Cognitive Appraisal, Stress State, and Cellular Immunity Responses Before and After Diagnosis of Breast Tumor

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In this investigation, we determined changes in psychoimmunological status and studied cognitive appraisal processes (Impact, Mastery, and Uncertainty perception) in a sample of 36 breast cancer patients and a comparison group of 36 matched benign tumor women. We also assessed psychological distress (stress, anxiety, depression), enumerative immune measures [white blood cell count (WBC), total lymphocytes, and NK cell percentages], and functional immune measures [lymphocyte proliferative responses to phytohemagglutinin (PHA) and concanavalin A (Con A)] the day before and 1 month after surgical biopsy, and we performed a 5-month follow-up psychological evaluation. Both groups showed significant pre-/postnotification improvement in psychological outcomes. Both the Cancer and the Benign groups showed significant pre-/postnotification changes in lymphocytes and NK cell percentages, while WBC and functional responses to Con A and PHA did not change in either group of subjects. Immune pre-post changes correlated with tumor appraisal pre-post changes (Impact and Mastery). Greater reported Mastery was also predictive of larger proliferative responses. Results suggest that the anticipation period of breast tumor diagnosis is more stressful than the postdiagnosis notification periods and that cognitive appraisal, such as Mastery perception, could mediate the adverse impact of the stressor on psychoimmune reactivity.

KEY WORDS: cognitive appraisal; stress; stressor; breast cancer; immunity; psychoneuroimmunology.

INTRODUCTION

A diagnosis of breast tumor constitutes an acute stressor and presents threats at many levels. It evokes fear of death, loss of body parts, loss of sexuality, and loss of independence in everyday functioning (Margolis *et al.*, 1989; Taylor *et al.*, 1984). Previous research suggests that receiving a diagnosis of breast cancer often produces severe distress (Meyerowitz, 1983). Among women with newly diagnosed

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Immunological Outcomes

Parallel to psychological outcomes, a MANOVA revealed significant multivariate effects on functional (Con A and PHA) and quantitative immune variables (WBC, Lymphocytes, NK) only for Notification (pre–post) effect $[F(5,20) = 3,96, P < 0.01]$. For enumerative immune assays, univariate ANOVAs revealed significant changes over the diagnosis notification period for both groups. From pre- to post-notification, there were decreases in Lymphocytes and increases in NK percentage of cells for both groups, $[F(1,63) = 8.51, P < 0.01,$ and $[F(1,31) = 32.07, P < 0.0001]$ (see Table II). These responses remained unchanged between notification periods for the WBC and the functional immune measures, Con A and PHA.

No immune differences were present between Cancer and Benign subjects after notification or at the 5-month follow-up point. At prenotification, the Benign group had marginally lower Con A responses than did the Cancer group, but the trend toward a between-group difference was no longer present after the diagnosis. The same pattern occurred for PHA response. Con A and PHA responses significantly correlated $(r = 0.83, P < 0.0001)$.

Table II. Repeated-Measures Analysis of Variance for Immunological Measures

| Variable | Mean (SE) | | F | | |
	Pre	Post	Group, Cancer/Benign	Notification, pre/post/ follow-up	Group × Notification
MANOVA					
Overall			1.48	3.96**	0.49
ANOVAs					
Lymphocytes (%)					
Cancer	40.59 (2.59)	36.17 (2.17)	2.77	8.51**	0.19
Benign	46.03 (2.50)	40.07 (2.10)			
NK (%)					
Cancer	7.33 (1.01)	11.13 (1.76)	3.35	32.07***	1.37
Benign	9.11 (1.19)	14.89 (1.49)			
PHA					
Cancer	5.04 (0.05)	5.02 (0.04)	1.70	0.23	1.56
Benign	4.94 (0.05)	4.99 (0.03)			
Con A					
Cancer	4.88 (0.06)	4.86 (0.05)	4.90*	0.76	1.34
Benign	4.70 (0.06)	4.80 (0.06)			
WBC					
Cancer	7547 (398)	7748 (523)	0.08	0.01	0.32
Benign	7581 (380)	7407 (499)			

Note. PHA, phytohemagglutinin; Con A, concanavalin A; WBC, white blood cells.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.0001$.

Cognitive Appraisal Process

As expected, a MANOVA revealed significant multivariate effects for the combined appraisal variables (Impact, Mastery, and Uncertainty) for Group [$F(3,65)$ = 8.66, P < 0.0001], Notification [$F(3,65)$ = 201.12, P < 0.0001], and Group × Notification [$F(3,65)$ = 11.15, P < 0.0001]. All factorial cognitive appraisal variables changed after notification of diagnosis. Specifically, Mastery increased [$F(1,66)$ = 12.39, P < 0.0001], Uncertainty decreased [$F(1,66)$ = 57.63, P < 0.0001], and Impact decreased [$F(1,66)$ = 14.28, P < 0.001]. For Mastery, as for PSM and BSIANX scores, ANOVAs revealed that both groups showed a similar pattern of increase in Mastery pre- to postnotification as well as at the 5-month follow-up [Group, $F(1,66)$ = 0.15, NS; Group × Notification, [$F(1,66)$ = 2.87, NS].

