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Letter to the Editor

Depression linked to cancer mortality not convincingly demonstrated

There is no consensus whether psychosocial factors influence cancer initiation and development. In my review based on 70 prospective studies, where the number of significant findings was counted, it was concluded that there was not any specific psychological factor that had convincingly been demonstrated to influence cancer development (Garssen, 2004). Recent meta-analyses have focused on specific psychological factors. For example, Duijts *et al*. (2003) concluded that death of a spouse reliably predicts breast cancer risk and Satin *et al*. (2009) showed that depression is related to cancer mortality, which was confirmed in a meta-analysis on a much larger set of studies, recently published in *Psychological Medicine* (Pinquart & Duberstein, 2010).

The inclusion of relevant confounding factors has always been a major topic of discussion in reviews, and studies have been criticized for their inadequate control for such factors. Pinquart & Duberstein (2010) surveyed the use of control for confounding variables and found no difference in the risk ratio for controlled studies and uncontrolled studies; both types of studies did find increased depression-related cancer mortality. This finding and the large number of studies summarized in their meta-analysis ($n=76$) certainly encourage us to be convinced about the effect of depression on cancer mortality. However, this conclusion is weakened by a number of critical remarks.

First, the number of studies that did find a significant relationship between depression and mortality is rather modest. I counted 75 publications (instead of 76), of which eight described the same study (Shekelle *et al*. 1981 and Persky *et al*. 1987; Watson *et al*. 1999, 2005; Chang *et al*. 2004*a*, *b*; Mainio, 2005, 2006), I rejected six studies that did not describe the subject or had fatal flaws in their design (Coryell, 1981; Tschuske *et al*. 2001; Litosfsky *et al*. 2004; Beresford *et al*. 2006; Stockler *et al*. 2007; Wilson *et al*. 2007), and could not trace two publications (Stein *et al*. 1989; Ehlers, 2002). Of the remaining 64 studies, only 22 (34%) observed a significant relationship (Derogatis *et al*. 1979; Leigh *et al*. 1987; Persky *et al*. 1987; Colon *et al*. 1991; Ratcliffe *et al*. 1995; Buccheri, 1998; Penninx *et al*. 1998; Loberiza *et al*. 2002; Stommel *et al*. 2002; Brown *et al*. 2003; Hjerl *et al*. 2003; Chang *et al*. 2004*b*; Goodwin *et al*. 2004; Hoodin *et al*. 2004; Mainio *et al*. 2006; Kawamura *et al*. 2007; Steel *et al*. 2007; Dalton *et al*. 2008; Grulke *et al*. 2008; Gantinji *et al*. 2009; Lloyd-Williams *et al*. 2009; Tian *et al*. 2009). I did not equate depression and helplessness in this analysis, as I have argued elsewhere that they are different concepts (Garssen, 2004). [For full references to the studies cited in this paragraph, see Pinquart & Duberstein (2010)].

Second, a relationship between depression and mortality is not necessarily evidence for an effect of depression on cancer mortality, because there are several other possible explanations, especially in terms of health behaviours. The largest study included in Pinquart & Duberstein's survey is the nation-wide study of the Danish population conducted by Dalton *et al*. (2008), which contributes 45% of the cancer patients involved in the present meta-analysis and 10% of the samples [the outcome of each type of cancer described in the Dalton *et al*. (2008) study is counted as one sample]. Although the meta-analysis of Pinquart & Duberstein (2010) focused on cancer mortality, it is illustrative to also describe the study by Dalton *et al*. (2008) with respect to cancer initiation.

Of the 21 types of cancer described in the study by Dalton *et al*. (2008), for six cancers it was shown that depression led to an increased chance of cancer incidence in men and/or women. Of these six types of cancer, three were related to tobacco smoking (cancer of the mouth and pharynx, oesophagus, and lung), which also had the largest incidence rate. With respect to the course of cancer, it appeared that the only cancer type showing shorter survival in depressed patients was stomach cancer, which is also a tobacco-related type of cancer. These findings suggest that a major part of the increased incidence and mortality rate of depression is linked to smoking. Although Pinquart & Duberstein (2010) found no difference in risk ratio for controlled and uncontrolled studies, they did not include smoking and alcohol consumption in their survey; thus it remains uncertain whether controlling for these important confounders would have drastically reduced the association between depression and survival in their meta-analysis.

