Environment International 86 (2016) 1–13

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

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

Geneviève Van Maele-Fabry [a,*], Noömi Lombaert [b], Dominique Lison [a]

[a] Université catholique de Louvain, SSS/IREC/LTAP (Louvain Center for Toxicology and Applied Pharmacology), Avenue E. Mounier 53, bte B1.52.12, B-1200 Brussels, Belgium
[b] International Zinc/Cadmium Association, Avenue de Tervueren 168/Box 4, B-1150 Brussels, Belgium

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form 5 October 2015
Accepted 5 October 2015
Available online 18 October 2015

Keywords:
Dietary cadmium
Breast cancer
Postmenopausal women
Systematic review
Meta-analysis

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.

* Corresponding author.
E-mail addresses: genevieve.vanmaele@uclouvain.be (G. Van Maele-Fabry), nlombaert@zinc.org (N. Lombaert), dominique.lison@uclouvain.be (D. Lison).

http://dx.doi.org/10.1016/j.envint.2015.10.003

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

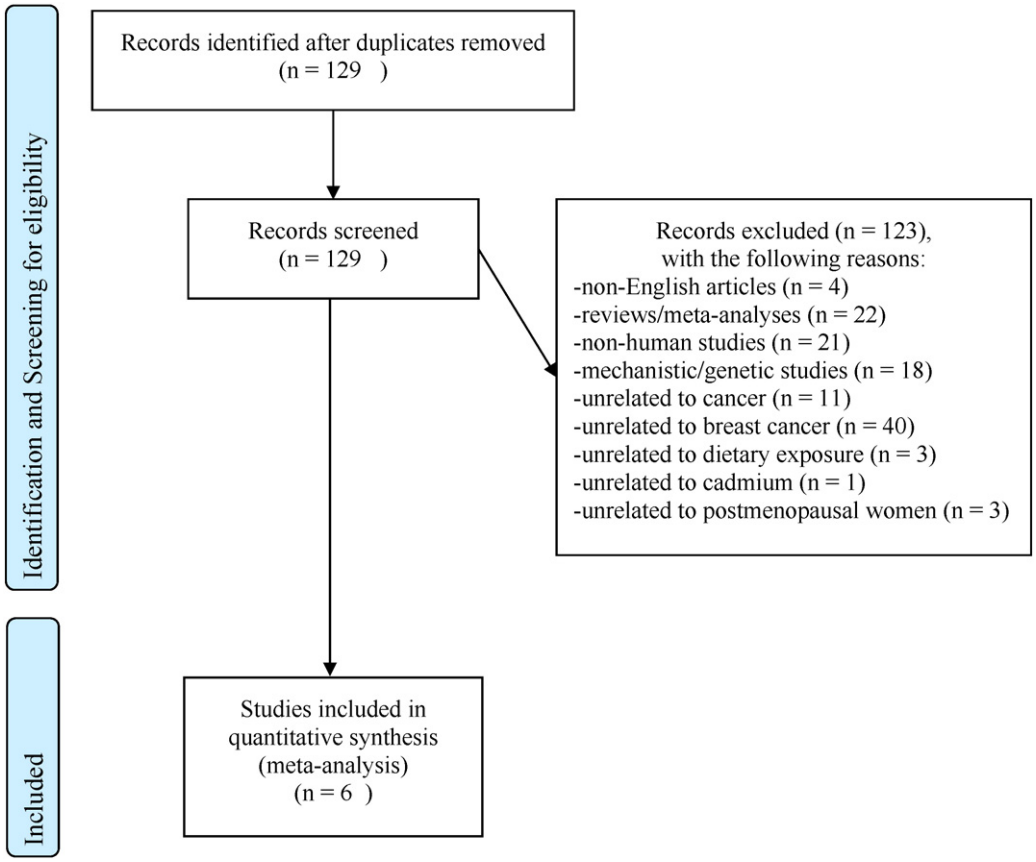

Fig. 1. Flow chart of study selection. Note: n = number of publications.

eligible for review, for the period 1966 to 31 January 2015. An electronic search using "("cadmium"[MeSH Terms] OR "cadmium"[All Fields]) AND ("diet"[MeSH Terms] OR "diet"[All Fields] OR "dietary"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])" was initially undertaken. This was supplemented with the reference lists of the relevant publications in an effort to identify all available literature that may not have been traced by our database searches. The search was limited to studies published in peer-reviewed journals as they are likely to be more reliable than unpublished reports.

2.1.2. Study selection

A study was considered eligible for further review if (i) it referred to dietary Cd exposure, (ii) if the outcome included breast cancer among postmenopausal women and (iii) if the study used a cohort or a case–control design. We excluded studies published in a non-English language, those that did not report original results (reviews, meta-analysis, case-reports, comments, letters, editorials, abstract), non-human studies, mechanistic studies as well as studies focusing on genetic data. Studies dealing with breast tumor cases among pre- and postmenopausal women combined with no separate reporting of postmenopausal women data were not selected, as well as those including subjects already included in another more complete or more recent publication examining a greater number of subjects or with longer follow-up duration.

The systematic review and identification of eligible publications was performed by 1 reviewer (GVMF).

2.2. Data extraction

A structured abstract was derived from each selected publication, including information on the study design and characteristics, location, exposure assessment and disease definition. Two authors (GVMF and NL) read the reports and independently extracted and tabulated the most relevant risk estimators, with their 95% CIs. The results of this exercise were compared between the authors and consensus was obtained before the meta-analysis.

2.3. Data analysis

The data analysis is the same as previously described in details in Van Maele-Fabry et al. (2010, 2012, 2013).

2.3.1. Evaluation of homogeneity

The significance of the between-study variance was evaluated with the ln(RR) or Q statistic test which has a χ^2 distribution with degrees of freedom equal to the number of studies pooled minus 1. The applied formula is: $\chi^2 = \Sigma w_i[\ln(RR)_i - \ln(RR)_p]^2$, for i = 1 to N, where N is the number of studies combined, RR_p is the overall pooled RR estimate, RR_i is the RR for the ith study and $w_i = 1 / V_i$ where V_i is the variance of the $\ln(RR)_i$. A low P value for this statistic indicates the presence of heterogeneity, which questions the validity of the pooled estimates (Clarke and Oxman, 2000; Lipsett and Campleman, 1999). When meta-analyses include small numbers of studies, the power of the test is low (Hardy and Thompson, 1998). An alternative approach to quantify the effect of heterogeneity, providing a measure of the degree of inconsistency in the results has been developed by Higgins et al. (2003). The quantity called I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 can be calculated as $I^2 = 100\% \times (Q - df) / Q$ where Q is Cochran's heterogeneity statistic and df the degree of freedom. Negative values of I^2 are put equal to zero so that I^2 lies between 0 and 100%. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

Table 1
Selected characteristics of the studies dealing with dietary cadmium exposure and risk of postmenopausal breast cancer.