For Uncertainty, an interaction between Group and Notification was present [$F(1,66)$ = 6.38, P < 0.01]. Inspection of cell means (see Fig. 1) showed that Uncertainty decreased in two ways. The Benign group significantly decreased in Uncertainty from prenotification to postnotification [$F(1,34)$ = 57.06, P < 0.0001]. In contrast, the Cancer group's improvement was noticeable only at follow-up [$F(1,33)$ = 42.66, P < .0001]. Furthermore, at postnotification, post hoc comparisons on means revealed that Uncertainty was significantly higher in the Cancer group (see Fig. 1) than in the Benign group, although these differences were not significant at follow-up.

Similar to Uncertainty, a significant Group × Notification interaction was also present on Impact [$F(1,66)$ = 6.95, P < 0.01]. Inspection of cell means (see Fig. 1) again revealed two different patterns. Within the Benign group, subjects significantly decreased their Impact perception, from prenotification to postnotification period [$F(1,34)$ = 17.64, P < 0.0001]. Within the Cancer group, a marginally significant difference in perceived Impact was again present only at follow-up [$F(1,33)$ = 6.97, P < 0.05]. In addition, Impact scores differed between groups at both postnotification periods.

Individual Differences Among Breast Cancer Patients

To study individual differences in psychoimmunological status among Breast Cancer patients, we computed multiple regression analyses. For the psychological state improvement (decrease in stress scores), tumor Impact and Uncertainty changes accounted for 31% of the PSM change variance and 16% of the BSIANX change variance (see Table III). A decrease in stress state correlated with decreases in Uncertainty and Impact perceptions. Concerning enumerative immune changes or postnotification functional status, Impact and Mastery perception changes accounted for 53% of NK count changes and 15% of Lymphocytes changes. Increases in NK cells and decreases in lymphocytes correlated positively with increases in Mastery and correlated negatively with changes in Impact perception. Furthermore, perception of Mastery was also a predictor for both postnotification blastogenesis measures; postnotification Mastery explained 20% of PHA variance and 16% of
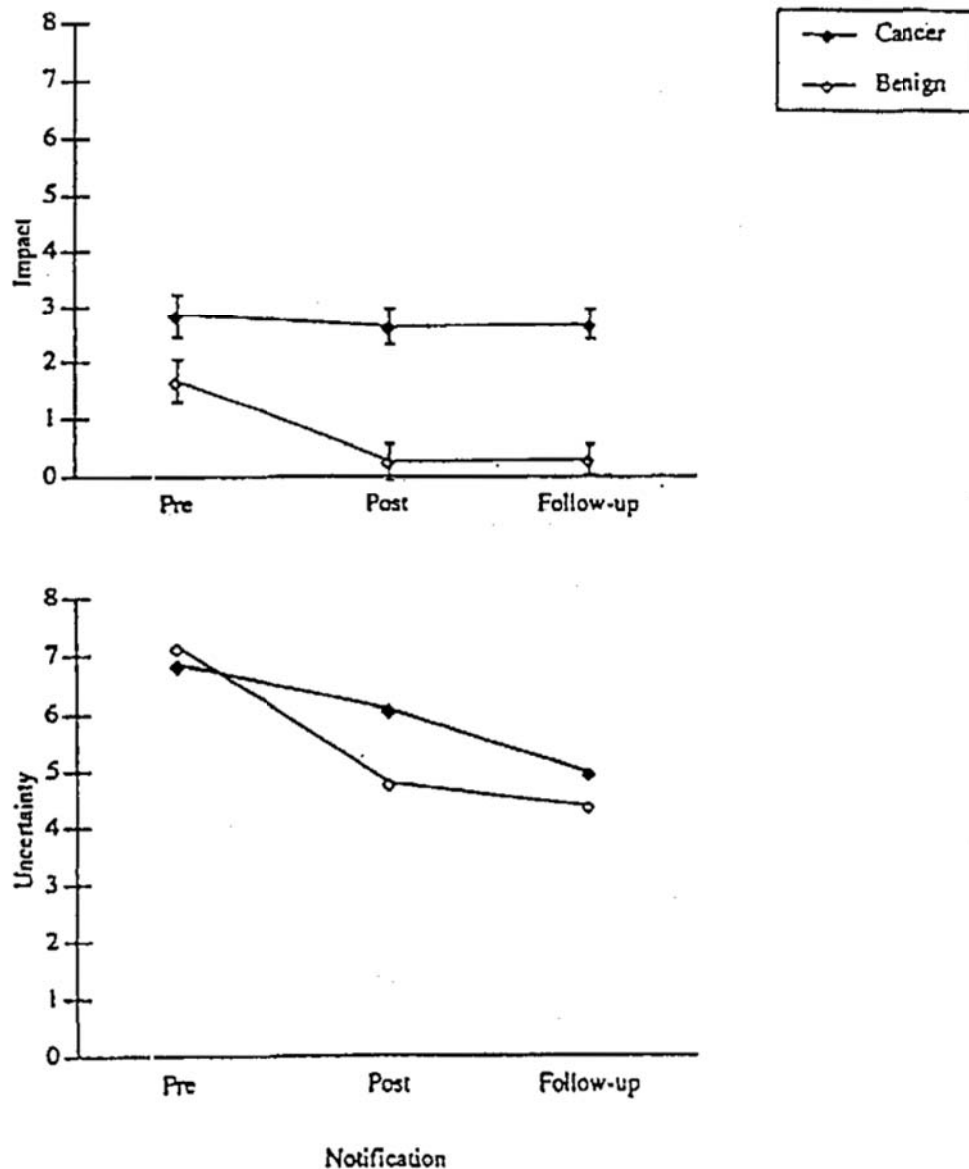
Fig. 1. Group × Notification interaction effects for Uncertainty and Impact appraisals.

