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Review article

Cadmium exposure and risk of breast cancer: A dose-response meta-analysis of cohort studies

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ABSTRACT

Background: Cadmium is a toxic heavy metal that has been implicated in breast cancer etiology, albeit with inconsistent results.
Objective: To investigate the shape of the relation between cadmium exposure and breast cancer incidence and mortality in cohort studies.
Data sources: Following a literature search through April 14, 2020, we carried out a systematic review and dose-response meta-analysis to investigate the shape of the relation between cadmium exposure (assessed either through diet or urine excretion) and disease incidence and mortality.
Study eligibility criteria: For inclusion, a study had to report incidence or mortality for breast cancer according to baseline cadmium exposure category; be a prospective cohort, case-cohort or nested case-control study with a minimum one-year follow-up, and reporting effect estimates for all exposure categories.
Study appraisal and synthesis methods: Studies were evaluated using the ROBINS-E risk of bias tool. The effects in humans were assessed quantitatively using one-stage dose-response meta-analysis in a random effects meta-analytical model.
Results: We identified 10 studies eligible for inclusion in the dose-response meta-analysis, six based on cadmium dietary intake, and four on urinary excretion levels. We found a marginal and imprecise positive relation between dietary cadmium intake and breast cancer, and no association when urinary cadmium excretion was used for exposure assessment. Compared to no exposure, at 20 μg/day of cadmium intake the summary risk ratio was 1.12 (95% confidence interval 0.80–1.56), while at 2 μg/g creatinine of cadmium excretion the summary risk ratio was 0.89 (95% confidence interval 0.38–2.14). Analysis restricted to post-menopausal women showed no association between either dietary or urinary cadmium and subsequent breast cancer incidence and mortality.
Limitations and conclusions: Overall, we found scant evidence of a positive association between cadmium and breast cancer. Available data were too limited to carry out stratified analyses according to age, smoking and hormone receptor status. Therefore, possible associations between cadmium exposure and breast cancer in selected subgroups cannot be entirely ruled out.

1. Introduction

Cadmium is a heavy metal toxic for humans with both natural and anthropogenic sources (ATSDR, 2012). In subjects not occupationally exposed, diet and smoking are the main sources of exposure (ATSDR, 2012; Filippini et al., 2018). In particular, higher levels of cadmium may occur in women due to increased absorption in relation to low levels of iron, and in older subjects due to accumulation of cadmium,

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particularly in liver and kidney (Berglund et al., 1994; Filippini et al., 2020; Jarup et al., 1983). Cadmium has been associated with increased risk of chronic diseases including cancer (Akesson et al., 2014; Filippini et al., 2019b; Satarug et al., 2017b; Tinkov et al., 2017; Tinkov et al., 2018). The International Agency for Research on Cancer classified cadmium as carcinogenic to humans (Group I) due to its capacity to increase risk of lung cancer, and possibly kidney and prostate cancer (IARC, 2012). Cadmium has also been suspected to increase the risk of several other cancers, including gynecologic ones (Adams et al., 2014; McElroy and Hunter, 2019; Vu et al., 2019). The latter association is made plausible by the estrogen-like properties exhibited by this metal (Ali et al., 2012; Ali et al., 2016; Kluxen et al., 2013), along with other mechanisms, including increased migration and epithelial-mesenchymal transition of breast cancer cell (Shan et al., 2018; Wang et al., 2019; Wei et al., 2018). In addition, cadmium has been associated with genotoxic effects through the production of reactive oxygen species (ROS), and with epigenetic alterations including DNA methylation and histone modification, leading to reduction of the antioxidative defense in breast cells (Cannino et al., 2008; Luevano and Damodaran, 2014). The possibility that cadmium exposure may increase the risk of breast cancer has been extensively investigated through recent epidemiological studies based on very different indicators of exposure, although with inconsistent results (Amadou et al., 2020; Gaudet et al., 2019; Grioni et al., 2019; Jablonska et al., 2017; Jouybari et al., 2018; Larsson et al., 2015; O'Brien et al., 2019; Strumylaite et al., 2019; Van Maele-Fabry et al., 2016; White et al., 2019a). These studies have been heterogeneous with reference to study design, indicators of cadmium exposure and outcome (incidence or mortality from breast cancer overall considered, or in relation to specific subtypes). Most epidemiological studies have based exposure assessment on dietary evaluation of cadmium intake or on urinary excretion of the heavy metal, which is the most reliable biomarker of exposure (Akesson et al., 2014; Satarug et al., 2017a). Case-control studies assessing this possible relationship have also been challenged for methodological reasons, since the disease-related metabolic alterations and an impairment in nutritional status may lead to changes in circulating levels of trace elements, including cadmium (Jablonska et al., 2017; Zaroukian et al., 2005), thus raising the issue of reverse causation.

