CADMIUM EXPOSURE AND RISK OF BREAST CANCER: A META-ANALYSIS

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Background and aims

Cadmium (Cd) is a toxic metal with estrogenic activity and established human carcinogenicity, but several uncertainties still exist about the amounts of relevant exposure and particularly the cancer types involved. Systematic review and meta-analysis were performed in order to investigate the role of cadmium on breast cancer incidence.

Methods

We carried out a systematic search in the PubMed-Medline database in April 2015, using as MeSH terms 'cadmium', 'breast cancer', or 'breast tumor'. Further inclusion criteria were: breast cancer as an outcome, cohort and case-control design, exposure assessment including dietary, urinary and air Cd (no blood-tissue), RR and corresponding 95% CI reported for highest versus lowest category.

Overall, 22 studies meet final inclusion criteria:

- ❑ Design: 8 cohort studies and 7 case-control studies.
- ❑ Exposure assessment: 7 (5-1) dietary intake, 7 (2-5) urine concentrations and 1 (1-0) air levels.

We performed a meta-analysis according to study design and type of Cd exposure assessment, using random-effects model considering the moderate heterogeneity between these investigations.

Results

The exposure assessment methodology influenced the meta-analysis results, which however generally indicated an increased risk of breast cancer. For studies using urine Cd concentrations for exposure assessment, we found a summary relative risk (RR) of 2.14 (95% CI 1.37-3.34) and 1.39 (0.67-2.92) for case-control and cohort studies, respectively (Figure 1). For cohort studies using dietary Cd intake for exposure assessment, summary RR was 1.00 (0.87-1.15) (Figure 2). Stratified analysis according to Estrogen Receptor (ER) status showed a summary RRs of 1.05 (0.94-1.16) and 1.00 (0.82-1.21) for positive and negative cancer types, respectively. Considering body mass index (BMI) as effect modifier, RR was 1.08 (0.96-1.23) and 0.99 (0.93-1.05) for BMI<25 and BMI≥25, respectively (Table 1). Funnel plots highlighted a little evidence of publication bias for case-control studies with Egger test intercept of 2.70 (95% CI 0.59, 4.81; *P=0.022*), while failed for cohort studies with intercept of 0.45 (-2.07, 2.99; *P=0.672*)(Figure 3). Finally, different average daily intake of cadmium in cohort studies are presented in order to analyze sources of heterogeneity (Figure 4).

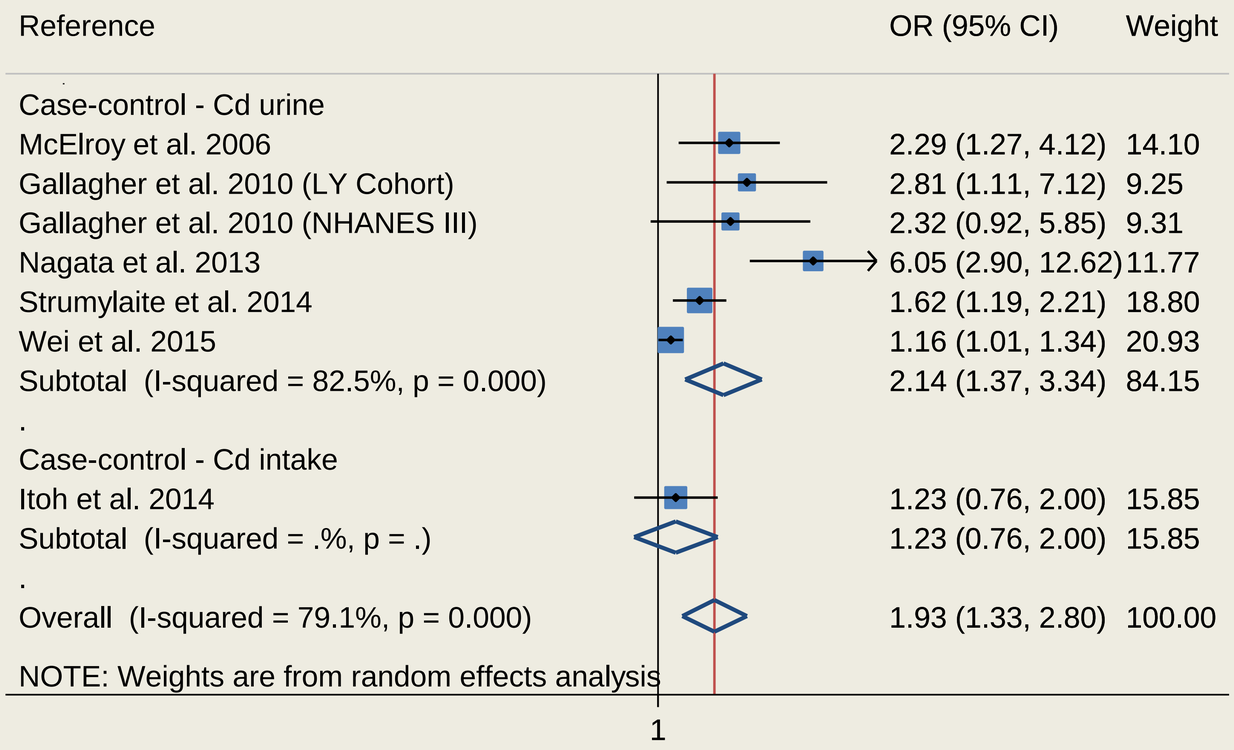

Figure 1. Forest plot of case-control studies according to exposure assessment method.

