Cancer Causes Control (2015) 26:1281–1288
DOI 10.1007/s10552-015-0621-5

ORIGINAL PAPER

Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence

Tim S. Nawrot[1,2] · Dries S. Martens[1] · Azusa Hara[3] · Michelle Plusquin[1] · Jaco Vangronsveld[1] · Harry A. Roels[1,5] · Jan A. Staessen[3,4]

Received: 29 December 2014 / Accepted: 12 June 2015 / Published online: 25 June 2015

Abstract

Background Recent studies are indicative of substantial progress in understanding the dose–response relation between the incidence of total and lung cancer and environmental cadmium exposure. We conducted a meta-analysis of population studies that examined the risk of cancer in relation to lifetime exposure to cadmium.

Methods We searched MEDLINE, Web of Science, and relevant reviews until August 2014 for studies on the association between cancer risk and cadmium exposure. Eligible studies had to include an estimate of lifetime exposure to cadmium as reflected by the urinary cadmium concentration and adjustment of the cancer risk at least for age and smoking. We pooled relative risk across the studies estimates for cancer and lung cancer using variance-weighted random-effect models and expressed association sizes for a twofold increase in urinary cadmium, thereby respecting the continuous nature of the association.

Results The meta-analysis included 20,459 participants from three prospective population studies. The average urinary cadmium concentration across populations ranged from 0.25 to 0.93 μg/g creatinine. The relative risk of total cancer, associated with a doubling of the urinary cadmium concentration, ranged across the different studies from 1.18 to 1.31, and the pooled relative risk was 1.22 (95 % CI 1.13–1.31; $p < 0.0001$). For lung cancer, the relative risk ranged from 1.21 to 1.70 for a doubling of the urinary cadmium concentration, while the pooled relative risk amounted to 1.68 (1.47–1.92; $p < 0.0001$). Excluding one study at the time did not move the pooled estimates outside the confidence interval of the overall estimate for all studies combined.

Conclusion The epidemiological evidence of the last decade consistently identifies low-level environmental exposure to cadmium as a risk factor for total cancer and lung cancer.

Keywords Cadmium · Epidemiology · Cancer · Lung cancer · Meta-analysis

✉ Tim S. Nawrot
tim.nawrot@uhasselt.be

[1] Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium

[2] Department of Public Health, Leuven University, Louvain, Belgium

[3] KU Leuven Department of Cardiovascular Sciences, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, University of Leuven, Louvain, Belgium

[4] VitaK Research and Development, Maastricht University, Maastricht, The Netherlands

[5] Louvain Centre for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium

Introduction

Cadmium is an ever-present and global environmental pollutant. During the twentieth century, the cadmium concentration in human bone rose tenfold in France [1]. Populations worldwide have a low-level intake through food and smoking of cigarettes, causing an age-related cumulative increase in the body burden of this toxic metal [2, 3]. Environmental exposure levels to cadmium, which are substantially above the background, occur in areas with current or historical industrial contamination, for instance, in regions of Belgium, Sweden, UK, Japan, and China [4].

Particulate matter (PM) air pollution through particles with an aerodynamic diameter <10 μm (PM_{10}) may serve as a vector of inhalation exposure to toxic metals such as cadmium. Moreover, the smallest particles of the PM_{10} fraction (<1 μm) can penetrate in the deep lung and may entail systemic consequences [5, 6].

The International Agency for Research on Cancer (IARC) classified cadmium as a cancer-causing agent in humans on the basis of elevated incidence of lung cancer in cohorts of workers with inhalation exposure to this metal [7]. The fact that the initial evidence on the carcinogenic effect of cadmium was obtained in the occupational setting led to an underestimation of alternative exposure sources in populations, for instance, via diet and inhalation of outdoor/indoor particulate matter. Indeed, the evidence available at the time of the 1993 IARC evaluation showed difficulties in reaching clear conclusions as pointed out by Nordberg [8]. In 2006, we were the first to provide prospective evidence for an association between lung cancer and environmental cadmium exposure [9]. In the last 5 years, five US studies [10–14] further reported on the association between cancer and urinary cadmium. Here, we investigated the strength and consistency of the putative role of low-dose environmental cadmium in association with increased total cancer and lung cancer. Therefore, we systematically reviewed the available evidence dealing with the impact of lifetime environmental cadmium exposure, as reflected by urinary cadmium (an individual biomarker of cadmium exposure), on the risk of total and lung cancer.