Due to lack of dose-response meta-analyses of cohort studies assessing the relation between cadmium exposure and breast cancer, and the recent availability of advanced biostatistical techniques which are being tested in risk assessment provided that enough studies with category-specific risk estimates are available (Adani et al., 2020; Crippa et al., 2019; Filippini et al., 2019a; Larsson and Orsini, 2018; Lugo et al., 2018; Vinceti et al., 2018), we carried out a dose-response meta-analysis to investigate the shape of the relation between dietary and urinary cadmium exposure with breast cancer incidence and mortality in prospective cohort studies.

2. Methods

2.1. Literature search

We performed online literature searches in the PubMed, Embase and Web of Science databases until 14 April 2020. The research question was configured according to PECOS statement (Population, Exposure, Comparator(s), Outcomes, and Study design - "Is cadmium exposure positively associated with female breast cancer incidence and mortality in prospective cohort studies, also taking into account the different levels of exposure?") (Morgan et al., 2018), by using search terms related to "cadmium" and "breast cancer". Details about the search terms are reported in Supplemental Table S1. Reference lists were further screened to identify additional literature, with the application of citation chasing techniques including reference list scanning of included studies and of previous reviews, as well as backward and forward citations of included studies (Booth, 2008; European network for Health Technology Assessment (EUnetHTA) 2017).

A study was considered eligible if: (1) exposure to cadmium was assessed through a long term indicator of exposure, i.e. assessment of dietary intake or urinary levels (Akesson et al., 2014; Nawrot et al., 2010); (2) the outcome of interest was breast cancer incidence and mortality; (3) it was a prospective cohort, case-cohort or nested case-control study with a minimum one-year follow-up; (4) risk estimates were provided using incident rate ratio (IRR), hazard ratio (HR), rate/risk ratio (RR) or odds ratio (OR), along with the corresponding 95% confidence interval (CI); and (5) effect estimates were reported for all exposure categories (either based on fixed cutpoint or percentiles), and not for some of them only, or for continuous exposure. Case-control studies with controls not recruited from the same cohort that generated the breast cancer cases, cross-sectional and animal studies were not considered. The studies were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org). At least two authors reviewed all titles and abstracts independently. When there was disagreement between two authors, a final decision was reached through the intervention of a third author. No language restriction was applied to the search strategy.

2.2. Risk of bias assessment

The quality of the included studies was assessed independently by all authors from the University of Modena and Reggio Emilia, the University of Athens, and the University of Porto, using the preliminary Risk of Bias (RoB) in Non-randomized Studies of Exposures (ROBINS-E) tool (Morgan et al., 2019). Seven domains were covered including: (1) bias due to confounding; (2) bias in selecting participants in the study; (3) bias in exposure classification; (4) bias due to departures from intended exposures; (5) bias due to missing data; (6) bias in outcome measurement; (7) bias in the selection of reported results. Each domain was characterized as low, moderate, serious or critical risk of bias. We report in Supplemental Table S2 the criteria for risk of bias evaluation. In case of disagreement between assessors, we assigned the rate which obtained the majority of the approvals.

2.3. Data extraction

The following data were extracted by two independent researchers (MIK, TF) and checked by a third author (CC) for each eligible study: (1) first author name; (2) publication year; (3) location; (4) duration of follow-up; (5) exposure of interest (dietary intake or urinary excretion of cadmium); (6) recruitment period; (7) date of outcome assessment; (8) information about the outcome of interest (breast cancer incidence and mortality); (9) cut-off values for each category of exposure; (10) number of cases; (11) sample size; (12) adjustment variables in multivariable analysis; (13) risk estimates with 95% CIs from the most adjusted model.

2.4. Data analysis

We performed a meta-analysis based on categorical exposure to cadmium, i.e. to the RRs from each study obtained by comparing the highest versus the lowest exposure category. When more than one study was carried out on the same cohort and used the same biomarker, we included in the analysis only the latest report. We applied a random effects model (DerSimonian and Laird, 1986), and we assessed heterogeneity using the I^2 statistic (Higgins et al., 2003).

We used the methodology established by Greenland and Longnecker (1992) and recently developed by Orsini et al. (2012) and Crippa et al. (2019) to explore the shape of the relation between exposure to cadmium and breast cancer, stratifying for exposure assessment method (reported dietary intake vs urinary excretion). For each exposure category, we extracted the mean or the median depending on the availability of the data provided by the authors. In cases where this

information was missing, we used the midpoint of each exposure strata. When the highest and lowest exposure categories were 'open', we used as boundary a value that was 20% and 15% higher or lower than the closest cutpoint. In order to investigate the association between exposure and the outcome of interest, we applied the one-stage approach for dose-response meta-analysis (Crippa et al., 2019; Orsini et al., 2012). We used a restricted cubic spline model with 3 knots at fixed percentiles (10, 50, and 90%) of the overall distribution of the dose according to Harrell's method (Harrell, 2001), and using a generalized least-squares regression taking into account the correlation within each set of published effect estimates (Crippa et al., 2019; Orsini et al., 2012). Furthermore, we pooled study-specific estimates using the restricted maximum likelihood method in a random-effects meta-analysis (Jackson et al., 2010; Orsini et al., 2006; Orsini et al., 2012). We also carried out a stratified analysis according to women's menopausal status.