Another behavioural factor that may explain the relationship between depression and survival is treatment adherence. It has convincingly been demonstrated that depressive patients follow medical prescription less regularly than other patients, and it has also been demonstrated that depression even makes the odds of non-adherence three times higher

(DiMatteo *et al*. 2000). It is therefore plausible that such undertreated conditions would affect outcomes in the long term. Also increasing the chances of an adverse outcome may be that depressive patients present at a later stage of cancer. Finally, it is possible that a lack of effective communication between the patient and medical doctor may delay medical treatment. In line with these expectations is the outcome of a study showing that women with a history of depression were less likely to receive treatment for their breast cancer consistent with consensus conference standards (Goodwin *et al*. 2004). Some of these possible health behaviour consequences of depression were also acknowledged by Pinquart & Duberstein (2010), but they did not include any treatment factors in their list of confounding variables.

There is a third explanation for the association between high levels of depression and increased cancer mortality. Nakaya *et al*. (2008) rightly argued that this association could be explained by clinical state, because a poor clinical state would be associated with depression and with later increased mortality. Indeed, many studies have demonstrated that the presence of somatic symptoms, such as pain, fatigue and dyspnoea, is strongly associated with level of depression, and is even one of the strongest predictors for psychological symptoms (Deimling *et al*. 2002; Kurtz *et al*. 2002; Stommel *et al*. 2004). Nakaya *et al*. (2008) showed that depression predicts mortality rate among lung cancer patients. However, when pain and dyspnoea were added to the regression analysis, the relationship was no longer significant. Another example is the study of Gripp *et al*. (2007) that found depression to be related to survival in univariate analyses, but no longer so in the multivariate analysis that included somatic symptoms and performance status. Another measure of clinical state mentioned by Nakaya *et al*. (2008) is performance status. Performance status appeared to be an important predictor for depression in many studies (for instance, Deimling *et al*. 2002; Stommel *et al*. 2004). A third confounding factor is co-morbidity, which is also associated with depression and with survival (Goodwin *et al*. 2004). So, to rule out the possibility that the depression–survival relationship is explained by a third factor, namely a bad clinical condition affecting both depression and survival, somatic symptoms, performance status and/or co-morbidity should be included as confounding factors. However, of the studies that found a relationship between depression and mortality, less than 15% controlled for these confounding factors.

Pinquart & Duberstein (2010) are aware of some of these problems by pointing at the possibility that associations between depression and mortality may reflect illness severity, but argue that studies having assessed depression years before cancer diagnosis found similar associations compared with studies that had assessed depression following cancer diagnosis. However, this is not a valid argument, as depression years before treatment is associated with depression during and after treatment (Kissane *et al*. 2004; Simonelli *et al*. 2008).

A last problem with many studies that have researched the role of psychological factors on cancer mortality, including the studies in Pinquart & Duberstein's (2010) meta-analysis, is that the studies rarely confirmed whether the cause of death was cancer. Depression increases the mortality rate for several medical diseases and other conditions (Kawamura *et al*. 2007).

The finding that depression is related to cancer mortality through its effects on health behaviours, such as smoking, alcohol consumption, treatment adherence and treatment delay, is clinically very relevant. However, many scientists and laymen appear more interested in the alternative pathway, namely that depression impairs immune function, which in turn predisposes a person to the initiation or progression of neoplastic disease. Unfortunately, the meta-analysis conducted by Pinquart & Duberstein (2010) does not prove that depression has any effect on cancer mortality beyond its influence on health behaviour.

Declaration of Interest

None.

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The authors reply

Meta-analysis and its discontents

For better or worse, meta-analyses are based on all available evidence. Taking a step back to the pre-meta-analytic era, Garssen's crude boxscore approach leads to the conclusion that 'only 34%' of the studies included in our meta-analysis found a significant effect. Presumably, he trots out this number to cast doubt on the robustness of the relationship between depression and mortality in cancer patients.

However, whether the effect size of an individual study reaches statistical significance largely depends on the sample size. Many included studies did not have sufficient sample sizes for detecting effects that are statistically significant. Meta-analysis allows the pooling of the results from many studies, so that the aggregate findings have greater statistical power. Therefore, meta-analyses are better suited for identifying small statistical effects than crude counting procedures like the one used by Garssen. The average risk ratios (RRs) of the four published meta-analyses on associations of depression and cancer mortality (McGee *et al*. 1994; Chida *et al*. 2008; Satin *et al*. 2009; Pinquart & Duberstein, 2010) varied between 1.08 and 1.39, which indicates that the relative mortality risk of depressed individuals is enhanced by 8 to 39%. Few readers would deny the clinical significance of the risk reduction that could potentially result from effective depression treatment.

Garssen's letter expresses concern that the association between depression and mortality may be based on the effect of third variables. Here, two kinds of cases would have to be distinguished. First, the association between depression and mortality might be based on an unmeasured confounding variable that affects both depression and mortality, such as stage of cancer or functional status. Second, the effect of cancer on mortality may be mediated by another variable. We are pleased that Garssen raised these important issues as we are now able to report new analyses.

