step. In the primary care setting, adding a question regarding assistance to the questionnaire, which was, "Is this something with which you would like help?" improved the screening performance (Arroll et al., 2005). Such a questionnaire may also give information about patients' needs, and adding a "help" question may be a clue to help us formulate our next step.

ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-aid for Cancer Research, Clinical Cancer Research, and Third Term Comprehensive 10-year Strategy for Cancer Control, from the Japanese Ministry of Health, Labor and Welfare.

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Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005537.

Psychotherapy for depression among incurable cancer patients.

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BACKGROUND: The most common psychiatric diagnosis among cancer patients is depression; this diagnosis is even more common among patients with advanced cancer. Psychotherapy is a patient-preferred and promising strategy for treating depression among cancer patients. Several systematic reviews have investigated the effectiveness of psychological treatment for depression among cancer patients. However, the findings are conflicting, and no review has focused on depression among patients with incurable cancer. OBJECTIVES: To investigate the effects of psychotherapy for treating depression among patients with advanced cancer by conducting a systematic review of randomized controlled trials (RCTs). SEARCH STRATEGY: We searched the Cochrane Pain, Palliative and Supportive Care Group Register, The Cochrane Controlled Trials Register, MEDLINE, EMBASE, CINAHL, and PsycINFO databases in September 2005. SELECTION CRITERIA: All relevant RCTs comparing any kind of psychotherapy with conventional treatment for adult patients with advanced cancer were eligible for inclusion. Two independent review authors identified relevant studies. DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data from the original reports using standardized data extraction forms. Two independent review authors also assessed the methodological quality of the selected studies according to the recommendations of a previous systematic review of psychological therapies for cancer patients that utilized ten internal validity indicators. The primary outcome was the standardized mean difference (SMD) of change between the baseline and immediate post-treatment scores. MAIN RESULTS: We identified a total of ten RCTs (total of 780 participants); data from six studies were used for meta-analyses (292 patients in the psychotherapy arm and 225 patients in the control arm). Among these six studies, four studies used supportive psychotherapy, one adopted cognitive behavioural therapy, and one adopted problem-solving therapy. When compared with treatment as usual, psychotherapy was associated with a significant decrease in depression score (SMD = -0.44, 95% confidence interval [CI] = -0.08 to -0.80). None of the studies focused on patients with clinically diagnosed depression. AUTHORS' CONCLUSIONS: Evidence from RCTs of moderate quality suggest that psychotherapy is useful for treating depressive states in advanced cancer patients. However, no evidence supports the effectiveness of psychotherapy for patients with clinically diagnosed depression.

PMID: 18425922 [PubMed - indexed for MEDLINE]

Palliative and Supportive Care (2008), **6**, 79–81. Printed in the USA.

DOI: 10.1017/S1478951508000114

CASE REPORT

A case of respiratory akathisia in a cancer patient: A case report

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(RECEIVED September 14, 2007; ACCEPTED October 16, 2007)

ABSTRACT

Objective: It has been reported that akathisia is a neurological side effect induced by antiemetic drugs and/or antipsychotics. Akathisia can occur in any area of the body, but respiratory akathisia is an unusual type of akathisia. Cases of respiratory akathisia in cancer patients taking antiemetic drugs have not previously been reported.

Methods: We report on a case of a cancer patient taking prochlorperazine as an antiemetic drug who experienced dyspnea accompanied by severe restlessness associated with respiration. By administration of biperiden, his restlessness in respiration and dyspnea promptly disappeared.

Results: This finding led us to conclude that this cancer patient was experiencing respiratory akathisia.

Significance of results: Respiratory akathisia is uncommon. It is important for cancer patients that dyspnea induced by disease progression be ruled out as a cause of the respiratory restlessness. It is necessary to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

KEYWORDS: Respiratory akathisia, Cancer, Antiemetic drug

INTRODUCTION

Akathisia is a neurological side effect produced by antipsychotic or antiemetic drug therapy (Blaisdell, 1994). The clinical picture of akathisia is a feeling of inner restlessness in the limbs, especially in the legs (Gibb & Lee, 1986). However, reports have indicated that akathisia can occur in any area of the body, such as the arms or abdomen (Raskin, 1972; Ratey & Salzman, 1984; Walters et al., 1989). A rare manifestation of akathisia reported by patients receiving antipsychotic treatment is an inner restlessness in respiration as dyspnea.

Prochlorperazine is an antiemetic agent frequently used by cancer patients taking opioids (e.g., morphine, oxycodone) for cancer pain. In oncological settings, prochlorperazine is used as an antiemetic drug for nausea, a side effect of opioid. It is a phenothiazine antiemetic that has central dopamine antagonist properties and that has been reported to cause acute extrapyramidal side effects,

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parkinsonism, dystonia, and akathisia (Bateman et al., 1989). It is well known that neuroleptic-induced akathisia may be difficult to recognize and can occur in the absence of other extrapyramidal signs. Furthermore, cases of akathisia due to antiemetic drugs used by cancer patients have been little reported.

CASE REPORT

The patient was an 66-year-old man with squamous cell carcinoma of the esophagus, stage II(T2N0M0). Due to his renal impairment and the presence of emphysema, surgical resection was not performed; furthermore, chemotherapy was not indicated. Therefore, he attempted radiation therapy and received a total dose of 70.2 Gy. He used opioid, 20 mg/day of morphine hydrochloride, for pain of esophagitis by irradiation, with taking prochlorperazine as an antiemetic drug. He complained of chest discomfort after receiving 5 mg/day of prochlorperazine p.o. for 3 weeks and was admitted to the hospital. When he arrived in the hospital, he acknowledged dyspnea with vague anxiety and a subjective restlessness in respiration, with a temperature of 36.8°C, blood pressure of 118/72 mm Hg, pulse 79 beats/min, respiratory rate 18 breaths/min. Resting room-air oxygen saturation was 98%. First, radiation pneumonitis was suspected, but chest X-ray was normal. He felt that he could not respire leisurely nor stop breathing at any time because of this restlessness in respiration. He denied restlessness in the limbs or other body areas except for the chest. He showed no signs or symptoms of parkinsonism. He was administered 5 mg of biperiden d.i.v.; his restlessness in respiration and dyspnea simultaneously disappeared approximately 1 h later (Hirose & Ashby, 2000). Subsequently, 6 mg of oral biperiden was added to the treatment regimen. The next day, the dyspnea with vague anxiety and other restless movements completely ceased. No signs or symptoms of akathisia have appeared in this patient since that time.

DISCUSSION

We reported respiratory akathisia in cancer patients taking prochlorperazine as antiemetics. This is the first report of respiratory akathisia recognized in cancer patients.

