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Research paper

Timing and risk of mood disorders requiring psychotropics in long-term survivors of adult cancers: A nationwide cohort study

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ABSTRACT

Background: The increasing number of long-term cancer survivors over the past few decades poses the challenge of mental health care needs. However, little is known about risks of mood disorders in long-term cancer survivors.

Methods: Long-term survivors (≥5 years) of adult cancers (LSAC) (n = 190,748) newly diagnosed between January 1, 2000 and December 31, 2007 were matched with one control. The primary outcome was diagnosis of mood disorders requiring psychotropics. Cumulative incidences and sub-hazard ratios (SHR) were calculated and multivariate analyses were conducted after accounting for mortality.

Results: The mood disorder risk was significantly higher in the LSAC cohort than in the control cohort (adjusted SHR = 1.16, 95% confidence interval [CI] = 1.13–1.18, $P < 0.001$). Patients with certain cancer types were at increased risk, particularly in the first 2 years after diagnosis. However, patients with head and neck cancers or esophageal cancers had a higher risk after the 5-year follow-up period. Multivariate analysis indicated that being female, aged 40–59 years, with more than two primary cancers, receiving two or more treatment modalities, having CCI scores higher than 3, a higher urbanization level, and lower monthly income were independently associated with an increased risk of mood disorders.

Limitations: Some potential confounders such as lifestyle factors were not available in the study.

Conclusion: These findings call for increased mental health awareness not only in the early years after the cancer diagnosis, but also during long-term follow-up for certain cancer subtypes.

1. Introduction

Owing to advances in cancer screening and treatment, the number of long-term survivors of adult cancers (LSAC; i.e., those alive for at least 5 years since diagnosis) has continued to increase over the past decade (Allemani et al., 2015). Whether the risk of mood disorders in LSAC is significantly different to that of the general population remains inconsistent (Adler and Page, 2008; Foster et al., 2009). A recent meta-analysis including studies with adult cancer survivors at least 2 years post diagnosis showed that the depression risk is significantly higher in patients within 2 years after the diagnosis (Mitchell et al., 2013). However, it might not be appropriate to apply this conclusion to all LSAC due to the highly diverse survivorship of patients with different cancer types (Addington-Hall, 2013). Further, the assessment of depression risk varies across studies due to differences in survey timing, cancer subtypes, patient characteristics, comorbidities, impacts from different treatment modalities, and study designs (Fossa et al., 2008; Foster et al., 2009; Hoffman et al., 2009; Mitchell et al., 2013). Consequently, we lack robust data to identify which LSAC are more likely to be depressed.

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The purpose of this study was to use Taiwan National Health Insurance Research Database (1) to compare the risk of mood disorders longitudinally over the course of survivorship between a nationally representative population of LSAC and the general population without cancers, and (2) to identify the sociodemographic and clinical factors associated with increased depression risk among LSAC.

2. Methods

2.1. Data source

Taiwan has implemented a national health insurance (NHI) program since 1995 to provide a compulsory universal health-care service that covered more than 99.6% of its 23 million Taiwanese citizens by the end of 2014 (National Health Insurance Administration, 2014). For research purposes, the comprehensive inpatient and outpatient medical claims records of demographic data, disease diagnoses (using the A code before 2000, and the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] classification after 2000), laboratory test items, treatment procedures, and drug prescriptions were included in National Health Insurance Research Database (NHIRD).

The Longitudinal Health Insurance Database 2000 (LHID 2000) is a longitudinal claims database derived from the NHIRD, including 1 million individuals who were randomly selected from the entire NHI enrollee population in the year 2000. The LHID is highly representative without significant differences in age, sex, or health-care costs compared to the entire NHI population (National Health Insurance Administration, 2010).

The LHID 2000 provides all the medical claims records longitudinally from 2000 to the end of 2012.

The present study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (104-9232B).

2.2. Study population and design

The LSAC cohort comprised patients who were newly diagnosed with cancer (A codes A090–A141 or ICD-9-CM codes 140–209) between January 1, 2000 and December 31, 2007. Patients younger than 20 years old on the day of the cancer diagnosis or who had a survival of less than 5 years were excluded. The index date was defined as the date on which the catastrophic illness certificate for cancer was issued. Since the LSAC cohort started from 2000, one control with at least a 5-year survival and without a diagnosis of cancer for each cancer patient was randomly selected from the LHID 2000, with frequency matching for age, sex, index date (within the same index month), and the Charlson comorbidity index (CCI) score (Table S1) (Deyo et al., 1992). To obtain the incidence of mood disorders after index date, we excluded subjects in both cohorts who were diagnosed with mood disorders before the index date.

