RESEARCH ARTICLE

Breast Cancer Frequency and Exposure to Cadmium: A Meta-Analysis and Systematic Review

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Abstract

Background: In this meta-analysis we review evidence suggesting that exposure to cadmium is a cause of breast cancer. Materials and Methods: We conducted Medline/PubMed and Scopus searches using selected MeSH keywords to identify papers published from January 1, 1980 through January 1, 2013. Data were merged and summary mean differences were estimated using either a random-effects model or a fixed-effects model. Results: There were 13 studies including 978 exposed cases and 1,279 controls. There was no statistically significant difference in the frequencies of breast cancer between cadmium-exposed and control groups, and the summary estimate of mean difference was 0.71 (95%CI: 0.33-1.08). However, stratification showed that there were statistically significant differences in the frequencies of breast cancer between cadmium-exposed and control groups among Asian compared with Caucasian population, and the summary estimates of mean difference were 1.45 (95%CI: 0.62-2.28) vs. 0.25 (95%CI: -0.09-0.6), respectively. There was a difference in the frequencies of breast cancer between cadmium-exposed and control groups in peripheral venous blood sampling methods, and the summary estimate of mean difference was 1.41 (95%CI: 0.46-2.37). Conclusions: Data indicate that the frequencies of breast cancer might be an indicator of early genetic effects for cadmium-exposed populations. However, our meta-analysis was performed on population-based studies; meta-analysis based on individual data might provide more precise and reliable results. Therefore, it is necessary to construct an international database on genetic damage among populations exposed to cadmium that may contain all raw data of studies examining genetic toxicity.

Keywords: Cadmium - breast cancer - meta-analysis - systematic review

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Introduction

Cadmium (Cd) is a human carcinogenic heavy metal, which is taken up from contaminated soil by a variety of vegetables and grains, as a result of industrial and agricultural activities (Jarup, 2003; Hellstrom et al., 2007; Jarup and Akesson, 2009; Peralta-Videa et al., 2009). In the human body, most of the Cd is bounded to low molecular weight proteins functioning in the essential metals such as zinc called metallothioneins (Freisinger and Vasak, 2013; Linsak et al., 2013). The Cd-metallothioneins complex is dispersed to different organs and tissues, and is eventually reabsorbed in kidneys, so Cd accumulates in tissues because of absence of mechanism for the excretion of this heavy metal from the body (Fujishiro et al., 2012; Tekin et al., 2012). Epidemiological evidences reported the relationship of occupational and dietary Cd exposure with various cancers such as pancreatic cancer (Ojajarvi et al., 2000; Schwartz and Reis, 2000). The possible mechanisms for Cd-induced cancer include induction of oxidative stress (Joseph et al., 2001; Shih et al., 2004), inhibition of DNA damaging repair (Jin et al., 2003), and apoptosis inhibition (Templeton and Liu, 2010).

Estrogen receptor (ER) plays a crucial role between different signaling pathways in breast cancer (Kok and Linn, 2010), besides some experimental studies offer evidence that Cd may act as a metallo-estrogen through mimicking the effect of estrogen on mammary gland (Johnson et al., 2003; Safe, 2003), or induces mitogenic signaling (Brama et al., 2007). Breast cancer is the second leading cause of the dead after lung cancer, with nearly 1.4 million new cases (Lopez et al., 2006). A few small case–control studies supported the role of Cd exposure in the development of breast cancer so far (McElroy et al., 2006; Gallagher et al., 2010). Furthermore, a few cohorts suggested the role of dietary Cd in the breast cancer (Adams et al., 2012; Julin et al., 2012).

In this meta-analysis we attempt to review evidence indicating that exposure to cadmium is a cause of breast cancer.

Materials and Methods

Literature source and searching methods

We conducted Medline/PubMed and Scopus searches using [“Cadmium” (Mesh) OR “Cadmium Chloride”

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(Mesh) OR "Cadmium Compounds" (Mesh) OR "Cadmium Poisoning" (Mesh)] AND "Breast Neoplasms" (Mesh) OR "Neoplasms" (Mesh) as keywords to search for papers published (from January 1, 1980 through January 1, 2013)]. Further publications were also recognized by retrieving the bibliographies of the retrieved papers through reference check method. The search and evaluation were done on May 2013.