It was necessary that other medical problems known to produce dyspnea, such as panic attacks and dyskinesia and dystonia or pulmonary diseases, could be ruled out as a cause of the respiratory restlessness (Hirose, 2000). In this case, the patient did not have anxiety about dying or a history of panic disorder before. Respiratory dyskinesia presents as involuntary movements of respiratory muscles, but not as a restless feeling in respiration, and is not improved on treatment with biperiden (Kruk et al., 1995; Esmail et al, 1999; Heard et al., 1999). Furthermore, in this case, dystonia was ruled out by the absence of tonic contractions of respiratory muscles (Dressler & Benecke, 2005).

Respiratory akathisia is uncommon, so one needs to ask specific questions about restlessness in breathing to recognize this type of akathisia. Therefore, if physicians is not aware of inner restlessness in respiration, it is possible that dyspnea in akathisia may be overlooked or misdiagnosed as a symptom of anxiety disorders, agitation, or respiratory symptoms of cancer itself (Hirose, 2000).

Antiemetics possessing a central antidopaminergic effect are suspected to have caused the akathisia (Seeman, 2002; Matsui-Sakata et al., 2005). Antiemetic-induced akathisia has been reported in cancer patients receiving metoclopramide or prochlorperazine to help control chemotherapy-related nausea and vomiting (Fleishman et al., 1994; Tsuji et al., 2006). In this case, prochlorperazine was used as an antiemetic drug for nausea and vomiting, a side effect of opioid.

Prochlorperazine is a phenothiazine antiemetic that has central dopamine antagonistic properties. It has been reported that the presumed community standard of prescribing prochlorperazine, dexamethasone, or a 5HT3 receptor antagonist after moderately high to highly emetogenic chemotherapy results in equivalent outcomes in terms of control of vomiting and measures of satisfaction and quality of life (Burris et al., 1996; Crucitt et al., 1996).

In Japan, many cancer patients taking opioids for cancer pain clinically use prochlorperazine as an antiemetic drug. Therefore, it should be noted that akathisia is considered a possible side effect during the management of cancer pain.

The clinicians' attitude toward akathisia is important to recognize. It is also important to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

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Palliative and Supportive Care (2008), **6**, 183–185. Printed in the USA.

doi:10.1017/S1478951508000278

CASE REPORT

Activation syndrome caused by paroxetine in a cancer patient

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(RECEIVED September 05, 2007; ACCEPTED October 15, 2007)

ABSTRACT

Individuals with cancer have two to four times an increased risk of depressive disorders compared to the general population. Depressive symptoms are related to impaired daily life functioning and a rise in health care utilization. Pharmacological treatments for depression are usually effective to reduce depressive symptoms, but sometimes lead to serious adverse reactions. We describe a cancer patient who developed sudden psychological and behavioral abnormalities after administration of the antidepressant paroxetine. Impulsive and aggressive symptoms are a so-called activation syndrome that can cause violent or suicidal tendencies. Palliative care staff should pay close attention to these potentially lethal reactions and make an immediate and correct diagnosis.

KEYWORDS: Activation syndrome, Selective serotonin reuptake inhibitors (SSRIs), Paroxetine, Cancer, Akathisia

INTRODUCTION

Recent reports have confirmed that selective serotonin reuptake inhibitors (SSRIs) cause adverse mental and behavioral reactions, so-called activation syndrome (Teicher et al., 1990; Breggin, 2003/2004). We describe a cancer patient who developed activation syndrome soon after receiving an SSRI, paroxetine.

CASE REPORT

A 60-year-old man was admitted to our cancer center for treatment of abdominal pain. The patient had been diagnosed with pancreas cancer 18 months previously and had received three courses of chemotherapy without success. The primal lesion in the pancreas had invaded the para-aortic lymph nodes, causing severe abdominal pain. He had been taking acetaminophen, morphine sulfate, and H2-blocker before and after admission without any adverse side effects. His hepatic and renal functions were well preserved. There was no clinical evidence of brain metastasis or neurological abnormality. He had never experienced a psychotic episode, although he had previously been quite sensitive and anxious about his physical condition. Other symptoms included hopelessness and passive suicidal thoughts due to unbearable pain without any suicidal attempts. The next day after admission, these complaints abated as he realized that his pain could be well controlled with intravenous administration of morphine chloride. His pain was finally well controlled with oral morphine sulfate on day 18 after admission. Nevertheless, he complained of several other symptoms, including depressive mood, anhedonia (he had no interest in investments although he used to be an ambitious shareholder), general fatigue, psychomotor retardation and insomnia.

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Based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), he was diagnosed with major depressive disorder by a psycho-oncologist. He was started on paroxetine 10 mg/day. The day after beginning paroxetine treatment (day 19 after admission), he became talkative and laughed frequently in conversation with his family. On day 2 after beginning administration, he appeared more outgoing and hyperactive (he went home, cooked, and did household chores, and came back to the hospital late at night). On day 3, he insisted on going to a hot spring instead of receiving cancer treatment. He had never showed such behavior before. In the morning on day 4, he abruptly complained of inner restlessness and inability to keep his feet still. He screamed incoherent bizarre ideas and expressed a strong urge to harm himself ("I want to stab my limbs or jump out of the window"). He appeared extremely agitated and showed akathisia-like movements of rocking his feet and head.

Paroxetine treatment was discontinued and levomepromazine (LPZ) was administered for 2 days (25 mg on that day and 15 mg the next day). His subjective complaints of mental and physical restlessness improved several hours after LPZ administration, but he still made inappropriate jokes and aggressive statements the next day. On day 3 after stopping paroxetine, he was quite calm but had a short episode of hyperventilation. His objective stimulated mental symptoms were alleviated 4 days after paroxetine was stopped. Over 1 month after the discontinuation of paroxetine, the patient made a full recovery from the stimulated state and was also free from the major depressive disorder.

DISCUSSION

Although abnormal psychomotor and behavioral conditions have been observed with SSRIs, to our knowledge, this is the first report of so-called activation syndrome in a cancer patient. In the issued advisory by the U.S. Food and Drug Administration, "activation" includes the following symptoms: irritability, anxiety, agitation, insomnia, panic attacks, hostility, impulsiveness, akathisia (severe restlessness occasionally leading to suicidal thoughts and attempts), hypomania, and mania. We would like to draw attention to this potentially lethal drug reaction. Depression is quite common during cancer treatment (Rodin et al., 2007) and SSRIs are more likely to be prescribed to cancer patients because of their fewer cardiovascular side effects compared to classic tricyclic antidepressants (MacGillivray et al., 2003).

On the other hand, several adverse reactions related to SSRIs have been reported, ranging from gastrointestinal symptoms, serotonin syndrome, and activation syndrome to suicidal thoughts and violent behavior (Wagstaff et al., 2002). Unfortunately, abnormal psychotic conditions are often under- and misdiagnosed in cancer treatment settings due to the difficulty of arranging psychiatric consultations (Culpepper et al., 2004); however, it is crucial for clinicians to be aware of the clinical features of activation syndrome because of easier opportunities for self-harm in general hospitals compared to psychiatric wards. In fact, our case would have jumped out of the hospital window if his family had not been with him.

