Editorial Commentary

Adverse impact of depression and anxiety on mortality in patients with breast cancer

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Depression and anxiety are common in patients with cancer. As in the reports regarding the association between depression and mortality in various physical conditions (1), there have been similar investigations of these issues in patients with cancer (2). However, these investigations have yielded mixed results regarding mortality, likely due to methodological differences among the studies. For example, the timing of diagnosis of psychiatric disease, i.e., before versus after the cancer diagnosis can affect the results (3). For the choice of assessment measures, the evidence for an association between depression and mortality was weaker in studies that used structured interviews than in those that used dimensional scales (1). Adjustment for confounding variables can also affect the results. The well-known prognostic factors in breast cancer are primary tumor size, presence of regional lymph nodes, distant metastases, histologic grade, and hormone receptor status. Other important confounding variables include social inequality, obesity, cigarette smoking, alcohol intake and exercise. These factors are not reliably documented in retrospective studies, unless drawn from large linkage studies such as those conducted by the Danish Cancer Society (4).

In a previous meta-analysis of 25 independent studies, the mortality rate was up to 39% above average in patients diagnosed with major or minor depression [unadjusted relative risk (RR), 1.39; 95% confidence interval (CI), 1.10–1.89] (5). Another recent meta-analysis by Wang and colleagues (2) of 51 cohort studies reported significant impacts of depression and/or anxiety on cancer-specific mortality (adjusted RR, 1.21; 95% CI, 1.16–1.26) and all-cause mortality in patients with various types of cancer (adjusted RR, 1.24; 95% CI, 1.13–1.35). However, in subgroup analysis of seven studies of breast cancer, depression and anxiety were not significantly associated with mortality.

Several biobehavioural pathways have been suggested to be possible links between psychological distress and tumour progression. Non-adherence to cancer treatment, including endocrine therapy, and negative lifestyle factors, such as smoking, physical inactivity and alcohol consumption, can impact cancer progression indirectly (4,6,7). Depression may impact the immune system of patients due to impaired activity of natural killer cells and cell-mediated immunity. Dysregulation of hypothalamic-pituitary-adrenal axis activity and activation of the automatic nervous system could increase inflammation and oxidative/nitrosative stress (6).

Given the concerns regarding the association between depression and mortality in patients with cancer, the question of whether treatment of depression could improve survival has been raised. There have been several

randomised controlled trials regarding the effects on mortality of psychosocial interventions in patients with comorbid cancer and depression, as a primary or secondary outcome, but the results were inconsistent; therefore, there is still debate concerning this issue (8,9). Meanwhile, there have been few investigations regarding the potential benefit of antidepressant treatment in survival in patients with cancer. Most studies used a retrospective design, which makes it difficult to identify causal relationships.

In breast cancer, there have been reports of an increased risk of mortality, rather than decreased mortality, associated with antidepressant use. Various types of antidepressants, e.g., selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), have been reported to increase breast cancer mortality in women, although conflicting results have been reported (10). Among the SSRIs, paroxetine has attracted attention with regard to increasing mortality in patients with breast cancer due to its possible interaction with tamoxifen *via* inhibition of the cytochrome P450 2D6 isoenzyme, its alteration of oestrogen responsiveness, or its oestrogenic effect (10). Although this has not yet been proven, it is prudent to exert caution when considering paroxetine and related SSRIs using the P450 2D6 metabolic pathway for patients with breast cancer.

Time of first-onset of mental illness in relation to cancer diagnosis

Shim *et al.* used National Health Insurance Service (NHIS) data from South Korea to examine the associations of depression, anxiety and antidepressant treatment with mortality in patients with breast cancer (11). The prevalence rates of depression and anxiety were lower than in previous studies performed in Western countries, and also much lower than in another nationwide South Korean study that used NHIS data (12). This could have been due to the exclusion of cases of depression or anxiety diagnosed 1 year before the breast cancer diagnosis. It is important to be specific regarding the timing of the depression/anxiety diagnosis in relation to that of cancer when investigating the impact of these comorbidities on mortality. The effects of mental disorders with first onset after cancer diagnosis may differ from those of recurrent mental disorders, with the former probably being a product of cancer-specific stress (3). In a nationwide cohort study, mental disorders with first onset after cancer diagnosis were shown to increase cancer-specific mortality, while recurrent mental disorders had no such effect (3).

