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Antidepressants and colorectal cancer: A population-based nested case-control study

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ABSTRACT

Background: Experimental evidence indicates that serotonin is associated with both proliferative and pro-carcinogenic effects on colorectal tumors. The present study aims to investigate the associations between antidepressant use and colorectal cancer in an epidemiological sample.

Methods: We conducted a population-based case-control study utilizing Taiwan's National Health Insurance Research Database (NHIRD). We identified 49,342 cases with colorectal cancer and 240,985 controls between 1997 and 2008. We conducted conditional logistic regression analyses to assess the association between antidepressant use and colorectal cancer risk. Sensitivity analyses were conducted to assess whether genotoxic antidepressants (i.e. antidepressants which may exert procarcinogenic effects) would increase risk for colorectal cancer.

Results: Selective serotonin reuptake inhibitors (adjusted OR=1.00, 95% CI=0.94–1.06), tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and serotonin antagonist and reuptake inhibitors were not associated with increased incidence of colorectal cancer. Monoamine oxidase inhibitors were, however, associated with an increased incidence of colorectal cancer (adjusted OR=1.22, 95% CI=1.06–1.41). Higher cumulative dose of mirtazapine was associated with a decreased incidence of colorectal cancer (adjusted OR=0.39, 95% CI=0.17–0.90). A small sample size of individuals who received mirtazapine, however, precludes definitive conclusions regarding protective effects with mirtazapine.

Limitations: We could not discern the effects of obesity and other risk factors for colorectal cancer from the NHIRD.

Conclusions: Contemporary first-line antidepressants (i.e. SSRI, SNRI), as well as older agents (i.e. TCA), are not associated with increased incidence of colorectal cancer.

1. Introduction

According to the World Health Organization (WHO), colorectal cancer was the third leading cancer-related cause of death among men and second leading cancer-related cause of death among women in 2012. Approximately 1.4 million new cases were diagnosed in 2012, and the incidence of colorectal cancer is increasing worldwide (Stewart and Wild, 2014).

The mechanisms of colorectal cancer are not fully understood, although there is evidence of a complex interaction between environ-

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mental carcinogens and genetic alterations that may facilitate the development of colonic dysplasia and cancer. Diet, lifestyle, smoking, alcohol use, and body mass index are thought to be associated with increased incidence of colorectal cancer. In addition, individuals with type 2 diabetes mellitus are at a higher risk of colorectal cancer (Wang et al., 2014).

Antidepressants are used widely in patients with cancer to treat various medical conditions such as mental disorders and cancer-associated pain (Riblet et al., 2014). Experimental evidence indicates that serotonin may be procarcinogenic and may increase risk for colorectal cancer due to its proliferative properties (Azmitia, 2001; Tutton and Barkla, 1986). Notwithstanding, results from preclinical studies evaluating the effect of serotonin-based antidepressants on colorectal cancer risk are mixed insofar as selective serotonin reuptake inhibitors (SSRIs) have been reported to have no effect on tumor growth in rodents (Gil-Ad et al., 2008; Tutton and Steel, 1979), to increase tumor growth (Bendele et al., 1992; Brandes et al., 1992; Freire-Garabal et al., 1998), and to decrease tumor growth in rodents (Abdul et al., 1995; Tutton and Barkla, 1982). It has also been reported (Taler et al., 2007) that SSRIs modulate immune systems via inhibition of the secretion of TH1 factor-tumor necrosis factor (TNF-α), promoting tumor necrosis. In addition, available evidence for tricyclic antidepressants (TCAs), albeit limited, (van Schaik and Graf, 1991) suggests that TCAs may be cytotoxic and induce non-oxidative apoptotic death of human HT29 colon carcinoma cells, an effect perhaps mediated via a non-mitochondrial pathway associated with cell-cycle progression. For example, Iishi et al. (1993) reported that the tricyclic antidepressant desipramine facilitated colon tumor growth via colon epithelial cell proliferation.

van Schaik and Graf (1991, 1993) classified TCAs as genotoxic and nongenotoxic based on observed somatic mutations in wing cells of *Drosophila melanogaster*. The studies support the hypothesis that an N atom in the heterocyclic 7-membered ring of the tricyclic molecule may be responsible for its genotoxic property. Nevertheless, a clinical study by Xu et al. (2006) reported no clear association between risk of colorectal cancer and TCA use. Results from a case-control study (Walker et al., 2011) reported directionally opposite results insofar as genotoxic or nongenotoxic TCA use was associated with a decreased incidence of colorectal cancer. In a separate cohort study (Walker et al., 2012), TCAs were associated with increased risk for colorectal cancer. In addition to genotoxic TCAs, available evidence suggests that select SSRIs (Alzahrani, 2012; Draz et al., 2009) (i.e. fluoxetine and sertraline) may also be associated with genotoxic effects which may portend procarcinogenic effects.

