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Risk of type 2 diabetes mellitus in female breast cancer patients treated with morphine: A retrospective population-based time-dependent cohort study

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ABSTRACT

Aims: We aimed to examine whether morphine treatment is associated with type 2 diabetes mellitus (T2DM) in female breast cancer patients.
Methods: We conducted a retrospective cohort analysis of the Longitudinal Health Insurance Database for Catastrophic Illness Patients in Taiwan. A total of 31,112 women with breast cancer without T2DM history during the period 2000–2005 were identified, divided into morphine and non-morphine users (8071 and 23,041 patients, respectively), and the hazard ratios of newly diagnosed T2DM during the period 2005–2010 were calculated. We used a Cox proportional hazard model with time-dependent exposure covariates to estimate the risk of T2DM. The dosage of morphine was counted as defined daily dose and its effect was assessed by multivariable Cox proportional hazard regression controlling age, Charlson comorbidity index, outpatient department visits, antipsychotics, and breast cancer drugs.
Results: Morphine users were 1.24 times more likely to suffer from T2DM than non-morphine users (95% CI = 1.04–1.49). Risk increased slightly with the morphine dosage, in patients aged 35–49 years, and with tamoxifen, aromatase inhibitors, and antipsychotics treatment.

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Conclusions: The incidence of T2DM is associated with morphine treatment in female breast cancer patients. A higher risk was observed in patients aged 35–49 years using higher dose of morphine, and may be increased by tamoxifen and aromatase inhibitors.

1. Introduction

A key element of the palliative care of cancer patients is the management of chronic pain [1]. Opioids continue to be a mainstay in the management of cancer pain in all treatment guidelines [2], and morphine is regarded as the ''gold standard'' [3–6]. Considered as broad-spectrum analgesics, opioids have multiple side effects and potential complications [7]. Our previous studies indicated that morphine treatment is associated with subdural hemorrhage [8], pulmonary embolism [9], and acute coronary syndrome [10] in cancer patients, as well as increased stroke incidence in prostate cancer patients [11].

Opioid modulation of key hypothalamic glucose sensing regions could influence overall glucose and energy homeostasis, and hence opioid use might lead to an increase in incidence of type 2 diabetes mellitus (T2DM) or obesity [12,13]. In vivo animal studies suggest that central administration of opiates acts indirectly via the sympathetic nervous system to cause hyperglycemia and impaired insulin secretion [14]. People addicted to heroin, metabolized to morphine in our body, have impaired insulin secretion to oral glucose, suggesting that a selective inhibition of glucose-induced insulin secretion is operative in these subjects, as in patients with T2DM [15]. Additionally, hyperglycemia is higher among opiate substance use disorder patients with diabetes, absolutely and age-dependently [16].

Given the role for opioid neural pathways in modulating key brain glucose sensing neurons and the increased incidence of hyperglycemia in opioid-dependent patients, we speculated an association between morphine treatment and subsequent development of T2DM. To address the potential problem of diabetic hyperglycemia induced by former morphine exposure, the hazard ratios of T2DM in female breast cancer patients treated with and without morphine were compared using the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Methods

2.1. Data source

We used the Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP) for this respective cohort study. The LHID-CIP is a part of NHIRD which was set up by Taiwan Bureau of National Health Insurance (TBNHI) and maintained by the National Health Research Institutes (NHRI). Identification of diseases in NHIRD was according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Over 99% of the population (about 23 million) joined in this single-payer National Health Insurance Program in Taiwan. Insurants with catastrophic illness diagnosis, such as breast cancer, could apply for a catastrophic illness certificate to have the right of copayment exemptions. These applications were formally reviewed by the specialist physicians. All medical visits, prescriptions, and surgery records including inpatient and outpatient claims for each insurant from 1996 to 2011 were documented in the LHID-CIP. To protect personal information, the identification of each insurant was scrambled by TBNHI and NHRI before data releasing to the research. Our study was also approved the Institutional Review Board in China Medical University Hospital.

2.2. Study subjects, outcomes, and potential risk factors

We selected adult women diagnosed with breast cancer (ICD-9-CM 174) during the period 2000–2005 as our study population. The date of breast cancer diagnosis was defined as the index date. Those with a history of diabetes (ICD-9-CM 250) or who had received morphine before the index date, follow-up period <30 days, or the interval between initial morphine treatment and T2DM diagnosis ≤ 30 days were excluded. All study subjects were followed from the index date to the date of first-time T2DM diagnosis (ICD-9-CM 250.x0, 250.x2), death, or end of study, whichever was earliest. The baseline condition of the study subjects was displayed using Charlson comorbidity index (CCI) score [17,18]. Because the study subjects were women with breast cancer, the CCI scores in this study did not include the cancer score. To decrease the potential detection bias, we considered the number of annual outpatient department (OPD) visits. We also included the hormone therapy medicines for breast cancer patients (tamoxifen, megestrol acetate, and aromatase inhibitors), as well as antipsychotics as potential risk factors.

2.3. Statistical analysis

Chi-square test was used to test the difference of different age groups (20–34, 35–49, 50–64, and ≥ 65 years-old), CCI scores (0, 1–2, 3–4, and ≥ 5), and medicine used (tamoxifen, megestrol acetate, aromatase inhibitors, and antipsychotics) between the morphine and non-morphine cohorts in the breast cancer women. We used *t*-test to measure the differences of mean age, mean CCI score, and mean number of annual OPD visits between morphine and non-morphine users. Because patients did not always receive drugs during the study period, the effect of the drug may be overestimated. In order to reduce the immortal time bias, we used the Cox proportional hazard model with time-dependent exposure covariates to estimate