Association of depressive and anxiety disorders with mortality in patients with breast cancer

Regarding patients with breast cancer, there have been some reports specifically related to the effects of depression and/or anxiety on the mortality rate (*Table 1*) (11,13-21). Among ten studies, three analyzed cancer-specific mortality and the others analyzed all-cause mortality. The study by Shim *et al.* also did not analyse cancer-specific mortality. When analyzing mortality, it is recommended to investigate cancer-specific mortality to identify the direct impact of depression on cancer outcomes, because depression is associated with a higher mortality rate in the general population (5). Even though the association of depression with cancer-specific mortality was not found to be significant, the association with all-cause mortality might be significant if non-cancer-related mortality had a sufficiently large effect size (22).

Including the study by Shim *et al.*, five studies investigated the impact of depression and anxiety on mortality (11,14,17,19,21). Only the study by Shim *et al.* analyzed the specific impacts of depression and anxiety and the impact of their co-occurrence. Depression and anxiety were independently associated with mortality in patients with breast cancer, and their co-occurrence further increased the risk (11).

As mentioned above, adjusting recognised confounding factors is also important. The results of the study by shim *et al.* were adjusted by sex, age, place of residence, income level, comorbid illness, type of breast cancer, disability, and receipt of chemotherapy/radiation therapy/hormonal therapy/target therapy (11). However, the results were not fully adjusted for several important confounding factors to analyze mortality. For example, the severity of cancer at first diagnosis is a risk factor for mortality that affects results. In a nationwide retrospective cohort study conducted in Denmark, preoperative depression was associated with elevated mortality in late-stage breast cancer, while postoperative depression was associated with increased mortality in early stage breast cancer (15). The study by Shim *et al.*, investigated the cancer type, i.e., cancer *vs.* carcinoma-in-situ, but did not differentiate between early *vs.* late breast cancer. Furthermore, significantly more carcinoma-in-situ cases were included in the non-depression/non-anxiety group than in the other groups. Although this difference was adjusted for by covariates, whether advanced cancer cases were similarly distributed between the groups remains unknown. Furthermore, other

Table 1 Summary of previous articles concerning the impact of depression and/or anxiety on mortality in patients with breast cancer

First author, year published	Sample size and stage of cancer	Study design	Assessment of depression/anxiety	Time of assessing depression/ anxiety	Duration of follow-up	Summary of findings	Other comments
Hjerl K, 2003	10,382 patients with early-stage BC and 10,211 patients with late-stage BC	Nationwide, retrospective cohort	Depressive disorders on ICD-8 code in the database	Preoperative *vs.* postoperative	5.5 years for early-stage/ 3.8 years for late-stage	Preoperative depression: higher risk of all-cause mortality in the late-stage group (RR, 1.34; 95% CI, 1.13–1.59); Postoperative depression: higher risk of all-cause mortality in the early-stage group (RR, 1.73; 95% CI, 1.30–2.28)	Depressive disorders: bipolar, unipolar, reactive, dysthymia, and anxiety disorders
Osborne RH, 2004	61 patients with early-stage BC	Prospective cohort	HADS	4 weeks or more since completion of chemotherapy	6.1–7.9 years	N.S. result for cancer-specific mortality	Minimizing illness adjustment predicted longer survival
Watson M, 2005	578 patients with stage I/II BC	Prospective cohort	HADS	4–12 weeks post-diagnosis of cancer	10 years	N.S. result for overall survival	Significant result on helplessness/ hopelessness
Groenvold M, 2007	1,588 patients with invasive BC	Prospective cohort	HADS	2 months after primary operation	12.9 years	N.S. result for overall survival	Emotional function predicted favourable overall survival
Vodermaier A, 2014	1,646 patients with stage I–IV BC	Prospective cohort	PSSCAN-depression subscale	After cancer diagnosis but before treatment initiation	76 months	In patients with curable cancer, depression predicted all-cause mortality (HR, 1.54; 95% CI, 1.06–2.25) but not cancer-specific mortality	N.S. result on metastatic disease
Vin-Raviv N, 2015	4,164 hospitalized patients with BC/4,164 matched control	Cross-Sectional	Depression and anxiety disorders on ICD-9 code in the database	Within investigation period	Within investigation period	Depression associated with lower all-cause mortality (adjusted OR, 0.68; 95% CI, 0.51–0.91)	N.S. result on anxiety disorders
Kanani R, 2016	77,173 patients with BC	Retrospective cohort	Mood disorders on ICD-10 code in the database	From 3 years before to a year following cancer diagnosis	5 year after cancer diagnosis	Depression predicted worse overall survival (HR, 1.33; 95%CI, 1.20–1.48)	Also investigated bipolar disorder, but N.S. result
Suppli NP, 2017	45,325 patients with early BC	Nationwide, retrospective cohort	Previous hospital contact for depression or history of treated with AD in the database	Before primary BC diagnosis	Between 1998–2011	Women who had used AD had worse overall survival (HR, 1.21; 95% CI, 1.14–1.28) and BC-specific mortality (HR, 1.11; 95% CI, 1.03–1.20)	Increased HRs for death by suicide for women who had used AD or had previous hospital contact for depression

