In this issue of the Journal, Tross et al. (1) report on an exceptionally fine study of the relationship between psychological distress and both disease-free and overall survival in women with stage II breast cancer. Their report is noteworthy not only for the rigor of its methods but especially for the open-minded and balanced way in which it is written. The authors found no relationship between psychological distress, as measured by the Symptom Check List-90-Revised (SCL-90-R), and recurrence of disease in or survival of patients with breast cancer. Their study was conducted on a large subsample of patients in the Cancer and Leukemia Group B (CALGB) national clinical trial of adjuvant therapy for stage II breast cancer. Two hundred eighty women, 31% of the total sample, were entered in the study. Even a casual examination of the survival curves for these women shows little support for the idea that distress, as measured by the SCL-90-R, is associated with longer or shorter disease-free or overall survival time.

In their report, Tross et al. note the limitations of their study. Although their study was prospective in design, the psychosocial component was apparently retrospective, a useful add-on to an intervention trial. Another important issue is sample bias. The authors were able to assess fewer than a third of the total sample, although it was a sizable number of women. Some of the reasons for this subsample selection, i.e., patient refusal and attrition, might have restricted the range of distress found, thereby reducing the ability of the study to detect a relationship between variance in distress and survival. Indeed, Tross et al. noted that the sample of patients was relatively nondepressed. Being depressed might be a reason for refusal to fill out additional questionnaires. Other reasons, such as a tendency to be uncooperative, have been reported to be associated with longer survival (2). Thus, patients who participated in the study might be self-selected for lacking the depression that might predict poorer outcome or the feistiness that other authors (1,3) have found to predict better outcome.

That said, there is little in the present data to encourage even the most optimistic advocates of the connection between psychosocial and medical variables. Similarly, Zonderman et al. (4) found no relationship between a diagnosis of depression and the incidence of cancer. These investigators did an excellent job of reviewing the literature on this topic in 1989. They noted that general measures of psychological distress, such as the SCL-90, do not seem to be associated with the rate of relapse of or mortality from cancer.

More specific constructs, such as suppression of distress, active coping strategies, and psychosocial intervention, should provide a more definitive test of the mind-body hypothesis. The sample population may have been composed of some people who genuinely were not distressed and others who were distressed but who attempted to suppress their awareness of it, so-called “repressors” (5). These latter people have been noted to be prone to somatic evidence of distress despite subjective denials. They have, for example, high cortisol levels in the morning (6). Speculation has long existed about, and recent findings offer support for, the hypothesis that it may be important to the physical health of cancer patients to express their emotions, receive support from others, and become assertive about their needs (7-12).

In our own studies of metastatic breast cancer patients (13), we have found that measuring distress is complex. People who try to suppress affect are, if anything, more anxious and depressed than those who score lower on a measure of defensiveness (13). Thus, the reported level of distress on a general measure like the SCL-90-R may reflect a genuine absence of anxiety, depression, and other symptoms; a lack of awareness of such problems; or the breakthrough of such symptoms despite genuine efforts to repress them. The theory holds that people of the latter type (i.e., those with substantial distress despite efforts to avoid coming to terms with that distress) are at most risk for stress-induced somatic symptoms. Conversely, studies have shown that coping styles predict medical outcome. British researchers (3,14,15) have found that an attitude characterized as a “fighting spirit” is associated with longer survival among breast cancer patients.

Tross et al. (1) call for more focused research that tests for the relationship between specific psychosocial constructs such as repression-sensitization, or fighting spirit, and disease progression. They also recommend further studies on the possible effects of psychological intervention on disease progression. This is quite a reasonable direction for future research. Indeed, two randomized prospective trials are under way in our laboratory; one is a multicenter trial for women with primary breast cancer, and the other is a single-site trial for women with metastatic breast cancer.

Tross et al. suggest that one possible mechanism for such survival differences is better adherence to aggressive treatment regimens. They cite the important study by Richardson et al. (16) that demonstrated that adherence to treatment by lymphoma and leukemia patients improved after an educational in-
tervention. In that study, patients receiving this psychological intervention lived longer, even when differences in adherence to treatment were controlled. As many as one quarter of cancer patients may fail to adhere to chemotherapy regimens (17). In a study of women with abnormal Pap smears requiring follow-up care, 29% of these women did not return for follow-up screening (18). Affective and cognitive disturbance, which is higher than normal among the physically ill (19), may account for some of this poor adherence to diagnostic screening or treatment, which could affect disease course.

If one takes the viewpoint that anxiety and depression might be natural responses to the diagnosis or progression of cancer but should not plausibly influence its course, then the present findings are expected, if not extremely interesting. However, if one believes that hormonal and other somatic aspects of depression, which include hypercortisolism (20,21), might exert some influence on tumor growth, the result would seem disappointing. Recently, a molecular mechanism was proposed whereby elevated levels of corticotropin-releasing hormone (CRH) could influence the expression of breast cancer oncogenes (22). Thus, stress or depression-induced overactivation of the CRH–adrenocorticotropic hormone (ACTH)–cortisol system (23,24) might be related to more rapid tumor progression, as has been shown in animals (25). Other mechanisms postulated include the immunosuppressive effects of glucocorticoids (26).

The role of the immune system in cancer surveillance and progression is complex, and it is not clear that laboratory studies indicating stress-induced immunosuppression, for example, are clinically meaningful (27). Nonetheless, a few clinical studies support the hypothesis. Conditioned immunosuppression has been observed in ovarian cancer patients undergoing chemotherapy (28). Natural killer (NK) cells have been implicated both in cancer progression and in response to psychosocial factors (29). NK cells are similar to lymphokine-activated killer (LAK) cells in having antitumor activity without recognition of tumor-specific antigens (30). Lower NK cytotoxic activity has been shown to predict disease recurrence in breast cancer (31), whereas perceived high social support from a spouse, an intimate other, or a physician or actively seeking social support has been shown to be related to higher NK activity in patients with stage I or II breast cancer (32). NK cells are known to kill many different types of tumor cells when tested either in vitro or in animals (33). Stress significantly decreases NK cytotoxicity, increases levels of cortisol and ACTH, and increases the metastatic spread of mammary tumor to the lung in rats (34). This could mean that the rate of disease progression, rather than the incidence of cancer, might more plausibly be influenced by depression.

For some, the question might be: Why should there be any relationship at all between psychological variables and disease progression? A growing interest in the interaction between psychological and medical variables in cancer is well served by studies like the one by Tross et al. (1), which rigorously examines possible relationships and serves to sensibly direct future research toward better defined psychological constructs and controlled intervention trials. Tross et al. make it clear that, for cancer patients, it is not simply mind over matter, but instead they point the way toward how in future research it may be possible to determine how mind does matter.

References
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(25) Sapolsky RM, Krey LC, McEwen BS. The adrenocortical stress-response: possible relationships and serves to sensibly direct future research toward better defined psychological constructs and controlled intervention trials. Tross et al. make it clear that, for cancer patients, it is not simply mind over matter, but instead they point the way toward how in future research it may be possible to determine how mind does matter.
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