Con A variance after partialling out the prenotification immunity value. WBC did not relate to cognitive appraisal.

In summary, the results did not support hypothesis 1, mainly confirmed hypothesis 2, and supported hypothesis 3. Cancer patients, relative to Benign patients, did not show a lower psychoimmunological status at the postnotification period. In fact, both groups improved psychological status and showed similar changes in their

Table III. Multiple Regression Analysis for Breast Cancer Group

	R^2 adj	F	Predictor	β Std. Est.	Partial R^2
ΔPSM[a]	0.31	6.20***	ΔImpact	0.44**	0.20
			ΔUncertainty	0.37**	0.12
			ΔMastery	0.25	0.06
ΔBSIANX[a]	0.16	4.35*	ΔUncertainty	0.39**	0.12
			ΔMastery	0.26	0.09
ΔLymphocytes[a]	0.15	3.37*	ΔMastery	0.43*	0.13
			ΔImpact	−0.28	0.08
ΔNK[a]	0.53	8.96**	ΔImpact	−0.90**	0.37
			ΔMastery	0.56**	0.23
PHA[b]	0.37	10.14***	(PHA pre)	0.37	0.22
			Mastery post	0.46**	0.20
Con A[b]	0.18	4.53**	(Con A pre)	0.18	0.07
			Mastery Post	0.41*	0.16

Note. PSM, psychological stress measure; BSIANX, Brief Symptom Inventory—Anxiety; PHA, phytohemagglutinin; Con A, concanavalin A.
[a]Predictors included in the regression: ΔImpact, ΔMastery, and ΔUncertainty.
[b]Predictors (prenotification value): Impact—Post, Mastery—Post, and Uncertainty—Post.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

immune status from pre- to postnotification periods. Similar to psychoimmune adjustment, both groups showed improvement in Mastery perception. However, following the diagnosis, the Cancer group demonstrated a higher perception of Impact and Uncertainty over the breast tumor compared to the Benign group. Finally, appraisal changes accounted for a significant amount of the psychological and immulogical changes.

DISCUSSION

Psychological Distress

At the postnotification period, we expected that the Benign group would show a better overall state (PSM, BSIANX, BSIDEP scores) than the Cancer group. Both groups showed pre- to postnotification decreases in stress and anxiety state levels. In fact, similar decreases in stress level were present in over 75% of the sample: 64% of the Cancer group and 86% of the Benign group. Among the remaining 36% of the cancer group, only 15% showed an increase in stress level. Similar observations were evident for anxiety state. In addition, the mean PSM, as well as the means of BSIANX and BSIDEP, observed in the Cancer group reached normal values about 2 weeks following diagnosis. No diagnosis effect was evident

either 2 weeks after cancer diagnosis or at 5-month follow-up. These findings are consistent with recent studies (Carver et al., 1993; Irvine et al., 1990; Stanton and Snider, 1993). Moreover, our longitudinal observations suggest that the anticipation period of the diagnosis of cancer or surgery appears to be more stressful than the 2-week period following the cancer diagnosis itself.

The fact that subjects are not likely to show major difficulties in adjustment does not mean that the tumor diagnosis is not stressful. The rapid adjustment seen among breast cancer patients as a group is not specific to this stressor. A similar pattern of rapid adjustment was also evident following notification of HIV-1 sero-positivity (Ironson et al., 1990). HIV+ notification is a severe stressor, and the psychological recuperation observed could be an adaptation process. This process is consistent with the Mobilization-Minimization theory of adaptation to negative life events (Taylor, 1991). According to this model, mobilization is the first response evoked by a negative event. For patients free of premorbid symptoms, rapidly following this mobilization are physiological, cognitive, emotional, and behavioral responses that attenuate and even nullify negative effects of the event.

Immunological Status

We also expected that changes in psychological distress would evident in immunological changes. As expected, the immune enumerative response seemed to parallel stress and anxiety states, and they seemed to relate more to the anticipation period of the diagnosis or surgery than to the short-term period following Cancer diagnosis. After notification, no immune differences were evident between groups. Anticipation of diagnosis appeared to be associated with a lower NK percentage in positive cells and a higher lymphocyte percentage. From pre- to postnotification, there were increases in NK-positive cells and decreases in lymphocyte percentage for both groups. Although it is difficult to interpret the significance of quantitative immune changes (Kiecolt-Glaser, 1988), naturally occurring stressors have consistently correlated with decreases in NK cell number (Herbert and Cohen, 1993), and the increase observed from pre- to postnotification could support the negative anticipation effect proposed earlier.

For the functional blastogenesis responses, only a marginally lower Con A response appeared to be associated with anticipation of diagnosis in the Benign group only. Despite the fact that lymphocyte proliferation assay using mitogens such as Con A and PHA has been a widely used method to monitor cell-mediated immunocompetence and the fact that it is particularly sensitive to psychological stress, there is a great deal of inter- and intravariability in these measures (Darko et al., 1991; Von Rood et al., 1991). Even when taking several precautions to optimize reliability (Fillion et al., 1994a), it is possible that high variability could mask the absence of group or notification effects. Furthermore, the stressor effect was barely evident for Con A responses and not for PHA responses, which is consistent with other findings that suggest a greater stress sensitivity for Con A (Weisse et al., 1990, Zakowski et al., 1992) and a need for other ways of measuring functional lymphocyte proliferation.