Reference Geographic location Type of study	Cohort description (study period)	Exposure assessment A. Source of exposure data B. Exposure category	Disease definition (case finding and case diagnosis)
Adams et al., 2012 USA (13-county area; western Washington State) VITamins And Lifestyle (VITAL) prospective cohort	– Participants: female members of the VITAL cohort aged 50–76 and living in the 13-county area in western Washington State covered by the SEER cancer registry. – Excluded women: with unknown breast cancer history or with a previous breast cancer history; women diagnosed after enrolment with rare breast cancer histologies (sarcoma, lymphoma, or phyllodes) and from death certificate only; because missing FFQ responses; because reporting <600 kcal or >4000 kcal daily intake; pre- and perimenopausal women and women with unknown menopausal status. – Enrolment: 2000–2002, analytic cohort = 30,543 postmenopausal women including 26,801with complete information on all covariates in the fully adjusted risk model. – FU: 200–2002 through December 31, 2009. Mean FU time of 7.5 years. – Incident breast cancer cases: 1026; of these, 899 had complete covariate information for adjusted analyses; ER status available for 880 cases (757 ER+, 123 ER−). – Mean estimated cadmium intake (SD) = 10.9 (4.9) μg/day; range: 0.5–55.7 μg/day.	A. Self-administered questionnaire (24-page) concerning diet, supplement use, lifestyle, demographics and health history. Assessment of dietary intake: food frequency questionnaire (FFQ), 120 food, food group and beverage items over the past one year (adjustment questions on types of foods and preparation techniques); FFQ analytic program calculates average annual servings of each FFQ food item adjusted to sex-specific portion sizes, and estimated nutrient intakes based on the Minnesota Nutrient Data System. Dietary cadmium intake estimated by combining FFQ responses with US Food and Drug Administration (US FDA) data on food cadmium content. Each of the 343 food and beverage line items on the VITAL FFQ was matched to one or more foods analyzed by US FDA and on food mapping created by the US FDA, for FFQ foods for which no closely similar food was analyzed by US FDA. Cadmium concentration for each food = arithmetic mean of cadmium content (mg/kg prepared weight) reported by US FDA for all sample of each food, 1991–2008. B. Quartile of dietary intake.	– Incidence of breast cancer was ascertained through linkage of the cohort to the western Washington Surveillance, Epidemiology, and End Results (SEER) cancer registry through December 31, 2009. – Information on ER (estrogen receptor) status in breast cancer tissue of breast cancer patients was retrieved from SEER.
Adams et al., 2014 US (40 clinical centers) Women's Health Initiative (WHI) Prospective study comprising observational study and randomized clinical trial	– Participants: postmenopausal women aged 50–79 years from the WHI study comprising randomized clinical trial and observational study. – Excluded women: with incomplete or invalid (total energy <600 or >5000 kcal/day) FFQ data or without follow-up information for cancer diagnosis; with a previous breast cancer history; (women with missing information on a given variable were included as a separate category for adjustment). – Enrolment: 1993–1998; 161,808 women enrolled; 150,889 women included in the breast cancer analyses. – FU: 1993–1998 through August 2009. Mean FU time of 10.5 years. – Incident breast cancer cases: 6658; ER status available for 6109 cases (5161 ER+, 948 ER−). – Mean estimated cadmium intake (median) = 10.9 (10.3) μg/day; range: 0.02–59.4 μg/day.	A. Self-administered questionnaire concerning dietary habits, lifestyle (tobacco use, alcohol use, dietary supplement use, physical activity), demographic characteristics, reproductive history (use of postmenopausal hormones) and medical history; anthropometric measurements taken at baseline clinic visits and BMI calculated. Assessment of dietary intake during the prior 3 months: food frequency questionnaire (FFQ), 122 food and beverage items comprising 302 individual food and beverage components. Dietary cadmium intake estimated by combining FFQ responses with US Food and Drug Administration data on food cadmium content. Each of the 302 food and beverage line items on the WHI FFQ was matched to one of the foods analyzed by US FDA and on food mapping created by the US FDA, for FFQ foods for which no closely similar food was analyzed by US FDA (to allow inclusion of participants at the Hawaii center, 27 additional component foods specific to the Hawaii FFQ were matched). Urinary cadmium and creatinine: cadmium concentration was measured in a subset (n = 1050) of urine samples; urine creatinine was also measured. B. Quintile of dietary intake (quartiles for some adjustments).	– Participants reported incident invasive breast, endometrial or ovarian cancer and WHI centrally adjudicated all cases through August 2009; physician review of medical records. – Information on ER (estrogen receptor) status in breast cancer tissue of breast cancer patients [ER+, N = 5161; ER−, N = 948].
Eriksen et al., 2014 Denmark Diet, Cancer and Health cohort (DCH) Prospective cohort study	– Participants: 57,053 individuals including 29,875 women aged 50–60 years, born in Denmark. – Excluded women: with a previous cancer diagnosis. – Enrolment: 1993–1997, restricted to postmenopausal at baseline with complete covariate information,	A. Self-administered, interviewer-checked 192 item semi-quantitative food frequency questionnaire (FFQ), over the past 12 months, covering also lifestyle habits (including present and previous smoking status), physical activity, reproductive history, health status and social factors.	– Danish Cancer Registry used to identify incident cases of cancer; information on ER status, PGR status and histology type was obtained from The Danish Breast Cancer Cooperative Group.

Table 1 (*continued*)

Reference Geographic location Type of study	Cohort description (study period)	Exposure assessment A. Source of exposure data B. Exposure category	Disease definition (case finding and case diagnosis)
	analytic cohort = 23,815 postmenopausal women. – FU: 1987–90 through December 31, 2010. Mean FU time of 13 years. – Incident breast cancer cases: 1390; ER status available for 1209 cases (981 ER+, 228 ER−); PGR status available for 671 cases (405 PGR+, 266 PGR−). – Mean dietary cadmium intake: 14 μg/day (5–95% percentiles = 8–22 μg cadmium/day).	Assessment of dietary intake: food monitoring data from the Danish Food Monitoring Programme for Nutrients and Contaminants (monitoring cycles running for 5-year periods), 1993–97 was used for the calculations. Dietary cadmium intake per day was obtained, for each participant in the DCH cohort, by adding the obtained cadmium concentration for each food item to the food table using the FoodCalc program. B. Tertile of dietary intake.	
Itoh et al., 2014 Japan (Nagano Prefecture, 4 hospitals) Hospital-based case–control study	– Participants: Japanese women aged 20–74 years (405 matched pairs) from May 2001 to September 2005 at four hospitals. – Excluded women: pairs of women with extremely low or high daily total energy intake (<500 kcal or ≥4000 kcal) were excluded. – Enrolment: 390 pairs used in the analyses including a total of 465 postmenopausal women (212 cases; 253 controls). – Postmenopausal women: incident breast cancer cases: 212; ER status available for 210 cases (156 ER+, 54 ER−); PGR status available for 210 cases (107 PGR+, 103 PGR−). – Mean estimated energy-adjusted cadmium intake in control subjects = 26.4 μg/day.	A. Self-administered questionnaire concerning demographic characteristics, anthropometric factors, smoking habits, family history of cancer, physical activity, medical history, menstrual and reproductive history. Assessment of dietary intake: 136-item semi-quantitative FFQ (evaluating average food intake over the last year); 10 frequency categories and relative sizes compared to standard portions (3 amounts: small, medium, large). Data used to calculate consumption for each food groups (g/day), nutrients (mg/day) and cadmium (μg/day). Cadmium content of food obtained from JECFA and the Committee on Pharmaceutical and Food Sanitation of the Ministry of Health, Labor and Welfare of Japan. 6 food groups selected: rice, wheat, soybeans, stem/root vegetables, leafy vegetables, other vegetables or fruits. Daily cadmium intake estimated by multiplying frequency of consumption by portion size and the average cadmium content in each food item. B. Tertile of dietary intake.	– Cases = women with newly arising, histologically confirmed invasive breast cancer admitted to any of the 4 hospitals during the survey period; controls = healthy subjects selected from among medical checkup examinees in 2 of the hospitals, who were confirmed to not have cancer; 1 control matched to 1 case by age (within 3 years) and residential area during the study period. – Information on ER (estrogen receptor) and PR (progesterone receptor) status in breast cancer tissue of breast cancer patients was obtained from medical records.
Julin et al., 2012 Sweden central counties : Västmanland and Uppsala Swedish Mammography CohortProspective cohort study	– Participants were women born between 1914 and 1948 invited to a mammography screening (n = 90,303); cohort established in 1987 to 1990. – Excluded women: with incorrect or missing national registration number, reporting implausible values for energy intake, with a previous cancer diagnosis, with diabetes. – Enrolment: 30,825 participants who were postmenopausal at baseline (1987–1990) + 27,705 who self--reported cessation of menstruation during follow-up + women classified as postmenopausal if they had had bilateral oophorectomy or were 55 year old or older. – Analytic cohort for the primary analysis = 55,987 postmenopausal women. – FU: 1987–1990 in Uppsala and January 1998 in Västmanland through December 31, 2008. Average of 12.2 years (712,075 person-years). – Incident breast cancer cases: 2112; ER status available for 1916 cases (1,626 ER+, 290 ER−). – Mean estimated energy-adjusted cadmium intake in the cohort = 15 μg/day ± 3.2 (SD).	A. Self-administered questionnaire concerning diet, lifestyle and reproductive factors; response rate being 74%. Uppsala (54% of the cohort): additional questionnaire including information on history of oral contraceptive use, postmenopausal hormone use, age at menarche and menopause. In 1997: second questionnaire sent to gain information on smoking status and details on reproductive factors; response rate being 70%. Assessment of dietary intake: 67-item food frequency questionnaire (FFQ); frequency of each item reported using 8 predefined categories (from never/seldom to 4 times a day). Average daily exposure to dietary cadmium estimated by multiplying the frequency of consumption by the age-specific portion sizes and the average cadmium content in each food item. Cadmium content of food obtained from the National Food Administration and from Finnish and Danish data (for pepper, spinach, leek and citrus fruits). Exposure from air contributes to less than 1% and community-provided tap water and water from private wells contribute on average with 0.2% of the total cadmium exposure. Cross classification of FFQ-estimated dietary cadmium and urinary cadmium concentration (reflecting the long-term kidney accumulation of the metal)	– Histology confirmed cases identified by linkage of the cohort to the National Cancer Registry. – ER status obtained from pathology logs at the Uppsala University Hospital (1987–1994) and from the Quality Registry at the Regional Oncology Centre (1994–2008). – Dates of death were ascertained by linkage to the Swedish Death Registry.