It is also important to make a correct diagnosis of activation and to distinguish it from worsening depression, which could lead to an increased dose of the inappropriate medication and worsen the condition. In previous reports, beta-adrenergic blockers and/or benzodiazepines are usually recommended for the management of SSRI-induced akathisia (Leo, 1996). Our patient required a major tranquilizer to control the intense impulse to self-harm. Although the underlying mechanisms of SSRI-induced akathisia remain uncertain, previous studies have suggested their possible pathophysiology (Lipinski et al., 1989). Our case showed immediate alleviation of the inner restlessness and characteristic leg movement after oral LPZ administration, which implies a different pathomechanism of akathisia between neuroleptics and SSRIs.

In summary, we experienced a cancer patient with paroxetine-induced activation syndrome. Not only oncologists but also staff who participate in palliative care medicine should be attentive to possible adverse mental and behavioral reactions during antidepressant treatment. These symptoms sometimes persist after discontinuation of SSRI and need additional treatment. The effects of neuroleptics on SSRI-induced akathisia may have some implications for their pathophysiological assessment.

ACKNOWLEDGMENTS

We thank the patient and his family for giving us kind suggestions.

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Jpn J Clin Oncol 2009;39(3)175–182
doi:10.1093/jjco/hyn157

Etiologies of Delirium and Their Relationship to Reversibility and Motor Subtype in Cancer Patients

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Received October 29, 2008; accepted December 17, 2008; published online February 3, 2009

Background: Delirium is one of the most commonly encountered complications in patients with cancer. The etiology of delirium in cancer is often multi-factorial, and few reports have examined the causes of delirium. This study investigated the causes of delirium and their association with reversibility and motor subtypes of delirium in cancer patients.
Methods: The subjects were inpatients with cancer who had been referred to our Department of Psychiatry and diagnosed with delirium by psychiatrists. The causes of delirium were determined using standard operationalized criteria. The association between delirium reversibility and each clinical factor was examined in detail and longitudinally.
Results: Data were available from a total of 100 patients. Among them, 58% had hyperactive delirium and 14% had hypoactive delirium. Delirium improved in 56% of the patients after 1 week of standard treatment. The most frequent causes of delirium were opioids (29%), inflammation (27%), dehydration and/or sodium level abnormalities (15%). While two or more causes were identified in 40% or more of the cases, the cause of delirium was not identified in 20% of the patients. Neither reversibility nor motor subtypes of delirium was associated with any specific etiological factor.
Conclusions: When treating delirium, prevalences of the causes of delirium, as identified in this study, should be kept in mind. Further research is required to investigate what specific treatments may facilitate the prompt recovery from delirium among cancer patients.

Key words: delirium – etiologies – cancer – general ward – reversibility – consultation-liaison

INTRODUCTION

Delirium is an acute and transient disturbance of cortical functioning that manifests as deficits in cognition, attention, consciousness and recent memory. Presenting symptoms and signs usually include insomnia with a disturbance or reversal of the sleep/awake cycle, psychomotor agitation or retardation and sometimes perceptual abnormalities such as illusions or hallucinations.

Delirium is one of the most commonly encountered complications in patients with cancer. It occurs in 25–40% of hospitalized patients and may be seen in up to 80% of patients in the terminal stage of their disease (1–6). Patients with delirium tend to require longer hospital stays and have higher mortality rates (2,7,8). In patients with cancer, delirium imposes an additional burden, as the consequent deficits in awareness and attention impede communication with their families and hinder participation in treatment decisions, counseling and symptom assessment (9–11).

One of the most important strategies for the management of delirium is the early identification of the potential cause of delirium and subsequent treatment. However, the causes of delirium are various, and their clinical identification is difficult. Very few studies have investigated the causes of delirium among cancer patients. In addition, to the best of our knowledge, few studies have examined the relation between the causes of delirium and reversibility. Lawlor et al. (2) investigated the cause of delirium among advanced cancer patients who had been admitted to an acute palliative care unit. They reported that the most common cause of delirium was opioids (76%) and psychoactive medications (21%). Furthermore, opioids and dehydration were associated with delirium reversibility, whereas hypoxic encephalopathy and metabolic factors were associated with the non-reversibility of

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delirium. Morita et al. (4) also investigated the pathologies and clinical features of terminal cancer patients with delirium who had been admitted to hospice care. They identified metabolic failure (e.g. hepatic failure, prerenal azotemia and hyperosomolality: 29%, 21% and 21%, respectively) and medication (25%) as the most common causes of delirium in this population. Furthermore, they suggested that delirium caused by medication and hypercalcemia is more likely to improve significantly with treatment. In addition, Gaudreau et al. (12,13) reported in a prospective cohort study that opioid exposure significantly increased the risk of delirium (odds ratio of 1.7) in hospitalized cancer patients.

In clinical oncology settings, the management of patients with delirium is often done through psychiatric consultation at the general wards. However, no studies have investigated the causes of delirium in psychiatric consultation settings. Because these previous studies described above were conducted in palliative care settings, the generalizability of their findings may be limited. For example, the active treatment is scarcely done there. In addition, the method used to identify the etiology of delirium was not clear, and operational diagnostic criteria such as the DSM were not applied in one study (14).

The clinical manifestations of delirium vary widely but may be classified as hyperactive, hypoactive or mixed subtypes, depending on the symptomatology, especially the level of psychomotor activity and alertness. Hyperactive patients are agitated, restless and very distracted, and they respond to stimuli with discrimination. These patients may even be physically combative. Hypoactive patients are quiet, inactive and lethargic, with an overall reduction in their responses to stimuli (15–18). Several studies have suggested that hyperactive, hypoactive and mixed delirium subgroups may differ according to etiology, pathophysiology, detection rates, delirium treatment experience and duration of episodes and outcome (19–22). As far as we know, few studies have addressed the association between the cause of delirium and the clinical subtype in cancer patients.

The purposes of this study were to determine the precipitating etiologic factors of delirium and the reversibility of delirium originating from each different cause in a psychiatric consultation setting. We also investigated the association between each precipitating factor and the clinical subtypes.

PATIENTS AND METHODS

Study Population

This study was conducted at Nagoya City University Hospital, an 808-bed teaching and tertiary care facility of the Nagoya City University Medical School in Aichi, Japan. The subjects included in this study were consecutive adult cancer patients who were referred to the Department of Psychiatry in a consultation-liaison setting between August 2005 and December 2007. All the patients had been hospitalized in general medical wards other than the psychiatric or pediatric wards.

The eligibility criteria were an age of 18 years or over, a confirmed diagnosis of cancer and fulfillment of the criteria for delirium according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) (23) as determined by a trained psychiatrist. The exclusion criteria were a post-operative period of within a fortnight, recent withdrawal from a respirator, underlying obvious dementia and the presence of intracranial disease such as brain metastasis or a cerebral vascular accident. Because this study aimed to examine the relationship between the cause of delirium and the responsiveness to treatment, cases whose delirium was thought to be associated with the above-mentioned exclusion criteria were excluded.

