

Breast Cancer Risk and Immune Responses in Healthy Women

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Purpose/Objectives: To summarize the findings of objective and subjective breast cancer risk assessments and their association with psychological distress and immune responses in healthy women with a family history of breast cancer.

Data Sources: Published articles and book chapters.

Data Synthesis: Healthy women with a family history of breast cancer have shown decreased immune responses (i.e., low natural killer cell activity and low Th1 cytokine production), exaggerated biopsiologic reactivity to stimuli, and increased psychological distress.

Conclusions: Objective and subjective breast cancer risk is associated with impaired immune responses and exaggerated biopsiologic responses in healthy women with a family history of breast cancer. Increased psychological distress can contribute further to negative immune responses. Additional studies are warranted to substantiate and extend the findings based on more comprehensive assessments of objective and subjective breast cancer risk.

Implications for Nursing: Biopsiologic assessment is a useful approach for nurses in early identification of women at risk for breast cancer and developing appropriate strategies to reduce the risk.

Key Points . . .

- ▶ The immune system is the major defense mechanism against tumor insult.
- ▶ The study of objective and subjective breast cancer risk on immune responses needs to be expanded.
- ▶ Impaired immune responses, either inherited or induced by psychological distress, may account for a mechanism underlying an increased risk of developing breast cancer in women with a family history of the disease.
- ▶ Selective impaired immune responses may serve as biopsiologic markers for early identification of women at increased risk for developing breast cancer.

Breast cancer is the most common cancer among American women, and an estimated 212,920 new cases will be diagnosed in 2006 (American Cancer Society [ACS], 2006). Despite advances in early detection and treatment, breast cancer remains the second-leading cause of cancer death among American women, and the incidence rate has continued to increase in the United States since the 1980s (ACS). Greater attention clearly is needed regarding early detection of at-risk women and risk reduction for breast cancer. One step toward that goal is a better understanding of breast cancer risk assessment and its relationship between breast cancer risk and immune responses.

Breast cancer is a multifactorial disease of gene-environment interactions. Breast cancer is categorized largely into hereditary and sporadic breast cancer based on its etiology. Hereditary breast cancer accounts for 5%–10% of all breast cancer cases (McCance & Jorde, 1998) and is accompanied by a strong genetic predisposition with inherited germline mutations, predominantly in the breast cancer susceptibility genes *BRCA1* and *BRCA2* (Pasacreta, 1999). Germline mutations are present in all cells of the body and can be passed on from one generation to the next. However, not all women with germline mutations develop breast cancer, indicating additional complexity and gene-environment interactions in the phenotypic expression of the disease. Most breast cancer is sporadic without genetic predisposition. In sporadic breast cancer, mutations in somatic cells are precipitated by envi-

ronmental factors (Pasacreta; Pharoah, Stratton, & Mackay, 1998), clearly indicating the significance of gene-environment interactions in the development of breast cancer.

The known breast cancer risk factors are female gender, age, family history of breast cancer, reproductive and menstrual history of early menarche, late menopause, late first live birth, current and previous hormone therapy, exposure to radiation, mammographic breast density, lifestyle factors (e.g., exercise, diet, alcohol intake), and history of benign breast disease (ACS, 2006). In particular, a family history of breast cancer increases the risk for developing the disease by two to three times (Pharoah, Day, Duffy, Easton, & Ponder, 1997; Slattery & Kerber, 1993). The risk for developing breast cancer is even greater if the affected relatives are younger, the number of affected relatives is larger, and the

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biologic relationship is closer (Pharoah et al., 1997, 2000). An estimated 6%–19% of the general population have a family history of breast cancer (i.e., having blood-related relatives diagnosed with breast cancer) (Hoskins et al., 1995). A positive family history of breast cancer contributes to sporadic and hereditary breast cancer because of shared genetic susceptibility or a shared environment and lifestyle within the family (Pharoah et al., 1998). Furthermore, a strong family history with early-onset or bilateral breast cancer, male breast cancer, two or more breast or ovarian cancer cases in first-degree relatives (i.e., parents, siblings, and children), and multiple breast or ovarian cancer cases across several generations suggest the presence of increased risk for hereditary breast cancer (Thull & Farengo-Clark, 2003). Having risk factors or a genetic predisposition, however, does not always predict the development of breast cancer (Mahon, 1998), and not all breast cancer risk factors may have been discovered.