Inclusion criteria

The studies should be published in English language, include cadmium exposure and breast cancer, must offer the exposed group and control group, The paper must offer the size of the sample, arithmetic means and standard deviations (SD). Accordingly, nonrelevant and repeated literatures were excluded.

Data extraction

The information including first authors, publication year, country, duration, arithmetic means and standard deviations, sample size of exposed group and control group from each selected study were retrieved. Features of individual studies were summarized in Table 1.

Quantitative data synthesis

To assess the relationship between breast cancer frequencies and exposure to Cd, we conducted a meta-analysis of available studies. Data were merged using either a random-effects model or a fixed-effects model (DerSimonian and Laird, 1986). The assessment of heterogeneity was done using the Cochrane Q statistics test. In case the effects are assumed to be homogenous a fixed-effects model is employed, hence a random-effects model is performed when they are heterogeneous. We computed the mean difference and 95% confidence interval (95%CI) for each study. Publication bias was observed using Egger's test, in which a regression model was established, using the standardized estimate of size effect as a dependent variable and the inverse of the standard error as an independent variable (Egger et al., 1997; Xu et al., 2009). Moreover, Begg's rank correlation test was used to check the publication bias (Begg and Mazumdar, 1994).

Statistical analysis

All of the statistical analyses were performed with STATA10.0 software package (STATA Corporation, College Station, Texas). All the tests were two-side, a p value of less than 0.05 for any test or model was considered to be statistically significant.

Results

Meta-analysis

There were 13 studies including 978 exposed cases and 1279 controls (Figure 1) (Antila et al., 1996; Ionescu et al., 2006; McElroy et al., 2006; Wu et al., 2006; Pasha et al., 2008; Strumylaite et al., 2008; Gallagher et al., 2010; Benderli Cihan et al., 2011; Saleh et al., 2011; Strumylaite et al., 2011; Kotsopoulos et al., 2012; Nagata et al., 2013). The characterization of all selected studies was summarized in Table 1.

Test of heterogeneity

The heterogeneity of studies on Cd was analyzed for the 13 selected studies. The results show that all meta-analysis on Cd frequencies in our studies had heterogeneity with p value less than 0.05 (Figure 2).

Table 1. Description of Included Studies

Author, year	Country	Sample Size		Cadmium (Mean±SD)		p value	Detection technique	Breast cancer stage	Control group
		Case	Control	Case	Control				
Nagata et al., 2013	Japan	153	431	2.72±2.01	2.09±1.82	<0.01	urine sampling	Mixed	Healthy
Kotsopoulos et al., 2012	Canada	48	96	1.09±0.28	1.03±0.42	0.43	peripheral venous blood	Mixed	Healthy
BenderliCihan et al., 2011	Turkey	52	52	0.441±0.486	0.175±0.206	<0.05	hair levels	III	Healthy
Saleh et al., 2011	Kuwait	50	150	5.87±1.53	3.81±1.9	<0.0001	peripheral venous blood	I	Healthy
Strumylaite et al., 2011	Lithuania	57	51	0.053±0.028	0.032±0.018	<0.001	peripheral venous blood	I	benign breast
Romanowicz-Makowska et al., 2011	Poland	67	19	0.61±0.24	0.76±0.38	<0.05	tissue samples	Mixed	Cancer-free
Gallagher et al., 2010	USA	100	98	0.058±0.050	0.041±0.050	0.001	peripheral venous blood	Mixed	Healthy
Pasha et al., 2008	Pakistan	53	61	1.21±2.64	0.58±1.12	<0.001	tissue samples	III	benign breast
Strumylaite et al., 2008	Lithuania	21	19	33.1±22.08	17.5±8.09	0.009	tissue samples	Mixed	benign breast
Ionescu et al., 2006	Germany	20	8	89.65±120.04	16.87±11.03	<0.001	tissue samples	Mixed	Healthy
Wu et al., 2006	Taiwan	68	26	2.28±0.28	1.13±0.42	<0.01	peripheral venous blood	Mixed	Healthy
McElroy et al., 2006	USA	246	254	0.45±0.28	0.42±0.19	0.653	urine specimen	Mixed	Healthy
Antila et al., 1996	Finland	43	32	20.4±17.5	31.7±39.4	0.581	tissue samples	Mixed	Healthy