Since this research was performed using data collected during routine clinical practice, informed consent and Institutional Review Board approval were not obtained.

Procedure

First, we evaluated the global condition of patients, the severity and motor subtypes of delirium and its precipitating factors at baseline (when the delirium was first diagnosed). At the same time, we also asked patients' physicians, nurses or caregivers about the overall physical functioning of the patients to evaluate patients' performance status. A structured evaluation was performed, and we evaluated the time–dosage relation between delirium and factors at the time of delirium deterioration. These evaluations were performed by two trained psychiatrists (R.S. and T.O.) Then, standard therapy for delirium (24) was performed. Two main approaches were utilized: symptomatic therapy using antipsychotics such as haloperidol or risperidone (25–31), and reporting the potential cause of delirium to the attending physician and requesting medical treatment, if possible. A follow-up investigation was conducted 1 week later, at which time the severity of the delirium and delirium-related factors were evaluated.

Precipitating Factors and Criteria for Cause Identification

To investigate the biological precipitating factors for the development of delirium, we utilized an *a priori* list of precipitating factors developed using literature references and examined all the listed items using a data entry sheet that we developed.

Each potential precipitating factor for delirium was assessed with regard to the following three criteria (2,7,32). Criterion 1 was the evidence of its presence based on specific clinical and laboratory data. Criterion 2 was a temporal association with the course of delirium consistent with a precipitating factor. Criterion 3 was the improvement of delirium or its non-improvement corresponding to evidence of amelioration or continuation, respectively, of the precipitating factor. When the factor met all three criteria, it was judged to be the most probable precipitating factor of

delirium and was defined as the 'cause' of delirium in this study. When only criteria 1 and 2 were recognized, that is, when delirium with a possible precipitating factor was encountered, the cause of the delirium was qualified as a 'possible factor'.

The following potential precipitating factors and their definitions were utilized in this study.

Psychoactive Medications and Other Drugs (e.g. Opioids, Benzodiazepines, Steroids, Anti-Cholinergic Agents, H2-blockers and Antiepileptic Agents)

Patients received a new psychoactive medication or an increased dosage of a medication known to cause delirium. The use of opioids, benzodiazepines and steroids was examined in each patient, since these drugs are frequently utilized.

Dehydration or Sodium Level Abnormality

A creatinine level higher than 1.3 or a urea nitrogen level of >20 mg/dL in the absence of bleeding into the gastrointestinal tract with hydration. Sodium levels of >150 mmol/L and <130 mmol/L were defined as hypernatremia and hyponatoremia, respectively.

Structural Brain Lesion

Evidence of CNS problems detected during the episode of delirium was obtained by checking for the occurrence of stroke or the presence of brain tumors, although patients with delirium superimposed on obvious dementia or confirmed intracranial lesions had been excluded from the study.

Alcohol or Other Substance Abuse

Withdrawal from alcohol or other drugs is a known cause of delirium, producing clinical evidence of autonomic hyperreactivity or seizure within 7 days of withdrawal.

Hypoxia

Oximetry levels of <90% while receiving room air or requiring an oxygen flow of at least 2 L/min to maintain oxygen saturation levels of at least 90% were regarded as evidence of hypoxic encephalopathy.

Metabolic Factors Like Liver or Renal Failure, Hypoglycemia

The following laboratory reference values were used for specific metabolic factors: aspartate aminotransferase levels of >40 U/L, alanine aminotransferase levels of >50 U/L, bilirubin levels of >1.1 mg/dL (hepatic impairment), a persistent creatinine level of >1.7 mg/dL (renal insufficiency) and a glucose level of <72 mg/dL (hypoglycemia).

Hypercalcemia

Hypercalcemia was recorded if the calcium levels (corrected for the albumin level) were >10.4 mg/dL.

Anemia

A hemoglobin level of <10 g/L was regarded as indicating anemia.

Clotting Abnormality

Laboratory evidence consisting of low platelet levels, prolonged prothrombin and partial thromboplastin times, and D-dimer levels of >0.5 mg/L.

Inflammation

Laboratory evidence consisting of a high white blood cell count or an elevated C-reactive protein level >0.4 mg/dL.

Reversibility of Delirium

Patient response to treatment for delirium was assessed using the DELIRIUM RATING SCALE REVISED 98 (DRS-R-98) (33) 1 week after the baseline assessment. The DRS-R-98 is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The severity scale has a possible range of 0–39 and the diagnostic scale has a range of 0–7. Although the DRS-R-98 is more suitable for diagnostic aims, the quantification of symptom severity using this scale is widely accepted in clinical settings. Using a DRS-R-98 severity score of 15/16 points as the cutoff for distinguishing delirium from other psychiatric disorders, a sensitivity of 92% and a specificity of 93% were obtained. According to this cutoff, a 'reversible case' was defined as a patient whose severity score had dropped to 15 or less at the time of the follow-up examination.

Motor Subtypes of Delirium

The motor subtypes of delirium (15–18) were evaluated using available data from clinical interviews, a review of the case records and information obtained from the medical staff. Clinical information used to determine the subtypes was gathered with regard to the mental status of the patient over several days and nights. The clinical subtypes were evaluated using the phenomenological subtypes initially described by Liptzin and Levkoff in 1992 (34). Using this standard, patients were classified as 'hyperactive' subtype if they had 3 or more of 16 items (such as hypervigilance, restlessness), patients were classified as 'hypoactive' subtype if they had 4 or more of 7 items (such as unawareness, decreased alertness) and patients were classified as 'mixed' subtype if they met the criteria for both hyperactive and hypoactive subtypes.

Statistical Analysis

When investigating the relation between cause and reversibility, we regarded the existence of each 'possible factor' as an independent variable and the reversibility of delirium as the dependent variable. We could not take 'cause of delirium' as independent variable in this analysis because its definition included judgment of reversibility (see the criteria used to identify the cause of delirium). When investigating the relation between the cause and the motor subtypes, we regarded the existence of each investigated factor as an independent variable and the subtype of delirium as the dependent variable. Patients with mixed-type delirium were excluded from these analyses to compare the two distinct delirium conditions.

In both analyses, the association between each possible independent and dependent factor was tested using an appropriate univariate analysis to determine the potential factors. Associated factors ($P < 0.10$) were retained. Then, we used a multivariate analysis to investigate these factors. Similarly, a univariate analysis was conducted using demographic data, such as age, sex, stage of cancer (we divided it into I–III and IV or recurrence, and treated it as category data) and performance status (PS) (we divided it into 0–2 and 3–4, and treated it as category data), and significant variables ($P < 0.1$) were entered into a stepwise multivariate logistic regression analysis to adjust potential confounding factors. A χ^2 test or Fisher exact test was used for the univariate analysis of categorical data. The relation between the number of causes and the reversibility of delirium was analyzed using a Mann–Whitney *U*-test. A Kaplan–Meier analysis was used to calculate the survival period from the beginning of psychiatric consultation until death. A two-tailed *P* value of <0.05 was regarded as significant in all of the statistical analyses. The statistical analysis was conducted using the SPSS ver.11.5 Japanese version for Windows.