We checked for the possible presence of publication bias using funnel plots for studies reporting highest versus lowest exposure. In sensitivity analyses, we used an alternative estimate (i.e. 15% instead of 20%) for the highest and lowest exposure categories with unknown mean/median values. We provided a graphical overlay of study-specific predicted curves including fixed and random effects showing the influence of variation across studies (Crippa et al., 2019), and we assessed the presence of a linear trend (Orsini et al., 2012). We used Stata 16.1 software (Stata Corp. TX, 2019) for all data analyses, and specifically the 'metan' and 'metafunnel' routines for highest versus lowest meta-analysis and 'mkspline', and 'drmeta' routines for the dose-response analysis.

We evaluated the overall certainty of the evidence according to the GRADE approach (Atkins et al., 2004), which takes in account issues related to both internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity such as directness of the results. We used the GRADEPro GDT (https://gradepro.org) to present a certainty assessment and summary of findings table. Finally, our review was implemented using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement checklist (Moher et al., 2011) reported in Supplemental Table S3.

3. Results

The PRISMA flow-chart of the literature search is presented in Fig. 1. We retrieved 752 unique studies, from which 718 were excluded after title and abstract screening, leaving 34 studies for full-text assessment. Based on full-text evaluation, we additionally excluded 24 studies, including one study (Adams et al., 2012b) carried out on the same population of one subsequently published study (Lin et al., 2013) we included in the review. Details of reasons for exclusion are reported in Fig. 1: excluded studies either did not employ a cohort design, or they solely provided information of possible mechanisms. Otherwise, they were reviews or conference abstracts of subsequent included studies. Finally, for lack of compliance with the study protocol we excluded the only one study assessing blood cadmium levels (Gaudet et al., 2019) and the four studies using environmental air cadmium for exposure assessment: one reporting correlations between air emissions and incidence of breast cancer across US states (Vu et al., 2019), one study not reporting cadmium levels across increasing categories of exposure (White et al., 2019a), and the remaining two studies implementing different and non-comparable assessment methods, namely non-cumulative (Liu et al., 2015) and cumulative cadmium exposure (Amadou et al., 2020).

Table 1 presents details about the characteristics of the eligible studies which we eventually considered in the dose-response meta-analysis. Five studies were conducted in the US (Adams et al., 2012a; Adams et al., 2014; Adams et al., 2016; Garcia-Esquinas et al., 2014; Lin et al., 2013), four in Europe (Eriksen et al., 2014; Eriksen et al., 2017; Grioni et al., 2019; Julin et al., 2012) and one in Japan (Sawada et al., 2012). We included four studies assessing cadmium exposure using urine levels (Adams et al., 2016; Eriksen et al., 2017; Garcia-Esquinas et al., 2014; Lin et al., 2013), and six using dietary intake (Adams et al., 2012a; Adams et al., 2014; Eriksen et al., 2014; Grioni et al., 2019; Julin et al., 2012; Sawada et al., 2012). Eight studies assessed breast cancer incidence (Adams et al., 2012a; Adams et al., 2014; Adams et al., 2016; Eriksen et al., 2014; Eriksen et al., 2017; Grioni et al., 2019; Julin et al., 2012; Sawada et al., 2012), and two mortality (Garcia-Esquinas et al., 2014; Lin et al., 2013).

Detailed and summary RoB assessment with single-item evaluation and overall study-level risk of bias is reported in Supplemental Tables S4 and S5. Overall, none of the included studies was at high risk of bias. All studies accounted for age and body mass index (or both height and weight). All studies but one (Julin et al., 2012) included smoking habits in the model, although the authors of this single study reported that the addition of smoking to the multivariable model did not substantially change estimates. One study did not adjust for the use hormone replacement therapy (Grioni et al., 2019). All studies assessing exposure through urine levels reported creatinine-adjusted values, while all but one (Eriksen et al., 2014) among studies using dietary intake presented energy-adjusted estimates and/or included total energy intake in the multivariable model. Two studies out of four (Garcia-Esquinas et al., 2014; Lin et al., 2013) using urinary cadmium excretion focused on breast cancer mortality, while all studies assessing dietary cadmium intake considered incidence as the outcome.

The meta-analysis comparing the highest versus the lowest exposure category showed no association of urine cadmium levels with incidence or mortality for breast cancer (RR = 1.01, 95% CI 0.70–1.47), as well as little evidence of a positive association with dietary intake (RR = 1.04, 95% CI 0.90–1.21 – Supplemental Fig. S1). In the dose-response meta-analysis, only two studies reported a median value for each exposure categories (Grioni et al., 2019; Sawada et al., 2012). In all other studies, we entered the mean values in intermediate categories and a value 20% higher or lower than the closest cutpoints in open boundaries. In the analysis considering all women independently from menopausal status (Fig. 2), we detected a null association between incidence and mortality for breast cancer and urinary cadmium (RR = 0.96, 95% CI 0.57–1.59, at 1 μg/g creatinine and 0.89, 95% CI 0.37–2.14 at 2 μg/g creatinine). Conversely, we found a marginal and statistically imprecise positive association between dietary cadmium and breast cancer (RR = 1.04, 95% CI 0.81–1.33 at 10 μg/day, and 1.12, 95% CI 0.80–1.56 at 20 μg/day).