Quantitative data synthesis

Therefore, we estimated the summary mean difference for them using a random-effects model (Table 2). There was no statistically significant difference in the frequencies of breast cancer between Cd-exposed and control groups, and the summary estimate of mean difference was 0.71 (95%CI: 0.33-1.08) (Figure 3). We stratified the studies by ethnicity including Asian and Caucasian (Figure 4). The stratification showed that there were statistically significant differences in the frequencies of breast cancer between Cd-exposed and control groups among Asian compared to Caucasian population, and the summary estimates of mean difference were 1.45 (95%CI: 0.62-2.28) vs. 0.25 (95%CI: -0.09-0.6), respectively (Figure 4). We also stratified the studies by different sampling method including hair, urine, tissue and peripheral venous blood (Figure 5). There were statistically significant differences in the frequencies of breast cancer between Cd-exposed and control groups in peripheral venous blood sampling methods, and the summary estimates of mean difference was 1.41 (95%CI: 0.46-2.37) (Figure 5).

Sensitivity analysis

We conducted the sensitivity analysis and found that subgroup analysis based on ethnicity (Asian versus Caucasian populations) and sampling techniques (Urine, tissue, hair and peripheral venous blood) did make a noticeable difference for the above analyses (Table 2). The summary estimates of mean difference of Asian population were higher compared with Caucasian population. Similarly, the summary estimate of mean difference of peripheral venous blood technique was higher compared with the rest three techniques.

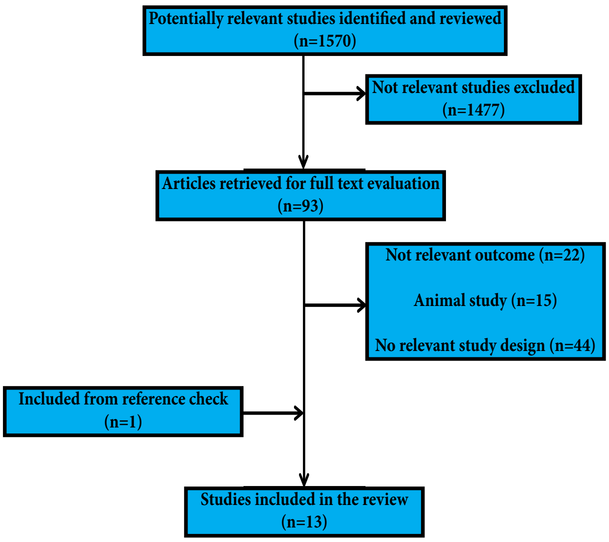

Figure 1. The Flow Diagram of Study Selection

Assessing publication bias

Publication bias was evaluated by Egger's test and Begg's test (Table 2). Both tests suggest that publication bias might not have a significant influence on summary estimate of Cd exposure among Caucasian population, and between different sampling techniques. Maybe, there was publication bias in meta-analysis for total population, because there was some uncertainty with the p value being less than 0.05 in either Egger's or Begg's tests, among Asian population.

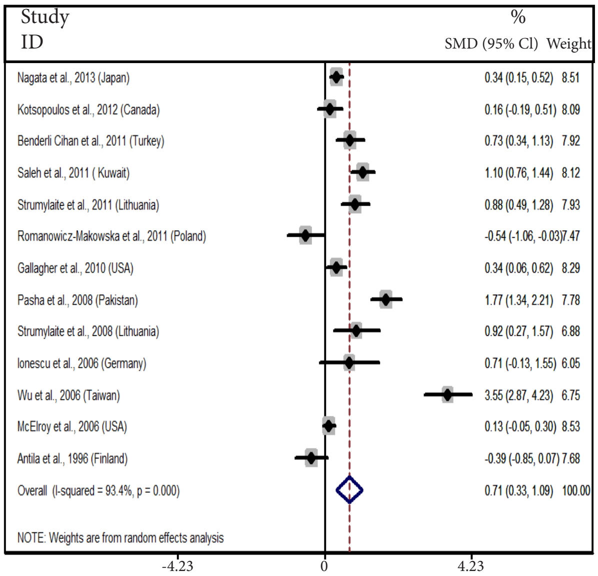

Figure 3. Meta-Analysis is Conducted on Cadmium among Total Breast Cancer Population. Each estimate of mean difference on cadmium is designated by a solid square, and the 95% confidence interval (95% CI) of each subgroup is shown by transverse line. The solid rhombus at the bottom is the pooled estimate of mean difference by random-effects model