Table 1 (*continued*)

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First author, year published	Sample size and stage of cancer	Study design	Assessment of depression/anxiety	Time of assessing depression/ anxiety	Duration of follow-up	Summary of findings	Other comments
Antoni MH, 2017	231 patients with non-metastatic BC (stage 0–IIIb)	Prospective cohort	HDRS	2–10 weeks after surgery	8–15 year	Mild/moderate depressive symptoms had shorter overall survival (HR, 2.56; 95% CI, 1.11–5.91) than non-depression group	Greater HDRS scores associated with shorter survival
Shim EJ, 2020	124,381 patients with BC	Nationwide retrospective cohort	Depression and anxiety disorders on ICD-10 code in the database	From 1 year before the cancer diagnosis	3.98–4.46 years	Depression and anxiety disorder associated with increased risk of all-cause mortality (HR, 1.26; 95% CI, 1.18–1.36 for depression; HR, 1.14; 95% CI, 1.08–1.22 for anxiety)	Sub-analysis for AD/BDZ group

AD, antidepressant; BC, breast cancer; BDZ, benzodiazepine; HADS, Hospital Anxiety and Depression Scale; HDRS, Hamilton Rating Scale for Depression; HR, hazards ratio; ICD, International Classification of Disease; N.S., not-significant; OR, odds ratio; PSSCAN, Psychosocial Screen for Cancer; RR, relative risk.

factors such as involvement of axillary lymph nodes, distant metastasis, and other socio-behavioral confounding factors were not investigated.

Impact of antidepressants on mortality in patients with breast cancer

Shim *et al.* reported that antidepressant treatment was related to reduced cancer mortality. This finding was unique and noteworthy, but caution is required in its interpretation. The study did not specifically focus on the impact of the treatment of depression or anxiety, but rather on the association of the use of psychiatric medication with mortality in patients with breast cancer. A few studies have investigated the associations between antidepressants and mortality in patients with cancer; the results varied between increased and decreased mortality (23,24). But regardless of the controversial results found in previous studies, it is necessary to pay attention to the application of "antidepressant treatment" used in the study of Shim and colleagues. The expression "antidepressant treatment" included not only "antidepressants" but also "anxiolytics", such as benzodiazepines in the study. This may answer the question raised by Chen *et al.* in a letter regarding why "antidepressants treatment" were administered to patients without formal depressive and anxiety disorders in that study (25): anxiolytics are widely recommended to control various symptoms other than anxiety or depression in patients with cancer. It ought not to be concluded that those antidepressants or benzodiazepines actually decreased the risk of mortality in patients with breast cancer because the mortality rate was increased in the patients receiving antidepressant treatment among a non-depressed and non-anxious group in the study of Shim *et al.* However, Shim *et al.* reported "antidepressant treatment" may attenuate the risk because the mortality rate was lower in the patients receiving antidepressant treatment among the group with the depression and anxiety, compared to one with the same diagnosis but not receiving antidepressant treatment. While this is quite encouraging, the paper did not provide the full results of pairwise comparisons, i.e., pairwise over strata, on the log-rank test to compare more than two groups. Only the results of a log-rank test comparing these groups with a reference group (i.e., a group without anxiety or depression that received no antidepressant treatment) were provided.

In a similar previous nationwide study, higher adherence to antidepressants was associated with decreased all-cause mortality in patients with various type of cancer (24).

However, among patients with breast cancer, the results differed from those of another population-based study which showed that patients with long-term SSRI use had higher mortality than their non-SSRI-using counterparts, regardless of any prior diagnosis of depression (23). Given the limitations inherent in the retrospective and/or observational designs of these studies, randomised controlled trials with mortality as the primary outcome are required for more definitive conclusions.

Conclusion and future directions

Determining the impact of mental illness on mortality in patients with breast cancer is very important. It is also important to determine whether appropriate mental health interventions could reduce mortality in these patients, but previous studies reported conflicting results and had methodological limitations. Nationwide studies using health insurance databases have the benefit of large sample sizes, but it is difficult to determine causal relationships and control variables in a retrospective design. However, the results could provide a basis for future prospective studies or randomised controlled trials. To investigate the impact on mortality, the timing of the depression/anxiety diagnosis relative to the cancer diagnosis, the cancer-specific mortality, and full adjustment for confounding variables are recommended.

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Footnote

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