Methods

Search strategy and study selection

We searched MEDLINE and Web of Science for studies assessing the prospective association between environmental cadmium exposure and total cancer and lung cancer. The search was conducted without language restrictions on all articles from the beginning of indexing in each database through August 2014. We initially used "cadmium," "epidemiology," and "cancer" as search terms. We also searched for studies including both terms "urinary cadmium" and "cancer." We also considered references in review articles found by our literature search. Our inclusion criteria were as follows: (1) total cancer or lung cancer as endpoint; (2) environmental exposure to cadmium; (3) urinary excretion of cadmium as a biomarker of lifetime cadmium exposure; and (4) adjustment for age and smoking. Our exclusion criteria were as follows: (1) study not conducted in the general population; (2) publications containing no original data, such as reviews, editorials, and commentaries; (3) case reports; and (4) mechanistic studies. In case that more than one study had been published based on the same population, we selected the publication with the longest follow-up period. Two investigators (T.S.N. and D.S.M.) independently abstracted study data from articles that met the inclusion criteria. For studies with multiple levels of adjustment, we used the hazard ratio obtained from the model adjusted for the most covariables. This meta-analysis complies with the preferred reporting items of the MOOSE statement for meta-analyses of observational studies [15].

Statistical analysis

A meta-analytical pooled-effect estimate was derived from the point estimate of each separate study weighted by the inverse of the variance ($1/SE^2$). We used random-effect estimates. The association between cancer and urinary cadmium is usually described by an exposure–response function that expresses the relative increase in cancer risk for a specific increment of urinary cadmium. The effect size was calculated as a relative risk for a doubling in the urinary cadmium concentration (RR^{log2}). If studies were not expressed on the log scale, the authors of the papers were contacted to express their results on log10 scale. The robustness of the findings was examined by recalculating the combined estimate while excluding one study at the time in order to evaluate the influence of individual studies on the combined effect size. If the resulting combined estimate lies outside the confidence interval of the overall estimate, then the excluded study has a disproportionate influence on the combined effect size. Furthermore, between-study heterogeneity was examined using the Cochran Q and I^2 test.

Results

We identified seven studies that investigated total cancer and lung cancer risk in association with individual lifetime exposure to cadmium as reflected by urinary cadmium and which also accounted for age and smoking (Fig. 1). The studies are listed in chronological order in Table 1. However, out of these seven reports, four were based on the NHANES III population [10, 11, 13, 14], and two studies [9, 16] comprised the follow-up of the initial Belgian CadmiBel Study. Of the reports based on the same population, those with the longest follow-up or no restrictions to specific inclusion, e.g., age groups, were included. Therefore, our meta-analysis consisted of two US populations, i.e., the NHANES III [10] and the Strong Heart Study [12], and the follow-up of the Belgian Cadmibel Study [9]