The average lifetime risk for breast cancer in American women is 13.22% (ACS, 2006). However, risk differs among individuals and needs to be assessed based on genetic and environmental background (Hutson, 2003; Mahon, 1998; Rebbeck, 1999). The Gail and Claus models are the two most common models used in breast cancer risk assessment. The models provide an objective assessment of breast cancer risk, but women typically have their own subjective assessment of risk (Rhodes, 2002), which frequently serves as a source of psychological distress (Bovbjerg & Valdimarsdottir, 2001; Zakowski et al., 1997). Psychological distress is known to influence various immune responses (Cohen et al., 2002; Cohen & Pollack, 2005); for example, women with breast cancer and their unaffected family members have decreased immune responses (Baxevanis et al., 1993; Shevde, Joshi, Shinde, & Nadkarni, 1998; Strayer, Carter, & Brodsky, 1986). Given the significant role of the immune system in tumor defense, the links between objective and subjective breast cancer risk and immune responses need to be examined further. Current research in this area is limited.

The purpose of this review is to summarize what is presently known about (a) immune responses in breast cancer; (b) breast cancer risk assessment; (c) the relationship between breast cancer risk and immune responses; (d) the relationship among breast cancer risk, psychological distress, and immune responses; and (e) recommendations for future research, focusing on healthy women with a family history of breast cancer.

Immune Responses

The Immune System

The immune system is the major defense mechanism against tumor insult. The highly integrated networks of cells, tissues, and organs collectively protect the body from the growth of tumor cells through nonspecific and specific (humoral and cellular) immune responses (Goldsby, Kindt, & Osborne, 2000). Decreased immune responses may lead to decreased immunosurveillance against tumor cells and increased risk of cancer development (Garssen & Goodkin, 1999; Trinchieri, 1989; Whiteside & Herberman, 1995). The immune system is responsive to psychosocial factors, and psychological distress is known to induce multiple immune alterations (Segerstrom & Miller, 2004; Zorrilla et al., 2001). A certain group of immune parameters are selected for their

relevance to tumor immunosurveillance and psychological distress for this review. The immune parameters include natural killer (NK) cell activity, lymphokine-activated killer (LAK) cell activity, T-lymphocyte proliferation, and cytokine production (Brittenden, Heys, Ross, & Eremin, 1996; Kang, 2003; Kiecolt-Glaser, Robles, Heffner, Loving, & Glaser, 2002).

NK cells play a major role in early immunosurveillance against tumor cells without prior sensitizations and restriction of major histocompatibility complex, which make NK cells particularly effective in early antitumor activity (Brittenden et al., 1996). When NK cells are incubated with a lymphokine or cytokine, such as interleukin-2 (IL-2) and interferon-gamma (IFN- γ), some cells proliferate and differentiate into aggressive killer cells with NK-like activity, referred to as LAK cells (Spaner, Radvanyi, & Miller, 1998). T cells are a major group of lymphocytes involved in specific immunity and are clustered into three major subtypes: T-helper, T-suppressor, and T-cytotoxic cells. T-helper cells are pivotal in initiating and sustaining immune responses, whereas T-suppressor cells downregulate the immune response preventing its overactivation; T-cytotoxic cells kill cells that express foreign or non-self antigens (Kang & Fox, 2001). Decreased T-lymphocyte proliferation reflects the downregulation of normal immune responses (Kiecolt-Glaser & Glaser, 1997).

Cytokines are immunopeptides that function as a major signal of cell-to-cell communications for immune activation and regulation. Many cells of the body can produce some cytokines, but T-helper cells are the major source of cytokines. T-helper cell cytokines are classified further into Th1 (e.g., IFN- γ , IL-2, IL-12), which primarily enhances cellular immunity, and Th2 (e.g., IL-4, IL-6, IL-10), which facilitates humoral immunity (Del Prete, Maggi, & Romagnani, 1994). The cytokines may have counterregulatory functions for each other, but the balance of Th1- and Th2-type cytokines is believed to be important in tumor defense (Paul & Seder, 1994).