In the dose-response meta-analysis restricted to post-menopausal women only, there was little evidence of any association between exposure and breast cancer either using dietary assessment methods or urinary excretion (Fig. 3). Conversely, the comparison of the highest versus lowest category in this subgroup indicated no association based on dietary cadmium, and a weak positive association based on urinary cadmium excretion (Supplemental Fig. S2). The analysis restricted to pre-menopausal women could only include two studies assessing dietary cadmium intake, fewer than the number needed for a dose-response spline regression analysis, but enough for a meta-analysis comparing extreme exposure categories. The latter analysis showed little association between exposure and breast cancer incidence (RR = 1.12, 95% CI 0.44–2.87 – Supplemental Fig. S3), based on opposite results in the two studies. For urinary cadmium, stratified analysis based on outcome assessment (incidence vs. mortality) showed limited evidence of any difference between the two outcomes, despite a slightly higher risk ratio for the latter (RR = 0.96, 95% CI 0.68–1.36; RR = 1.18, 95% CI 0.32–4.33, respectively – Supplemental Fig. S4). In a sensitivity analysis entering a ± 15% value instead of 20% for open boundaries in exposure categories, we found comparable results (Supplemental Fig. S5).

We also reported study-specific dose-response relations from leave-one-out analysis in addition to the overall dose-response meta-analyses, which were particularly heterogeneous for estimates based on dietary