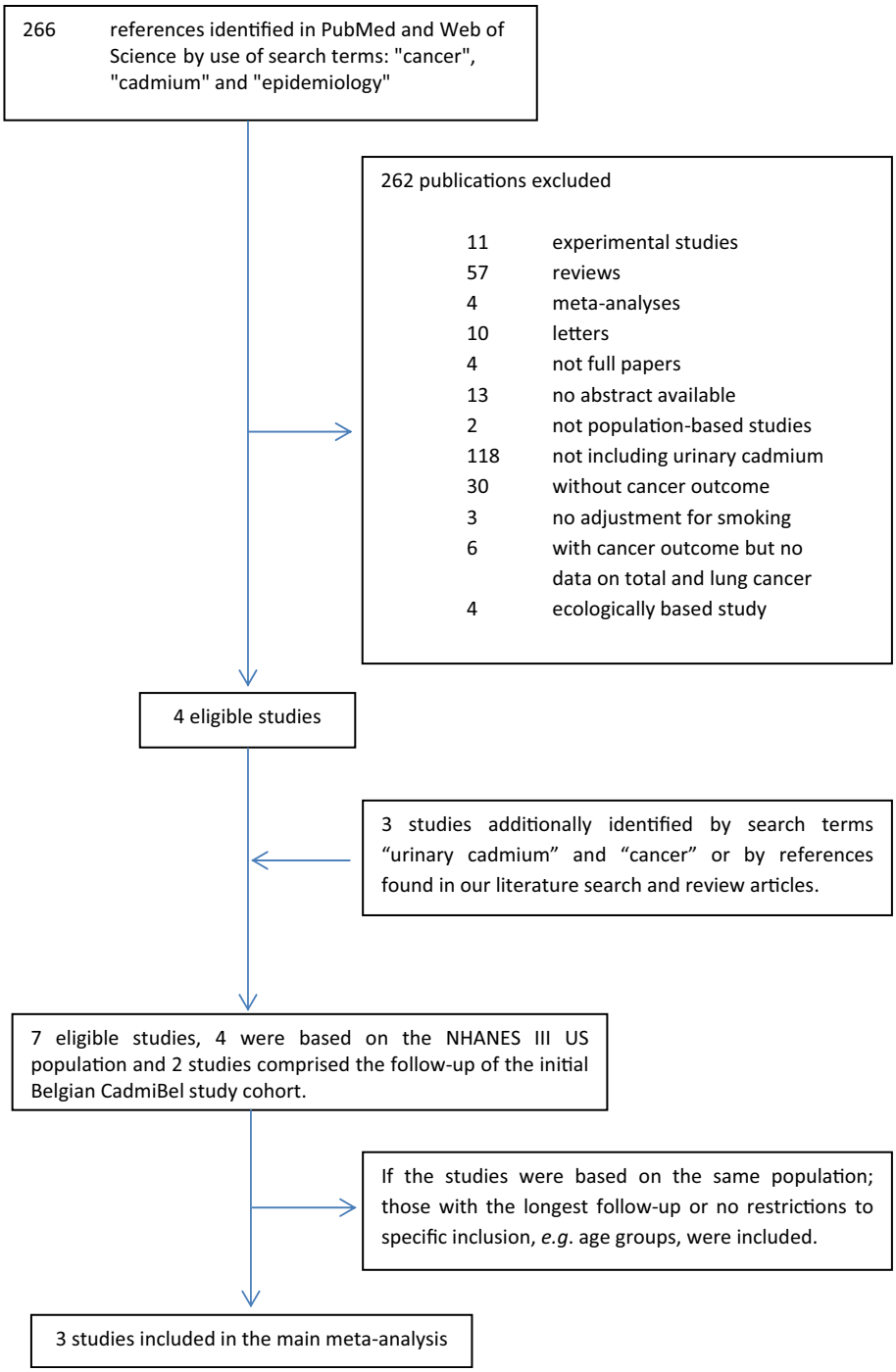

Fig. 1 Flowchart of study inclusion

together comprising 20,459 participants. The three study populations had a similar sex distribution (range 41–48 % men), and their average urinary cadmium concentration ranged from 0.25 to 0.93 μg/g creatinine. In all reports, the results were adjusted for age and smoking and either adjusted or stratified for sex. Two studies [10, 12] reported stratified analysis for smokers and non-smokers in a sub-analysis and were used in a sensitivity analysis to show the robustness of the available data.

Cochran Q statistics did not indicate incomparability of the studies' results either for total cancer ($p = 0.84$) or for lung cancer ($p = 0.41$). For a doubling of urinary cadmium, the pooled relative risk of total cancer (Fig. 2) was 1.22 (95 % CI 1.13–1.31; $p < 0.0001$), while for lung cancer (Fig. 3), it was 1.68 (95 % CI 1.47–1.92; $p < 0.0001$).