Immune Responses in Breast Cancer

Although some reports are conflicting, a general consensus acknowledges that women with breast cancer have significantly lower immune responses than healthy women in various immune parameters. Women with breast cancer, for example, have lower NK cell activity than healthy women in general populations prior to their surgery or treatment (Baxevanis et al., 1993; Shevde, Joshi, Dudhat, Hawaldar, & Nadkarni, 1999). Shevde, Rao, et al. (1998) reported that women with breast cancer, including those before surgery and adjuvant treatment as well as those at least one year after treatment, demonstrated lower NK cell activity than healthy controls. In addition, preoperative immune findings indicate that women with the most advanced stage (stage IV) of breast cancer had the lowest NK cell activity compared with women with stages I–III and healthy controls (Konjevic & Spuzic, 1993), suggesting a greater immune impairment with advances in breast cancer stage. When women who were disease free after treatment for breast cancer had the highest quartile of NK cell activity at baseline, they survived longer without metastasis than women having the lowest quartile of NK cell activity, demonstrating baseline NK cell activity as a possible prognostic indicator (Pross & Lotzova, 1993).

The findings of LAK cell activity were similar to those of NK cell activity. Before surgery and cancer treatment, women

with breast cancer have lower LAK cell activity compared with women with nonmalignant breast tumors (Sachs et al., 1995) and healthy individuals (Baxevanis et al., 1993). Furthermore, lower LAK cell activity was related to an increased number of lymph nodes involved (Sachs et al.).

For T-cell responses, preoperative T-lymphocyte proliferation responses were lower in women with breast cancer than healthy controls, and lower T-cell responses were related to the advanced stage of the disease indicated by larger tumor size and positive lymph node status (Shevde et al., 1999; Wiltshcke et al., 1995). In addition, Wiltshcke et al. found that women who showed a reduction in T-lymphocyte proliferation in the first year following surgery had a higher incidence of metastasis during the subsequent three-year period than those who showed an increase in the T-cell response.

Similarly, women with breast cancer showed lower Th1-type cytokine levels, such as IFN- γ , IL-2, and IL-12, before surgery and treatment compared with healthy controls (Campbell, Scott, Maecker, Park, & Esserman, 2005; Merendino et al., 1999). Lower IL-2 levels were associated with a higher rate of breast cancer relapse during a follow-up period (i.e., 10–12 months) in women who were treated for breast cancer and disease-free for more than six months following the completion of cancer treatment (Arduino et al., 1996).

The findings collectively indicate that women with breast cancer have multiple impairments in the immune system, although the causality between impaired immune responses and breast cancer development needs to be determined further. Given the complexity of the immune system and the effects of tumor and antitumor treatment on the immune system, debate is ongoing as to whether the suppressed immune responses are a cause of the disease or a result of the course of disease (Brittenden et al., 1996; Whiteside & Herberman, 1995). The limited sample sizes for most of the studies further restrict reliable interpretations of the findings (Andersen, Kiecolt-Glaser, & Glaser, 1994; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Prospective and longitudinal studies with large sample sizes would help to clarify the debate. Long-term follow-up investigations of impaired and dysregulated immune responses in healthy individuals at increased cancer risk may provide important insight to the link of immune responses and susceptibility for cancer development (Cohen, 1994).

Psychological Distress and Immune Impairment in Breast Cancer

Psychological characteristics have been shown to influence immune responses in patients with cancer and healthy individuals. Psychological distress (e.g., depression, anxiety, intrusive thoughts) has been inversely associated with preoperative and pretreatment immune function, such as NK and LAK cell activity, in women with breast cancer (Sachs et al., 1995; Tjemsland, Soreide, Matre, & Malt, 1997). In women who had recent breast cancer surgery, higher levels of psychological distress (intrusive and avoidant thoughts concerning cancer) were associated with lower NK cell activity, decreased LAK cell activity, and diminished T-lymphocyte proliferation prior to adjuvant therapy (Andersen et al., 1998). The findings indicate that psychological distress is associated with reductions in multiple immune responses during the early course of breast cancer.

The magnitude of immune responses to the same distressful situation may vary among individuals (Zorrilla et al., 2001).

Personal appraisal and perception of the situation (Lazarus & Folkman, 1984) and coexisting physical health conditions (McEwen, 1998) may be key factors in interindividual variability. Neuroendocrine pathways or the sensitivity of the immune system may mediate the variability in the link between psychological distress and immune responses (Cohen, 1994). An understanding of objective and subjective breast cancer risk and psychological distress and their relationships with immune responses in healthy individuals at increased risk would help to advance knowledge in this area.