(*continued on next page*)

Table 1 (*continued*)

Reference Geographic location Type of study	Cohort description (study period)	Exposure assessment A. Source of exposure data B. Exposure category	Disease definition (case finding and case diagnosis)
		resulted in 51% sensitivity and 58% specificity. B. Tertile of dietary intake (estimated daily cadmium intake adjusted for total energy intake of 1700 kcal [mean of the cohort]).	
Sawada et al., 2012 Japan The Japan Public Health Center--based Prospective study (2 cohorts): cohort I (Iwate, Akita, Nagano, Okinawa, *Tokyo excluded in this study*), cohort II (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, Osaka) Population-based prospective study	– Participants were men and women 45–74 years of age (n = 98,519 [46,033 men + 52,486 women]) drawn from Japan Public Health Centers. – Excluded subjects: those with a history of cancer, those who reported extreme total energy intake (<990 kcal/day or ≥4204 kcal/day in men and <843 kcal/day or ≥3686 kcal/day in women); all subjects in Tokyo because incidence data were not available; – Analytic cohort for the primary analysis = 90,383 subjects including 5849 with cancer. – Enrolment: Prospective study conducted in 2 cohorts initiated in 1990 (cohort I; 5-year FU: 1995) and 1993 (cohort II; 5-year FU: 1998). – FU: until 31 December 2006 (average FU period: 9-year). – Newly diagnosed cases of cancer: N = 5849 (3586 men, 2263 women including 402 breast cancers [18%]). – Average estimated energy-adjusted cadmium intake in the cohort = 26.5 μg/day.	A. Self-administered questionnaire (FFQ) at baseline and after a 5-year FU with more comprehensive information on food-intake frequency than the first one (5-year FU used as baseline to assess dietary exposure). Questionnaire included information on medical history and lifestyle factors (smoking, alcohol consumption). Assessment of dietary intake: 138 food and beverage FFQ items with standard portions/units (specified for each food items in 3 amounts: small, medium, large) and 9 frequency categories. Assessment of cadmium dietary intake: from 6 food groups (rice, wheat, soybeans, stem/root vegetables, leafy vegetables, other vegetables or fruits), based on the questionnaire data. Cadmium intake calculated by multiplying the average cadmium concentration in each item (based on reports from the Join FAO/WHO Expert Committee on Food Additives and the Committee on Pharmaceutical and Food Sanitation of the Ministry of Health, Labor and Welfare of Japan) by the quantity of each item. Exposure from air contributes to less than 1% and cadmium in drinking water is limited to less than 0.01 mg/L → cadmium intake via water and air were ignored. B. Tertile of cadmium intake for breast cancer, with the lowest consumption category as the reference. Estimated daily cadmium intake was adjusted for total energy intake.	– Incident cancers were identified by reports from hospitals (64%), registries (26%), death certificates (10%) and responses to questionnaires and others (0.2%). – Cases were coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3).

Abbreviations: FAO/WHO, Food and Agriculture Organization/World Health Organization; FFQ, food frequency questionnaire; FU, follow-up; ICD-O-3, the International Classification of Diseases for Oncology, third edition; JECFA, the Joint FAO/WHO Expert Committee on Food Additives; SEER, Surveillance, Epidemiology, and End Results (cancer registry); US FDA, United States Food and Drug Administration; VITAL, VITamins And Lifestyle; and WHI, Women's Health Initiative.

Table 2
Estimated cadmium dietary intakes in the studies included in the meta-analysis and in the respective general populations.

Reference	Geographic location	Mean Cd intake in the cohort (μg/day)	Mean Cd intake in the general population (μg/day)
Adams et al., 2012	USA	10.9 (SD: 4.9) Range: 0.5–55.7	9.39[a]
Adams et al., 2014	USA	10.9 Median: 10.3 Range: 0.02–59.4	9.39[a]
Eriksen et al., 2014	Denmark	14 5–95% percentiles: 8–22	16 (1993–1997)[b] 10 (1998–2003)[c] 10.8 (2004–2011)[c]
Julin et al., 2012	Sweden	Energy-adjusted: 15 ± 3.2	~15[d]
Itoh et al., 2014	Japan	Energy-adjusted in controls: 26.4*	25.5[e]
Sawada et al., 2012	Japan	Energy-adjusted: 26.5**	25.5[e] 25.9[f]

* Women pre-and postmenopausal.
** The cohort included men + women.
[a] Egan et al. (2007) (women: 60–65 years).
[b] Larsen et al. (2002) (men + women).
[c] National Food Institute (2013) (men + women).
[d] Järup et al. (1998) (men + women).
[e] Watanabe et al. (2000) (women).
[f] Ikeda et al. (1999) (women).

Table 3
Data summary from studies on dietary cadmium intake and postmenopausal women breast cancer.

References	Geographic location	Exposure	N. of cases (/controls)	Estimator of relative risk	Risk estimator data [95% CI]	Adjustment/ matching
Adams et al. (2012)	USA (13-county area in western Washington State) [VITAL cohort] Prospective cohort	[mean μg/day (SD)]		HR		Age and total energy intake
		Quartile 1 [5.8 (1.2)]	276		Reference	
		Quartile 2 [8.8 (0.7)]	248		0.85 [0.71–1.03]	
		Quartile 3 [11.6 (0.9)]	258		0.88 [0.72–1.08]	
		Quartile 4 [17.4 (4.3)]	244		0.84 [0.67–1.06]	
		Per μg/day	1026		0.99 [0.97–1.01]	
		Quartile 1	232		Reference	Age, total energy intake, education, race,
		Quartile 2	213		0.91 [0.73–1.15]	HRT use, vegetable consumption
		Quartile 3	230		1.03 [0.79–1.35]	(excluding potatoes), potato consumption,
		Quartile 4	224		1.00 [0.72–1.41]	whole grain consumption, cigarette
		Per μg/day	899		1.00 [0.98–1.02]	smoking, BMI, physical activity, alcohol
		[range: 0.5–55.7 μg/day; mean: 10.9 (SD:4.9) μg/day]				consumption, age at first childbirth, multivitamin use, mammography
		ER+ tumors	757		1.0 [0.98–1.03]	Remark: to test for the difference in
		ER− tumors	123		0.94 [0.89–1.01]	association of cadmium with ER+ and
		Also stratifications for smoking, HRT, BMI, parity, vegetable consumption, regular multivitamin use, total zinc intake, total iron intake, total calcium intake				ER− tumors, the dataset was reformulated as a case–control study
Adams et al. (2014)	USA (40 clinical centers) [WHI: Women's Health Initiative] Prospective study	[μg/day]		HR		Total energy intake (residual method), age and study component (observational, clinical trial)
		Quintile 1 [<7.10]	1198		Reference	
		Quintile 2 [7.10–9.24]	1378		0.96 [0.89–1.04]	
		Quintile 3 [9.24–11.35]	1338		0.98 [0.91–1.06]	
		Quintile 4 [11.35–14.21]	1416		1.00 [0.93–1.08]	
		Quintile 5 [>14.21]	1328		0.96 [0.89–1.03]	
					p-Trend: 0.63	
		Quintile 1			Reference	+Body mass index, smoking, alcohol
		Quintile 2			0.93 [0.86–1.00]	consumption, race/ethnicity, education,
		Quintile 3			0.94 [0.87–1.02]	physical activity, age at first birth, age at
		Quintile 4			0.96 [0.89–1.04]	menarche, age at menopause, unoppose E
		Quintile 5			0.93 [0.86–1.00]	use, E + PG use, mammography 2 years
					p-Trend: 0.20	prior to baseline
		Quintile 1			Reference	+Daily vegetables serving, daily grain
		Quintile 2			0.92 [0.85–1.00]	servings
		Quintile 3			0.93 [0.86–1.02]	
		Quintile 4			0.94 [0.86–1.03]	
		Quintile 5			0.90 [0.81–1.00]	
					p-Trend: 0.12	
Eriksen et al. (2014)	Denmark; [Diet, Cancer and Health cohort]Prospective cohort study	[μg/day]		IRR		Age is underlying time-scale. Adjusted for
		Tertile 1 [<11.9]	468		Reference	educational level, smoking status, number
		Tertile 2 [11.9–15.3]	461		0.96 [0.85–1.10]	of births, age at first birth, HRT status, HRT
		Tertile 3 [>15.3]	461		0.97 [0.85–1.11]	use, age at menarche, BMI, height, physical
		Per 10 μg Cd/day	1390		0.99 [0.87–1.13]	activity and alcohol intake.
		Per 10 μg Cd/day				
		ER+ tumors	981		1.0 [0.85–1.15]	
		ER− tumors	228		0.88 [0.62–1.22]	
		Also stratifications for PGR, histology, education, smoking, HRT, BMI, total zinc intake, total iron intake				
Itoh et al. (2014)	Japan (4 hospitals in Nagano Prefecture) Case–control study	[Median intake: μg/day]		OR		Age, residential area, moderate physical
		Low tertile [21.4]	68/70		1.00	activity in the past 5 years, smoking status,
		Middle tertile [26.2]	66/89		1.01 [0.60–1.71]	family history for breast cancer, number of
		High tertile [31.5]	78/94		1.49 [0.84–2.64]	births, isoflavone intake, vegetable intake,
					p-Trend: 0.16	total energy intake
		Continuous intake			**1.06 [1.01–1.11]**	
				OR		
		ER+ tumors				
		Low tertile [21.4]	43		1.00	
		Middle tertile [26.2]	48		1.16 [0.65–2.07]	
		High tertile [31.5]	65		**1.94 [1.04–3.63]**	
					p-Trend: 0.032*	
		Continuous intake			**1.08 [1.03–1.14]**	
		ER− tumors				
		Low tertile [21.4]	25		1.00	
		Middle tertile [26.2]	17		0.69 [0.32–1.48]	
		High tertile [31.5]	12		0.62 [0.25–1.51]	
					p-Trend: 0.28	
		Continuous intake			0.99 [0.92–1.06]	
		Also stratifications for PGR status				