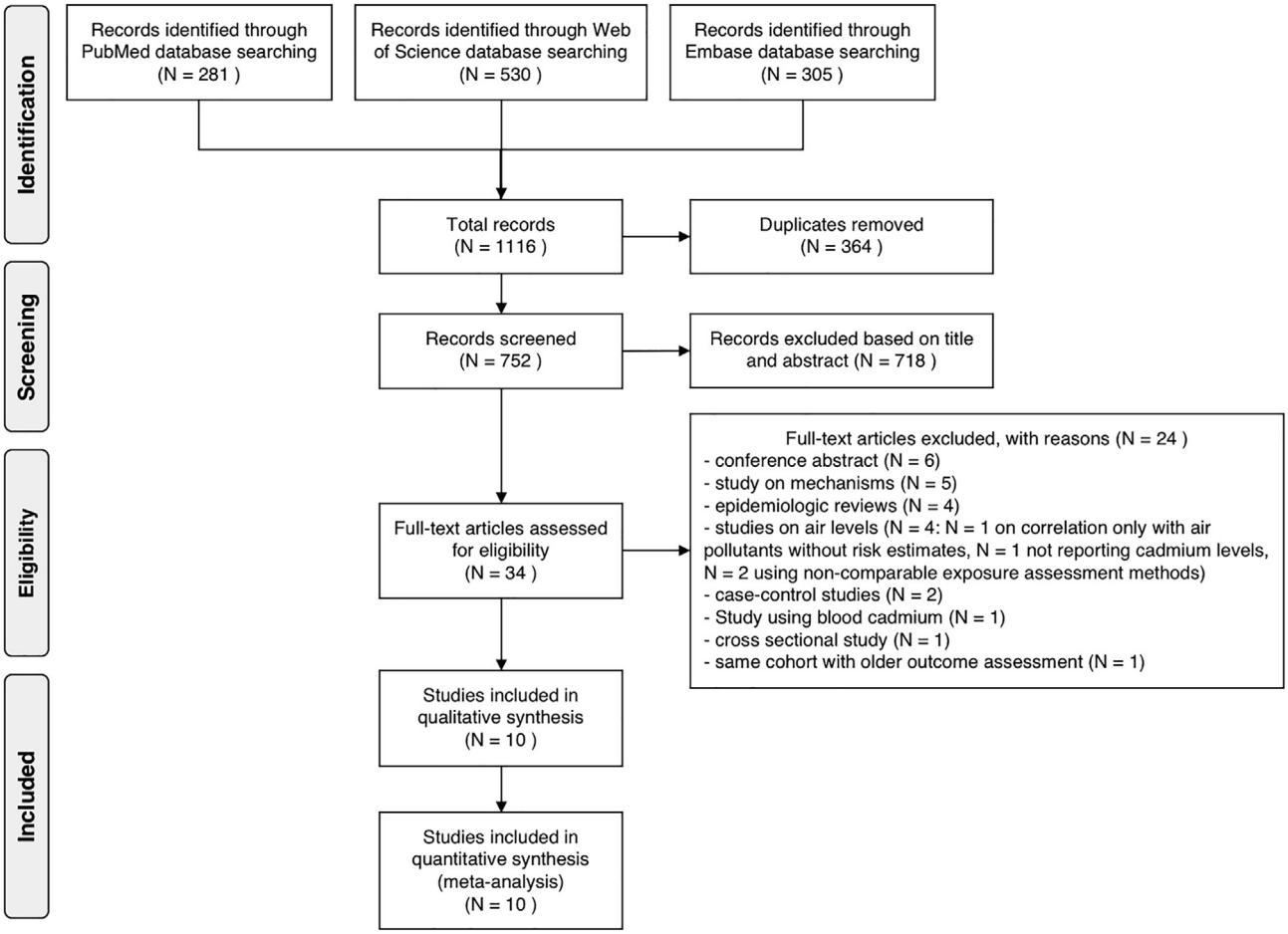

Fig. 1. Flow-chart of systematic literature search on cadmium exposure and breast cancer until 14 April 2020.

cadmium (Supplemental Fig. S6). Linear regression analysis of the relation between cadmium exposure and breast cancer showed a substantially comparable pattern compared with the overall spline analysis (Supplemental Fig. S7).

Funnel plots based on the different exposure assessment methods showed a substantially symmetric distribution and yielded little evidence of publication bias. Due to the low number of publications, however, such bias could not be entirely ruled out (Supplemental Fig. S8).

Finally, the GRADE assessment showed low-certainty of the evidence for an enhanced breast cancer incidence and mortality induced by both dietary and urinary cadmium exposure, due to directness of the exposure assessment based on cadmium evaluation, a generally imprecise effect due to the width of 95% confidence interval, lack of serious risk of bias, no substantial publication bias, and the presence of a moderate/serious inconsistency of results, an imprecise and not large effect with no dose-response gradient (Table 2).

4. Discussion

Overall, we did not find evidence to link higher cadmium exposure to an enhanced incidence and mortality for breast cancer, both in dichotomous, traditional meta-analysis and in dose-response spline regression meta-analysis. In the latter, we found some though very imprecise evidence of a weak positive association for the highest dietary cadmium intake (above 20 μg/day approximately). However, this finding was not replicated by the analysis based on the biomarker, that is cadmium urinary excretion. This indicator had a major advantage: it took into account all sources of exposure, including active and passive smoking and more generally air pollution, as well as long-term and slow cadmium release by organs such as the kidneys (Akesson et al., 2014; Satarug et al., 2017a). Therefore, estimates based on dietary intake assessment could have been biased by methodological limitations in the evaluation of exposure including exposure misclassification due to changes of dietary habits over time. In fact, these studies considered exposure at a single point in time, which cannot probably reflect exposure variation over a long period of time (Filippini et al., 2016; Satarug et al., 2017a), and in addition they could have suffered from residual, unmeasured confounding. An alternative hypothesis is that a positive association actually existed between cadmium dietary intake and cancer risk, but that such association is no longer detectable when exposure assessment is based on a biomarker such as urinary cadmium, either for limitations of the biomarker or for residual confounding. However, urinary cadmium is considered to be a reliable biomarker of exposure to this heavy metal (Akesson et al., 2014; Satarug et al., 2017a). Also, generally high correlation is found between urinary cadmium levels in samples collected in the same subjects 4–6 years apart (Meliker et al., 2019). Nonetheless, we cannot entirely rule out that factors such as changes in smoking habits or occurrence of diseases characterized by increased excretion of proteins may produce short-term changes in urinary cadmium levels, thus influencing exposure assessment based on urinary cadmium excretion (Vacchi-Suzzi et al., 2016).

The absence of evidence for an association between overall cadmium exposure and breast cancer was even stronger when we limited the analysis to studies in post-menopausal women only. This is in keeping with the hypothesis that breast cancer risk factors or effect modification by age could differ according to age of disease onset or

Table 1
Characteristics of the studies included in the review.