Breast Cancer Risk Assessment: Objective Versus Subjective

Breast cancer risk can be determined prior to the development of the disease by various genetic and biologic characteristics, personal health habits, lifestyle, or environmental factors (Lancaster, 2005). In the past, family history of breast cancer was a major source of breast cancer risk assessment, guiding the interpretation of the genetic and environmental context of disease (Loescher, 1999; Pharoah et al., 2000; Slattery & Kerber, 1993). Most data about a family history of cancer or breast cancer were obtained from self-reports based on individual memory and recall, raising concerns about the accuracy of data, especially cancer history in more distant relatives (Kerber & Slattery, 1997; Parent, Ghadirian, Lacroix, & Perret, 1997). Although many studies are examining genetic linkages to family history, the interactions of family history of breast cancer with other environmental risk factors have not been investigated adequately, partly because of the limited availability of comprehensive risk assessment models. A comprehensive model of breast cancer risk assessment should include many more relevant risk factors of breast cancer that are not included in the current assessment models. Also, models should provide a way of combining multiple risk factors into a composite estimate of the overall risk for developing breast cancer that can be useful for clinical counseling of women at risk (Sakorafas, Krespis, & Pavlakis, 2002).

Objective Breast Cancer Risk Assessment

Among several breast cancer risk assessment models, the Gail and Claus models are used most commonly, with each model having unique characteristics based on a different combination of risk factors (Baltzell & Wrensch, 2005; Domchek et al., 2003). The Gail model (Gail et al., 1989) may be more appropriate for women at risk for sporadic breast cancer, whereas the Claus model (Claus, Risch, & Thompson, 1994) may be a better assessment tool for women at risk for hereditary breast cancer (Brown, 2005). The Gail model estimates breast cancer risk based on the number of female first-degree relatives (mother, sisters, daughters) with breast cancer, the number of breast biopsies, age at first live birth, current age, age at menarche, atypical hyperplasia in biopsy, and race or ethnicity. The Gail model, however, does not consider a relative's age at diagnosis, second-degree relatives (grandmothers, aunts, nieces), paternal relatives, bilateral breast cancer, family history of ovarian cancer, or personal history of lobular neoplasia. In contrast, the Claus model is based on the assumed prevalence of a highly penetrant breast cancer susceptibility gene and incorporates greater details of family history of breast cancer in extended families. It assesses the family history of breast cancer in maternal and paternal first- and second-degree relatives as

well as the age of the relative at diagnosis of breast cancer. The Claus model neglects other common hormonal and clinical risk factors included in the Gail model and bilateral breast cancer in a family, thereby frequently underestimating risk in women with these types of risk factors (Euhus, 2001). In general, the Claus model is more useful for women with at least one female first- or second-degree relative with breast cancer, whereas the Gail model is more appropriate for women having risk factors other than a family history of breast cancer (Armstrong, Eisen, & Weber, 2000; Sakorafas et al., 2002). Because both models were developed from data on predominantly Caucasian women, their applicability to women of other ethnic backgrounds has been questioned (Bondy & Newman, 2003; Euhus).

The Gail and Claus models were developed before the discovery of *BRCA1* and *BRCA2* genes; as a result, the models do not directly address the probability of carrying genetic mutations. The BRCAPRO model (Parmigiani, Berry, & Aguilar, 1998) and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model (Antoniou et al., 2002; Antoniou, Pharoah, Smith, & Easton, 2004) have been developed to predict the carrier probabilities for genetic mutations in breast cancer susceptibility genes, mainly *BRCA1* and *BRCA2*. Although the BRCAPRO model considers the simultaneous effects of *BRCA1* and *BRCA2* only in calculating an individual's risk of carrying a mutation in these genes and of developing breast cancer, the BOADICEA model incorporates the simultaneous effects of *BRCA1*, *BRCA2*, and other low-penetrance genes on breast cancer risk into the risk estimation of carrying *BRCA1* and *BRCA2* mutations and of developing breast or ovarian cancer. The BOADICEA model provides a more comprehensive assessment of objective breast cancer risk based on genetic mutations. A summary for the comparison of the four risk assessment models is presented in Table 1.