(continued on next page)

Table 3 (*continued*)

References	Geographic location	Exposure	N. of cases (/controls)	Estimator of relative risk	Risk estimator data [95% CI]	Adjustment/ matching
Julin et al. (2012)	Sweden central counties: Västmanland and Uppsala [Swedish Mammography Cohort] Prospective cohort	[intake: μg/day] (median)		RR (highest tertile/lower)		
		Low tertile [<13 (12)]	677		1.00	Age
		Middle tertile [13–16 (15)]	691		1.00 [0.90–1.11]	
		High tertile [>16 (17)]	744		1.06 [0.95–1.17]	
					p-Trend: 0.25	
		Low tertile [<13 (12)]	677		1.00	Age, adult height, BMI, >12 years of education, use of oral contraceptives, use of postmenopausal hormones, age at menarche, age at menopause, parity, age at first birth, alcohol consumption, glycemic load, total energy intake.
		Middle tertile [13–16 (15)]	691		1.00 [0.90–1.11]	
		High tertile [>16 (17)]	744		1.05 [0.95–1.17]	
					p-Trend: 0.26	
		Low tertile [<13 (12)]	677		1.00	+ Intake of whole grain and vegetables in tertiles
		Middle tertile [13–16 (15)]	691		1.06 [0.95–1.18]	
		High tertile [>16 (17)]	744		**1.21 [1.07–1.36]**	
					p-Trend: 0.02*	
					(p < 0.05)	
		ER+ tumors				Age, adult height, BMI, >12 years of education, use of oral contraceptives, use of postmenopausal hormones, age at menarche, age at menopause, parity, age at first birth, alcohol consumption, glycemic load, total energy intake + intake of whole grain and vegetables in tertiles
		Low tertile [<13 (12)]	538		1.00	
		Middle tertile [13–16 (15)]	520		1.01 [0.89–1.15]	
		High tertile [>16 (17)]	568		**1.19 [1.03–1.36]**	
					p-Trend: 0.02*	
		ER− tumors				
		Low tertile [<13 (12)]	83		1.00	
		Middle tertile [13–16 (15)]	101		1.22 [0.90–1.66]	
		High tertile [>16 (17)]	106		1.33 [0.95–1.87]	
					p-Trend: 0.60	
		Also data only for lean and normal weight postmenopausal women				
Sawada et al. (2012)	Japan (2 cohorts — I: 5 public health center areas (Iwate, Akita, Nagano, Okinawa, *Tokyo excluded in the present study*); II: 6 areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, Osaka)) [The Japan Public Health Center-based Prospective Study] Prospective cohort	[Median intake: μg/day]		HR (highest vs lowest cadmium intake group)		Age, area, BMI, smoking status, frequency of alcohol intake, leisure-time physical activity, intake of meat, soybean, vegetable, fruit, menopausal status, use of exogenous female hormones
		Low tertile [19.2]	? < 124		1.00	
		Middle tertile [24.9]	? < 141		1.35 [0.95–1.90]	
		High tertile [32.3]	? < 137		0.95 [0.62–1.46]	
						Remark: risk estimator data was for postmenopausal women only but reported numbers of cases are for pre- + postmenopausal women [percentage of postmenopausal women = from 75 to 82%].

Abbreviations: BMI, body mass index; CI, confidence interval; E, estrogen; ER+ or ER−, estrogen receptor status; HR, hazard ratio; HRT, hormone replacement therapy; IRR, incidence rate ratio; OR, odds ratio; PG, progesterone; PGR, progesterone receptor status; RR, rate ratio; and SD, standard deviation.
Bold data indicates significant at risk estimators when the 95% CI do not include 1.
* statistically significant.

Confidence limits of I^2 reflecting uncertainty in the extent of heterogeneity were calculated as proposed by Higgins and Thompson (2002).

2.3.2. Statistical pooling

When there was little variation between studies ($I^2 \leq 25\%$; Higgins et al., 2003), we calculated RRs and CIs according to a fixed model which assumes that results across studies differ only by sampling error. The study variance (V_i) was calculated, using the CI given, according to the equation $V_i = [(\ln(CI_{upper}) - \ln(CI_{lower})) / 3.92]^2$. As detailed by Stewart et al. (1999) and Dennis (2000), the maximum likelihood estimate of the pooled RR in the fixed effect model is the $\exp(\ln(RR)_p)$. The pooled $\ln(RR)_p$ equals $\Sigma[\ln(RR)_i / V_i] / [\Sigma(1 / V_i)]$, where V_i is the variance for an individual study as described above and $\ln(RR)_i$ is the log RR estimate for study i. This is a variance-weighted least square mean. The variance of the pooled $\ln(RR)_p$, $Var(\ln(RR)_p)$ or V_p is given by: $[SE(\ln(RR)_p)]^2 = [\Sigma(1 / V_i)]^{-1}$ where SE is the standard error. The pooled variance is used to calculate a 95% CI around the pooled RR estimate.

When data are heterogeneous ($I^2 > 25\%$) or if there is reason to believe that publication bias exists, the random effects model is more appropriate. Under this model, the point estimate of the pooled effect measure and its CI incorporate the additional variability due to between-study variance (τ^2). Random effects models were applied, using the method described by DerSimonian and Laird (1986) who proposed a non-iterative estimator of τ^2 defined as $est(\tau^2) = \max\{0, [Q - (k - 1)] / [\Sigma w_i - (\Sigma(w_i^2)) / \Sigma w_i\}$ where Q is the heterogeneity statistic, k is the total number of studies, and w_i are the inverse variance weights for ln(RR). Potential sources of heterogeneity were evaluated by subset analyses.

The meta-analysis including all studies for dietary Cd intake and postmenopausal women breast cancer is illustrated by a forest plot where the confidence interval for each study is represented by a horizontal line and the point estimate by a square. The size of the square corresponds to the weight of the study in the meta-analysis. The confidence interval for the total is symbolized by a diamond.

2.3.3. Publication bias

Potential publication bias due to study size (tendency for the smaller studies to show larger effects) was explored by plotting the natural logarithm of the estimate of RR (ln RR) versus the inverse of standard error (1/SE). Funnel plot asymmetry was tested using the linear regression method suggested by Egger et al. (1997).

Other selection biases (like language bias) and other factors such as differences in study quality or study heterogeneity may also produce asymmetry in funnel plots (Rothstein et al., 2005).

Table 4
Dietary cadmium exposure and risk of postmenopausal breast cancer: meta-analyses after stratification of the studies.