2.3. Study outcome

The study outcome was the occurrence of newly diagnosed mood disorders requiring antipsychotropic drugs after the index date. To reduce misclassification, we defined the mood disorders as requiring two or more outpatient visits or one hospitalization with diagnoses of major depression (ICD-9-CM codes 296.2 and 296.3), depressive disorder (ICD-9-CM codes 300.4 and 311), and bipolar disease (ICD-9-CM codes 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, and 296.8), and having been prescribed psychotropic agents for at least 30 days. We identified these drugs in accordance with the Anatomical Therapeutic Chemical Classification System (Table S2). All subjects were followed up from the index date until the development of mood disorders, death, withdrawal from the NHI, or the study's end (December 31, 2012).

2.4. Covariates

We examined the effect of sociodemographic variables including age, sex, income level, and urbanization level. Given that a number of comorbidities are potential confounders, we used the modified CCI score as an overall measure of comorbidity severity, using the ICD-9-CM codes and subgrouping the scores as follows: 0–3, 4–6, 7–9, and ≥10 (Deyo et al., 1992; Polsky et al., 2005). According to the literature, cancer-related covariates such as cancer subtype (ICD-9-CM 140–209), treatment modality (surgery, radiotherapy, and chemotherapy), and multiple primary cancers were analyzed (Andrykowski, 2012; Torres et al., 2013).

2.5. Statistical analyses

Standardized mean difference (SMD) rather than statistical testing was used to compare sociodemographic characteristics and comorbidities between the two study groups, because balance of covariates between the two study groups is a property of the sample and not of an underlying population. For the SMD, an absolute value of ≤0.1 indicates a negligible difference in potential confounders between the two study groups (Austin, 2011). The incidence rates (per 1000 person-years) were calculated for each cohort by sex, age, site-specific cancers, mood disorder subtype, and follow-up years. Due to the substantial mortality among cancer patients, we used the Fine-Gray competing risk regression model which posits the hazard of the subdistribution for mood disorder, known as the sub-hazard, and treats death from any other cause as competing risk rather than censored. The sub-hazard ratios (SHRs) with a 95% confidence interval (CI) for mood disorders were obtained in the Fine-Gray model which included covariates of interest (Fine and Gray, 1999). All data analyses were conducted using the SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at a two-sided α of 0.05.

3. Results

3.1. Demographic characteristics of the two study cohorts

Between 2000 and 2007, we identified 564,887 patients with newly diagnosed cancer from the NHIRD. Of these, 7337 patients younger than 20 years, 340,371 patients with survival of less than 5 years after diagnosis, and 15,471 patients diagnosed with mood disorders before enrollment were excluded. A total of 190,748 patients (94.6%) in the LSAC cohort had a 1:1 matched control from the LHID 2000 (Figure S1). Because of the matching nature of the two study groups, their age, sex, and CCI scores were similar. Comorbidities, urbanization level, and monthly income at the index date were all similar between the two study groups (Table S3).

The median follow-up times were 8.13 and 8.49 years for the LSAC and matched control cohort, respectively. Among the LSAC cohort, the three most common cancers were breast cancers (20%), colorectal cancers (15.3%), and head and neck cancers (13%). Surgery alone was the main treatment modality (31.3%); followed by surgery and chemotherapy (15%); surgery, radiation, and chemotherapy (12.9%); and radiation with chemotherapy (9.4%). Notably, 14.3% of the LSAC cohort did not receive any of the treatments mentioned above (Figure S2A and B).

3.2. Risk and timing of mood disorders among the two study cohorts

After the index date, the incidence of mood disorders was significantly higher in the LSAC cohort (8.38 per 1000 person-years) as compared to that in the control cohort (7.21 per 1000 person-years), with an SHR of 1.13 (95% CI = 1.11–1.16, $P < 0.001$). In terms of mood disorder subtypes, the risks of major depression and depression disorder were higher in the LSAC cohort, while the risk of bipolar