Reference	Region	Cohort	Recruitment period	Outcome: date - duration follow-up	Cases/ population	Population (age range)	Cadmium levels	Adjustment factors
Dietary cadmium								
(Adams et al., 2012a)	US	VITamins And Lifestyle (VITAL) cohort	2000–2002	Incidence: 31 December 2009–7.5 years	899/26,801	All post-menopausal women (50–76)	Mean (SD): 10.9 (4.9), range 0.5–55.7 μg/day	age, total energy intake, education, race, hormone replacement therapy use (combined estrogen and progesterone), vegetable consumption (excluding potatoes), potato consumption, whole grain consumption, cigarette smoking, body mass index, physical activity, alcohol consumption, age at first childbirth, multivitamin use, and mammography
(Adams et al., 2014)	US	Women's Health Initiative (WHI)	1993–1998	Incidence: August 2009–10.5 years	6,658/150,889	All post-menopausal women (50–79)	Mean: 10.9, range 0.02–59.4 μg/day	total energy intake (residual method), age and study component (observational, clinical trial), body mass index, smoking, alcohol consumption, race/ethnicity, education, physical activity, age at first birth, age at menarche, age at menopause, unopposed estrogen use, estrogen and progesterone use, mammography 2 years before baseline, daily vegetable servings, and daily grain servings
(Eriksen et al., 2014)	Denmark	Danish Diet Cancer and Health Cohort (DCH)	1993–1997	Incidence: 31 December 2010–13 years	1,390/23,815	All post-menopausal (50–65)	Median (5th-95th): 13.4 (8–22) (μg/day)	age, educational level, smoking status, number of births, age at first birth, hormone replacement therapy status and use, age at menarche, body mass index, height, physical activity, and alcohol intake
(Julin et al., 2012)	Sweden	Swedish Mammography Cohort (SMC)	1987–1990	Incidence: 31 December 2008–12.2 years	2,112/55,987	All post-menopausal (42–76)	Mean (SD): 15 (3.2) μg/day	age, adult height, body mass index, > 12 years of education, use of oral contraceptives, use of post-menopausal hormones, age at menarche, age at menopause, parity, age at first birth, alcohol consumption, glycemic load, and total energy intake
(Sawada et al., 2012)	Japan	Japan Public Health Center-based Prospective Studies I and II	1990 (I) 1993–1993 (II)	Incidence: 31 December 2006–9 years	402/48,351	Pre- and post-menopausal (45–74)	Mean: 26.5 μg/day	age, area, body mass index, smoking status, frequency of alcohol intake, leisure-time physical activity, intake of meat, soybean, vegetable, and fruit, menopausal status, and use of exogenous female hormones, residual method for energy adjustment of cadmium intake
(Grioni et al., 2019)	Italy	hormones, diet, and the etiology of breast cancer (ORDET)	1987–1992	Incidence: 31 December 2012–22.1 years	481/8,924	Pre- and post-menopausal (34–70)	Mean (SD): 7.8 (1.4), range 0.5 to 16.1 μg/day	age, energy intake, menopausal status, age at menarche, height, body mass index, age at first childbirth, smoking status, years of education, alcohol, vegetable intake, dietary iron, calcium, and zinc
Urinary cadmium								
(Adams et al., 2016)	US	Women's Health Initiative (WHI)	1993–1998	Incidence: 30 September 2010–13.2 years	508/1,050	All post-menopausal women (50–79)	Mean (SD): 0.63 (0.50), median (IQR): 0.51 (0.33–0.77) μg/g creatinine)	age, WHI study component (Observational Study or ClinicalTrials), age at first birth, age at menopause, family history of breast cancer, smoking status, pack-years of smoking, body mass index, education, alcohol consumption, WHI Hormone Therapy Trial arm, and hormone therapy use
(Eriksen et al., 2017)	Denmark	Danish Diet Cancer and Health Cohort (DCH)	1993–1997	Incidence: 31 December 2011 - > 13 years	900/23,379 (898 nested)	All post-menopausal (50–65)	Median (5th-95th): 0.54 (0.14–1.94) μg/g creatinine)	age (by matching), educational level, number of births, age at first birth, hormone replacement therapy status and use, height, weight, physical activity, and alcohol intake, smoking status, intensity and duration
(Garcia-Esquinas et al., 2014)	US	Strong Heart Study (SHS)	1989–1991	Mortality: 31 December 2008–17.2 years	25/2,254	Pre- and post-menopausal (45–74)	Median (IQR): 0.93 (0.61–1.46) μg/g creatinine)	age, smoking status, cigarette pack-years, body mass index, menopausal status, parity, and hormonal replacement therapy
(Lin et al., 2013)	US		1988–1994	Mortality: 31 December 2007–12.4 years	26/2,730	All post-menopausal (≥50)	Median (IQR): 0.77 (0.47–1.27) μg/g creatinine)	stratified by age at baseline and adjusted for race/birthplace and the following covariates ascertained

(*continued on next page*)

Table 1 (*continued*)

Reference	Region	Cohort	Recruitment period	Outcome: date - follow-up	duration	Cases/ population	Population (age range)	Cadmium levels	Adjustment factors
		Third National Health and Nutrition Examination Survey (NHANES III)							at baseline: family history of breast cancer, age at menarche, age at first full term pregnancy, the combined variable of menopausal status and hormone therapy use status, alcohol consumption, total pack years of smoking, strenuous physical activity. and body mass index