Stratifications	N. studies	Meta-RR	[95% CI]	χ^2 Woolf	p-Value	I^2 (%)	95% UI
All studies (1)	6	1.03	[0.89–1.19]	15.521	0.836×10^{-2}	68	24–86
Study design							
Cohort (2)	5	1.01	[0.88–1.16]	13.752	0.813×10^{-2}	71	26–89
Case–control (3)	1	/	/	/	/	/	/
ER status							
ER+ (4)	4	1.08	[0.95–1.22]	10.08	0.018	70	15–90
ER− (5)	4	0.98	[0.81–1.17]	4.951	0.175	39	0–79
PGR status							
PGR+ (6)	2	1.04	[0.60–1.80]	2.501	0.114	60	0–91
PGR− (7)	2	1.15	[0.88–1.49]	0.163	0.686	0	ND
Smoking status							
Never (8)	2	1.01	[0.98–1.04]	0.909	0.340	0	ND
Ever (9)	2	0.99	[0.96–1.01]	0.136	0.712	0	ND
HRT use							
Never (10)	2	0.99	[0.97–1.02]	0.009	0.924	0	ND
Ever (11)	2	1.00	[0.97–1.02]	0.295	0.587	0	ND
BMI							
<25 kg/m^2 (12)	2	1.01	[0.99–1.04]	0.580	0.446	0	ND
≥25 kg/m^2 (13)	2	0.98	[0.92–1.04]	1.171	0.279	0	ND
Zinc°							
Low (14)	2	1.02	[0.98–1.06]	0.032	0.858	0	ND
High (15)	2	1.00	[0.98–1.02]	0.054	0.817	0	ND
Iron°							
Low (16)	2	1.00	[0.95–1.06]	0.000	/	/	ND
High (17)	2	1.00	[0.98–1.02]	0.014	0.906	0	ND
Geographic location							
Europe	2	1.09	[0.87–1.35]	5.834	0.0157	82	28–96
USA	2	0.91	[0.82–1.00]	0.344	0.558	0	ND
Japan	2	1.14	[0.74–1.76]	1.522	0.217	34	ND
Sensitivity study							
All studies less Adams et al. (2012)* (18)	5	1.04	[0.88–1.21]	15.515	0.374×10^{-2}	74	36–90
All studies less Itoh et al. (2014)** (19)	5	1.01	[0.88–1.16]	13.752	0.813×10^{-2}	71	26–89
All studies less Adams et al. (2012)* and Itoh et al. (2014)** (20)	4	1.01	[0.86–1.19]	13.750	0.327×10^{-2}	78	41–92

Abbreviations: N. studies, number of studies; meta-RR, meta-rate ratio; 95% CI, 95% confidence interval; 95% UI, 95% uncertainty interval; and ND, not defined (could not be calculated).
Notes: where studies reported results for tertiles/quartiles/quintiles, the data for the highest were used. Where results were reported for several levels of adjustment, the data adjusted for the larger number of parameters was used.
Included studies were:
(1): Adams et al. (2012), Adams et al. (2014), Eriksen et al. (2014), Itoh et al. (2014), Julin et al. (2012), and Sawada et al. (2012).
(2): Adams et al. (2012), Adams et al. (2014), Eriksen et al. (2014), Julin et al. (2012), and Sawada et al. (2012).
(3): Itoh et al. (2014).
(4): Adams et al. (2012), Eriksen et al. (2014), Itoh et al. (2014), and Julin et al. (2012).
(5): Adams et al. (2012), Eriksen et al. (2014), Itoh et al. (2014), and Julin et al. (2012).
(6): Eriksen et al. (2014) and Itoh et al. (2014).
(7): Eriksen et al. (2014) and Itoh et al. (2014).
(8) to (17): Adams et al. (2012) and Eriksen et al. (2014).
(18): Adams et al. (2014), Eriksen et al. (2014), Itoh et al. (2014), Julin et al. (2012), and Sawada et al. (2012).
(19): Adams et al. (2012), Adams et al. (2014), Eriksen et al. (2014), Julin et al. (2012), and Sawada et al. (2012).
(20): Adams et al. (2014), Eriksen et al. (2014), Julin et al. (2012), and Sawada et al. (2012).
° Total intake from diet and supplement and multivitamins, cut-offs correspond to lowest quartile among all participants (Adams et al., 2012) or to the median (Eriksen et al., 2014).
* Adams et al. (2014) study participants were from 40 clinical centers across the USA, one center being located in Seattle (Western Washington state) and the participants of the study of Adams et al. (2012) were from 13-county areas in Western Washington state. As redundancy between some data from Adams et al. (2012) and Adams et al. (2014) cannot be excluded, sensitivity analysis was performed excluding the study of Adams et al. (2012).
** The participants of the study of Sawada et al. (2012) were from 9 Public Health Center areas including Nagano and the Itoh's study participants are from 4 hospitals in Nagano Prefecture. As redundancy between some data from Itoh et al. (2014) and Sawada et al. (2012) cannot be excluded, sensitivity analysis was performed excluding the study of Itoh et al. (2014).

2.3.4. Sensitivity analyses

To determine the robustness of the findings as well as to determine whether some of the decisions made had a major effect on the results of the review, sensitivity analyses were conducted. The meta-analysis of all studies was performed using both fixed and random effect methods. When redundancy between some data from different studies could not be totally excluded, sensitivity analysis was performed by excluding the smaller studies.

3. Results

3.1. Literature selection and study characteristics

The study selection process is summarized in the flow chart in Fig. 1. A total of 129 articles were retrieved from MEDLINE and hand searching in the reference lists of the relevant publications. Among these studies, 123 were excluded as they did not fulfill the inclusion criteria because they were non-English articles (n = 4), non-human studies (n = 21), or because they were reviews and/or meta-analyses (n = 22), mechanistic and genetic studies (n = 18), studies unrelated to cancer and breast cancer (n = 51), unrelated to dietary exposure (n = 3), unrelated to Cd (n = 1) or unrelated to postmenopausal women (n = 3).

The 6 remaining studies were included in present analyses. Five cohort studies (Adams et al., 2012; Adams et al., 2014; Eriksen et al., 2014; Julin et al., 2012; Sawada et al., 2012) and one case–control study (Itoh et al., 2014) were identified as fulfilling the inclusion criteria.

Table 1 provides selected characteristics of the studies included in the analysis. They were published between 2012 and 2014. The case–control study and 1 cohort study were from Japan, 2 cohort studies were from North America and 2 cohort studies from Europe.

The mean estimated Cd intake in the cohorts were between 10.9 and 15 μg/day in the European and North American cohorts and of 26.4 and 26.5 μg/day for the Japanese studies (Table 2).

Dietary intakes were assessed in all studies by using a self-administered food frequency questionnaire (FFQ) including between 67 and 192 items. Exposure categories were presented as tertiles, quartiles and quintiles. Case numbers and estimators of the relative risk (along with their CIs) for postmenopausal women to develop breast cancer after exposure to Cd were extracted from individual studies and presented in Table 3 according to the exposure. Estimators of relative risk used by the primary authors included rate ratio (RR), hazard ratio (HR), odds ratio (OR), incidence rate ratio (IRR).

3.2. Data synthesis

3.2.1. Meta-analyses

Table 4 summarizes the results of the different meta-analyses performed. The meta-rate ratio calculated according to the random effect model was 1.03 (95% CI: 0.89–1.19) for all included studies. A forest plot of the 6 studies is reported on Fig. 2.

The meta-rate ratio revealed a slight non-statistically significant increased risk of breast cancer among postmenopausal women exposed to Cd through the diet. However, the high heterogeneity and degree of inconsistency among the 6 relative risk estimates (p value of 0.836×10^{-2} and I^2 of 68%) argued against an overall meta-analysis of the data. Further analyses were therefore carried out to identify the sources of heterogeneity, stratifying studies according to different variables including tumor ER status, PGR status, smoking status, HRT use, BMI, zinc intake, iron intake and geographic location. No significant positive association between dietary Cd exposure and breast cancer in postmenopausal women was found in any subgroup.

Stratification by study design did not reveal inconsistency among studies with a cohort design.

No statistically increased risk of breast cancer was found after stratification by estrogen receptor status (ER+ or ER−). Less inconsistency/heterogeneity between study results was observed when combining data from the four studies reporting on ER− tumors (p value of 0.175 and I^2 of 39%) than when combining data from the four studies reporting on ER+ tumors (p value of 0.0179 and I^2 of 70%). Stratification according to the PGR status resulted in consistency among studies for PGR− ($I^2 = 0$; n = 2 only) but not for PGR+ as well as for Japanese and American studies but not for the European studies. Heterogeneity and inconsistency were drastically reduced after stratification for smoking status, HRT use, BMI status, zinc and iron intake but only 2 studies were available for each subgroup.

3.2.2. Sensitivity analyses

The meta-analysis performed on all studies using fixed or random effects models yielded very similar results (fixed model, mRR: 1.01, 95% CI: 0.95–1.08; random model, mRR: 1.03, 95% CI: 0.89–1.19).

