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Anti-depressant therapy and cancer risk: A nested case-control study

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Abstract
Previous studies demonstrated a possible association between anti-depressant therapy with selective serotonin reuptake inhibitors (SSRI) and tricyclic anti-depressants (TCA), several genetic and hormonal pathways and cancer risk, with inconsistent results. Exposure to serotonin-norepinephrine reuptake inhibitors (SNRI) was not studied extensively. We sought to evaluate the association between exposure to SSRIs, TCAs and SNRIs and the five most common solid tumors. We conducted nested case-control studies using a large UK population-representative database. Cases were those with any medical code for the specific malignancy. For every case, four controls matched on age, sex, practice site, and duration of follow-up before index date were selected using incidence-density sampling. Exposure of interest was SSRI, SNRI or TCA therapy before index date. Odds ratios (ORs) and 95% CIs were estimated for each anti-depressant class using conditional logistic-regression analysis, adjusted for potential confounders, such as obesity, smoking history and alcohol consumption.

Results: 109,096 cancer patients and 426,402 matched controls were included. Current SSRI users with treatment initiation > one year before index date had modestly higher risk for lung and breast cancers with ORs of 1.27 (95% CI 1.16–1.38) and 1.12 (95% CI 1.06–1.18), respectively. Among current TCA users, there was a higher risk only for lung cancers with OR of 1.45 (95% CI 1.31–1.6). There was no statistically significant association between current SNRI therapy and cancer risk.

Discussion: Treatment with SSRI and TCA might be associated with increased lung cancer risk.

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SSRI therapy might be associated with modest increase in breast cancer risk.

1. Introduction

Anti-depressants are among the most commonly prescribed drugs in western countries, with over 10% of the US population receiving at least one prescription every year (National Center for Health Statistics, 2010). It is also the most frequently used medication by individuals aged 18–44 years (National Center for Health Statistics, 2010, Zhong et al., 2013). The three main anti-depressant classes include selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA). Anti-depressants are commonly used in cancer patients for treatment of anxiety and depression as well as for disease and therapy induced complications, such as neuropathic pain and hot flushes (Loprinzi et al., 2002; Smith et al., 2013).

Since the early 90's several studies, both in tumor cell cultures and animal models, raised a possible association between anti-depressants and cancer risk, mainly in breast and colorectal tumors and five TCAs were found to be genotoxic (van Schaik and Graf, 1991). In the breast, the SSRI fluoxetine and the TCA amitriptyline were shown to promote the growth of mammary tumors in animal models by binding to intracellular histamine receptors (Brandes et al., 1985; 1992). Other works evaluated the possible association between increase in prolactin levels secondary to SSRI exposure and breast cancer risk (Ashbury et al., 2012). In the colon, fluoxetine was shown to decrease the proliferation of colon cancer and exert an anti-angiogenic response (Kannen et al., 2011; Kannen et al. (2012); Stepulak et al., 2008; Tutton and Barkla., 1982). TCA were also shown to have cytotoxic effects on human HT29 colon carcinoma cells by inducing apoptosis (Arimochi and Morita, 2006). Recently, the SSRI citalopram was found to reduce tumor size and metastases in a mouse model of colorectal cancer (CRC), possibly through inhibition of TGF-β (van Noort et al., 2014).

Past epidemiologic studies that evaluated the association between anti-depressant exposure and breast cancer risk were inconclusive and demonstrated high (Ashbury et al., 2012; Cotterchio et al., 2000; Sharpe et al., 2002), low (Coogan et al., 2005) or no change in risk (Ashbury et al., 2010; Coogan et al., 2008; Eom et al., 2012; González-Pérez and García Rodríguez, 2005, Haque et al., 2005; Kelly et al., 1999; Moorman et al., 2003; Moorman et al., 2005; Tamim et al., 2006). Several of those studies demonstrated an association with duration of therapy (Coogan et al., 2005) or use of TCAs that were defined as genotoxic (Sharpe et al., 2002). For CRC, three previous studies demonstrated decreased risk with SSRI exposure or overall anti-depressant therapy (Chubak et al., 2011; Coogan et al., 2009; Xu et al., 2006) while other studies showed no change in risk (Cronin-Fenton et al., 2011; Lee et al., 2012) or even increased risk (Haukka et al., 2010). Three studies that included lung cancer patients demonstrated no change in cancer risk (Haukka et al., 2010; Walker et al., 2011) or mild increase following exposure to TCA (Toh et al., 2007). One study that focused on prostate cancer patients presented mild increase in cancer risk with TCA (Tamim et al., 2008) however another study showed no similar change in risk (Toh et al., 2007). Overall, those studies had several important limitations including lack of adjustment for common cancer risk factors, confounding by indication, protopathic bias, small sample size and use of questionnaires to assess exposure to anti-depressant therapy. According to our knowledge, to date no large population study evaluated cancer risk among users of SNRI.

In view of the high prevalence of anti-depressant use, and their possible biological activity in cancer related pathways, the current large population representative study evaluated the well-adjusted association between exposure to all three major anti-depressant classes and the five most prevalent solid tumors in the general UK population (lung, breast, prostate, colorectal and melanoma).

2. Experimental procedures

2.1. Study design

We conducted nested case-control studies using The Health Improvement Network (THIN) database. We focused on melanoma, lung, breast, prostate and colorectal cancers. The study was approved by the Institutional Review Board at the University of Pennsylvania and by the Scientific Review Committee of THIN.

2.2. Data source

THIN is a large population-representative electronic medical records database from the UK that contains comprehensive medical records for approximately 10 million patients under the care of general practitioners in the UK. THIN includes information on patients' demographics, socioeconomic status, medical diagnoses, drug prescriptions and lab results. Registration date is defined as the date when patients were first registered with a practice in THIN and Vision date is the date that a practice began using in-practice Vision software which collects information for the THIN database (Maguire et al., 2009). Data quality is monitored through routine analysis of the entered data (Bourke et al., 2004; Lewis et al., 2007). The database has been previously used for pharmaco-epidemiology studies, showing excellent quality of information (Blak et al., 2011; Hollowell, 1997).

2.3. Study cohort

All people receiving medical care from 1995 to 2013 from a THIN practitioner were eligible for inclusion. Patients without acceptable medical records (i.e., incomplete documentation or out of sequence date of birth, registration date, date of death, or date of exit from the database) were excluded. In order to focus our

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