RESULTS

Patient Characteristics

Among the 112 delirious patients who met the inclusion criteria, 12 patients were excluded from the analysis (10 cases died soon after entry and 2 moved within 1 week of entry). The characteristics of the remaining 100 patients are summarized in Table 1. The mean patient age was 68 years (SD = 12 years), and 69% of the patients were male. About three-quarters of the patients had metastatic or recurrent cancer. More than three-quarters of the subjects had serious physical impairments (PS = 3–4). The median survival time after the diagnosis of delirium was 39 days (inter-quartile range = 124 days). Fifty-eight percent, 26% and 14% of the patients had hyperactive, mixed and hypoactive delirium subtypes, respectively.

Table 1. Demographic data ($N = 100$)

	N	%
Age (years)	Mean 68 (SD = 12), median 70	
Male	69	69
Clinical stage		
I	3	3
II	1	1
III	8	8
IV (metastasis)	48	48
Recurrence	27	27
Other	13	13
Performance status (ECOG)		
1	7	7
2	15	15
3	46	46
4	32	32
Primary cancer site		
Lung	24	24
Esophagus	15	15
Malignant lymphoma	10	10
Stomach	9	9
Colon	8	8
Survival time (days)	Median 39 (IQR = 124)	
DRS-R-98 severity score (points)	Mean 20 (SD = 6)	
Subtype of delirium		
Hyperactive delirium	58	58
Hypoactive delirium	14	14
Mixed type delirium	26	26
Others (unspecified)	2	2

DRS-R-98, Delirium Rating Scale-Revised-98; ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; SD, standard deviation.

Prevalence of Precipitating Factors

The most common cause of delirium was opioids (29%) (Table 2). The use of benzodiazepines and steroids was also identified in 14% and 9% of the subjects, respectively, and the use of psychoactive drugs accounted for ~50% of all causes of delirium. Inflammation reaction, dehydration and sodium abnormality, and metabolism abnormality were recognized in 27%, 15% and 15% of the cases, respectively. Hypercalcemia, anemia, hypoxemia and a clotting abnormality were also observed in <10% of the patients.

Association between the Reversibility of Delirium and the Presence of Each Precipitating Factor

The delirium of 56 patients (56%) who underwent standard treatment improved within 1 week after the baseline examination (Table 2). Delirium caused by opioids was significantly

Table 2. Causes of delirium and reversibility ($N = 100$)

Precipitating factors	Identified cause		Including possible factors[a]		Reversed ($N = 56$)		Non-reversed ($N = 44$)		OR (95% CI)	P value
	N	%	N	%	N	%	N	%		
Opioids	29	29	36	36	15	27	21	48	2.5 (1.1–5.3)	0.03
Inflammation	27	27	43	43	29	36	23	52	2.0 (0.9–4.4)	0.10
Dehydration and sodium abnormality	15	15	24	24	12	21	12	27	1.4 (0.55–3.5)	0.50
Metabolism abnormality	15	15	22	23	9	16	13	30	2.2 (0.84–5.7)	0.10
Benzodiazepines	14	14	19	19	11	20	8	18	0.90 (0.33–2.5)	0.85
Steroids	9	9	14	14	8	14	6	14	0.95 (0.30–3.0)	0.93
Hypercalcemia	8	8	13	13	7	13	6	14	1.1 (.34–3.6)	0.87
Anemia	7	7	15	15	6	11	9	21	2.1 (0.70–6.6)	0.18
Hypoxemia	6	6	8	8	3	5	5	11	2.3 (0.51–10)	0.30
Clotting abnormality	6	6	10	10	3	5	7	16	3.3 (0.81–14)	0.10
No cause apparent	20	20	—	—	17	30	3	15	0.17 (0.05–0.62)	0.005

[a]Divided into two groups of reversible and non-reversible and then analyzed by independent variable 'possible factors'.
OR, odds ratio; 95% CI, 95% confidence interval.

Table 3. Number of precipitating factors and reversibility ($N = 100$)

Number of causes	All cases		Reversed ($P < 0.001$)[a] ($N = 56$)		Non-reversed ($P < 0.001$)[a] ($N = 44$)	
	N	%	N	%	N	%
Unidentified[b]	20	20	17	85	3	15
1	38	38	26	68	12	32
2	23	23	9	39	14	61
3	14	14	3	21	11	79
4	5	5	1	20	4	80

[a]Mann–Whitney U-test.
[b]Unidentified data were analyzed as missing data.

more unlikely to respond to treatment than delirium caused by other factors, as shown using a univariate analysis ($P = 0.03$). However, this significant difference disappeared after adjustments for PS, clinical stage and demographic data were made using a multivariate analysis. The results indicated that only poor physical functioning was a significant predictor of a poor prognosis for delirium.

Number of Causes and Reversibility of Delirium

The reversibility of delirium was significantly influenced by the number of causes (Table 3).

Association between Motor Subtypes of Delirium and the Presence of Each Precipitating Factor

No significant relations between motor subtypes of delirium and causes of delirium were seen (Table 4).

DISCUSSION

This is the first study to investigate the causes of delirium and their associations with reversibility and motor subtype in cancer patients who were admitted to a general ward. Medicines, such as opioids, and inflammation were the most common causes of delirium. None of the investigated factors showed a significant association with reversibility or clinical subtype.

Medicines, including opioids, were the most frequently identified causes of delirium in cancer patients hospitalized in general wards, consistent with the findings of previous studies performed in different clinical oncology settings. Since pain is a prevalent symptom and opioids are widely used to alleviate pain in cancer patients, opioid-induced delirium is probably the most common cause of delirium in an oncology setting. Infection, dehydration and sodium level abnormality were the next most common causes of delirium.

Table 4. Relation between causes of delirium and clinical subtype

	Hyperactive ($N = 58$)		Hypoactive ($N = 14$)		P value
	N	%	N	%	
Opioids	13	22	6	43	0.16
Inflammation	16	28	2	14	0.49
Dehydration and sodium abnormality	9	16	1	7	0.68
Metabolism abnormality	8	14	1	7	0.68
Benzodiazepines	11	19	2	14	1.00
Steroids	4	7	1	7	1.00
Hypercalcemia	3	5	1	7	1.00
Anemia	4	7	1	7	1.00
Hypoxemia	5	9	0	0	0.58
Clotting abnormality	2	3	2	14	0.17

Fisher's exact test was performed using the hyperactive and hypoactive conditions.