Omitting studies with potentially redundant data (Adams et al., 2012 and Itoh et al. 2014) did not substantially modify the results (n = 4) (mRR: 1.01; 95% CI: 0.86–1.19) (Table 4).

3.2.3. Funnel plots and asymmetry

Funnel plot of ln(RR) versus 1/SE for the meta-analysis including all studies was constructed (Fig. 3). The visual inspection of this figure did not clearly allow detecting asymmetry arising from a lack of small studies with low RR estimators. The statistical analysis provided by the linear regression method of Egger et al. (1997) did not yield evidence of asymmetry (intercept: 0.787; 95% CI: −3.873 to 5.448) (p > 0.20).

4. Discussion

Only few studies linking dietary Cd exposure to breast cancer risk are available. Two meta-analyses were performed on data from studies including women irrespective of their hormonal status (Cho et al., 2013; Wu et al., 2015). In a subgroup analysis of their updated meta-analysis, Wu et al. (2015) combined data from 4 studies concerning postmenopausal women. The present study is, to our knowledge, the first comprehensive meta-analysis focusing exclusively on postmenopausal women and combining data from 6 studies on dietary Cd exposure and breast cancer risk.

The overall results from this meta-analysis do not suggest evidence of an association between dietary exposure to Cd and breast cancer in postmenopausal women. The risk was not statistically significant and did not vary substantially when using the fixed model or when omitting studies with potential redundancy. However, the strong heterogeneity and degree of inconsistency existing among the 6 individual risk estimates argues against conducting an overall meta-analysis, and the interpretation must be done with caution. Several differences among individual studies that may account for this heterogeneity were analyzed, including study design, geographic location or ethnicity, breast cancer type, influence of other risk factors for breast cancer like smoking status, high BMI and HRT or elements interacting with the absorption of Cd (zinc, iron).

Grouping of the studies by geographic location strongly reduced heterogeneity among Japanese studies and evidence of heterogeneity was no more observed among American studies. The main source of heterogeneity comes from the European studies. This was already observed in the meta-analysis of Wu et al. (2015) including pre- and postmenopausal women and heterogeneity was explained by the differences in adjustment factors considered in the two European studies. In a meta-analysis on breast cancer (all women) and exposure (from all sources) to Cd estimated by using different sampling methods (including hair, urine, tissue and peripheral venous blood), higher frequencies of breast cancer were observed among Cd exposed Asians compared with Caucasian population (Rahim et al., 2013). We investigated if heterogeneity could be due to ethnicity differences by combining studies with Caucasian populations (USA and European) but heterogeneity was not reduced (meta-RR: 1.02; 95% CI: 0.87–1.19; I^2: 78%).

Although breast cancers constitute a heterogeneous group of neoplasms, most epidemiologic research to date has viewed breast cancer as a single disease with the risk of diluting or masking associations for a specific form of breast cancer. Breast cancers can be classified according to the expression of estrogen receptor (ER) and/or progesterone receptor (PGR) that have different clinical, pathologic, and molecular features, and it has been suggested that breast cancers stratified by hormone receptor status are also etiologically distinct diseases (Althuis et al., 2004). Assessing risk factors for breast cancers stratified by pathologic features has raised increasing interest and showed, as an example, that reproduction-related exposures (risk factors for breast cancer) tended to be associated with increased risk of ER-positive but not ER-negative tumors. ER status was reported in 4 studies included in our meta-analysis and an elective impact of Cd exposure did not appear in ER+ tumors. After stratification of the two studies reporting tumor PGR status, no evidence of heterogeneity remained for PGR− grouping although high heterogeneity was observed for PGR+. A similar pattern of lack of evidence was observed in all other groups analyzed and stratified for risk factors including smoking status, HRT use and BMI. The combined risk estimates were close to 1, none of them being statistically significant.

The accumulation of Cd in tissues and organs of environmentally exposed individuals results most probably from the efficient absorption and systemic transport of Cd, by mechanisms developed for essential metals, most likely to be zinc (Zn^{2+}), iron (Fe^{2+}), manganese (Mn^{2+}), and calcium (Ca^{2+}) (Satarug et al., 2010). There is some mechanistic evidence that Cd competes with these metals and calcium for binding sites on cellular proteins (metallothionein) (Klaassen et al., 1999, 2009). One would expect that the association between dietary Cd intake and breast cancer would be the strongest among women with low levels of zinc, iron or calcium intake. Comparing studies that

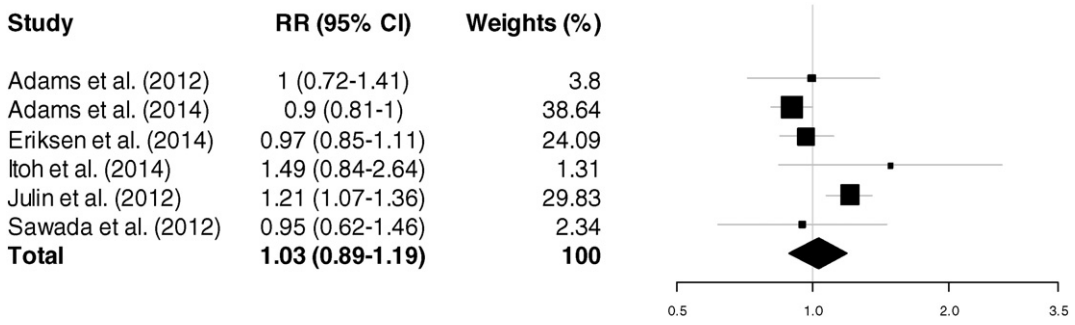

Fig. 2. Forest plot of studies on dietary exposure to cadmium and breast cancer in postmenopausal women (random effect model). Note. Estimators of RR and 95% confidence intervals (CI) of studies included in the meta-analysis "all studies" are presented. Each estimator was assigned a weight (w_i) equal to the inverse square of its standard error (SE): $w_i = 1 / (SE)^2$.

reported low and high levels of zinc or iron did not reveal risk differences. No evidence of heterogeneity was observed whatever the subgroup.

It has, however, to be stressed that the low number of studies included in the stratifications led to restricted statistical power and less precise risk estimates in some analyses.

One strength of our study is that it focuses on postmenopausal women. This study population is the most appropriate to investigate the possible impact of exogenous factors with estrogenic activity, like Cd, on breast cancer as, after menopause, exogenous estrogens are predominant. Restricting the analysis to postmenopausal women limits the impact of endogenous estrogens (produced by the ovaries) potentially unmasking the possible estrogenic influence of Cd (Strumylaite et al., 2010). Another strength of our meta-analysis is that 5 out of the 6 available studies have a prospective cohort design which reduced the recall and selection bias. Publication bias is a serious concern in meta-analysis that can be detected by funnel plot asymmetry. We found no evidence of publication bias. All included studies are recent (2012–2014) and properly conducted. For each study, estimated Cd intake is in great agreement with the mean intake reported for the general population of the respective countries (Table 2). Furthermore, several factors that may have influenced the effect of dietary Cd exposure on the development of breast cancer have been investigated, including study design, geographic location or ethnicity, breast cancer type, smoker status, high BMI, HRT, zinc and iron.

The major limitation of all included studies is the non-ability of accurately assessing individual dietary Cd intake. All these studies assessed Cd dietary intake by combining FFQ responses with national data on food Cd content. Misclassification of estimated dietary Cd may have been introduced from multiple sources including social desirability bias and poor recall bias. FFQ responses may not reflect long term dietary patterns of exposure as FFQ asked about diet in short periods prior to enrollment (3 months, 1 year). In addition, as reported by Adams et al. (2012), Cd content in food items is subject to variations as the amount of Cd absorbed by plants depends on growing location,

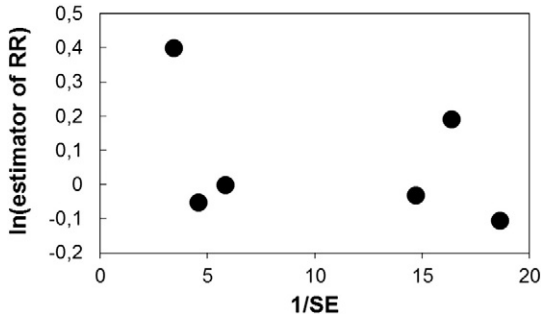

Fig. 3. Funnel plot of all studies on dietary exposure to cadmium and breast cancer in postmenopausal women. Note. Funnel plot of logarithms of relative risk (RR) estimates vs the inverse of their standard errors (1/SE) (ln of the 6 studies combined = 0.0291).