Subjective Breast Cancer Risk Assessment

Regardless of the levels of objective breast cancer risk, every woman typically has her own subjective assessment of risk (Rhodes, 2002). Although objective risk assessment is based on the known risk factors of breast cancer, subjective risk assessment can be influenced strongly by personal belief and perception about breast cancer (Champion, 1999; Slovic, 1987). Objective components of breast cancer risk (e.g., the presence of actual breast cancer risk factor) also may influence a person's subjective risk assessment (Lancaster, 2005). For instance, women with a family history of breast cancer have shown significantly higher levels of subjective breast cancer risk compared with women without any family history (Erblich, Montgomery, Valdimarsdottir, Cloitre, & Bovbjerg, 2003; Valdimarsdottir et al., 1995; Zakowski et al., 1997). Zakowski et al. demonstrated a significant positive correlation between subjective and objective risk assessment from the Claus model that mainly relies on a family history of breast cancer. Evidence also exists that most women tend to overestimate their subjective breast cancer risk regardless of a family history of the disease (Davids, Schapira, McAuliffe, & Nattinger, 2004; Mouchawar, Byers, Cutter, Dignan, & Michael, 1999), suggesting that other factors contribute to subjective risk assessment. The overestimated subjective assessment of breast cancer risk was associated with increased psychological distress (Meiser et al., 2001; van Dooren et al.,

Table 1. Summary of Factors Included in Four Breast Cancer Risk Assessment Models

Factor	Model			
	Gail	Claus	BRCAPRO	BOADICEA
Age	X	X	X	X
Race or ethnicity	X	–	–	–
Family history of breast cancer				
First-degree relatives	X	X	X	X
Second-degree relatives	–	X	X	–
Age at onset of cancer	–	X	X	X
Bilateral breast cancer	–	–	X	–
Male breast cancer	–	–	X	–
Family history of ovarian cancer	–	–	X	X
Hormonal factors				
Age at menarche	X	–	–	–
Age at first live birth	X	–	–	–
Personal breast disease				
Number of breast biopsies	X	–	–	–
Atypical hyperplasia	X	–	–	–
Genetic factors				
<i>BRCA1</i>	–	–	X	X
<i>BRCA2</i>	–	–	X	X
Other low-penetrant genes	–	–	–	X

BOADICEA—Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm

2004; Zakowski et al.), particularly in women who cared for their mother and experienced the mother's death from breast cancer (Erblich, Bovbjerg, & Valdimarsdottir, 2000; Zakowski et al.). No correlation was found between objective breast cancer risk assessment and psychological distress (Zakowski et al.). Close associations between subjective risk assessment and psychological distress suggest that healthy women with heightened subjective breast cancer risk assessment may experience increased immune impairment because of high psychological distress.

Breast Cancer Risk and Immune Responses in Healthy Women

Objective Breast Cancer Risk and Immune Responses

Only a few researchers have investigated the immune-cancer link among healthy individuals at increased risk for developing any cancer. In earlier studies, healthy individuals with a family history of various types of cancer, including breast cancer, have lower levels of NK cell activity than individuals without a family history of cancer (Bovbjerg & Valdimarsdottir, 1993; Hersey, Edwards, Honeyman, & McCarthy, 1979; Strayer, Carter, Mayberry, Pequignot, & Brodsky, 1984; Strayer et al., 1986). Hersey et al. observed that a high proportion of patients with familial melanoma and their clinically asymptomatic first-degree relatives had lower levels of NK cell activity compared with patients with nonfamilial melanoma and their first-degree relatives, despite the fact that all patients were clinically free of melanoma at the time of the study. The levels of NK cell activity in the patients

who previously had the disease were significantly correlated with NK cell activity of their unaffected first-degree relatives, suggesting genetic or environmental determination in the family. Strayer et al. (1984) reported that healthy individuals with a high incidence of mixed types of cancer in the family (i.e., three or more cases among grandparents, parents, and siblings) had lower NK cell activity than individuals with a low incidence of cancer in the family (two or fewer cases). The findings remained stable after controlling for the effects of gender and smoking. In a subsequent study, Strayer et al. (1986) also found that healthy individuals at high risk for breast cancer (i.e., one case or more of breast cancer in first-degree relatives or two cases or more in second-degree relatives) had lower NK cell activity than those at low risk for the disease (i.e., no cases of breast cancer in first-degree relatives and one case or none among second-degree relatives). Even after controlling for the influence of psychological distress on NK cell activity, women with a family history of various types of cancer in first-degree relatives still demonstrated lower NK cell activity than those without any family history of cancer in first-degree relatives (Bovbjerg & Valdimarsdottir, 1993).