These factors have also been previously reported as potentially important causes of delirium in cancer patients. Thus, the current study, as well as previous studies, demonstrates that opioids, infection, dehydration and mineral imbalances are common causes of delirium in cancer patients, regardless of the clinical setting. In this regard, opioid-induced delirium (76%) was commonly observed in a study by Lawlor et al. (2) (see the Introduction section). On the other hand, we cannot claim, based on the present findings, that these factors, when present, will commonly cause delirium.

The cause of delirium could not be identified in ~20% of the cases. Although we utilized a structured assessment of the causes of delirium in the current study, a more comprehensive evaluation may be necessary. Because some recent studies have suggested other possible causes of delirium, such as vitamin B1 deficiency (35), in cancer patients, our method might have failed to recognize the causes of delirium comprehensively. Antagonistically, high rate of unknown cause was may reflect the quite stringent criteria for attribution of cause in the methods. Some delirium might occur in cancer patients as a result of the accumulation of multiple mild abnormalities or potential factors. Furthermore, 1 week follow might not be long enough to see a reversal in delirium. On the other hand, multiple causes were identified in ~40% of the cases. According to data obtained in palliative care settings, Lawlor et al. and Morita et al. reported that the causes of delirium could not be identified in 1% and 7% of the cases, respectively. And, they also reported that the median number of identified factors were 3 and 2, respectively. These findings suggest that the causes of delirium observed in a general medical ward setting may vary to a greater extent than those in a palliative care setting, and medical staff members should pay attention to a broader range of possible causes.

The current study did not find an association between specific delirium-precipitating factors and delirium reversibility, and only physical functioning independently influenced the reversibility of delirium. Insomuch as patients receiving opioids in general wards may have a more critical physical condition, the influence of opioids on delirium may have been indirect. On the other hand, some previous studies conducted in palliative care settings have reported that delirium induced by medicines, such as opioids, is more likely to be reversible than delirium induced by other causes (2,4,16,17). Several possible explanations for the observed difference exist. First of all, the treatment interventions after the cause of the delirium had been identified may have differed. Namely, we only notified each patient's physician of the precipitating factors of delirium; whether any intervention was subsequently provided depended on the physician's practice. On the other hand, previous studies in palliative care settings applied more active and structured interventions, such as opioid rotation. The fact that delirium could not be improved in patients with multiple identified causes of delirium may indicate that delirium resulting from multiple causes is more difficult to recover from. In addition, more opioid-induced delirium occurred in a PCU setting study, suggesting that if opioids are widely used, the reversibility of delirium may increase.

The delirium which had many causes was hard to recover in this study. It may be because in the delirium developing from complicated causes, namely the delirium with many causes, it was difficult to treat its precipitating factors. In addition, the patients with delirium developing from complicated causes had such bad physical conditions that the condition was hardly reversible.

No specific delirium-precipitating factors were associated with the motor subtypes of delirium in the present study. Morita et al. (4) only just reported that hyperactive symptoms were significantly associated with drug-induced delirium, whereas dehydration-related pathologies were significantly associated with hypoactivity in a palliative care setting. Thus, the findings regarding the association between the cause of delirium and the motor subtype are inconsistent. In addition, the motor subtype of delirium may result from other factors (e.g. complicated clinical factors, biological factors, the patient's condition and the interaction of factors), rather than the causes that were investigated. Furthermore, the definition of delirium subtypes is problematic, and the operational definitions of the subtypes vary among study (36). To clarify the association between causal factors and the delirium subtype, further studies that overcome these issues are needed. On the other hand, the sample in this study had a high percentage of hyperactive cases contrasts with other studies of cancer patients. The exclusion of cases with dementia may also have reduced the frequency of hypoactive delirium. In addition, the reversibility of delirium was higher than other studies, again possibly related to high frequency of hyperactive delirium where prognosis seemed better.

The current study has several advantages. One advantage was the investigational setting, as our study was performed in a general ward. Thus, our findings may be easier to generalize than those obtained in palliative care settings. Additionally, with regard to identifying the cause of the delirium, the time–dosage relation was judged more strictly than in other studies. Furthermore, clear subtype criteria that were independent of severity-of-illness evaluations and evaluations of cognitive function were used for the subtype evaluation.

This study also has several limitations. First, the referred patient sample may have been influenced by a physician bias. In particular, hypoactive delirium can be easily overlooked by physicians, and this may have led to a selection bias among the subjects. Second, the sample size is relatively small which may account for the lack of positive findings. In particular, the relation between the cause of delirium and the delirium subtype may have been distorted as there were very few cases of hypoactive delirium; consequently, significant features may have been overlooked. Furthermore, in our study, the treatment protocol was not standardized and approaches to delirium depended on the physician's practice or interest. This may have biased the assessment of its reversibility.

In conclusion, medication-induced delirium, especially opioid-induced delirium, is commonly observed in cancer patients hospitalized in general wards. Although opioids are a very important medication for cancer patients, their use must be carefully observed when medical examinations are performed in psychiatric consultation service. In addition, the causes of delirium were not association with delirium reversibility or the motor subtype of delirium. Additional research and biological classification are needed in the future.

Funding

This study was supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Labor, Health and Welfare.

Conflict of interest statement

None declared.

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Mental Vulnerability and Survival After Cancer

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Background: It has been hypothesized that personality traits affect survival after cancer, but studies have produced inconsistent results. This study examined the association between mental vulnerability and survival after cancer in Denmark in a prospective cohort study.
Methods: Between 1976 and 2001, 12733 residents of Copenhagen completed a questionnaire eliciting information on a 12-item mental vulnerability scale, as well as various personal data. Follow-up in the Danish Cancer Registry until 2003 identified 884 incident cases of primary cancer, and follow-up for death from the date of cancer diagnosis until 2003 identified 382 deaths. Mental vulnerability scores were divided into 4 approximately equal-sized groups. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of all-cause mortality.
Results: Multivariate HR for all-cause mortality for persons in the highest category of mental vulnerability compared with those at the lowest was 1.1 (95% confidence interval = 0.9–1.5).
Conclusion: We found no support for the hypothesis that mental vulnerability is associated with survival after cancer diagnosis.

It has been hypothesized that personality traits affect the risk for cancer incidence by altering immune and endocrine function.[1–3] However, several well-conducted prospective studies have not confirmed this hypothesis.[4–9] The role of personality traits in survival after cancer[10] has been addressed in at least 7 studies.[11–17] Three studies supported an association: higher scores of "lie scale,"[11] introversion,[12] and neuroticism[13] were associated with poor survival after cancer. All studies, however, had important limitations, including failure to control for cigarette smoking or alcohol consumption,[11,12,14,15] clinical status,[15] and comorbidity[11–13,15,17]; personality traits measured prior to the diagnosis of cancer[11,12,14,15,17]; and use of small samples (5 of the 7 studies had fewer than 200 study subjects).[11–15]

Mental vulnerability is defined as a tendency to experience psychosomatic symptoms, mental symptoms, or negative reactions in social interactions.[18–20] Mental vulnerability represents a reaction pattern that is closely related to personality traits such as neuroticism.[21] No study had previously investigated the association between mental vulnerability and survival after cancer. We conducted a large, population-based prospective cohort study in Denmark to explore this relationship.