agricultural conditions as well as crop varietals (Arao and Ae, 2003; Peralta-Videa et al., 2009). Overall, measurement error in assessing of dietary Cd would be non-differential in these prospective studies and could have introduced substantial bias towards a finding of no association (Freedman et al., 2011). As a consequence, whether the no increased risk reflects a true lack of association with breast cancer or whether the results reflect non-differential exposure measurement error in the estimation of dietary Cd intake concealing a true association remains unclear. Cadmium in urine reflects the body burden and is believed to be an objective indicator for the cumulative long term exposure (Lauwerys et al., 1994). Three case–control studies (McElroy et al., 2006; Gallagher et al., 2010; Wei et al., 2015) and one prospective mortality cohort study (García-Esquinas et al., 2014) reported data on the association between urinary Cd and breast cancer among women populations including more than 85% postmenopausal women. One retrospective case–control study showed significant increased risk of breast cancer among one of their two studied populations (Gallagher et al., 2010). However, as in this study urinary Cd concentration was measured after cancer diagnosis, it has been suggested by Adams et al. (2012, 2014) that cancer treatment and changes in lifestyles due to disease status may have influenced Cd excretion. Non-significant risks were observed for the second population studied by Gallagher as well as in the two others case–control studies (McElroy et al., 2006; Wei et al., 2015). Non-significantly decreased risk was reported in the prospective mortality study (García-Esquinas et al., 2014). Apparent discrepancies among the results of these studies need further explorations. A more valid assessment of Cd exposure would be a direct measure of Cd body burden (provided by urine Cd concentration) at enrollment, before cancer diagnosis as it has be done by Wei et al. (2015).

Another limitation, also underlined by Julin et al. (2012) and common to all studies included in our meta-analysis, is that they could be subject to unmeasured confounding. Furthermore, all included studies were conducted in developed countries and in spite of the fact that they are relatively similar in exposure assessment and in study design, they represent countries with differences in dietary habits, quality of Cd monitoring data, Cd pollution levels which could have impacted these studies differently. Notably, when compared internationally, the dietary Cd intake in Japan is higher than in other countries (Table 2) but no significantly increased risk was observed in this population.

5. Conclusion

We did not detect a statistically significant increased risk of breast cancer among postmenopausal women related to dietary Cd intake. Subgroup analyses allowed identifying several sources of inconsistency between studies including geographical location, tumor ER, PGR and smoker status, HRT use, BMI, zinc and iron absorption. As studies estimating the dietary Cd intake in relation to breast cancer have only been performed during the last few years, the number of available studies is limited and stratifications led to restricted statistical power and less precise risk estimates. The concern for an increased risk of breast

cancer caused by the estrogenic activity of Cd needs further investigations with a focus on improved accuracy of individual dietary Cd intakes and differentiation of breast cancers by pathologic features.

Conflict of interest statement

This study was conducted with financial support from the International Zinc/Cadmium Association (Research agreement NP 2006 - 9/01/2015), and reflects only authors' views. NL is employed by the International Zinc/Cadmium Association.

Role of the funding source

This study was conducted with financial support from the International Zinc/Cadmium Association.

References

Adams, S.V., Newcomb, P.A., White, E., 2012. Dietary cadmium and risk of invasive postmenopausal breast cancer in the VITAL cohort. Cancer Causes Control 23, 845–854.
Adams, S.V., Quraishi, S.M., Shafer, M.M., Passarelli, M.N., Freney, E.P., Chlebowski, R.T., et al., 2014. Dietary cadmium exposure and risk of breast, endometrial, and ovarian cancer in the Women's Health Initiative. Environ. Health Perspect. 122 (6), 594–600.
Agency for Toxic Substances and Disease Registry, 2011. Potential for human exposure. Toxicological Profile for Cadmium, pp. 277–331 Available: http://www.atsdr.cdc.gov/toxprofiles/tp5-c6.pdf.
Akesson, A., Berglund, M., Schutz, A., Bjellerup, P., Bremme, K., Vahter, M., 2002. Cadmium exposure in pregnancy and lactation in relation to iron status. Am. J. Public Health 92, 284–287.
Akesson, A., Julin, B., Wolk, A., 2008. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. Cancer Res. 68, 6435–6441.
Ali, I., Penttinen-Damdimopoulou, P.E., Makela, S.I., Berglund, M., Stenius, U., Akesson, A., et al., 2010. Estrogen-like effects of cadmium in vivo do not appear to be mediated via the classical estrogen receptor transcriptional pathway. Environ. Health Perspect. 118, 1389–1394.
Althuis, M.D., Fergenbaum, J.H., Garcia-Closas, M., Brinton, L.A., Madigan, M.P., Sherman, M.E., 2004. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Epidemiol. Biomarkers Prev. 13 (10), 1558–1568.
Arao, T., Ae, N., 2003. Genotypic variations in cadmium levels of rice grain. Soil Sci. Plant Nutr. 49 (4), 473–479.
Benbrahim-Tallaa, L., Tokar, E.J., Diwan, B.A., Dill, A.L., Coppin, J.F., Waalkes, M.P., 2009. Cadmium malignantly transforms normal human breast epithelial cells into a basal-like phenotype. Environ. Health Perspect. 117, 1847–1852.
Berglund, M., Akesson, A., Nermell, B., Vahter, M., 1994. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ. Health Perspect. 102, 1058–1066.
Bertin, G., Averbeck, D., 2006. Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie 88, 1549–1559.
Brama, M., Gnessi, L., Basciani, S., Cerulli, N., Politi, L., et al., 2007. Cadmium induces mitogenic signaling in breast cancer cell by an ERalpha-dependent mechanism. Mol. Cell. Endocrinol. 264, 102–108.
Cho, Y.A., Kim, J., Wood, H.D., Kang, M., 2013. Dietary cadmium intake and the risk of cancer: a meta-analysis. PLoS One 8, e75087.
Clarke M, Oxman AD (eds). Cochrane Reviewers' Handbook 4.1 (update June 2000). In: Review Manager (RevMan) (computer program). Version 4.1. The Cochrane Collaboration 2000, Oxford, England; 2000.
CCC, Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment; Public Health England. Cadmium: general information. In: Guidance, Cadmium: health effects, incident management and toxicology. 2014. Available: https://www.gov.uk/government/publications/cadmium-properties-incident-management-and-toxicology.
Dennis, L.K., 2000. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. Prostate 42 (1), 56–66.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.
Egan, S.K., Bolger, P.M., Carrington, C.D., 2007. Update of US FDA's Total Diet Study food list and diets. J. Expo. Sci. Environ. Epidemiol. 17 (6), 573–582.
Egger, M., Davey, S.G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.
Eriksen, K.T., Halkjær, J., Sørensen, M., Meliker, J.R., McElroy, J.A., Tjønneland, A., Raaschou-Nielsen, O., 2014. Dietary cadmium intake and risk of breast, endometrial and ovarian cancer in Danish postmenopausal women: a prospective cohort study. PLoS One 9 (6), e100815.
Freedman, L.S., Schatzkin, A., Midthune, D., Kipnis, V., 2011. Dealing with dietary measurement error in nutritional cohort studies. J. Natl. Cancer Inst. 103 (14), 1086–1092.
Gallagher, C.M., Chen, J.J., Kovach, J.S., 2010. Environmental cadmium and breast cancer risk. Aging 2 (11), 804–814.
García-Esquinas, E., Pollan, M., Tellez-Plaza, M., Francesconi, K.A., Goessler, W., Guallar, E., Umans, J.G., Yeh, J., Best, L.G., Navas-Acien, A., 2014. Cadmium exposure and cancer mortality in a prospective cohort: the strong heart study. Environ. Health Perspect. 122 (4), 363–370.
Garcia-Morales, P., Saceda, M., Kenney, N., Kim, N., Salomon, D.S., et al., 1994. Effect of cadmium on estrogen receptor levels and estrogen-induced responses in human breast cancer cells. J. Biol. Chem. 269, 16896–16901.
Godt, J., Scheidig, F., Grosse-Siestrup, C., Esche, V., Brandenburg, P., et al., 2006. The toxicity of cadmium and resulting hazards for human health. J. Occup. Med. Toxicol. 1, 22.
Hardy, R.J., Thompson, S.G., 1998. Detecting and describing heterogeneity in meta-analysis. Stat. Med. 17 (8), 841–856.
Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.
Ikeda, M., Zhang, Z.W., Higashikawa, K., Watanabe, T., Shimbo, S., Moon, C.S., Nakatsuka, H., Matsuda-Inoguchi, N., 1999. Background exposure of general women populations in Japan to cadmium in the environment and possible health effects. Toxicol. Lett. 108 (2–3), 161–166.
International Agency for Research on Cancer. Cadmium and cadmium compounds. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Review of Human Carcinogens; arsenic, metals, fibres and dusts. 2012; Vol. 100c.
Itoh, H., Iwasaki, M., Sawada, N., Tabachi, R., Kasuga, Y., et al., 2014. Dietary cadmium intake and breast cancer risk in Japanese women: a case–control study. Int. J. Hyg. Environ. Health 217, 70–77.
Järup, L., Akesson, A., 2009. Current status of cadmium as an environmental health problem. Toxicol. Appl. Pharmacol. 238, 201–208.
Järup, L., Berglund, M., Elinder, C.H., Nordberg, G., Vahter, M., 1998. Health effects of cadmium exposure. a review of the literature and a risk estimate. Scand. J. Work Environ. Health 24 (Suppl. 1), 1–52.
Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., Forman, D., 2011. Global cancer statistics. Cancer J. Clin. 61, 69–90.
Jin, Y.H., Clark, A.B., Slebos, R.J., Al-Refai, H., Taylor, J.A., Kunkel, T.A., et al., 2003. Cadmium is a mutagen that acts by inhibiting mismatch repair. Nat. Genet. 34, 326–329.
Johnson, M.D., Kenney, N., Stoica, A., Hilakivi-Clarke, L., Singh, B., et al., 2003. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nat. Med. 9, 1081–1084.
Joseph, P., 2009. Mechanisms of cadmium carcinogenesis. Toxicol. Appl. Pharmacol. 238, 272–279.
Julin, B., Wolk, A., Bergkvist, L., Bottai, M., Akesson, A., et al., 2012. Dietary cadmium exposure and risk of postmenopausal breast cancer: a population-based prospective cohort study. Cancer Res. 72, 1459–1466.
Klaassen, C.D., 1981. Pharmacokinetics in metal toxicity. Fundam. Appl. Toxicol. 1, 353–357.
Klaassen, C.D., Liu, J., Choudhuri, S., 1999. Metallothionein: an intracellular protein to protect against cadmium toxicity. Annu. Rev. Pharmacol. Toxicol. 39, 267–294.
Klaassen, C.D., Liu, J., Diwan, B.A., 2009. Metallothionein protection of cadmium toxicity. Toxicol. Appl. Pharmacol. 238 (3), 215–220.
Larsen, E.H., Andersen, N.L., Moller, A., Petersen, A., Mortensen, G.K., Petersen, J., 2002. Monitoring the content and intake of trace elements from food in Denmark. Food Addit. Contam. 19 (1), 33–46.
Lauwerys, R.R., Bernard, A.M., Roels, H.A., Buchet, J.P., 1994. Cadmium: exposure markers as predictors of nephrotoxic effects. Clin. Chem. 40 (7 Pt 2), 1391–1394.
Lipsett, M., Campleman, S., 1999. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am. J. Public Health 89 (7), 1009–1017.
Liu, Z., Yu, X., Shaikh, Z.A., 2008. Rapid activation of ERK1/2 and AKT in human breast cancer cells by cadmium. Toxicol. Appl. Pharmacol. 228, 286–294.
Luevano, J., Damodaran, C., 2014. A review of molecular events of cadmium-induced carcinogenesis. J. Environ. Pathol. Toxicol. Oncol. 33 (3), 183–194.
Martinez-Campa, C., Alonso-Gonzales, C., Mediavilla, M.D., Cos, S., Gonzales, A., et al., 2006. Melatonin inhibits both ER alpha activation and breast cancer cell proliferation induced by a metalloestrogen, cadmium. J. Pineal Res. 40, 291–296.
McElroy, J.A., Shafer, M.M., Trentham-Dietz, A., Hampton, J.M., Newcomb, P.A., 2006. Cadmium exposure and breast cancer risk. J. Natl. Cancer Inst. 98 (12), 869–873.
National Food Institute, Technical University of Denmark. Chemical contaminants 2004–2011. Food monitoring 2004–2011. 2013. Report available at www.food.dtu.dk.
Peralta-Videa, J.R., Lopez, M.L., Narayan, M., Saupe, G., Gardea-Torresdey, J., 2009. The biochemistry of environmental heavy metal uptake by plants: implications for the food chain. Int. J. Biochem. Cell Biol. 41 (8–9), 1665–1677.
Rahim, F., Jalali, A., Tangestani, R., 2013. Breast cancer frequency and exposure to cadmium: a meta-analysis and systematic review. Asian Pac. J. Cancer Prev. 14 (7), 4283–4287.
Rothstein, H.R., Sutton, A.J., Borenstein, M., 2005. Publication Bias in Meta-analysis. Prevention, Assessment and Adjustment. John Wiley & Sons Ltd., The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England.
Safe, S., 2003. Cadmium's disguise dupes the estrogen receptor. Nat. Med. 9, 1000–1001.
Sartor, F., Rondia, D., Claes, F., Buchet, J.P., Ducoffre, G., et al., 1992. Factors influencing the cadmium body burden in a population study. IARC Sci. Publ. 118, 101–106.
Satarug, S., Moore, M.R., 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ. Health Perspect. 112 (10), 1099–1103.
Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. Environ. Health Perspect. 18, 182–190.
Sawada, N., Iwasaki, M., Inoue, M., Takachi, R., Sasazuki, S., et al., 2012. Long-term dietary cadmium intake and cancer incidence. Epidemiology 23, 368–376.