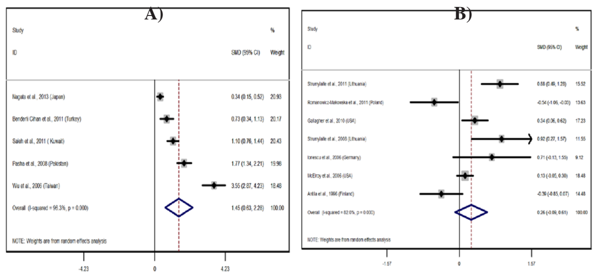

Figure 4. Meta-Analysis is Conducted on Cadmium among Different Ethnicity. A) Asian and B) Caucasian**.** Each estimate of mean difference on cadmium is designated by a solid square, and the 95% confidence interval of each subgroup is shown by transverse line. The solid rhombus at the bottom is the pooled estimate of mean difference by random-effects model

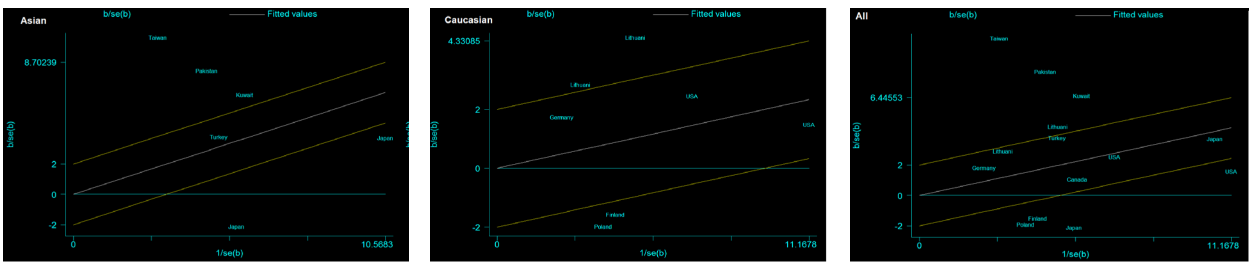

Figure 2. Assessing the Heterogeneity of All Sample Population and Subgroups (Asian and Caucasian)

Table 2. Summary Results of Meta-Analysis on Breast Cancer Induced by Cadmium

Population	Exposed/Control	Heterogeneity test		Hypothesis test		df	Egger test		Begg test (95% CI)		Summary estimates of
		Q	p	Z	p		t	p	Z	p	mean difference
Total	978/1279	182.4	<0.0001	3.7	<0.0001	12	1.69	0.12	0.98	0.329	0.71 (0.33-1.08)
Stratification by sampling											
Urine	399/685	2.62	0.106	2.17	0.03	1	--	--	1	0.317	0.23 (0.02-0.44)
Peripheral venous blood	323/421	74.35	<0.0001	2.9	0.004	3	4.63	0.044	1.36	0.174	1.41 (0.46-2.37)
Tissue	204/139	64.64	<0.0001	0.97	0.332	4	-0.07	0.946	0.49	0.624	0.48 (-0.49-1.47)
Hair*	52/52	0	--	3.62	0	0	--	--	--	--	----------
Stratification by ethnicity											
Asian	376/720	108.43	<0.0001	3.45	0.001	4	4.31	0.023	1.96	0.05	1.45 (0.62-2.28)
Caucasian	602/577	33.33	<0.0001	1.45	0.147	6	0.38	0.718	0.15	0.881	0.25 (-0.09-0.60)