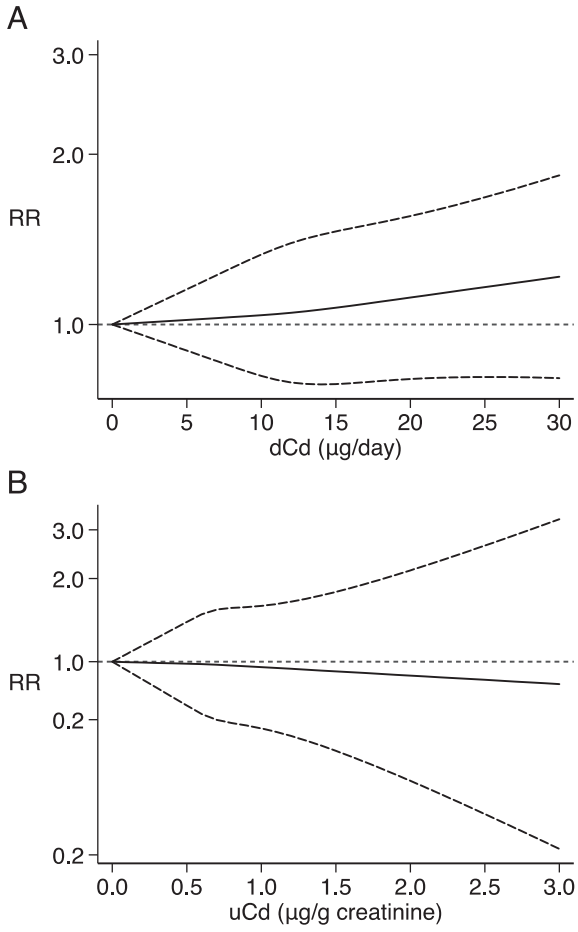

Fig. 2. Dose-response meta-analysis between cadmium exposure and breast cancer using dietary intake – dCd (A) or urine levels – uCd (B) in all women. Spline curve (solid line) with 95% confidence limits (dashed lines). RR: risk ratio.

menopausal status (Strumylaite et al., 2010). In such a subgroup, in fact, dietary cadmium also showed little association with breast cancer. Conversely, we could not carry out a specific analysis for pre-menopausal women due to a lack of data for the latter. However, the dichotomous meta-analysis based on the comparison of extreme categories of exposure for pre-menopausal women did not yield results suggestive of an association in this subgroup as well.

The substantial lack of association between cadmium exposure and breast cancer incidence and mortality we detected in this dose-response meta-analysis is not entirely surprising, given the most recent results of other studies testing this association based on exposure assessment with blood or air cadmium levels (Amadou et al., 2020; Gaudet et al., 2019; Liu et al., 2015; Vu et al., 2019; White et al., 2019b). In particular, the only study on breast cancer that assessed cadmium exposure using blood levels drawn from three different cohorts (Gaudet et al., 2019) found an inverse association RR = 0.59 (95% CI 0.39–0.91) when comparing the highest versus the lowest exposure category. In addition, despite some biological plausibility of such association based on some toxic properties of the heavy metal, such as estrogenicity, reactive oxygen species production and DNA damage (Akesson et al., 2014), other studies highlighted cadmium properties compatible with even a reduced risk of breast cancer. Such effects are cadmium-induced lower estradiol levels or adverse effects of the metal on angiogenesis and cell viability, properties which might explain recently reported inverse associations between cadmium exposure and breast cancer (Amadou et al., 2020; Gaudet et al., 2019).

Because of the lack of data, we could not assess using dose-response

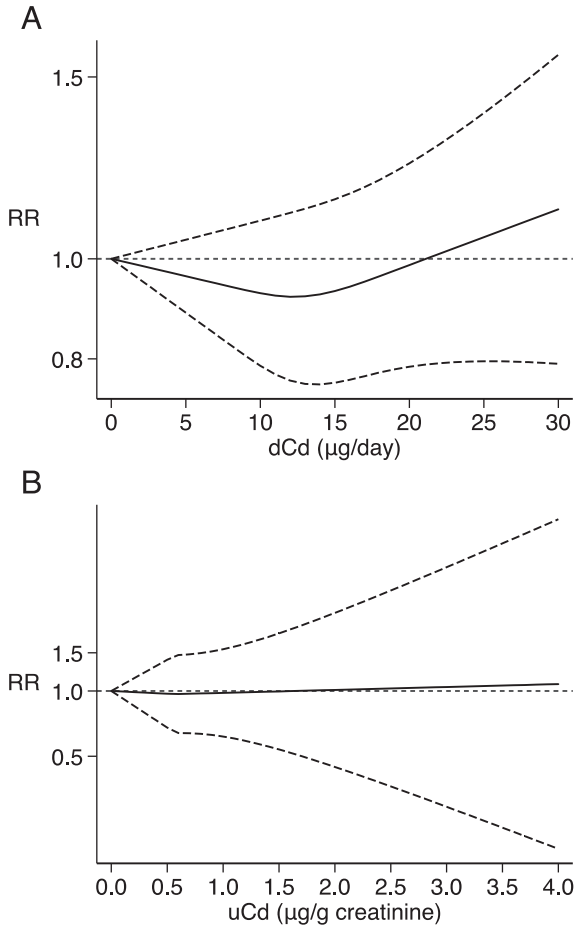

Fig. 3. Dose-response meta-analysis between cadmium exposure and breast cancer using dietary intake – dCd (A) or urine levels –uCd (B) in post-menopausal women. Spline curve (solid line) with 95% confidence limits (dashed lines). RR: risk ratio.

meta-analysis the role of confounding factors such as body mass index and smoking habits or whether cadmium exposure may play a role in the induction of specific breast cancer subtypes based on hormone receptor status. This is particularly so if cancer subtypes are rare enough compared with the remaining disease forms and therefore unable to modify the overall shape of the relation. Some studies suggested that the hormone receptor status of breast cancer may modify the association, although other reports found little support for this (Amadou et al., 2020; Grioni et al., 2019; Julin et al., 2012; Van Maele-Fabry et al., 2016). In addition, our meta-analysis included studies assessing both breast cancer incidence and mortality and this may have introduced some heterogeneity in the summary risk estimates, since different etiological factors may be implicated in the onset of or the death from breast cancer.