METHODS

Study Population

The sample was based on 6 studies conducted at the Copenhagen County Research Center for Prevention and Health (eTable 1, http://links.lww.com/EDE/A337). The populations were sampled randomly in southwestern Copenhagen County, and 12,733 men and women participated in a general health examination (eTable 2 and eFigure, http://links.lww.com/EDE/A337).

Health Data

Data on mental vulnerability, sex, age, education, comorbidity, and physical activity, as well as tobacco and alcohol consumption, were obtained from questionnaires. Body mass index in kg/m^2 was calculated from self-reported data on height and weight.[22–24]

Mental Vulnerability Scale

In 1981 Kühl and Martini developed a 22-item scale, which was later reduced to a 12-item scale on the basis of validity tests.[18,25] On the basis of theoretical considerations, 3 new scales (psychosomatic symptoms, interpersonal problems and mental symptoms) were then designed from the 22 items selected.[18] In this study, we used both the 3 newly validated scales and the 12-item scale (eAppendix, http://links.lww.com/EDE/A337).

Linkage to Registries

Data for all members of the study population were linked to the Central Population Register for verification of

Submitted 22 July 2008; accepted 7 January 2009.
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Supported by the Foundation for Promotion of Cancer Research (Japan) for the 3rd Term Comprehensive 10-year Strategy for Control, and the Psychosocial Research Committee at the Danish Cancer Society, Denmark.
SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).
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ISSN: 1044-3983/09/2006-0916
DOI: 10.1097/EDE.0b013e3181b5f3b0

the personal identification number and for information on vital statistics and migration. Subsequently, the study cohort was linked to the Danish Cancer Registry for information on date of diagnosis of the tumor and details about the tumor.[26] Tumors are coded according to a modified Danish version of the International Classification of Diseases, Seventh Revision.[26] Finally, the study cohort was linked to the Danish Registry of Causes of Death.[27] Cause of death was coded according to a modified Danish version of the International Classification of Diseases, Tenth Revision.[28]

Follow-up

The 12,733 persons in the study cohort were followed for cancer from the date of the interview until the date of first cancer (other than nonmelanoma skin cancer), date of emigration, date of death or 31 December 2003, whichever came first. We identified 1085 incident cases of cancer. We then excluded 33 persons who had not answered the mental vulnerability questions and 168 persons without information on cancer stage, leaving 884 cancer cases for analysis. These persons were followed up for death from the date of cancer diagnosis until date of emigration, date of death or 31 December 2003, whichever came first. A total of 382 deaths were identified (eFigure, http://links.lww.com/EDE/A337).

Statistical Analyses

Analyses were conducted with the 12 item scale as an ordinal variable, and the scores for mental vulnerability (0–12) were divided into 4 approximately equal-sized groups (quartiles). For all 3 subscales, we chose a cut-off point of 0 and ≥1, because the distributions were not normal, and the proportion of persons with score 0 was high (62%–70%). Kaplan-Meier analyses were used to obtain estimates of survival. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed as the death rates among persons in each quartile of mental vulnerability score divided by the death rate among persons in the lowest quartile. Both deaths from all causes and cancer-related death were used as end-points. We conducted a stratified analysis of HR of death according to the duration between mental vulnerability assessment and cancer diagnosis. A Cox proportional hazard model was used to estimate HRs for mental vulnerability.[29] Multivariate HRs were adjusted for sex, age at cancer diagnosis, study cohort, body mass index in kg/m^2, marital status, length of education in years, smoking status, alcohol consumption, physical activity in leisure time, a history of comorbidity, and a history of depression, cancer site, and cancer type.

RESULTS

The 884 incident cases of primary cancer accrued a total of 3736 person-years of follow-up, with a mean follow-up of 4 years (range, 0–23 years). Persons with higher scores of the mental vulnerability were more likely to be women, unmarried, and nondrinkers; to have cancer in hormone-related organs; to have a low level of physical activity; and to have a history of comorbidity and depression (eTable 2, http://links.lww.com/EDE/A337).

Kaplan-Meier plots showed no clear association between score on the 12 item scale and overall survival (Figure). Sex and age-adjusted analyses showed no association between mental vulnerability and the overall risk of death. The HR for death from all causes for persons in the highest category of mental vulnerability, compared with those at the lowest was 1.2 (95% CI = 0.9–1.5) (Table). After control for potential confounders, the association between scores and risk of death was further reduced (HR = 1.1 [0.9–1.5]). When cancer-related death was used as an end-point, the adjusted HR for persons in the highest category of mental vulnerability compared with those in the lowest was 1.1 (0.8–1.5). In multivariate analyses, we found no associations between any mental vulnerability subscale and the risk for death from all causes or from cancer.

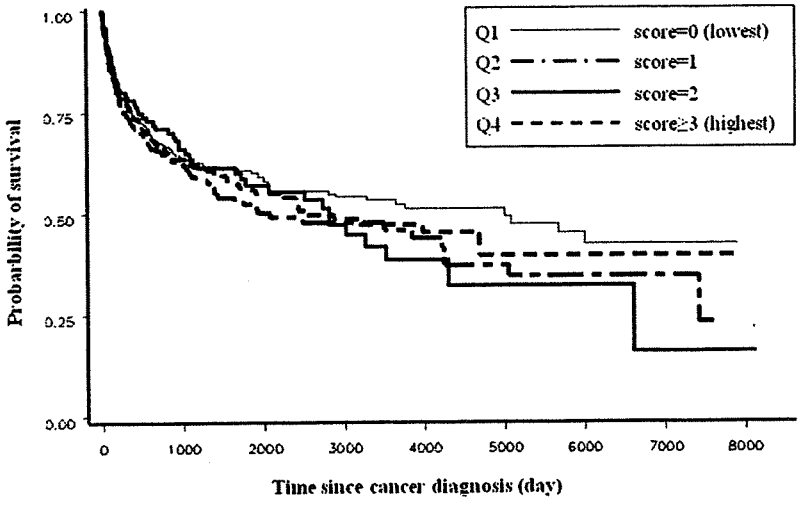

FIGURE. Overall survival according to the 12-item mental vulnerability scale.