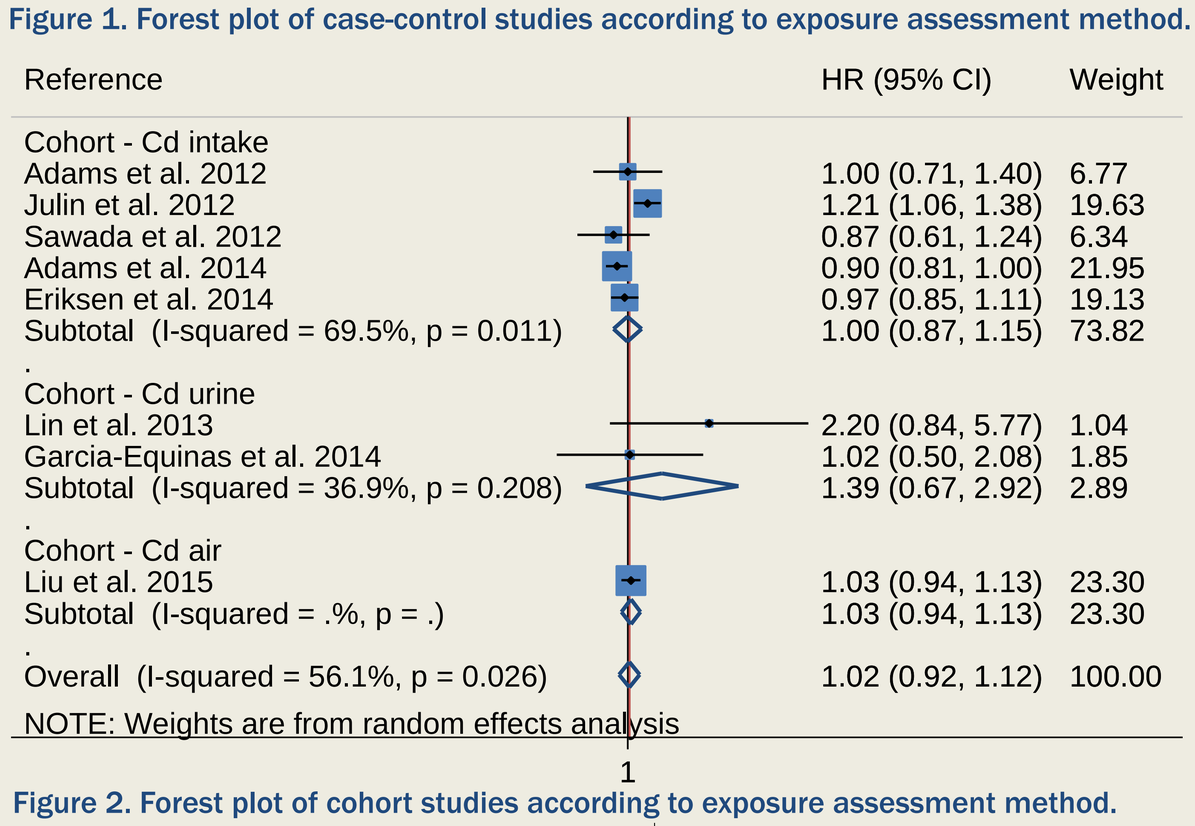

Figure 2. Forest plot of cohort studies according to exposure assessment method.