Cognitive Appraisal Changes

Interestingly, it was impossible to distinguish the Cancer and Benign groups from their psychological or immune status following diagnosis. Our results also failed to distinguish the groups from their perception of Mastery. Following notification of tumor diagnosis, both groups improved their sense of Mastery over the tumor. Mastery obtained from the SARS is attributable primarily to perceived control and perceived ability to cope. Therefore, an increase in sense of Mastery over the tumor could indicate an increase in perceived control over the situation and may relate to better adjustment. This interpretation is consistent with other findings showing that perception of control is a good predictor of psychological adjustment among Cancer subjects (Taylor et al., 1984; Timko and Janoff-Bulman, 1985).

Improvement over time was also evident from decrease in Uncertainty and Impact perceptions, although some Group × Notification interactions were present. After diagnosis, the Cancer group showed significantly higher Impact and higher Uncertainty associated with their breast tumor then did the Benign group. Impact, which could correspond to Lazarus's construct of primary appraisal, may relate to passive coping and difficulty in breast cancer adjustment (Stanton and Snider, 1993). Uncertainty may relate to lower optimism (Mishel et al., 1984), and lower optimism may also relate to difficulty in breast cancer adjustment (Carver et al., 1993; Mishel et al., 1984). The higher perceived level of Impact and Uncertainty observed in the present study suggests that Cancer patients, although not distressed, could be more vulnerable to adjustment difficulty than are Benign patients, especially during the first month following diagnosis. Furthermore, the profile of change is consistent with longitudinal appraisal changes reported following breast cancer diagnosis (Stanton and Snider, 1993) as well as with changes observed during different stressful transactions (Carver and Scheier, 1994; Folkman and Lazarus, 1985). These significant changes in cognitive appraisal variables support the notion that cognitive appraisal is a dynamic unfolding process (Lazarus and Folkman, 1984).

Individual Differences in Psychoimmunological Status

According to this transactional stress model (Lazarus and Folkman, 1984), we also expected that individual differences in psychological distress changes and individual differences in immune changes would correlate with changes in stressor appraisal. As expected, our results showed that as psychological distress decreased, stressor appraisals of the breast tumor changed. Our results also showed positive relationships between decreased psychological stress and decreased perceptions of Uncertainty and Impact. As expected, regression analysis revealed that stressor appraisal changes—mainly Impact and Uncertainty pre-post delta scores—accounted for 31% of the variance of the PSM improvement. Even if Uncertainty and Impact were still high in the Cancer group in general, the patients who improved their cognitive appraisal also improved their psychological status.

Furthermore, regression analyses revealed that changes in Impact and changes in Mastery accounted for 52% of the variance of the NK changes. Regression analy-

ses also revealed that Mastery was the best predictor of postdiagnosis lymphocyte proliferation. After partialling out the prenotification value of the PHA and the Con A responses, Mastery perception of cancer diagnosis accounted for 21% of the postnotification variance of PHA responses and 16% of the Con A responses. As already mentioned, Mastery consists mostly of perceived control, and perceived control may operate as a cognitive mediator of active coping strategies associated with good adjustment to breast cancer (Taylor et al., 1984). Mastery corresponds to the construct of secondary appraisal proposed by Lazarus, and research has also linked second appraisal to active coping (Lazarus and Folkman, 1984). Therefore, to explain the link between Perception of Mastery and immune functioning, we speculate that Mastery possibly operates as a cognitive mediator of active coping. This interpretation is consistent with PNI experimental studies suggesting that immunomodulation observed during a specific stressful transaction correlates with energy mobilization or active coping (Manuck et al., 1991; Naliboff et al., 1991; Wiedenfeld et al., 1990).

Methodological Limitations

We must note some limitations of the present study. First, the great effort devoted to increase the internal validity of the protocol limits generalizability to early breast cancer patients. On the other hand, this limitation had the positive consequence of providing a homogeneous sample, which allowed for better psychological and immunological comparisons than would have been possible with a heterogeneous sample. A second limitation lies in the quasi-experimental nature of the study, which limits conclusions of causality. These conclusions also remain limited because of the absence of a control group. Subjects with a benign diagnosis certainly constitute an excellent surgical comparison group, but a group of women having other types of surgery would have been an additional useful group. Such a control group would help delineate the anticipation effect. This limitation is especially restrictive concerning the immune changes. It is possible that the more extensive surgery received by Cancer patients relative to Benign patients was responsible for a greater immune mobilization. Nonetheless, NK changes observed in the Cancer group significantly correlated with Impact and Mastery changes. Finally, another limitation is the choice of immune measures. The lymphocyte proliferation assay shows an important variability problem and remains a nonspecific in vitro assay. Mitogens stimulate a higher proportion of cell division than antigens usually do in vivo. Used as an index of immune function, PHA or Con A lymphoproliferative response is sufficient to exclude severe cell-mediated immunodeficiencies, but it is not necessarily an indicator of cancer proneness. In comparison, NK enumeration has a better reliability and seems more directly linked to immune defense against cancer cells (Whiteside and Herberman, 1989). The CD57 monoclonal used here provides a good label for NK cells, but it would have been useful to add CD56 and CD16 markers. However, these specific immune measure limitations exemplify a general need in PNI studies to validate new immune measures and new combinations of assays or to improve current techniques. In particular, a reliability

study on NK cytotoxicity assay as a functional immune measure is necessary. Despite these limitations, the results clearly show the importance of including cognitive appraisals to understand the variability in individual psychological and immunological responses during a specific stressful transaction such as breast cancer diagnosis.