The early findings of low NK cell activity in healthy individuals with a family history of cancer raised a question as to whether impaired immune responses were inherited or were more pervasive in other multiple immune effector mechanisms, including an imbalance between Th1 and Th2 cytokines (Sredni et al., 1996). Dubey, Alper, Mirza, Awdeh, and Yunis (1994) found that low NK cell activity could be inherited as a recessive trait linked to the major histocompatibility complex gene, which was estimated in as many as 30% of Caucasians. Similarly, a wide range of impaired immune responses was found in unaffected members of families with a strong family history of breast cancer. Unaffected family members with a family history of breast cancer in at least two generations had significantly lower NK cell activity, lower T-lymphocyte proliferation response, lower T-cytotoxic lymphocyte function, and impaired lymphocyte responses to IFN- α and IL-12 compared with healthy controls without any family history of cancer (Shevde, Joshi, Advani, & Nadkarni, 1998; Shevde, Joshi, Shinde, et al., 1998; Shevde, Rao, et al., 1998). In a more recent study, Cohen et al. (2002) reported that daughters of women with breast cancer had significantly lower NK cell activity, lower LAK cell activity, and lower secretion of Th1-type cytokines (IL-2, IL-12, and IFN- γ), compared with controls who had healthy mothers. However, whether impaired immune responses are derived from objective or subjective breast cancer risk or both is unclear. In any case, immune impairments may be a potential mechanism facilitating a phenotypic expression of breast cancer in women at increased risk for breast cancer. More studies are warranted to substantiate the findings. A summary of immune profiles in women with a family history of breast cancer is presented in Figure 1.

Objective Breast Cancer Risk and Genetic Instability

Some researchers extended their investigations to cytogenetics, cellular aspects of the chromosome. Rao, Joshi, Shinde, Advani, and Ghosh (1996) reported that a lymphocyte culture from an unaffected family member with a family history of breast cancer showed constitutive genetic instability or chromosomal anomalies, such as premature separation of centromeres and aneuploidy. Genetic instability is known to play

Decreased Immune Responses

- NK cell activity ↓
- LAK cell activity ↓
- T-lymphocyte proliferation ↓
- Th1 cytokine production ↓
 - IFN- γ ↓
 - IL-2 ↓
 - IL-12 ↓

Increased Genetic Instability

- Cytogenetic anomalies ↑
- Deficient DNA repair capacity ↑

Increased Stress Hormones

- Cortisol ↑
- Catecholamine ↑

Increased Immune Reactivity to Acute Stressors

- NK cell activity ↑
- NK cell numbers ↑

Increased Neuroendocrine Reactivity to Acute Stressors

- Change in heart rate ↑
- Change in cortisol ↑
- Change in epinephrine ↑
- Change in norepinephrine ↑

↑—increase; ↓—decrease; IFN—interferon; IL—interleukin; LAK—lymphocyte-activated killer; NK—natural killer; Th1—T-helper type 1 cell

Figure 1. Biopsychologic Characteristics of Healthy Women With a Family History of Breast Cancer Compared With Healthy Controls With No Family History of Breast Cancer

a significant role in early events of carcinogenesis. Women with breast cancer and their first-degree relatives also have shown more deficient DNA repair capacity compared with healthy controls without any family history of cancer (Kovacs & Almendral, 1987; Parshad et al., 1996). Rao, Pai, Shinde, and Ghosh (1998) found that, compared with healthy controls without any family history, unaffected individuals with a family history of breast cancer had cytogenetic anomalies, as well as deficient DNA repair capacity, demonstrating genetic instability. Shevde, Rao, et al. (1998) also reported that, in addition to immune impairments, a significant number of unaffected family members with a family history of breast cancer had increased cytogenetic anomalies in their lymphocyte cultures compared with healthy controls without any family history of cancer. Taken together, individuals with cytogenetic anomalies and immune impairments may be at greater risk for cancer than those with only one or none of the anomalies. If the findings are substantiated in more studies, immune and cytogenetic parameters may become useful biopsychologic markers for women at risk of breast cancer.

