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Review article

Dietary exposure to cadmium and risk of breast cancer in postmenopausal women: A systematic review and meta-analysis

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ABSTRACT

Background: With tobacco smoking, diet is the main source of cadmium (Cd) exposure in the general population. The carcinogenic and estrogenic activities of Cd make it a contaminant of potential concern for hormone-dependent cancers including breast cancer. Postmenopausal women represent the most appropriate population to investigate the possible impact of exogenous factors with potential estrogenic activity on breast cancer as, after menopause, their estrogenic influence is predominant.
Objectives: We systematically reviewed available studies on the association between dietary exposure to Cd and breast cancer focusing on postmenopausal women. A meta-analysis combining the risk estimators was performed and potential sources of between studies heterogeneity were traced.
Methods: Studies were searched from MEDLINE through 31 January 2015 and from the reference lists of relevant publications. Six eligible studies published between 2012 and 2014 were identified and relative risk estimates were extracted. Meta-rate ratio estimates (mRR) were calculated according to fixed and random-effect models. Meta-analyses were performed on the whole set of data and separate analyses were conducted after stratification for study design, geographic location, use of hormone replacement therapy (HRT), tumor estrogen receptor status (ER+ or ER−), progesterone receptor status (PGR+ or PGR−), body mass index (BMI), smoker status, zinc or iron intake.
Results: No statistically significant increased risk of breast cancer was observed when all studies were combined (mRR = 1.03; 95% confidence interval [CI]: 0.89–1.19). Several sources of heterogeneity and inconsistency were identified, including smoker status, HRT use, BMI, zinc and iron intake. Inconsistency was also strongly reduced when only considering ER−, PGR−, tumors subgroups from USA and from Japan. The risks were, however, not substantially modified after stratifications. No evidence of publication bias was found.
Conclusion: The present study does not provide support for the hypothesis that dietary exposure to Cd increases the risk of breast cancer in postmenopausal women. Misclassification in dietary Cd assessment in primary studies could have biased the results towards a finding of no association.

Contents

Abbreviations: BMI, body mass index; Cd, cadmium; 95% CI, 95% confidence interval; ER+/−, tumor estrogen receptor status; HR, hazard ratio; HRT, hormone replacement therapy; IRR, incidence rate ratio; MA, meta-analysis; mRR, meta-rate ratio; OR, odds ratio; $PGR^{+/-}$, tumor progesterone receptor status; RR, relative risk; 95% UI, 95% uncertainty interval.

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1. Introduction

Cadmium is a widespread metallic element occurring in the environment naturally (e.g., volcanic activity, weathering of Cd-containing rocks, and sea spray), and as a pollutant emanating from industrial (e.g., batteries, coatings, and plastic stabilizers), agricultural (e.g., contamination of phosphate fertilizers), and other sources (e.g., release from motor vehicle fuel combustion and tire wear) (Agency for Toxic Substances and Disease Registry, 2011; CCC, 2014). Environmental pollution and particularly soil contamination by Cd represents a health problem because grains, leafy and root vegetables bioconcentrate Cd, resulting in significant sources of Cd exposure for the general population through diet and tobacco smoking (Satarug and Moore, 2004; Järup and Akesson, 2009). However, recent data on Cd concentrations in crops and food argue in favor of a decreasing trend and the recently revised input/output scenarios for EU agricultural soils conclude that the current net balance of Cd in EU soils is negative (Six and Smolders, 2014).

Cadmium concentrations in food vary considerably, but, generally, fiber rich foods like cereals, vegetables and shellfish are the major contributors to Cd intake in humans. In many countries, rice is the dominating source of exposure and significantly contributes to Cd exposure (Vahter et al., 2007). The average Cd intake from food varies internationally from 8 to 25 μg/day and daily Cd exposure can double in smokers (Sartor et al., 1992). Approximately 5% of Cd ingested in food is absorbed, depending on the nutritional status (Godt et al., 2006). Only a small fraction of inhaled or ingested Cd is excreted, resulting in increasing body burden over time (Klaassen, 1981). Cd is taken up by transport mechanisms developed for essential metals, most likely zinc (Zn^{2+}), iron (Fe^{2+}), manganese (Mn^{2+}), and calcium (Ca^{2+}) (Satarug et al., 2010). Cadmium absorption is potentiated by a low iron store status (Akesson et al., 2002; Berglund et al., 1994).