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breast cancer, as many as one third may experience considerable psychological morbidity in the first 2 years after initial treatment (Maunsell et al., 1992). Interest in the role of stress in cancer has increased, as a number of studies in psychoneuroimmunology (PNI) have demonstrated links between stressful life events and altered immune functioning (Ader et al., 1991; for reviews see Fillion et al., 1994b; Herbert and Cohen, 1993). Acute stressors appear associated with decrements in two kinds of immune assays: enumerative and functional (Herbert and Cohen, 1993). The primary enumerative assays simply count the number of white blood cells (WBC) in the peripheral blood. Stressor exposure positively relates to the number of circulating white blood cells and negatively relates to the number of several lymphocytes or large granular lymphocytes subsets (Herbert and Cohen, 1993). Namely, changes in natural killer (NK) cell count (CD56+ or CD57+) often occur during stressful experiences (Herbert and Cohen, 1993; Kiecolt-Glaser et al., 1984). For instance, the percentage of NK cells decreases during naturalistic stressors, such as academic examinations (Glaser et al., 1985) and human immunodeficiency virus type 1 (HIV-1) + seronotification (Antoni et al., 1991; Ironson et al., 1990). In addition, decrements in NK cells occur in depressed persons (Weisse, 1992) and in separated or divorced women (Kiecolt-Glaser et al., 1987). In terms of testing the functional capacity of human immune cells, T-lymphocyte mitogens, such as concanavalin A (Con A) and phytohemagglutinin (PHA), have been the focus of extensive study in PNI research. Lymphocyte proliferation assays are particularly sensitive to naturally occurring stressors, such as bereavement (Irwin et al., 1987), divorce (Kiecolt-Glaser et al., 1987), and academic examinations (Halvorsen and Vassend, 1987; Kiecolt-Glaser et al., 1986; Workman and LaVia, 1987), as well as chronic stressors (e.g., unemployment) (Arnetz et al., 1991) and clinical states (e.g., depression) (Weisse, 1992). To our knowledge, no PNI study has directly investigated the impact of breast cancer diagnosis on psychoimmunological status.

During a stressful transaction, such as breast cancer diagnosis notification, individuals do appear to differ in the way they adapt to this acute stressor (Carver et al., 1993). To explain individual differences, the transactional stress model (Lazarus and Folkman, 1984; Lazarus and Launier, 1978) proposes that cognitive appraisal constitutes a critical mediator. Cognitive appraisal is a multidimensional construct including two principal factors: primary appraisal, which reflects the perception of the nature and degree of risk associated with the stressor; and secondary appraisal, which reflects perception of the resources or abilities to cope with this event (Lazarus and Folkman, 1984). When perception of demands imposed by a stressor tax or exceed a person's ability estimate to cope, maladaptive coping strategies and psychological stress responses could develop (Lazarus and Folkman, 1984). Psychological stress, in turn, influences immune function through autonomic nervous system activation or hormone-mediated alteration of immune cells (Ader et al., 1991; Herbert and Cohen, 1993). Patients who view their breast tumor as threatening and uncontrollable may employ maladaptive coping strategies, such as denial or emotional avoidance, or increase their use of alcohol or medication. These maladaptive strategies may compromise psychological adjustment, future illness behaviors, immune system functioning, and cancer progression (Dunkel-Schetter et al., 1992; for review, see Ironson et al., 1995). Recent studies have shown that some women free of pre-

morbid psychiatric disorders are unlikely to develop psychological symptoms following breast cancer diagnosis (for review, see Irvine et al., 1990). However, greater perception of threat (Stanton and Snider, 1993) and lower appraisal of control (Taylor et al., 1984; Timko and Janoff-Bulman, 1985) appear to be associated with higher psychological distress. Furthermore, one study linked use of denial as a passive coping style with lower proliferative responses to PHA (Biondi et al., 1987), and some studies have reported positive relationships between active coping responses to breast cancer and greater NK cell activity (NKCA) (Levy et al., 1985, 1987, 1990).

In addition, many studies have demonstrated that cognitive appraisal affects neurohormonal responses to stressors (for review see Lazarus and Folkman, 1984). Recently, one study revealed cardiac reactivity positively relates to challenge appraisal and negatively relates to threat appraisal (Tomaka et al., 1993). There is also evidence that immunological aberrations relate to the way in which individuals respond to stressor exposure. Decreases in lymphocyte proliferation to Con A and PHA and an increase in NK cells may result after exposure to experimental stressors (Bachen et al., 1992; Manuck et al., 1991; Naliboff et al., 1991; Weisse et al., 1990), and changes in immune functioning occur mainly among individuals who also show heightened responses on a composite index of cardiac reactivity (Bachen et al., 1992; Manuck et al., 1991; Zakowski et al., 1992). Furthermore, different stressors previously shown to elicit different hemodynamic response patterns (Hurwitz et al., 1993) also elicit different immune responses (Starr et al., 1996). These studies suggest that the changes in immune system observed during stressor exposure may be due, in part, to the same factors affecting high sympathetic activation responses, such as stressor appraisal (Frankenhaeuser, 1982; Obrist et al., 1978). Therefore, the cognitive appraisal process could be mediating the psychological and immunological impact of receiving a cancer diagnosis.

