factors are known to increase breast cancer risk, including high–animal fat diets, alcohol, and exposure to organochlorine-based pesticides, including DDT and its metabolites. Some of these chemicals have inflammatory immune system effects of their own. There are likely racial and socioeconomic disparities in exposure to toxins and a high-fat diet.

Racial Disparities in Breast Cancer and Immune Status: African American Women Have More Aggressive Breast Cancer—Although African American women are less likely to be diagnosed with breast cancer than Caucasian women, they are more likely to die from it.[56–62] African American women typically have breast carcinomas that exhibit more aggressive breast tumor characteristics,[56,63–66] have later-stage tumors at diagnosis,[56,64–67] present with larger tumors,[62,64,65,68,69] have a greater likelihood of having positive lymph node involvement,[65,66] have higher histologic and nuclear grade tumors,[63,65,66] have lower socio-economic status,[65,70,71] are more likely to be ER^- and/or progesterone receptor negative (PR^-),[56,63,65,66,68,72,73] have higher S phase and mitotic indexes,[63,66] have higher body mass index and obesity rates, are diagnosed at a younger age,[62,65–67,74] are more likely to have inflammatory breast cancers,[60] and are less likely to survive a breast cancer diagnosis. Proposed explanations for the observed survival rate discrepancy have included race [58,59,61,62,67,74–76]; socio-economic status [58,65,67,70,71,77,78]; disease stage at diagnosis[56,64–67]; access to equal care[57,62]; insurance status[57]; tumor characteristics[56,60,62–69,72,73,79]; timing between symptom detection, diagnosis, and treatment[69,73]; obesity[65,80,81]; and cultural factors.[67] Yet the results from many of these studies have been contradictory, and research examining additional factors is needed to better understand the observed survival rate discrepancy between populations.

African American Women Have Higher Mortality from Breast Cancer: Lower socioeconomic status has been linked to decreased cancer screenings, more advanced tumor

stage at diagnosis, longer delays between diagnosis and treatment, and decreased survival rates.[67,70,77,78] Inconsistent results have been reported as to the effect of race on survival prognosis. Several studies reported that when disease stage and treatment were equivalent, survival disparities between African American and Caucasian women were no longer statistically significant.[70,74,75,80] Conversely, other studies have concluded that racial disparities in survival rates persist despite diagnosis at equivalent stages and comparable treatment.[58,59,61,62] African American women treated in the US military equal-access medical system who received standardized cancer treatment had an increased survival rate when compared with other African American women nationally but continued to have a decreased survival rate when compared with their Caucasian counterparts receiving the same standardized military medical care.[62] In a large, population-based study of 135,424 women, Joslyn and West reported that significant racial disparities in survival remained even after controlling for additional risk factors.[67]

African American Women Have a Greater Risk of Inflammatory Breast Cancer: Differences in breast tumor biology have been consistently reported between African American and Caucasian populations. African American women more commonly have breast carcinomas that exhibit more aggressive characteristics, such as inflammatory breast cancers.[56,60,63,65,66,72,73] Data from the Surveillance, Epidemiology and End Results (SEER) registries database (collected from 1988 through 2000) revealed that African American women were more likely to have inflammatory breast cancer than Caucasian women. The average survival time for African American women with inflammatory breast cancer was 2 years, whereas Caucasian women survived an average of 3 years.[60]

Steroid Hormone Receptor Site-Negative Cancers and Gene Mutations Are More Common in African American Women—Chu and colleagues and Gapstur and colleagues identified disparities in ER and PR status between racial groups. ER^-/PR^- tumors occurred more frequently in African American populations than in Caucasian populations, even after adjusting for tumor size, tumor histology, and patient age.[68,72] Mehrotra and colleagues found that when compared with Caucasian women with ER^-/PR^- status, African American women with ER^-/PR^- status displayed an increased expression of gene methylation in four of five genes investigated and had a higher prevalence of multiple methylation genes per tumor.[78] The hypermethylation-mediated inactivation of gene expression may provide a molecular explanation for observed tumor growth–promoting factors. Different rates of methylation occurrence between racial populations may explain some of the distinct clinical and pathologic tumor features observed more frequently in African American women.

African American women also exhibit a greater prevalence of *P53* mutations than their Caucasian counterparts.[65,83] Alterations in *P53*, a tumor suppressor gene, have been shown to have a deleterious effect on breast cancer prognosis.[84] Caleffi and colleagues found an increased proportion of *P53* mutations, identified by deoxyribonucleic acid (DNA) sequencing, in African American women compared with Caucasian women.[83] Racial differences in *P53* expression remained even after adjusting for prognostic and other factors.[65] Differences in the biology of breast cancer between black and white populations support the hypothesis that race is an independent risk factor in determining prognosis.