TABLE. Hazard Ratio (HR) and 95% Confidence Interval (95% CI) of Death From All-cause and Cancer-related Death According to Mental Vulnerability Among 884 Persons Diagnosed With Cancer, Denmark

	Mental Vulnerability (12-item scale)				Mental Vulnerability, 3-Subscales					
	Q1 (Lowest)	Q2	Q3	Q4 (Highest)	Psychosomatic Symptoms		Interpersonal Problems		Psychological Symptoms	
Score	0	1	2	≥3	0	≥1	0	≥1	0	≥1
All subjects (n = 884)										
No. person-years of follow-up	1575	782	496	883	2374	1362	2374	1362	2696	1040
No. of deaths (death from all-causes/cancer-related death)	143/94	93/63	57/35	89/59	247/164	135/87	247/164	135/87	258/170	124/81
Crude mortality rate (per 1000 person years)	91	119	115	101	104	99	104	99	96	119
Sex- and age-adjusted HR (95% CI) for deaths from all causes	1.0[a]	1.1 (0.9–1.5)	1.2 (0.9–1.7)	1.2 (0.9–1.5)	1.0[a]	1.4 (1.2–1.8)	1.0[a]	0.9 (0.7–1.1)	1.0[a]	1.2 (1.0–1.5)
Multivariate HR[b] (95% CI) for deaths from all causes	1.0[a]	1.0 (0.8–1.3)	1.0 (0.7–1.4)	1.1 (0.9–1.5)	1.0[a]	1.2 (1.0–1.5)	1.0[a]	0.9 (0.7–1.1)	1.0[a]	1.0 (0.8–1.2)
Multivariate HR[b] (95% CI) for cancer-related deaths	1.0[a]	1.1 (0.8–1.5)	0.9 (0.6–1.4)	1.1 (0.8–1.5)	1.0[a]	1.2 (0.9–1.5)	1.0[a]	0.9 (0.7–1.2)	1.0[a]	1.0 (0.7–1.3)
Subjects diagnosed within 3 years of the mental vulnerability assessment (n = 157)[c]										
Multivariate HR[b] (95% CI) for death from all-cause	1.0[a]	1.9 (0.8–4.1)	1.8 (0.7–4.3)	1.2 (0.5–2.9)	1.0[a]	1.4 (0.7–2.8)	1.0[a]	0.9 (0.5–1.6)	1.0[a]	1.1 (0.6–2.1)
Multivariate HR[b] (95% CI) for cancer-related death	1.0[a]	1.7 (0.6–4.5)	2.1 (0.7–6.0)	1.3 (0.4–3.7)	1.0[a]	1.6 (0.6–3.8)	1.0[a]	0.7 (0.3–1.6)	1.0[a]	0.9 (0.4–2.1)
Subjects diagnosed later than 3 years from the mental vulnerability assessment (n = 727)[d]										
Multivariate HR[b] (95% CI) for death from all-cause	1.0[a]	1.0 (0.7–1.3)	1.0 (0.7–1.4)	1.1 (0.8–1.5)	1.0[a]	1.1 (0.8–1.5)	1.0[a]	0.9 (0.7–1.2)	1.0[a]	1.0 (0.8–1.3)
Multivariate HR[b] (95% CI) for cancer-related death	1.0[a]	1.0 (0.7–1.5)	0.8 (0.5–1.3)	1.0 (0.7–1.5)	1.0[a]	1.1 (0.8–1.4)	1.0[a]	0.9 (0.7–1.3)	1.0[a]	1.0 (0.7–1.3)

[a]Reference category.

[b]Multivariate HRs were adjusted for sex and age at cancer diagnosis (continuous variable), study cohort (1936 cohort, MONICA 1, MONICA 3, Allergi 90 Cohort, Allergi 97 Cohort, and DAN-THYR), body mass index in kg/m^2 (<18.5, 18.5–24.9, or 25.0≤), marital status (married, widowed/divorced, or single), length of education in years (≤12 years or 13≤ years), smoking status (never, ex-, or current), alcohol consumption (0, 1–14, or 15≤ units/week), physical activity in leisure time (sit still, walk, or do exercise/sports), a history of comorbidity[b] (any or none), and a history of depression (present or absent), cancer site (hormone-related organs, virus-related and immune-related malignancies, digestive organs [excluding liver], respiratory organs, or other sites), and cancer type (in situ or localized, regional invasion, or distant metastasis). Comorbidity was measured by the following question: "Has a doctor ever told you that you have: coronary thrombosis, heart disease, high blood pressure, cerebral thrombosis, brain hemorrhage, diabetes, or bronchitis?"

[c]69 deaths from all causes and 52 cancer-related deaths.

[d]313 deaths from all causes and 199 cancer-related deaths.

Some differences were seen when analyses were stratified according to the time elapsed between mental vulnerability assessment and cancer diagnosis. Among persons diagnosed within 3 years of the mental vulnerability assessment, those who scored high on mental vulnerability had a slightly increased risk of death from all causes, compared with persons who had low scores. No increased risk was observed among persons diagnosed later than 3 years after the mental vulnerability assessment.

We further conducted analyses stratified by sex, and there was no association between mental vulnerability and risk for death among either men or women (data not shown).

DISCUSSION

In this large prospective cohort study, we found no support for the hypothesis that mental vulnerability is associated with survival after cancer.

Three studies have reported positive associations between personality traits and survival after cancer.[11–13] The design of these studies had some limitations, including small numbers of participants, making chance a possible explanation for the overall results. Furthermore, the mental vulnerability scale and each of the personality traits represent different ways of assessing personality.

In one previous study, Nakaya et al[13] indicated that neuroticism was positively associated with death from all-cause only among women. The present study did not support the hypothesis of a sex difference in the association between personality traits and survival after cancer.

This study had several methodologic advantages over previous studies. First, we had the largest number of cancer cases used yet to explore this question. Secondly, we controlled extensively for potential confounding variables, including cigarette smoking and alcohol consumption, clinical status and comorbidity, which have been shown to be associated with survival after cancer.[30–32] Thirdly, we took into account the duration of time between mental vulnerability assessment and cancer diagnosis, which did seem to play a role. The slightly increased risk of all-cause mortality observed among persons diagnosed within 3 years of the mental vulnerability assessments suggests that mental vulnerability assessments could have been affected by subclinical symptoms of as-yet-undiagnosed cancers.[4] It is also possible that mental vulnerability is not a stable personality trait, resulting in increasing measurement error with increasing time since the measurement. One limitation in the current study is that we had no information on health behavior after the cancer diagnosis or on compliance with treatment, which could have affected survival.

In an earlier prospective study, subjects with high scores on mental vulnerability had increased cancer mortality compared with subjects with low scores among the general Danish populations.[20] Cancer-related death was used as the end-point, and it was difficult to distinguish between mental vulnerability associated with cancer incidence and with the survival. This may explain the differences in results between the previous and present studies.

Although we found no support for the hypothesis that mental vulnerability is associated with survival after cancer, we cannot rule out associations with other personality traits.

ACKNOWLEDGMENTS

We thank Visti B. Larsen of the Department of Psychosocial Cancer Research, Institute of Cancer Epidemiology, Danish Cancer Society, for his assistance with the statistical analyses.

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