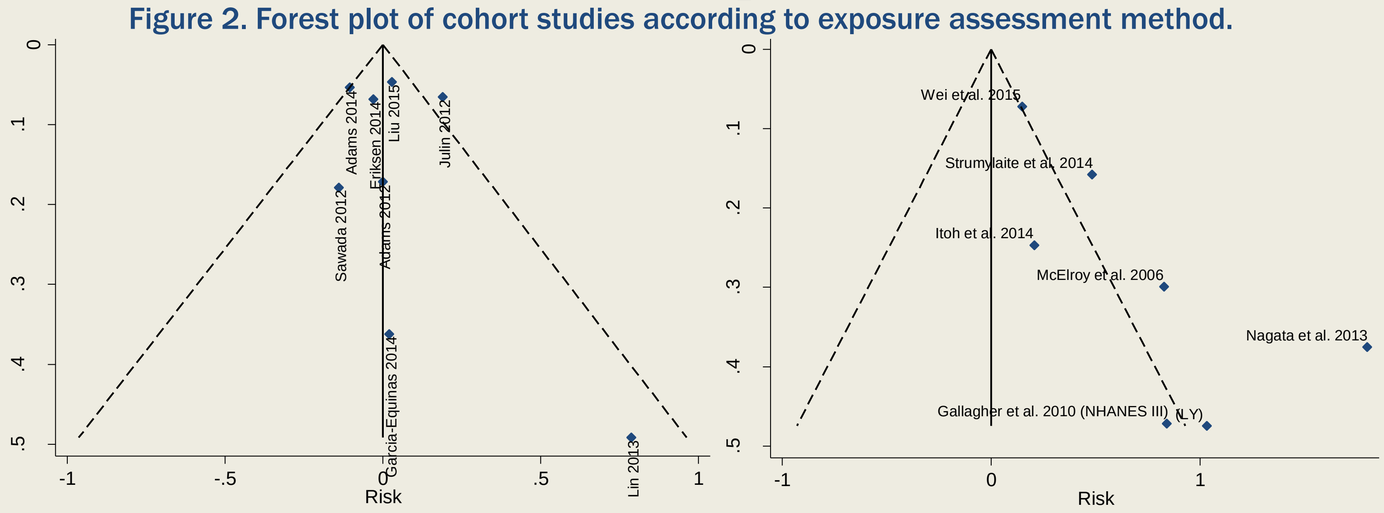

Figure 3. Funnel plot with pseudo 95% CI of case-control and cohort studies.

Categories	Strata	N	RR	95% CI	I^2
Study design	cohort	8	1.04	(0.94, 1.17)	63.0%
	case-control	6	1.93	(1.33, 2.80)	79.1%
Exp. assessment	dietary intake	6	1.01	(0.89, 1.15)	63.9%
	urine	7	1.95	(1.34, 2.83)	76.8%
	air	1	1.03	(0.94, 1.13)	-
ER status	ER+	3	1.05	(0.94, 1.16)	65.7%
	ER-	3	1.00	(0.82, 1.21)	51.2%
PR status	PR+	1	0.85	(0.67, 1.08)	-
	PR-	1	1.12	(0.84, 1.49)	-
Menopausal status	post-menop.	5	1.01	(0.88, 1.16)	68.2%
	pre-menop.	1	0.66	(0.31, 1.41)	-
BMI	<25	3	1.08	(0.96, 1.23)	67.2%
	≥25	3	0.99	(0.93, 1.05)	15.8%
Smoking habits	non-smoker	2	1.01	(0.98, 1.04)	0.0%
	smoker	2	0.99	(0.96, 1.01)	0.0%
	ex-smoker	1	0.85	(0.66, 1.10)	-
Geographic area	North America	7	1.16	(0.95, 1.41)	68.8%
	Europe	3	1.20	(0.95, 1.51)	82.3%
	Asia	4	1.48	(0.90, 2.43)	86.3%

Table 1. Stratified meta-analysis for overall studies.

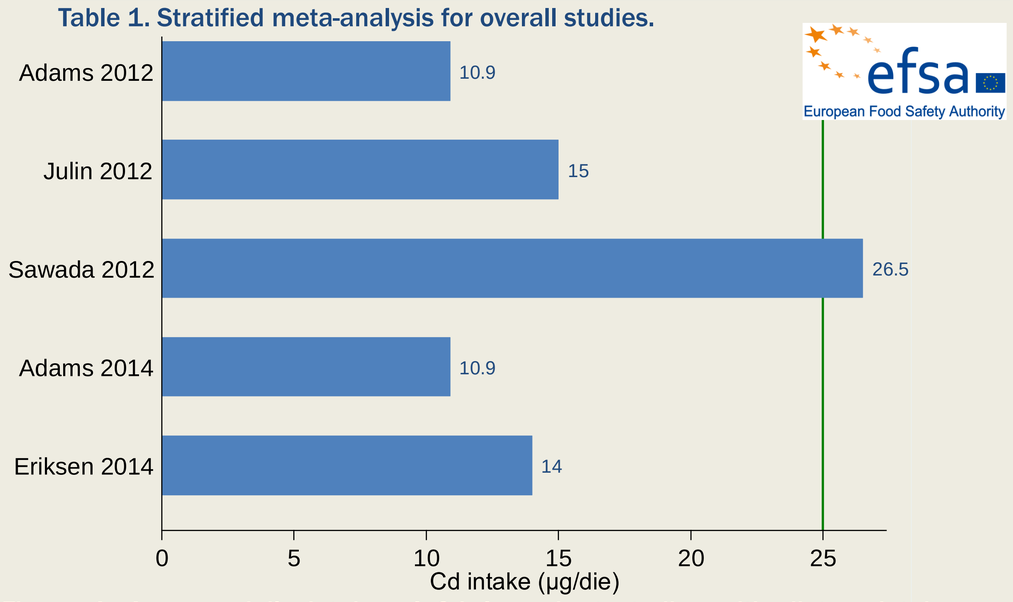

Figure 4. Average daily intake of Cd for cohort studies with dietary intake as exposure assessment. EFSA tolerable intake of 25 µg/die is shown by the green line.

Conclusions

Despite the limitations of this meta-analysis, such as the differences in exposure assessment methods and the statistical imprecision of the point estimates, overall results appear to suggest a direct association between cadmium exposure and breast cancer, with higher RR in subgroups such as ER-positive, and normal weight women.

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