The literature on cancer suggests that the breast tumor diagnosis period is particularly stressful, and PNI research has demonstrated that naturally occurring stressors negatively affect immune system functioning. Using a longitudinal quasi-experimental design, we examined changes in psychological distress and immunological functioning before and after surgical breast biopsy. Controlling for the stage of the disease and its impact on immunity, our first hypothesis was that notification of a breast cancer diagnosis would affect both psychological and immunological status. At the postnotification period, we expected that the Benign group would show a better psychoimmunological status than the Cancer group, as measured by the psychological (lower depression, anxiety and stress scores) and immunological (higher NK cell number and proliferative responses) variables. Our second hypothesis was that notification of a cancer diagnosis would negatively affect cognitive appraisal of the breast tumor. At the postnotification, we expected that the Cancer group would show a higher perception of threat (high Impact and high Uncertainty) and a lower perception of control (low sense of Mastery) over the breast tumor compared to the Benign group.

Finally, investigators have observed individual differences in psychological adjustment to breast cancer. The evidence that cognitive appraisal acts as a determinant of how well subjects adjust to stressful transactions provided a basis for our third hypothesis. We expected that individual differences observed among breast

cancer patients in their psychological distress and their immune functioning would relate to their cognitive appraisal of the tumor. Stress, depression, anxiety, and immune changes would be more likely when subjects appraised a tumor as highly threatening (high Impact and high Uncertainty) and uncontrollable (low Mastery) than when subjects appraised a tumor as low in threat and controllable.

METHOD

Subjects

We recruited women from surgery oncology departments of two hospitals in Montreal during a 12-month period. The inclusion criteria were as follows: (a) admission to the hospital for a breast surgical biopsy; (b) likely to perceive oneself as at risk to receive a benign or an early stage cancer diagnosis (suspicious mammogram or very small detected lump); (c) unaware of one's own tumor diagnosis; (d) having no previous cancer history; (e) a Caucasian woman (to control for ethnicity impact on immune functioning); (f) able to participate in the entire study (living in or near Montreal); (g) willing to refrain from alcohol or medication use for 24 hr prior to blood samples; and (h) not having any other health problem or chronic illness affecting the immune system, such as chronic fatigue syndrome, acute or chronic hepatitis, type I diabetes, asthma, autoimmune disease, or untreated thyroid problem. Of the 181 women who satisfied these criteria, 120 elected to participate. We excluded 6 of them after rechecking the inclusion criteria, and 10 refused to stay involved in the longitudinal study. The resulting sample contained a total of 104 women.

Cancer Group

The Cancer group consisted of 36 patients with early-stage breast cancer (Stage I or II) selected from 37 subjects who received a diagnosis of breast cancer. Research suggests that there is no difference in immune system functioning between early stage disease and benign disease (Mandeville et al., 1982). Therefore, we excluded one patient because she received a stage III diagnosis. Cancer cells had invaded the axillary lymph nodes in 17% of the patients. Only two older women, at their request, had undergone mastectomy. Concerning adjuvant therapy, 89% received radiotherapy, 50% hormonotherapy, and 8% chemotherapy. Initial analyses revealed that none of these medical variables varied at any assessment period in association with psychoimmune variables. Consequently, we did not include these medical variables in subsequent analyses.

Benign Group

The Benign group consisted of a matched sample of 36 subjects selected from the 67 subjects who received a diagnosis of benign disease. We individually matched

the selected patients to patients from the Cancer group on four socioeconomic variables: age, education, marital status, and income.

After matching, the two groups did not differ significantly in age (M = 56 years, range = 36 to 70 years), family income (27%, $0–20,000; 36%, $20,000–30,000; 20%, $30,000–40,000; 17%, > $40,000), educational level (24%, grade school; 51%, high school; 25%, college and beyond), or marital status (14%, single; 54%, married; 32%, widowed or divorced). Matching on age also provided an indirect control for menopausal status.

Psychological Outcomes

Psychological Stress Measure (PSM)

The psychological stress measure (PSM; Lemyre et al., 1990) is a self-report instrument assessing a unidimensional construct of the subjective experience of feeling stressed. The PSM, first designed for use with the normal French Canadian population (Lemyre, 1986; Lemyre and Tessier, 1988), provides information on three aspects of the stress response: physiological, cognitive-affective, and behavioral. A single score, obtained by summing the 25 items (Likert scale from 1 to 8), may vary from 25 to 200 as the stress state level increases; the mean of the normative population is around 75. Test–retest reliability of the PSM has been studied at two weeks ($r = 0.68$), 3 months ($r = 0.67$), and 6 months ($r = 0.61$). Data on content and construct validity, normal distribution, internal consistency ($\alpha = 0.92$), and factorial structure, as well as on discriminant and concurrent validity, appear in studies elsewhere with a representative sample of the population ($n = 1520$) (Fillion et al., 1989; Lemyre et al., 1990). The PSM correlates highly with other measures of distress (such as the Derogatis Brief Symptom Inventory, $r = 0.76$), measures of anxiety (such as Spielberger's State Inventory, $r = 0.73$), and depression (Beck Depression Inventory, $r = 0.75$) (Tessier et al., 1990).