Xu et al. (2006) performed a population-based case-control study, documenting decreased incidence of colorectal cancer associated with high daily doses of SSRI ($> 6.0\times10^{-6}$ mol per day) for 5 years or less. A separate study (Coogan et al.., 2009) reported that regular SSRI use (i.e. a minimum of 3 continuous months), but not regular TCA use, significantly reduced colorectal cancer risk. In addition, Chubak et al. (2011) reported a trend suggestive of reduced risk of colorectal cancer following antidepressant use in small sample. In addition, a large population-based case-control study by Cronin-Fenton et al. (2011) reported no association between colorectal risk and TCA, SSRI, or other antidepressant class prescription.

The foregoing studies have provided inconsistent or contradictory evidence as to whether an association exists between antidepressant use and cancer risk. In addition, the potential carcinogenic risk associated with other antidepressant classes, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), or serotonin antagonist and reuptake inhibitors (SARIs), have not been sufficiently studied. Against this background, we performed a large-scale analysis by using data from a cross-national population-based database of Taiwan to investigate the carcinogenic or protective effects of antidepressants from several classes on the risk of colorectal cancers.

2. Methods

2.1. Source population

The National Health Insurance (NHI) program was launched on March 1, 1995 by Taiwan's government. By December 2008, 99.5% of the population of Taiwan (i.e. approximately 22 million individuals) were enrolled in the NHI program. The National Health Insurance Research Database (NHIRD), derived from the original claim data of the NHI program, includes ambulatory care, hospital inpatient care, and prescription claims data. The population of this study was derived from the NHIRD between January 1, 1997 and December 31, 2008. The study dataset includes no patient identification information; thereby rendering it unnecessary to obtain approval of an institution review board.

In Taiwan, diagnoses of cancer, including colorectal cancer, are supported by confirmatory pathology analysis. Insured patients with colorectal cancer are eligible to register with the Catastrophic Illness Registry and apply for a catastrophic illness certificate. The issuance of the certificate requires a diagnosis of a catastrophic illness by physicians and a formal review by the Bureau of National Health Insurance, comprised of a panel of medical experts.

2.2. Cases and controls

Cases of colorectal cancer were operationalized using the International Classification of Diseases, Ninth Revision (ICD-9) codes 153 and 154 and confirmed using the Catastrophic Illness Registry Dataset. For each colorectal cancer case, we used an incidence density sampling method (Wacholder et al., 1992) and randomly selected 5 controls without colorectal cancer diagnosis. The dataset for the control population of 1 million samples was randomly selected from the complete NHI dataset, and individuals who did not have a diagnosis of cancer were selected for the control population. The controls were individually matched age- (i.e., with the same birth calendar year) and sex-matched to the cases.

2.3. Exposure assessment

Antidepressants were classified as an SSRI (i.e. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), an SNRI (i.e. duloxetine, and venlafaxine), a NaSSA (i.e. mirtazapine), a TCA (i.e. amitriptyline, clomipramine, dothiepin, doxepin, imipramine, maprotilinem, and melitracen), an SARI (i.e. trazodone), or an MAOI (i.e.moclobemide, clorgyline, tranylcypromine, isocarboxacid, phenelzine, and selegiline).

Each patient's exposure to antidepressants was quantified using the World Health Organization's Defined Daily Dose [DDD] (WHO, 2012). Cumulative doses were graded into the following: equal to or greater than 28 DDD (≧28DDD); equal to or greater than 84 DDD (≧84DDD); equal to or greater than 168 DDD (≧168DDD); and equal to or greater than 336 DDD (≧336DDD). In order to minimize protopathic effect, we excluded antidepressant exposure in the year directly preceding the index date (Rothman, 1981).

We adjusted for the potentially confounding effects of other administered drugs, including aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and statins, exceeding 1 DDD and prescribed 365 days prior to the index date were evaluated as part of the analysis.

2.4. Data analyses

Descriptive statistics of colorectal cancer cases and controls are reported, including demographic characteristics, healthcare system use, comorbid diseases, and exposure to potentially confounding drugs.