The robustness of the findings was further examined by removing one study at the time from the analysis and

Table 1 Characteristics of the studies on total cancer and lung cancer reporting lifetime exposure to cadmium

Authors	Study[a]	Population	Number of participants	Age (years)	Men (%)	Urinary cadmium, μg/g creatinine	Total cancer: *n* (%)	Lung cancer: *n* (%)	Follow-up time (years)
Nawrot et al. [9]	Cadmium in Belgium Study (CadmiBel)	Population from cadmium contaminated and reference area, Belgium prospective cohort study	994	46 (range 20–91)	47	0.82[b,c]	Fatal: 50 (5.0 %) Non-fatal: 20 (2.0 %)	Fatal: 18 (1.8 %) Non-fatal: 1 (0.1 %)	17.2
Nawrot et al. [16]	CadmiBel	Population from cadmium contaminated and reference area, Belgium prospective cohort study	956	47 (range 22–91)[c]	45	0.78[b,c]	Fatal: 54 (5.6 %)	Fatal: 17 (1.8 %)	20.3
Menke et al. [14]	Third National Health and Nutrition Examination Survey (NHANES III)	US population	13,958	~≥30	47	Men: 0.28[c] Women: 0.40[c]	Men fatal:266 (3.6 %) Women fatal:173 (2.6 %)	N/A	Persons alive: 9.0 Persons died: 5.1
Adams et al. [10]	NHANES III	US population mortality follow-up	15,673	≥17	48	Men: 0.25 (95 % CI 0.24–0.27)[c] Women: 0.35 (0.33–0.38)[c]	Men fatal: 420 (5.6 %) Women fatal: 303 (4 %)	Men fatal: 131 (1.8 %) Women fatal: 76 (0.9 %)	13.6
Lin et al. [13]	NHANES III	Subgroup NHANES III: non-Hispanic whites, non-Hispanic blacks, Mexican Americans, 50 years and older	5,204	63 (IQR 56–70)	48	Men: 0.58 (0.33–0.96)[d] Women: 0.77 (0.47–1.27)[d]	Men fatal: 339 (14 %) Women fatal: 230 (8 %)	Men fatal: 98 (4 %) Women fatal: 57 (2 %)	12.4
Cheung et al. [11]	NHANES III	US population mortality follow-up	20,050	~40	47	8.22 nmol/l (not creatinine standardized)	Number not given for the specific group analyzed	N/A	Not analyzed using the prospective nature
García-Esquinas et al. [12]	Strong Heart Study (SHS)	13 US Indian communities aged between 45 and 75 years prospective study	3,792	56.2 (SD 0.13)	41	0.93 (0.55–1.63)[d]	Fatal: 375 (9.9 %)	Fatal: 77 (2.0 %)	17.2

[a] Studies selected on the basis of individual lifetime exposure of cadmium as expressed by urinary cadmium and adjustment for age and smoking

[b] Recalculated concentration initially expressed as nmol cadmium/mmol creatinine for 24-h urinary excretion