Brief Symptom Inventory (BSIANX and BSIDEP)

The Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983) is a self-report questionnaire of psychopathology. It includes 53 items, rated 0 to 4. The BSI aims at measuring severity of psychopathology, including anxiety (BSIANX) and depressive symptoms (BSIDEP). We included only these two subscales and derived their scores according to the usual procedure described by the authors (Derogatis and Melisaratos, 1983). The BSI has established validity data from a sample of 719 persons from a nonclinical population and 343 psychiatric inpatients. The authors report several studies that attest to the validity and reliability of the measure on different psychiatric and medical populations. The French version used in this study has a good validity and reliability (Fortin and Coutu-Wakulczyk, 1985).

Immunological Outcomes

We chose the measures used in this study for their known sensitivity to psychological stressors and/or their relevance to breast cancer disease. They consisted of three enumerative measures—white blood cell count (WBC), percentage of lymphocytes, and NK cells in peripheral blood—and two functional measures—lymphocyte proliferative responses to Con A and PHA. In order to control for circadian variations, oncology nurses collected all blood samples between 0800 and 0830. The same technician performed all assays on the same day as sampled and under the same storage conditions. We had total and differential counts performed on each sample using an autoanalyzer standard technique. We determined enumeration of cytotoxic cells, which included NK cells, by a whole-blood direct immunofluorescence technique and used commercially available monoclonal antibodies (anti-CD57; Amac Inc., Westbrook, ME) conjugated with fluorescein isothyocine (FITC) to identify CD57 markers. We also used a negative control [an isotypic antibody (IgG1)] in this study to gate non-specific background fluorescence during flow cytometry. Aliquots of blood were incubated for 15 min with the corresponding antibody at room temperature. We then lysed red blood cells and centrifuged the samples, washed twice with PBS, with the percentage of positive cells determined by flow cytometry (EPICS, Coulter, Canada).

For the functional measures, we isolated mononuclear leukocytes from peripheral blood by density-gradient centrifugation (Ficoll–Hypaque density 0.1077; Sigma, St. Louis, MO) and then cultured them for 3 days in RPM1 1640, 10% bovine serum, 100 µg/ml penicillin G, and 100 µg streptomycin at one optimal concentration after dose–response curve controls (2.5 µg/ml for PHA HA-16, Wellcome Diagnostics, Dartford, England, and 10 µg/ml for Con A, Calbiochem, Behring Corp., La Jolla, CA). Pre establishing the dose–response curve increases stability, as reported elsewhere (Fillion et al., 1994a). We conducted triplicates for each condition. Results represent the total tritiated-thymidine incorporated during the last 16 hr of incubation, and we performed a log transformation. In order to improve stability and to obtain a better reliability coefficient (Fillion et al., 1994a), we used for calculation only the counts per minute (Cpm) of the stimulated cultures (reliability G coefficients: $G = 0.59$ for PHA, $G = 0.48$ for Con A).

Mediator Variables

Subjective Appraisal Ratings of Stressor (SARS)

We measured cognitive appraisal using the SARS (Lemyre, 1986). We selected the revised version (Biron, 1992), which consists of 10 items rated from 1 to 8 (Likert scale) and assesses cognitive appraisals of a specific potentially stressful event in terms of Negative Consequences, Positive Consequences, Loss, Danger, Failure, Challenge, Control, Coping Capability, Unknown, and Importance. Depending on the type of stressor studied, the SARS scores could include two or three factors (Biron, 1992). The first two factors, Impact and Mastery, correspond theoretically to the first and second appraisals of the transactional stress model

(Fillion, 1993; Lemyre, 1986). The third factor, Uncertainty, is generally observable following acute events; items are more likely to load on the Impact component in chronic situations (Biron, 1992; Lemyre, 1986). Before using the SARS in this study, we performed a test–retest study (Fillion, 1993) on 90 observations (three stressor appraisals associated with acute cancer concerns: tumor, surgery, and adjuvant treatment) to verify the psychometric qualities and feasibility with a cancer population ($n = 30$). For this initial validity study and for the current longitudinal study, we derived regression weights from a principal-component analysis of the 10-item SARS. On both occasions, the factor structure (after varimax rotation) revealed three consistent factors (eigenvalue > 1) explaining 60 % of the variance as reported previously (Biron, 1992; Lemyre, 1986). We named factors following Lemyre's work, namely, Impact, Mastery, and Uncertainty. In order for the constructs to be the same across notification period, we held factor loadings stationary across time (Tisak, 1993). At the prenotification periods, patients answered the 10-item SARS concerning the stressor *Breast Tumor and Risk of Receiving a Breast Cancer Diagnosis*. At the postnotification and follow-up period, Benign and Cancer patients answered the same 10 questions concerning the stressor *Breast Tumor and Diagnosis*.

Control Variables

Health-Related Variables

Subjects fasted for 12 hr and refrained from alcohol, caffeine, and unprescribed medication use for 24 hr prior to blood sampling. We measured alcohol, tobacco, and caffeine intake by self-report. Prior to blood collection, a registered nurse recorded prescribed medications and symptoms of viral or bacterial infection for the previous 2 weeks. We obtained other information concerning inclusion criteria from medical surgery and oncology files.