Scottenfeld, D., Fraumeni Jr., J.F., 2006. Cancer Epidemiology and Prevention. 3rd ed. Oxford University Press, New York, NY.
Six, L., Smolders, E., 2014. Future trends in soil cadmium concentration under current cadmium fluxes to European agricultural soils. Sci. Total Environ. 485–486, 319–328.
Stewart, R.E., Dennis, L.K., Dawson, D.V., Resnick, M.I., 1999. A meta-analysis of risk estimates for prostate cancer related to tire and rubber manufacturing operations. J. Occup. Environ. Med. 41 (12), 1079–1084.
Stoica, A., Katzenellenbogen, B.S., Martin, M.B., 2000. Activation of estrogen receptor-alpha by the heavy metal cadmium. Mol. Endocrinol. 14, 545–553.
Strumylaite, L., Mechonosina, K., Tamasauskas, S., 2010. Environmental factors and breast cancer. Medicina (Kaunas) 46, 867–873.
Templeton, D.M., Liu, Y., 2010. Multiple roles of cadmium in cell death and survival. Chem. Biol. Interact. 188, 267–275.
Vahter, M., Akesson, A., Lidén, C., Ceccatelli, S., Berglund, M., 2007. Gender differences in the disposition and toxicity of metals. Environ. Res. 104 (1), 85–95.
Van Maele-Fabry, G., Lantin, A.-C., Hoet, P., Lison, D., 2010. Childhood leukaemia and parental occupational exposure to pesticides: a systematic review ans meta-analysis. Cancer Causes Control 21, 787–809.
Van Maele-Fabry, G., Hoet, P., Vilain, F., Lison, D., 2012. Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies. Environ. Int. 46, 30–43.
Van Maele-Fabry, G., Hoet, P., Lison, D., 2013. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. Environ. Int. 56, 19–31.
Waalkes, M.P., 2003. Cadmium carcinogenesis. Mutat. Res. 533, 107–120.
Watanabe, T., Zhang, Z.W., Moon, C.S., Shimbo, S., Nakatsuka, H., Matsuda-Inoguchi, N., Higashikawa, K., Ikeda, M., 2000. Cadmium exposure of women in general populations in Japan during 1991–1997 compared with 1977–1981. Int. Arch. Occup. Environ. Health 73 (1), 26–34.
Wei, X.L., He, J.R., Cen, Y.L., Su, Y., Chen, L.J., Lin, Y., Wu, B.H., Su, F.X., Tang, L.Y., Ren, Z.F., 2015. Modified effect of urinary cadmium on breast cancer risk by selenium. Clin. Chim. Acta 438, 80–85.
Wilson, V.S., Bobseine, K., Gray Jr., L.E., 2004. Development and characterization of a cell line that stably expresses an estrogen-responsive luciferase reporter for the detection of estrogen receptor agonist and antagonists. Toxicol. Sci. 81, 69–77.
Wu, X., Zhu, X., Xie, M., 2015. Association between dietary cadmium exposure and breast cancer risk: an updated meta-analysis of observational studies. Med. Sci. Monit. 21, 769–775.
Zang, Y., Odwin-Dacosta, S., Yager, J.D., 2009. Effects of cadmium on estrogen receptor mediated signaling and estrogen induced DNA synthesis in T47D human breast cancer cells. Toxicol. Lett. 184, 134–138.