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CORRESPONDENCE

To the Editor:

Jacobs' and Bovasso's (**30**, 669–678) recent paper set out to determine whether early bereavement or chronic depression are associated with breast cancer. As part of the rationale for carrying out this study, they state that a recent meta-analysis found that recent adverse life events were not found to be causative factor in the development of breast cancer (Petticrew *et al*. 1999). This is misleading, as the meta-analysis was not confined to studies of recent stress, but included primary studies of the association between stress at any time in the life course. It included for example studies with assessment periods of 15 years and more. The results of the meta-analysis therefore are not limited to recent stressors.

Jacobs and Bovasso also reported that early maternal death was significantly associated with breast cancer hospitalization (OR = 2·56; 95% CI 1·59 to 4·35), and expressed the hope that future research might involve a meta-analysis of other prospective studies. The aforementioned meta-analysis did in fact do this, by separately analysing studies of bereavement and cancer risk, and found no overall association between bereavement and breast cancer when the higher quality studies were pooled (OR = 0·90; 95% CI 0·57 to 1·45). We have pooled the results from Jacobs' and Bovasso's new study with the odds ratios (OR) of the two other higher quality studies that were included in the meta-analysis (Kvikstad *et al*. 1994; Roberts *et al*. 1996) and have carried out a new meta-analysis. This shows an increase in the summary OR, but does not change the overall conclusions (random effects summary OR = 1·22; 95% CI 0·70, 2·13). This finding is in line with the negative results of the large prospective study of Jones *et al*. (1984), which used cancer registry data, and showed no significant effect of widowhood on risk of registration from breast cancer, or death of breast cancer, reporting RRs of 1·25 (95% CI 0·7–2·4) and 1·44 (95% CI 0·8, 2·7) respectively.

The overall association found by our re-analysis is in any case weak enough to be due to undetected biases in the primary studies (Rothman & Greenland, 1998), including publication bias (Song *et al*. 2000). In the current study, there are several other potential sources of bias. One of these considered by the authors: the use of self-reported information on hospitalization from breast cancer. However, self-reported hospitalization from breast cancer does appear to be very accurate, (Bergman *et al*. 1998) supporting the authors' contention that the bias introduced through error from self-reports is low. A more important source of bias however lies in the use of self-report data on family history of cancer, the accuracy of which varies depending on the cancer: this information is most accurate for breast cancer (Parent *et al*. 1997) but increasingly less accurate for other forms of cancer (Aitken *et al*. 1995; Paganini-Hill & Chao, 1993). In addition, the authors' Cox regression analysis only adjusted for self-reported family history of breast cancer, and the possibility that breast cancer risk is higher for those with a family history of cancer at other sites should also be considered. For example, associations between breast, ovarian and other cancers within families have been linked to BRCA1 and BRCA2 gene mutations (Poole *et al*. 1999). The observed increased risk of breast cancer may therefore be partly due to a positive family history of other cancers, which appears not to have been adjusted for in the analysis.

The authors also suggest that researchers can only speculate on how exactly depression or bereavement might be a causative factor or facilitator of cancer. As one possible mechanism they suggest the role of grief in suppressing NK and T cell activity. Such speculation may be interesting, and may even suggest biologically plausible causal pathways, but the acid test is whether the totality of the evidence suggests a causal association, and as shown above, it does not. Researchers might also speculate on the biological plausibility of an immune system in which NK and T cells appear able to differentiate between death of a mother, the death of other loved ones, and other forms of psychological stress.

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One notable feature of the studies to date is the high degree of heterogeneity among their results, with some studies reporting increased risk and some reporting reduced risk associated with stressful life events. Future research could usefully investigate in a systematic fashion the factors that underlie this heterogeneity (such as features of the study populations, and methodological aspects of the primary studies).

Finally, Protheroe and colleagues recently reported the results of a case–control study which examined recent stress and found no association with breast cancer (Protheroe *et al.* 1999). They concluded that women with breast cancer can be told that life stresses are unlikely to have played an important part in the development of their disease. There is still no convincing reason to alter this advice.

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The Authors reply:

Stress must be severe and chronic, persisting for years if not decades in order be a risk factor for cancer onset. Furthermore, our study neither hypothesized or found that less intense or shorter term depression, death of a spouse or divorce or any relatively recent stresses were predictors of breast cancer development. Those findings would have contradicted the basis of our study. We found only that severe and chronic depression that has persisted for decades, and the loss of a mother in childhood increased breast cancer risk. Chronic depression persists for years and in some cases the entire life span. Maternal death in childhood frequently involves other stressful complications such as family discord, increased and unsatisfied demands for parental attention and less financial resources (Hepworth & Ryder, 1984). The adverse affects of maternal death continuing for at least several years afterward have been well documented (Berlinsky & Biller, 1982). Our findings are consistent with the current views in physiological research that the causative factors of breast cancer develop over a period of 20 or more years. (Harris *et al.* 1993). This biological basis has influenced ourselves and other researchers (McGee *et al.* 1996) to emphasize that chronic and severe stress originating near, or before, that period is more likely to be a possible risk factor than relatively recent stresses.