*Only a single study has been found

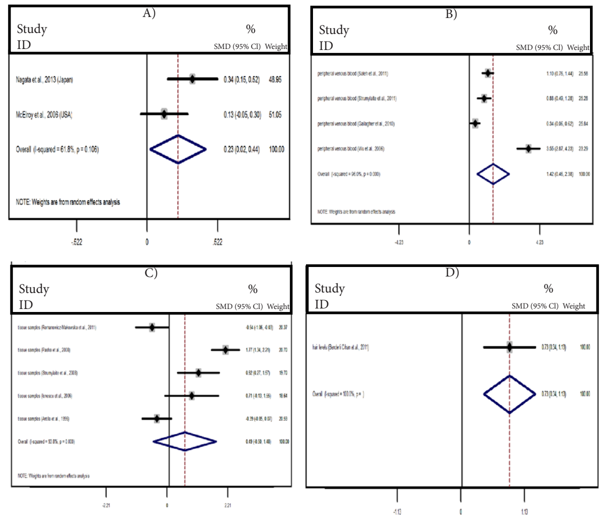

Figure 5. Meta-Analysis is Conducted on Cadmium among Different Sampling Technique. A) Urine, B) Peripheral blood, C) Tissue and D) Hair. Each estimate of mean difference on cadmium is designated by a solid square, and the 95% confidence interval of each subgroup is shown by transverse line. The solid rhombus at the bottom is the pooled estimate of mean difference by random-effects model

Discussion

Our meta-analysis shows that the frequencies of breast cancer were not significantly higher in the Cd-exposed group than the controls using random-effects model, where the summary estimate of mean difference was 0.71 (95%CI: 0.33-1.08). Our findings indicate that exposure to Cd could not induce significantly the breast cancer, which might be an indicator of noncarcinogenic effects for Cd-exposed population.

One complication of industrialization of the societies is the consumption of chemicals, trace elements and heavy metals, which are often very dangerous and lethal. Moreover, given the increasing prevalence of diseases caused by such environmental pollutants the main question is whether there are heavy metals in agricultural products or not? We found the association between Cd concentration and breast cancer in Asian and Caucasian populations. This is in agreement with a study among Caucasian (American) population that showed that a 2.7-fold increased risk of breast cancer was associated with cadmium exposure (McElroy et al., 2006). Other study revealed a similar magnitude (2.8-fold) of associations in (American) population (Gallagher et al., 2010). Other Study on Asian (Kuwait) population, investigated the blood level of Cd in stage I breast cancer patients, and reported that breast cancer patients seem to have abnormal levels of Cd compared to healthy controls (Saleh et al., 2011). Our meta-analysis showed the mean difference between cancer patients and healthy controls was more significant in Asian population than Caucasian. Over the last few decades, the increased awareness of health problem related to heavy metal contamination leads to decrease in those emissions in some industrialized countries (Hjortenkrans et al., 2006), but, in developing countries anthropogenic sources still have been increasing in response to rapid urbanization and industrialization (Govil et al., 2008). Different nutritional behaviors and industrialization between Asian and Caucasian populations may lead to different exposure and risk of breast cancer related to heavy metal contaminations.

Increasing the usage of Cd has directed to extensive contamination of the environment that affects human health as a consequence of industrial developments. Lethal or chronic Cd exposures and it's toxicity and damage to mammalian organs, mostly from dietary sources, seem to be the real challenge in the 21st century in a global health setting (Thevenod and Lee, 2013). Several lines of epidemiologic evidences from exposed people in polluted and contaminated areas have suggested a positive association between Cd and risk of several type cancers such as pancreas, prostate and endometrial (Akesson et al., 2008; Julin et al., 2012; Luckett et al., 2012; Sawada et al., 2012).

Chen et al, in a hospital-based, case-control study compared the blood and urine Cd levels among prostate cancer patients, and claimed that higher blood and urine Cd levels tended to be associated with advanced cancer phenotypes. They also showed that urine Cd levels were higher the blood levels in cases (Chen et al., 2009). The present meta-analysis showed the mean difference between breast cancer patients and healthy controls was significantly more in the blood than tissue and urine samples.

In conclusion, the current meta-analysis results show a significant increase in frequencies of breast cancer in Cd-exposed population. However, our meta-analysis was performed on population-based studies; meta-analysis based on individual data might provide more precise and reliable results. Therefore, it is necessary to construct an international database on genetic damage among population exposed to Cd that may contain all raw data of studies examining Cd-genetic toxicity.

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