Breast Cancer Risk, Psychological Distress, and Immune Responses

Subjective Breast Cancer Risk, Psychological Distress, and Immune Responses

Regardless of the actual objective risk of breast cancer, healthy women with a family history of breast cancer are shown to have significantly elevated levels of psychological distress

(e.g., intrusive thoughts) compared with those without any family history (Erblich et al., 2003; Kim, Duhamel, Valdimarsdottir, & Bovbjerg, 2005; Valdimarsdottir et al., 1995; Zakowski et al., 1997), identifying a family history of breast cancer as a potent chronic stressor (Bovbjerg & Valdimarsdottir, 2001). Similarly, a family history of breast cancer has been related to higher levels of subjective breast cancer risk, leading to increased levels of psychological distress (Valdimarsdottir et al., 1995; Zakowski et al.). Psychological distress is known to decrease various immune responses in healthy and ill populations (Bovbjerg & Valdimarsdottir, 1993; Cohen et al., 2002; Cohen & Pollack, 2005; Sachs et al., 1995; Tjemland et al., 1997) and can lead to negative health behaviors (e.g., smoking, drinking) (Bovbjerg & Valdimarsdottir, 2001; Trinchieri, 1989). Bovbjerg and Valdimarsdottir (1993) examined the associations among psychological (e.g., emotional distress) and behavioral variables (e.g., alcohol consumption) and NK cell activity in healthy women with a family history of various types of cancer. Women with a family history of cancer in first-degree relatives showed higher levels of distress at the time of a blood draw than those without any family history of cancer that were inversely related to the levels of NK cell activity. No differences existed in demographic or behavioral variables between women with and without a family history of cancer in first-degree relatives. In addition, decreased NK cell activity in women with a family history of cancer in first-degree relatives was independent of psychological distress. The findings indicate that a family history of cancer and psychological distress have direct negative effects on NK cell activity, a combination of which can be particularly detrimental to immune responses. Whether the combined effect is additive or synergistic needs to be tested further.

Some additional efforts have been undertaken to explore psychological and biopsychologic characteristics and their relationships in women with a family history of breast cancer, especially in first-degree relatives. Cohen et al. (2002) examined the relationship between psychological distress and immune function in daughters of women with breast cancer compared with controls whose mothers were healthy and never had cancer. Levels of stress hormones, such as plasma cortisol and urinary catecholamine, in daughters of women with breast cancer were higher than those in controls, validating the higher levels of psychological distress in these women. NK cell activity and *in vitro* Th1-type cytokine secretion were inversely correlated with the degree of psychological distress and the level of stress hormones in blood or urine (Cohen et al.). In a recent study, daughters of women with breast cancer and higher distress had lower IL-2-induced NK cell activity (i.e., LAK cell activity) and lower *in vitro* IL-2 and IL-12 secretion than those with lower distress, and the levels of stress hormones mediated the relationship between daughters' levels of distress and their immune functions (Cohen & Pollack, 2005). Together, the findings indicated that increased psychological distress in daughters of women with breast cancer can further impair the immune function, which may contribute to additional increases in breast cancer risk. Subjective risk assessment for breast cancer, however, was not measured directly in the studies.

Biopsychologic Reactivity to Distress

Evidence suggests that chronic distress can affect biopsychologic "reactivity" to unrelated acute stressors in

humans (Cacioppo et al., 2000; Pike et al., 1997), although the effects appear to be more variable across studies. For example, Valdimarsdottir et al. (2002) found that women at risk for familial breast cancer had larger increases in self-reported distress, heart rate, NK cell activity, and NK cell numbers when challenged with laboratory stressors (speech and mental arithmetic tasks) compared with women with normal risk. The researchers used the Claus model to classify women into positive and negative familial risk groups using a cut-off score of 11% lifetime risk. Using the same classification, Gold, Zakowski, Valdimarsdottir, and Bovbjerg (2003) found that women at risk for familial breast cancer showed greater epinephrine and cortisol reactivity to the acute laboratory stressors than those at normal risk. Elevated plasma epinephrine in women at risk for familial breast cancer was sustained at 15 minutes following the termination of stressors, whereas plasma epinephrine in the counterpart had returned to baseline. The findings suggest that women at risk for familial breast cancer may have elevated biopsychologic reactivity to classic laboratory stressors under controlled experimental conditions compared with those at normal breast cancer risk. Moreover, the exaggerated reactivity in NK cell responses may indicate a heightened immune dysregulation among women at risk for familial breast cancer, although the role of the immune reactivity in cancer is not fully understood (Valdimarsdottir et al., 2002).

