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Research paper

Risk of mood disorders in patients with colorectal cancer

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ABSTRACT

Background: To assess the risk of mood disorders among patients with colorectal cancer (CRC), a population-based cohort study was performed using the Taiwanese National Health Insurance Research Database.

Methods: The study cohort included 27242 patients diagnosed with CRC between January 1, 2000 and December 31, 2010. Four insurants from the general population without CRC were frequency matched to each case by age, sex, and index year/month to create the control group. Cox's proportional hazard regression model with hazard ratios (HRs) and 95% confidence intervals (CIs) was conducted to estimate the impact of CRC on the risk of mood disorders.

Results: Patients with CRC exhibited a significantly higher risk of developing mood disorders (adjusted HR = 3.05, 95% CI = 2.89–3.20) compared with the control group. This phenomenon was also observed for each type of mood disorder (depression, bipolar disease and anxiety), as well as across different subgroups by patient characteristics. However, a follow-up time longer than 1 year was more likely to have significantly increased risks, and we unexpectedly found that some treatments in CRC patients tended to have a decreased risk of anxiety compared to their counterparts.

Conclusion: The findings of this population-based cohort study suggest that patients with CRC are at a higher risk of mood disorders, especially when follow-up time is longer than 1 year, but various treatments may inversely affect this association.

1. Introduction

Cancer has been the leading cause of mortality among the general population in Taiwan since 1982 (Cancer Statistics Annual Report: Taiwan Cancer Registry). The incidence of cancer is rising continuously as the population rapidly ages and it constitutes an enormous burden in Taiwan. Colorectal cancer (CRC) remained the most common type of cancer in Taiwan for the eighth consecutive year. The average incidence rate from 2002 to 2012 was increased by 4.3% and 1.4% annually for colon cancer and rectal cancer, respectively (Chiang et al., 2016). The age-adjusted incidence rates for colon and rectal cancer were 37.72 and 22.84 per 100,000 people in 2012 (Chiang et al., 2016).

Mood disorders are a category of illnesses that includes major depressive disorder and bipolar disorder. A major depressive disorder is frequent in the general population and the Global Burden of Disease 2010 study identified depressive disorders as a leading cause of burden (Ferrari et al., 2013). Liao et al. found a low prevalence (1.2%) of major depressive disorder in Taiwanese adults and suggested that the pattern of low help-seeking behavior and profound functional impairment indicates much room for improvement in the early detection and intervention of major depression in this population (Liao et al., 2012). Bipolar disorder, formerly called manic depression, causes extreme mood swings ranging from a manic to a depressive state. Both depression and bipolar disorders are commonly associated with anxiety disorders (Preti et al., 2016; Mystakidou et al., 2005). An anxiety disorder is a feeling of nervousness, apprehension, fear, or worry. It is a chronic disorder and highly prevalent in the adult population. The prevalence of lifetime anxiety among the general population was around 5% in western countries in 2002 (Grant et al., 2005; Wittchen et al., 1994). In Taiwan, Hwu et al. found that the life time prevalence

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of anxiety differed considerably according to geographic sampling area, ranging from 3.7% to 10.5% (Hwu et al., 1989). Anxiety has a detrimental impact on health outcomes, such as increased risk of respiratory resistance in asthma and coronary heart disease (Roest et al., 2010; Ritz et al., 2000).

Depression, anxiety, and bipolar disorders are not uncommon among patients diagnosed with cancer (Nikbakhsh et al., 2014; Linden et al., 2012; Jadoon et al., 2010). In fact, it has been suggested that ongoing medical and psychosocial effects of cancer as well as its related treatments may lead to long-term psychological morbidity in cancer survivors (Khan et al., 2010; Aziz, 2002). Emotional distress was thought as the sixth vital sign in cancer care (Bultz and Carlson, 2005). Several individual cancer sites have been explored to evaluate the risk of subsequent depression and anxiety (Schwarz et al., 2008; Watson et al., 2005; Lintz et al., 2003; Aukst Margetić et al., 2013; Tavoli et al., 2007). However, only a limited number of papers focused on the issue of mood disorder risk among patients with CRC (Kurtz et al., 2002a, 2002b; Sehlo and Al Ahwal, 2013; Stommel et al., 2004). Considering that CRC is the most common cancer seen in Taiwan, with a relatively better prognosis compared to lung and liver cancers (high incidence in Taiwan), it would be interesting to know the psychosocial sequelae of CRC patients. In this study, we tried to determine whether CRC is a risk factor in the development of mood disorders, with the possible association that it's a temporary phenomenon or longer lasting, and if the cancer-related treatments aggravate the risks of mood disorders.