[c] Geometric mean

[d] Median and IQR

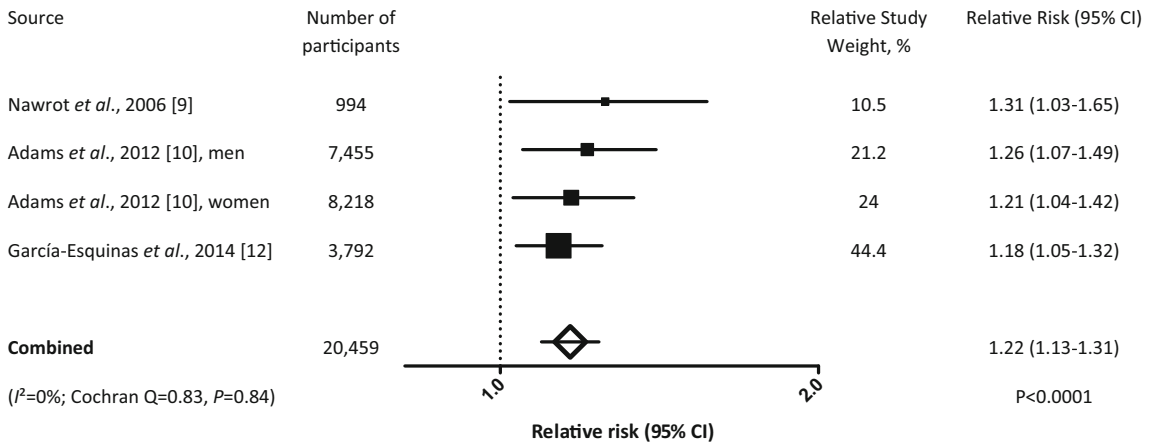

Fig. 2 Forest plot of relative risk (95 % CI) of total cancer associated with a doubling of urinary cadmium. *Squares* represent individual studies. The size of each *square* represents the inverse of the variance

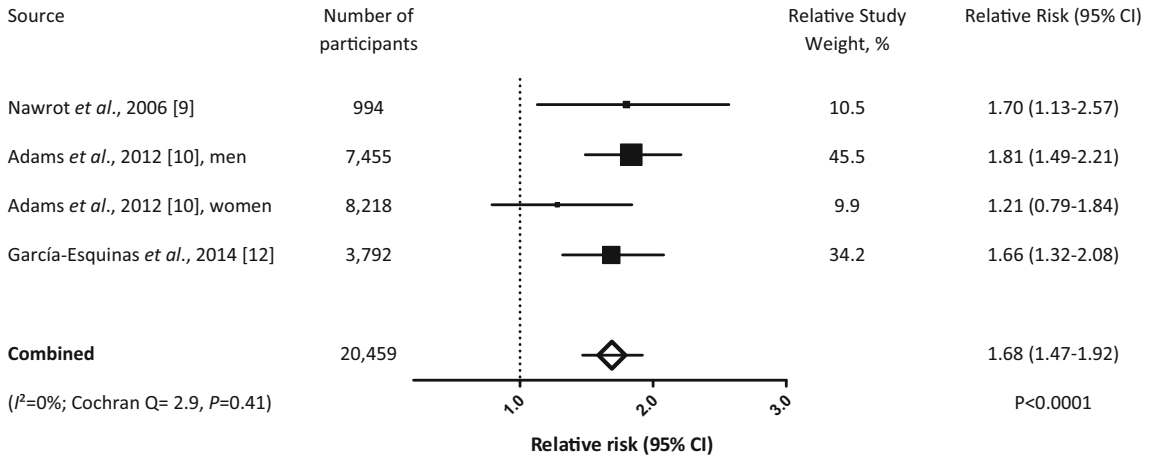

Fig. 3 Forest plot of relative risk (95 % CI) of lung cancer associated with a doubling of urinary cadmium. *Squares* represent individual studies. The size of each *square* represents the inverse of the variance

recalculating the combined effect. This procedure did not move the combined estimate outside the confidence interval of the overall estimate.

Replacing the US NHANES III study of Adams et al. [10] by that of Menke et al. [14] did not change the combined estimate for total cancer risk meaningfully [combined risk: 1.30 (95 % CI 1.11–1.52; $p = 0.0012$)]. The Belgian Cadmibel Study included both fatal and non-fatal events [9], but restricting the Belgian data to fatal events only [16] resulted in a combined estimate for total cancer of 1.22 (95 % CI 1.13–1.32; $p < 0.0001$) and for lung cancer of 1.67 (95 % CI 1.46–1.91; $p = 0.0001$). García-Esquinas et al. [12] and Adams et al. [10] conducted a subanalysis in which smokers at baseline were excluded or only never-smokers were included, respectively. The sensitivity analysis of the two subgroups resulted for a doubling of urinary cadmium in a pooled relative risk of 1.07 (95 % CI 0.96–1.20; $p = 0.21$) for total cancer and 1.58 (95 % CI 1.08–2.31; $p = 0.018$) for lung cancer.