African American women tended to carry more allelic variants responsible for increasing the expression of proinflammatory cytokines and decreasing the expression of immunosuppressant cytokines.[71] Comparing African American and Caucasian populations, Martin and colleagues reported substantial differences in the allele frequencies of 13 of 17 immunomodulatory genes tested.[85] This study implies that African American populations may have different genetically predisposed immune system responses to disease than Caucasian populations. These differences could potentially contribute to the more unfavorable disease outcomes observed in

breast cancer. Results from genetic research demonstrate disparities in immune system function between different racial populations. The diversity in the expression of proinflammatory cytokines may be connected to the observed survival rate differences between Caucasian and African American women.

African American Women Are More Likely to Be Leukopenic and Receive Less Dose-Dense Chemotherapy—In studies of healthy populations, African American women were found to have lower WBC and absolute neutrophil counts than women of European American ancestry.[86] Depressed WBC and neutrophil counts in African American women have important clinical results. Owing to a lower baseline WBC count, African American women with breast cancer required a longer duration of chemotherapy treatment than Caucasian women, resulting in overall lower–dose intensity treatments.[87]

Research Is Needed on Breast Cancer in African American Women—African American women have more severe breast cancer at diagnosis and are more likely to die of breast cancer compared with white women. African American women, both healthy and those with breast cancer, have genetic, immune system status, and cytokine differences from Caucasian women. These discrepancies may be partially, perhaps largely, the result of disparities in socioeconomic status, access to health care, exposure to gene-modifying toxic and proinflammatory chemicals, and immune system status at diagnosis. Some of the immune system disparities may be related mechanistically to the immunosuppressive action of sustained stress-related cortisol production. Much more research is needed to explain the biologic causes and consequences of racial breast cancer disparities. Such research should include the effect of racial and poverty-related stress on the immune system and the effect of cortisol and other stress hormones on the incidence rates of breast cancer.

Do Women with Immunologic Disorders Have a Higher Risk of Breast Cancer?

If immune system dysfunction has a role in the pathophysiology of breast cancer, then women with other diseases involving immune system dysfunction may have different relative risks for breast cancer. We have compared breast cancer incidence in six diseases known to be causally linked to immune dysregulation: autoimmune thyroiditis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and leukemia.

Women with breast cancer have elevated thyroid autoantibody titers compared with noncancer patients and colon cancer patients.[88] It is not known if high rates of autoimmune thyroiditis are the result of breast cancer treatment, possibly radiotherapy, or the result of a shared common causal factor.

Breast cancer risk, but not overall cancer risk, is higher in women with multiple sclerosis.[89] This increased risk of breast cancer in women with multiple sclerosis was not related to reduced parity or delayed first child birth.

Patients with SLE have an increased risk of malignancy, with breast, lung, and gynecologic malignancies being the most common cancers observed in the Chicago Lupus Cohort (N = 616).[90] Breast cancer was significantly increased in the women in this cohort. Women with lupus also have an increased risk of breast cancer, even after controlling for hormone replacement therapy and oral contraceptive history.[91] The increased risk of breast cancer in an SLE cohort was not completely explained by the usual factors in the Gail model. Other factors, such as carcinogenic exposures from alkylating agents and immunosuppressive drugs and the immune system dysregulation of SLE itself, may be contributory.[92]

In the Danish Cancer Registry, women with rheumatoid arthritis were more likely to have colorectal cancer, lymphoma, and lung cancer but were less likely to be diagnosed with breast cancer.[93] Sarcoidosis is an idiopathic systemic inflammatory granulomatous disorder involving epithelioid and multinucleated giant cells. Breast cancer rates in women with sarcoidosis do not differ from the expected frequency for all women.[94] Oluwole and colleagues reported that neither the rate of breast cancer nor the 5-year survival differed from those of non-HIV-infected women.[95]

Some but not all immunologic disorders are associated with an increased risk of breast cancer. Women with autoimmune thyroiditis, multiple sclerosis, and lupus have a higher risk of breast cancer, but it is not clear yet whether some of this risk is due to the immunosuppressive treatments used in these disorders or the immune system dysfunction itself. There is no evidence that rheumatoid arthritis, sarcoidosis, or HIV infection puts women at higher risk of developing breast cancer.

Immunologic Consequences of Conventional Breast Cancer Treatment

Immunologic Effects of Chemotherapy and Radiotherapy—Cyclophosphamide-methotrexate-5-fluorouracil (CMF) chemotherapy regimens have been shown to significantly decrease both spontaneous and IFN-stimulated NK cell activities. NK cell activity against the K562 cell line in patients who had received adjuvant chemotherapy combined with radiotherapy was significantly lower than that of patients after radiotherapy alone or that of healthy controls.[96] Tsavaris and colleagues studied the immunologic effects of taxane-based chemotherapy on 30 women with advanced breast cancer.6 Sera were collected before the start of chemotherapy and after the last treatment cycle and were compared with those from healthy controls. Compared with healthy controls, these breast cancer patients had depressed. NK cell LAK cytotoxicity and depressed GM-CSF, IL-2, IL-6, and TNF-α. Both paditaxel and docetaxel increased NK and LAK cell activity and increased IL-6, GM-CSF, and IFN-γ levels while decreasing IL-1 and TNF-α levels. A better clinical response in these metastatic breast cancer patients was associated with greater increases in serum IFN-γ, IL-2, IL-6, and GM-CSF cytokine levels and enhancement of peripheral blood mononuclear cell NK and LAK cell activity.