In natural daily life, women with at least a first-degree relative with breast cancer showed a greater percentage increase in urinary epinephrine and norepinephrine levels from sleep to work hours and were more reactive to work distress than women without any first-degree relative with cancer (James, van Berge-Landry, Valdimarsdottir, Montgomery, & Bovbjerg, 2004). The cortisol responses to daily life distress also were exaggerated in women with a family history of breast cancer in first-degree relatives (Dettenborn et al., 2005). Women with a family history of breast cancer may experience routine exaggerated biopsychologic responses to psychological distress, and repetition of such exaggerated reactivity may lead to a cumulative wear and tear of the body, compromising health over time (McEwen, 1998).

Recommendations for Future Research

The study findings indicate that unaffected healthy women with a family history of breast cancer have lower immune responses, more cytogenetic anomalies, greater psychological distress, and exaggerated biopsychologic reactivity to stressors than their counterparts with no family history of cancer or breast cancer. Lower immune responses may be attributed to inherited characteristics as well as increased psychological distress in women with a family history of breast cancer. Immune impairments along with anomalies of cytogenetics and biopsychologic reactivity may serve as a mechanism contributing to an increased risk of developing breast cancer. Immune and cytogenetic parameters may be useful biomarkers for identifying women at increased risk for developing breast cancer. Most studies, however, have been cross-sectional and correlational, with relatively small samples; thus, the causality could not be determined clearly between immune and cytogenetic impairments and the development of breast cancer. Because of the long duration required in the development of cancer, direct causality often

is difficult to establish. Nevertheless, large-scale prospective studies will help to determine the role of immune impairments and other biopsychologic responses on the actual development of breast cancer in women at increased risk. The number of studies conducted in this area is relatively small; therefore, more studies are necessary to substantiate and extend the previous findings.

Healthy women with a family history of breast cancer have been found to have increased psychological distress along with an exaggerated, subjective assessment of breast cancer risk. In the field of psychoneuroimmunology, psychological distress is known to induce significant alterations in various immune responses in laboratory and natural settings (Segerstrom & Miller, 2004; Zorrilla et al., 2001). In general, however, the effects of psychological distress on immune responses and immune reactivity rarely have been investigated in women with a family history of breast cancer. Although heightened subjective assessment of breast cancer risk was associated with increased psychological distress in women with a family history of breast cancer, studies are lacking that examine the link among subjective risk, psychological distress, and immune responses. In addition, an appropriate study design may help to explain separate contributions of objective and subjective breast cancer risk and psychological distress on immune responses. The findings, in turn, would clarify what interventions need to be developed for at-risk women to reduce immune impairments.

A family history of breast cancer has been used to represent objective assessment of breast cancer risk but has been defined inconsistently across the studies. Collective empirical evidence suggests that a family history of breast cancer may influence subjective risk appraisal and psychological distress as well as objective breast cancer risk assessment. A simple classification by a family history alone may not

advance understanding of the relationship between specific types of breast cancer risk and immune responses. A clear conceptual differentiation between objective and subjective breast cancer risk and a more comprehensive model of objective breast cancer risk assessment would advance the knowledge in this field. Although the Gail and Claus models have been used widely and new models are being developed, the models remain limited in providing a comprehensive assessment for objective breast cancer risk. More comprehensive assessment models should include multiple risk factors for breast cancer. In addition, future studies need to determine interactions of objective and subjective breast cancer risk with psychosocial profiles on biopsychologic responses in women at risk.

The significance of exaggerated immune and neuroendocrine reactivity in unaffected healthy women with a family history of breast cancer is unclear. Given the possibilities of long-term and repeated insults on the body over time, the cumulative effect of exaggerated responses on defense mechanisms needs to be investigated using a prospective longitudinal design. The effect on the defense mechanisms may be greater when several mechanisms are impacted simultaneously. Nurse scholars are well positioned to undertake research in the area of relating objective and subjective breast cancer risk with psychosocial issues such as distress and biopsychologic responses for women at risk for breast cancer. Given the clinical significance of breast cancer in women's health, greater attention needs to be directed at early identification of women at risk as well as risk reduction for breast cancer before its expression. Biopsychologic assessment is a critical tool in that endeavor.

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