Contextual Variables

In order to control the social context of the specific stressful transaction, subjects answered the Life Events and Difficulty Schedule (LEDS) retrospectively at follow-up. The LEDS (Brown and Harris, 1978) is an investigator-based measure of life events. Trained researchers (at Dr. Lemyre's research laboratory in Quebec City) identified and rated the severity of stressors following the procedure described by the authors (Brown and Harris, 1978). The semistructured interview includes a standard set of questions, allowing interviewers to identify and describe in contextual terms all events and difficulties experienced by subjects over the 12-month period preceding tumor diagnosis.

Over the diagnosis pre- and postnotification periods, initial analyses failed to reveal between-group differences among these health-related and contextual variables. Consequently, we did not include these variables in subsequent analyses.

Design

This is a 2×3 quasi-experimental design, with the quasi-experimental condition (cancer vs. benign diagnosis) as the between-group factor and notification period (pre, post, and follow-up) as the within-group factor. Psychological outcomes (stress, anxiety, and depression) as well as mediator variables (Impact, Mastery and Uncertainty) were available at all three notification periods. We measured immune outcomes before and after notification.

Procedure

We recruited subjects from two hospitals in Montreal over a 1-year period. All women hospitalized for a surgical breast biopsy who met the inclusion criteria were introduced to the first author during or just after meeting with medical and surgical staff. Subjects received a full explanation of the research procedure, research requirements, and issues of confidentiality. Researchers explained that the purpose of the study was to acquire knowledge about the relationship between immunity and psychological stress experienced during a specific stressful period. More than 80% of the women agreed to participate and scheduled interviews. We obtained blood samplings and psychological evaluations (outcomes and mediators) the day before the surgical biopsy and 1 month after biopsy (to control for menstrual cycle and to allow enough time to recuperate from surgery). The postnotification period took place approximately 2 weeks after diagnosis notification from the surgeon. For Cancer patients, we performed postsurgery interviews and blood sample collections before radiotherapy or any other adjuvant treatment (chemotherapy or hormonal therapy). We performed no subsequent immune measurement after cancer patients received adjuvant therapies. Subjects completed a psychological evaluation (outcome and mediator variables) 5 months after the biopsy. At that time, 85% of the Cancer patients had completed their treatment.

Statistical Analysis

We tested the first two hypotheses using multivariate repeated-measures analysis of variance (MANOVAs). Using the Group × Notification interaction, we tested the hypotheses that the cancer group, compared to the benign group, would show (a) poorer adjustment in a number of outcome variables [psychological distress (PSM, BSIANX, BSIDEP) and immune status (NK cells, PHA and Con A responses)] and (b) different appraisal processes (higher Impact and lower Mastery). Following these overall analyses, we computed univariate repeated-measures analyses of variance (ANOVAs), with α reduced from 0.05 to 0.01 to control for type I error. When significant ANOVA findings were present, we performed interaction analysis and planned post hoc comparisons.

Finally, to study individual differences among Breast Cancer psychoimmunological status and test the third hypothesis—that changes in cognitive appraisal variables would correlate with changes in psychoimmunological outcome variables—we computed separate multiple regression analyses. We used regressions to predict delta

scores (difference scores) between pre and post status from delta-score pre-/post-cognitive appraisal predictors. Where no significant pre-post changes in status were present, we performed regression analyses to predict postnotification status from postnotification cognitive appraisals, after controlling for prenotification values.

RESULTS

Psychological Outcomes

On overall psychological outcomes, a MANOVA revealed significant multivariate effects over the diagnosis notification period (pre-post) [$F(3,66) = 112,55, p < 0.0001$]. Univariate ANOVAs specified that both groups showed a significant decrease in stress scores (PSM) from pre- to postnotification [$F(1,68) = 8.10, p < 0.001$] as well as a significant decrease in anxiety scores (BSIANX) from pre- to postnotification [$F(1,68) = 10.29, p < 0.0001$] (see Table I).

Surprisingly, no psychological differences were present between Cancer and Benign subjects after notification or at the 5-month follow-up. Both groups displayed postnotification psychological stress scores similar to those observed among the general population of women in Quebec (means around 75) (Lemyre et al., 1990).

Table I. Repeated-Measures Analysis of Variance for Psychological Measures

	Mean (SE)			F		
Variable	Pre	Post	Follow-up	Group, Cancer/ Benign	Notification, pre/post/ follow-up	Group × notification
			MANOVA			
Overall				1.07	112.55**	0.69
			ANOVAs			
PSM						
Cancer	80 (5)	75 (5)	70 (5)	0.22	8.10*	1.99
Benign	86 (5)	71 (5)	77 (5)			
t	NS	NS	NS			
BSIANX						
Cancer	0.84 (0.11)	0.59 (0.11)	0.44 (0.13)	0.77	10.29**	0.90
Benign	0.53 (0.11)	0.63 (0.11)	0.68 (0.13)			
t	NS	NS	NS			
BSIDEP						
Cancer	0.54 (0.09)	0.48 (0.12)	0.44 (0.12)	1.95	2.32	0.61
Benign	0.79 (0.09)	0.57 (0.12)	0.64 (0.12)			
t	NS	NS	NS			

Note. PSM, psychological stress measure; BSIANX, Brief Symptom Inventory—Anxiety; BSIDEP, Brief Symptom Inventory—Depression.
*$P < 0.001$.
**$P < 0.0001$.