With regard to the first case, we had reported that there are significant associations of depression and length of survival in studies that controlled for possible confounders (cancer site, stage, functional status, medical co-morbidities, age and socio-economic status) and in those that did not. Due to space limitations, we had not reported separate analyses for each confounder. We now report that the results are identical for individual confounders. For example, depression relates to cancer mortality in studies that controlled for cancer stage [RR 1.24, 95% confidence interval (CI) 1.14–1.14] and in those studies that did not (RR 1.25, 95% CI 1.03–1.53). Similarly, studies that controlled for performance status (RR 1.43, 95% CI 1.19–1.73) do not differ in effect sizes from those that did not (RR 1.20, 95% CI 1.10–1.32). Further, results were identical for studies that controlled for co-morbidities (RR 1.26, 95% CI 1.07–1.48) and that did not control for this variable (RR 1.24, 95% CI 1.14–1.36).

In addition, because we found significant associations of depression with cancer survival even in studies that assessed depression years before cancer diagnosis, we stated that the association between depression and mortality is unlikely to reflect the confounding effect of cancer severity. Garssen believes

that this would not be a valid argument as depression may show stability over time. However, stable depression may be a risk factor for a diagnostic delay which could be a possible mediator of the association between depression and mortality of cancer patients (Desai *et al*. 1999).

Garssen suggests that tobacco smoking and alcohol consumption may have also confounded the association, though it is possible that these health behaviours actually mediate the effect of depression on mortality. As only six studies provided information about smoking habits and alcohol use, we excluded these variables from our meta-analysis. Nonetheless, we report here the presence of an association of depression and mortality in studies that controlled for tobacco smoking and alcohol use (RR 1.44, 95% CI 1.11–1.88) and in those studies that did not control for this variable (RR 1.22, 95% CI 1.13–1.32). Thus, the observed association between depression and mortality cannot be explained by higher tobacco smoking of depressed individuals. We also had not included treatment adherence as a potential confounder in our meta-analysis because this variable was rarely assessed in the available studies. However, as depressed individuals may receive less than optimal cancer therapy (Goodwin *et al*. 2004), we are able to compare studies that controlled for the receipt of therapy (e.g. chemotherapy, radiation). Again, studies that control for that variable (RR 1.25, 95% CI 1.11–1.41) and those that do not (RR 1.23, 95% CI 1.11–1.35) show similar effect sizes.

Garssen refers to variables that may mediate the association between cancer and mortality, such as treatment adherence or lack of effective communication between the patient and physician. We and the authors of the other meta-analyses have mentioned these possible mediators, in addition to other explanations (e.g. effects of cancer on the neuroendocrine and immunological functions). However, even if an association between depression and mortality were fully mediated by health behaviours – as Garssen implies – we agree with him that the association of depression and mortality is still practically important. Identifying and treating depression could be expected to have positive effects on health behaviours and compliance (DiMatteo *et al*. 2000), which again may influence cancer survival.

A main problem that cannot be solved by meta-analyses or narrative reviews of prospective studies on the association of depression with cancer mortality is the fact that prospective studies cannot provide a strict test for causal relationships, as there is still a risk that unmeasured third variables might cause the observed association between depression and mortality. The best test of causal effects of depression would be controlled trials that randomly assign depressed cancer patients to a depression treatment (medication, psychotherapy) or a structurally equivalent control condition. Because the size of the association between depression and mortality of cancer patients is small and as not all participants may respond well to the depression intervention, such studies should have large sample sizes. If survival is greater among those assigned to the depression treatment, and this advantage is mediated by a reduction in depression symptoms, there would be no better demonstration of the practical value of meta-analysis. Other mediators, such as health behaviours or immunological processes, could also be examined for a deeper scientific understanding of the basic mechanisms by which depression reduction confers a survival advantage.

In replying to his letter, and in an effort to ensure that we are not merely talking past each other, we would like to remind Garssen that our meta-analysis was merely intended to document the presence and strength of associations between depression and cancer mortality. It was not designed to examine whether 'psychosocial factors influence cancer initiation and development'. Nor was it intended to examine the effects of depression on cause-specific mortality. Finally, it was not an attempt to 'prove that depression has any effect on cancer mortality beyond its influence on health behaviour'. Leaving aside the elusive question of scientific proof, our meta-analysis cannot yield insights into underlying physiological mechanisms by which mortality can be accelerated. That question can only be examined in a controlled experimental setting and there is nothing in our paper that would have led a careful reader to conclude that we believe otherwise.

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