Ubiquitous exposure to low levels of Cd has raised concerns about adverse health effects. Cadmium has been classified as a group 1 human carcinogen with sufficient evidence for the lung and limited evidence for prostate and kidney (IARC, 2012). The molecular mechanisms involved in the carcinogenic activity of Cd are poorly understood. Possible general and tissue specific molecular mechanisms as well as epigenetic modifications that follow chronic exposure to Cd in breast, prostate and lung cancers have been recently reviewed by Luevano and Damodaran (2014). Several mechanisms of Cd carcinogenesis have been proposed but the most important appears to be oxidative stress (Joseph, 2009) because of its involvement into aberrant gene expression, DNA damage, altered DNA damage repair (Jin et al., 2003), and enhanced proliferation and/or depressed apoptosis (Waalkes, 2003; Joseph, 2009; Templeton and Liu, 2010). As mitochondria are known as intracellular targets for Cd and are central to the formation of excess reactive oxygen species, their implication is highly possible (Luevano and Damodaran, 2014). In addition, as reported by Julin et al. (2012), both in vivo and in vitro studies provide evidence that Cd may act as a metalloestrogen (Johnson et al., 2003; Safe, 2003; Brama et al., 2007; Zang et al., 2009; Garcia-Morales et al., 1994; Ali et al., 2010). Cadmium was discovered to exert estrogenic activities, such as stimulation of the proliferation of breast cancer cells (Brama et al., 2007; Martinez-Campa et al., 2006), activation and increased expression of estrogen regulated genes (Garcia-Morales et al., 1994; Liu et al., 2008) and activation of the estrogen receptor (ER)-alpha (Garcia-Morales et al., 1994; Martinez-Campa et al., 2006; Stoica et al., 2000; Wilson et al., 2004) supporting the hypothesis that this metal can potentially induce the development of hormone-dependent tumors in humans, including breast, uterus and prostate cancers (Akesson et al., 2008; Benbrahim-Tallaa et al., 2009; Bertin and Averbeck, 2006). Cd has been shown to upregulate progesterone receptor (PGR) levels in breast cancer cells, this induction being blocked by anti-estrogen (Garcia-Morales et al., 1994). The combination of carcinogenic and estrogenic activities makes Cd a contaminant of high concern for hormone-dependent cancers.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide (Jemal et al., 2011). Risk factors for this cancer include elements related to reproductive life and cumulative exposure to estrogens, e.g., early age at menarche, nulliparity, late age at first pregnancy, short lactation, late menopause, use of hormone replacement therapy (HRT), high BMI, low physical activity and family history (inheritance) of breast cancer. Associations were also reported with high alcohol consumption, radiation exposure, high socioeconomic status and higher educational levels (Scottenfeld and Fraumeni, 2006; Strumylaite et al., 2010).

Several epidemiological studies investigating the association between dietary Cd exposure and hormone-related cancers have reported conflicting results. A first meta-analysis (MA) (Cho et al., 2013) showed a statistically significant positive association between dietary Cd intake and breast cancer in women. In a re-evaluation including two additional cohort studies, the positive association was no more statistically significant (Wu et al., 2015). Detecting the activity of estrogenic chemicals in epidemiological studies is, however, not trivial because of the contribution of endogenous estrogens. After menopause, exogenous estrogens are predominant and contribute to breast cancer risk (Strumylaite et al., 2010). The potential estrogenic influence of Cd should, therefore, be better detected in postmenopausal women.

The aim of our study is to re-assess the association between dietary Cd intake and the risk of breast cancer, by combining the data on postmenopausal women in a MA. In addition, as heterogeneity has been reported in the previous MA, we conducted sub-group analyses to identify possible source(s) of heterogeneity.

2. Materials and methods

2.1. Study identification and selection

2.1.1. Study identification

A search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted using the PubMed interface to identify publications