It is also possible that chemotherapy has beneficial effects on immune status in breast cancer patients. Cyclophosphamide, for example, has been shown to suppress T reg cells. For this reason, the University of Washington Tumor Vaccine Group pretreats women receiving their *HER2/neu* vaccine with cyclophosphamide to suppress T reg cells. Taxanes as well have been shown to increase NK cell activity in breast cancer patients.6,[97] Trastuzumab (Herceptin) also has been shown to stimulate NK cell activity.[98]

Although some chemotherapy agents, especially the taxanes, have immune system–enhancing activity, radiotherapy has been shown to suppress most immune markers. In a study of 27 patients with several types of adenocarcinoma, radiotherapy alone decreased WBC and lymphocyte counts, as well as NK cell activity.[99] Breast irradiation produces significant leukopenia in both young and older women with breast cancer.[100] Patients undergoing radiation therapy for solid tumors show a decreased number of T lymphocytes and an altered helper to suppressor ratio.[101] What is not yet known is whether the radiotherapy-related lymphopenia represents a decrease in T reg cells.

Immunologic Disorders Associated with Breast Cancer Treatment—Myelodysplastic syndrome (MDS) is a severe immnunologic complication in breast cancer patients and has been related to several chemotherapy drugs and to radiotherapy of the breast. The 10-year incidence of secondary acute myelogenous leukemia (AML) or MDS after systemic chemotherapy is approximately 1.5%.[102] Breast cancer patients given mitoxantrone

with methotrexate or methotrexate and mitomycin had a 10 times higher risk of subsequent MDS or AML compared with that seen in the general population.103 The dose of doxorubicin or epirubicin, chemotherapy agents used in combination with cyclophosphamide, is also related to the risk of MDS in breast cancer patients.104

The relative risk of chemotherapy treatment–related AML and MDS was correlated with dose density rather than cumulative dose of standard doxorubicin and cyclophosphamide. Administration of G-CSF may also be independently associated with the risk of AML and MDS in breast cancer patients.[105] The use of G-CSF was associated with a doubling in the risk of subsequent AML or MDS.[106] In another study, the risk of developing AML or MDS increased in relation to planned epirubicin dose per cycle. Higher doses of epirubicin and cyclophosphamide were associated with greater 8-year cumulative risk.[104] Breast radiotherapy has also been associated with an increased risk of AML and MDS.[105]

Does Immune System Status Following Completion of Standard Therapy Predict Risk of Recurrence?

Research is just beginning to address this question. Some data from head and neck cancer suggest that high NK cell activity status predicts a lower risk of recurrence following standard treatment. Preliminary data from breast cancer patients suggest that taxane-based therapy is as effective as adjunctive breast cancer treatment owing to its cytotoxic activity and its immunomodulatory effects on NK cell activity and T-cell cytokine secretion.[6] Research at the University of Minnesota and Bastyr University Developmental Clinical Research Center, funded by the National Center for Complementary and Alternative Medicine (NCCAM), reported that a 6-week course of standard radiotherapy results in lymphopenia, low NK cell activity, low macrophage phagocytic activity, and depressed TNF-α production. Immune system defects were more severe in patients who received locoregional radiotherapy compared with breast radiotherapy only.[107]

Summary

Given the evidence discussed in this article, the hypothesis that immune system status is implicated in prevention of breast cancer relapse deserves consideration and further investigation. Both chemotherapy and radiotherapy have immunologic consequences in breast cancer patients. Some rare consequences, such as leukemia and MDS, are dire. Other immunologic effects of chemotherapy drugs, such as the taxanes, may be beneficial to immune system mechanisms underlying an effective host response to cancer treatment. In the future, chemotherapy choice may be based not just on chemosensitivity testing but also on immune system status and the specific immune system deficits of the patients. We still do not know if immune system status following completion of standard treatment has a role in preventing a recurrence of breast cancer after primary treatment. Immunologic research suggests that innovative immunotherapies should be targeted to improve Th1 activity, increase NK cell activity, and suppress T reg cells. A central hypothesis of the NCCAM-funded University of Minnesota and Bastyr University Developmental Center is that improving immune status following breast cancer treatment using plant-based therapies may improve disease-free survival.

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