We consider the dose-response modelling of the association between cadmium exposure and breast cancer incidence and mortality as main strength of this review. To the best of our knowledge, this was performed only once, based on urinary cadmium excretion only and on a smaller number of studies compared with those we could retrieve (Larsson et al., 2015). Conversely, we must acknowledge some heterogeneity among the included studies: this includes the use of mortality as a surrogate for incidence in two of the four studies based on urinary cadmium. Unfortunately, only two studies investigated the association between urinary cadmium excretion and breast cancer incidence, hampering us from carrying out the dose-response analysis excluding breast cancer mortality. Also, the higher heterogeneity may be due to different menopausal status of studies populations. However,

Table 2
Summary of findings table. Research question: "Is cadmium exposure positively associated with female breast cancer incidence and mortality in prospective cohort studies, also taking into account the different levels of exposure?". Assessment in all women, divided by exposure assessment methods: dietary cadmium (dCd) and urinary excretion (uCd).

Certainty assessment								Summary of findings					Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		No. of patients		Effect		Certainty	
								Cadmium	Low exposure	Relative (95% CI)	Absolute (95% CI)		
6	Observational (cohort) dCd	Not serious	Serious[a]	Not serious	Serious[b]	No publication bias detected, not large effect, no serious confounding, no dose-response gradient.		2987/293835 (1.0%)	2791/296133 (0.9%)	**RR 1.04** (0.90 to 1.21)	**38 more per 100.000** (from 94 fewer to 198 more)	+ VERY LOW	IMPORTANT[c]
4	Observational (cohort) uCd	Not serious	Serious[a]	Not serious	Serious[b]	No publication bias detected, not large effect, no serious confounding, no dose-response gradient		443/2480 (17.9%)	409/2021 (20.2%)	**RR 1.01** (0.70 to 1.47)	**202 more per 100.000** (from 6.071 fewer to 9.512 more)	+ VERY LOW	IMPORTANT[c]

[a] Heterogeneity greater than moderate.
[b] Serious imprecision due to the width of 95% confidence interval.
[c] Important since breast cancer is one of the most prevalent malignancy and the leading cause of death from cancer among women, but not critical due to the presence of therapeutic alternatives positively affecting disease prognosis.

the subgroup analysis suggested no major effects of this potential source of heterogeneity on the summary risk estimates, while such estimates were statistically too unstable to rule out slightly positive associations. Another limitation of our assessment may derive from the inclusion of vegetable consumption in the potential confounders adjusted for some studies based on dietary cadmium assessment (Adams et al., 2012a; Adams et al., 2014; Grioni et al., 2019; Sawada et al., 2012), and of smoking in all studies based on urinary cadmium. These two are the most important sources of cadmium exposure in non-occupationally exposed individuals (ATSDR, 2012; Filippini et al., 2018; IARC, 2012). Therefore, adjustment for these factors, despite improving confounding control, may have led to overadjustment by decreasing the gradient in exposure, thus contributing to the lack of detection of any relation between exposure and risk in both the single studies and our meta-analysis. Unfortunately, risk estimates stratified by smoking or vegetable intake were not available in sufficient numbers to carry out dose-response meta-analyses in selected subgroups, such as non-smokers or smokers. However, there was some sparse evidence of possible relations in such subgroups in single studies, such as the increased breast cancer risk found in smokers with the highest urinary cadmium levels but not in never-smokers in the study by Eriksen et al. (Eriksen et al., 2017), suggesting the need to further investigate this issue. We cannot also rule out that some non-differential exposure misclassification may have occurred, likely biasing the risk estimates towards the null and hampering the detection of any possible weak association between cadmium and breast cancer. We also note that several case-control studies have reported increased odds of breast cancer in women with the highest cadmium exposure as compared to those in the lowest exposure categories (Gallagher et al., 2010; Itoh et al., 2014; McElroy et al., 2006; Nagata et al., 2013; Strumylaite et al., 2019). This study design is however hampered by sources of bias, including (but not limited to) reverse causation due to dietary changes in patients or disease-induced changes in cadmium metabolism.

5. Conclusions

Overall, we found no relation between the investigated levels of cadmium exposure and breast cancer incidence and mortality. Nevertheless, due to the lack of enough data on smoking and hormone receptor status to carry out stratified analyses, possible associations between cadmium exposure and breast cancer in selected subgroups cannot be entirely ruled out.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105879.

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