Petticrew and Sutton's combining of our findings on chronic and severe stresses with relatively recent stresses that we specifically noted as unlikely to increase cancer risk in an inappropriate test of our research. Petticrew and Sutton pooled the results of our study with

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Kvikstad *et al*. (1994) and Roberts *et al*. (1996), which focused on death of a spouse and divorce as risk factors, neither of which were found to be significant risk factors in our study nor were expected to be significant. Our position that adverse emotions must be acute and persist for years to affect risk for breast cancer onset is in accord with the oncology research. (Harris *et al*. 1993). We hypothesized and found that women with chronic and severe depression were at greater risk for breast cancer development, but that woman with briefer episodes or shorter histories of depression were not at greater risk. Bereaved and divorced women may experience depression as a result of these life events but rarely continues for a decade or longer. As noted earlier, the severe effects of the loss of the mother on a child and subsequent complications persisting for several years have been clearly documented. Also, the loss of a mother is far more likely than loss of a spouse to occur decades before cancer onset. In addition, we are further perplexed by the specific choices of Kvikstad *et al*. (1994) and Roberts *et al*. (1996) as studies as to be combined in a meta-analysis with our research, since neither study chosen by Petticrew and Sutton assesses or tests the variables that we have found to be relevant. A meta-analysis, which combined our findings with two studies whose purpose and hypotheses are contrary to the basis of our study, does not provide a valid test of our hypotheses, and cannot yield meaningful results. In our study, we cited Petticrew *et al*. (1999) meta-analysis as representative of the position that relatively recent stresses do not affect breast cancer risk. This was not misleading since their meta-analysis consists largely of studies assessing recent life events between 1 and 6 years prior to breast cancer onset, and does not separately analyse chronic and severe stresses. As noted earlier, the inappropriate combination of variables and studies does not adequately, of fairly, test the role of severe, long-term and chronic stress. Since most of studies included in their meta-analysis involve relatively recent stress, their conclusion that long-term stresses are not associated with breast cancer risk is unwarranted. Secondly, the studies used in their data analysis are of mixed quality, particularly those pertaining to long-term events. Prior to citing Petticrew *et al*. (1999) article, we described the numerous methodological problems that characterized the research on psycho-social stress and its relation to breast cancer. These flaws negatively affect studies that examine the association of psycho-social variables with breast cancer and may account for much of the heterogeneity among studies assessing risk that Petticrew and Sutton remarked upon at the end of their commentary.

In addition to Petticrew and Sutton's misapplication of meta-analysis, we feel that a number of their comments about our study are mistaken and/or misleading. Petticrew and Sutton cited Poole *et al*.'s (1999) speculation that breast cancer might be genetically linked to other forms of cancer, and suggested the possibility that we did not control for family history of cancer, however this is simply not the case. Our study did control for family history of breast cancer, as well as those of the colon, large intestine and rectum. We found that the various other histories of cancer did not significantly predict breast cancer hospitalization, and thus we did not adjust our risk estimates for these factors.

Also, Petticrew and Sutton have chosen to present our statement that 'researchers can only speculate' on depression's role in cancer development as a statement of fact when it is obviously presented as speculation. We felt that at some point in the discussion, that speculation on possible ways that depressions might be involved in cancer development was logical and to some extent almost obligatory, at least it merited a single paragraph in the discussion section. We remarked on depression and grief having similar effects on the immune system by lowering natural killer (NK) and T cell populations, which the immune system needs to fight disease. Furthermore, there is considerable high quality research which suggests that chronic depression and grief have numerous physiological consequences that are likely to affect cancer development (Calabrese *et al*. 1987; Evans *et al*. 1992; Sachs *et al*. 1995). Our position is that depression and grief must have originated early enough to be involved in the early stages of cancer, as well as be severe and chronic in order to significantly affect the immune system. Our speculation is not related to the immune system differentiating between 'death of a mother and death of other loved

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ones', as Petticrew and Sutton seem to propose, but that depression and grief that is long-standing, chronic and severe is far more likely to damage the immune system than stress of shorter duration.

Petticrew and Sutton conclude their commentary by suggesting that researchers who argued that stress might be related to cancer risk, deprive women of the assurance that life's stress was not related to the development of their disease. The goal of research, which attempts to specify the types of stress related to cancer onset, is to direct medical attention toward individuals who are at greater risk. If chronic and severe depression increases breast cancer risk, then physicians need to assist individuals in this risk group. In the United States, physicians are probably too hesitant to order breast cancer screening (Vernon *et al.* 1990; Weinberger *et al.* 1992) and must often contend with insurance agencies and HMOs who are reluctant to pay for early or repeated testing. Furthermore, in addition to the possibility of increase risk for onset, physicians might need to be particularly attentive to depressives, since depression is frequently associated with delay in seeking medical attention for cancer symptoms. Desai *et al.*'s (1999) longitudinal study found that individuals with histories of major depression were more likely to have their cancer diagnosed in a later stage than the non-depressed or those with other affective disorders. We hope that our research when appropriately combined with other prospective studies will provide additional evidence that will help at risk groups receive tests and early medical attention.

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