2. Methods

2.1. Data source

Taiwan Bureau of National Health Insurance (BNHI) established a single-payer National Health Insurance (NHI) program on March 1, 1995 and covers nearly all (99%) 23.7 million residents of Taiwan (Database NHIR). The Taiwan National Health Insurance Research Database (NHIRD) contains the de-identified medical claims records, compiled by the Taiwan National Health Research Institutes (NHRI). The details of the NHI program and NHIRD were well written in previous studies (Chou et al., 2016; Lin et al., 2016). Diagnoses in this NHIRD were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115-CR1). The IRB also specifically waived the consent requirement.

2.2. Sampled participants

Patients newly diagnosed with CRC (ICD-9-CM codes 153.0, 153.1, 153.2, 153.3, 153.4, 153.6, 153.7, 154.0, 154.1) including proximal colon (ICD-9-CM codes 153.0, 153.1, 153.4, 153.6), distal colon (ICD-9-CM codes 153.2, 153.3, 153.7), and rectum (ICD-9-CM codes 154.0, 154.1) from 2000 to 2010 were identified from the Registry of Catastrophic Illnesses Patient Database (RCIPD), a sub-datasets of NHIRD for this study. The index date was defined as the day of diagnosing CRC. For each corresponding CRC patient, 4 non-CRC subjects were randomly selected from NHIRD without CRC and frequency-matched by age (based on 5-y spans), sex, and the year and month of CRC diagnosis. The index date for non-CRC subjects was a randomly appointed day with the same index year and the same month of the matched CRC cases. Cohorts with a history of other cancer (ICD-9-CM codes 140–152, 1535, 1538, 1539, 1542, 1543, 1548, 155–208), depressive disorder (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), bipolar disorder (ICD-9-CM codes 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80, and 296.89), or anxiety disorder (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 309.81) before the index date and younger than 20 years of age were excluded.

2.3. Outcome and relevant variables

Mood disorders (ICD-9-CM codes 296.0, 296.1, 296.2, 296.3, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80, 296.89, 300.4, 300.0, 300.2, 300.3, 308.3, 309.81, and 311) including depressive disorder, bipolar disorder, and anxiety disorder were defined as the endpoint of this study. All of the included patients were followed from the index date to the occurrence of the endpoint, withdrawal from the NHI program, or until the end of December 31, 2011. The sociodemographic factors, comorbidities, and treatments that may be associated with mood disorders were also identified. These include age ($\leq$49 y, 50–64 y, $\geq$65 y), sex, occupation (white collar, blue collar, and others), urbanization level (Level 1 was the highest level of urbanization and Level 4 was the lowest), monthly income-related insured amount ($<$15,000, 15,000–19,999, $\geq$20,000) (New Taiwan Dollars [NTD] per month), and comorbidities with hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–414), congestive heart failure (ICD-9-CM code 428), cerebrovascular disease (ICD-9-CM codes 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), chronic kidney disease (ICD-9-CM codes 580–589), and liver cirrhosis (ICD-9-CM code 571). The CRC-related treatments (including colostomy, radiotherapy, and chemotherapy) were also considered.

2.4. Statistical analysis

Distributions of socio-demographic factors, including age, sex, occupation, urbanization level, monthly income-related insured amount, comorbidity, and treatment, were compared between the CRC and the non-CRC cohorts using the chi-square test. For continuous variables, we conducted the Student's *t*-test to compare the CRC and non-CRC cohorts. The cumulative incidence of mood disorders between the CRC and the non-CRC cohorts were calculated using the Kaplan-Meier method and the difference was evaluated using the log-rank test. The follow-up period (in person-years) was used to estimate incidence density rates (per 1000 person-y) of mood disorders according to age, sex, occupation, urbanization level, monthly income-related insured amount, and comorbidity. To evaluate the risk of mood disorders for the CRC patient compared with non-CRC cohort, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using univariable and multivariable Cox proportional hazard models. The multivariate models were simultaneously adjusted for age, sex, occupation, urbanization level, monthly income-related insured amount, and comorbidities of hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, cerebrovascular disease, COPD, chronic kidney disease, and liver cirrhosis. Further analyses were performed to assess whether the association with mood disorders varied according to the length of the follow-up period and patients with different treatments. We also evaluated if patients with CRC exhibit different risks of developing mood disorders (including depressive disorder, bipolar disorder, and anxiety disorder) based on different tumor locations (proximal colon, distal colon, and rectum). Data management and analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC, USA). All *P* values were 2 tailed and a *P* value $<$ 0.05 was considered significant.

3. Results

The study subjects were composed of 27242 patients in the CRC cohort and 108046 persons in the non-CRC cohort. The mean age of the CRC cohort was 64.2 years and that of the non-CRC cohort was 63.5 years, with approximately 51% of the patients aged $\geq$65 years and most were men (approximately 61%) (Table 1). Most of the occupations in both cohorts were white-collar jobs (45.5% vs 43.4%), and the cohorts preferred to reside in urbanized areas (51.1% vs 56.1%). The