Discussion

Based on meta-analytical evidence, we found a consistent pattern of prospective evidence of total cancer and lung cancer incidence in association with lifetime environmental exposure to cadmium as reflected by urinary cadmium. This finding is based on 20,459 study participants from investigations in Belgium and USA. Each doubling in urinary cadmium resulted in a pooled estimated relative risk increase of 22 % ($p < 0.0001$) in total cancer incidence and 68 % ($p < 0.0001$) for lung cancer risk. To take advantage of the continuous nature of the exposure, we expressed the pooled risk for a doubling of the urinary cadmium concentration rather than contrasting the risk

between study-specific groups, e.g., tertiles. Our meta-analytical estimates fully support the 1993 decision by the International Agency for Research on Cancer [7] to classify cadmium as a human carcinogen based on epidemiological studies in workers.

Our meta-analysis including prospective population-based studies is in line with systematic evidence in workers. As reviewed by Verougstraete and colleagues [17], several [18–21], albeit not all, studies [22] showed a positive association between the risk of lung cancer and occupational exposure to cadmium. The combined estimate showed an increased risk of 20 % in workers exposed to cadmium compared with those not exposed [17].

There is mechanistic evidence to support a causal association between cadmium and cancer. In vitro studies have shown plausible toxicodynamic pathways, such as increased oxidative stress [23, 24], modified activity of transcription factors [25], and inhibition of DNA repair [23, 26]. Most errors that arise during DNA replication can be corrected by DNA polymerase proofreading or by post-replication mismatch repair. Inactivation of the DNA repair machinery is an important primary effect, because repair systems are required to deal with the continuous DNA damage associated with normal cell function. The latter mechanism might indeed be relevant for environmental exposure because Jin et al. [26] found that chronic exposure of yeast to environmentally relevant concentrations of cadmium can result in extreme hypermutability. The DNA mismatch repair system was already inhibited by 28 % at cadmium concentrations as low as 5 μM; for comparison, even in non-smokers, the human lungs accumulate cadmium to concentrations of 0.9–6 μM [26]. In addition to changes in DNA repair, growing evidence shows that cadmium exposure entails changes in epigenetic signature: Gene-specific DNA hypermethylation and gene silencing involving the tumor suppressor genes p16INK4a, RASSF1A, and MT-1 have been observed in cells chronically exposed to cadmium [27].

Previous studies in Japanese populations showed associations between mortality and environmental exposure to cadmium [28–32]. However, there exist important differences between the Japanese observations and the recent population-based findings from the USA and Belgium. First, the median urinary cadmium levels in the Japanese studies were very high, ranging from 4.6 to 12.1 μg/g creatinine [28–31], which might explain the increased mortality from nephritis and nephrosis [32]. For comparison, the median urinary cadmium at baseline was 0.82 μg/g creatinine in the Cadmibel Study [9] and 0.25–0.34 μg/g creatinine in the NHANESIII survey [10, 14], while in the Strong Heart Study [12] (American Indian communities), the urinary cadmium was higher and averaged 0.93 μg/g creatinine. Furthermore, the Japanese studies [28–30] provided standardized mortality rates instead of hazard rates or relative risks or did not adjust for smoking and therefore were not included in the current meta-analysis to prevent heterogeneity.

An important issue is whether the cadmium-induced cancers are independent from smoking. Indeed, smokers absorb amounts of cadmium comparable with those from dietary sources (about 1–3 μg of cadmium per day) [33]. However, theoretical [34] and empirical [35, 36] calculations have shown that if a disease-inducing factor increases the risk of the disease with 40 % or more (relative risk: 1.40), the residual confounding by smoking cannot reduce the finding to a non-statistical significant association. Note that for a doubling in urinary cadmium (continuous scale), our pooled RR for lung cancer was 1.68 and therefore strong enough to resist potential residual confounding. That, as to the development of cancer, the risk of environmental cadmium exposure in the population at large acts independently of tobacco smoke exposure is further supported in the current meta-analysis by providing a pooled hazard rate in the sensitivity analysis based on inclusion of only non-smokers. This subgroup analysis still showed a statistically significant pooled relative risk of lung cancer.

The rate of cadmium absorption increases if the iron status is low. The duodenal iron transporter is induced by iron deficiency, which leads to an increased intestinal absorption of dietary cadmium. This is probably the main reason why the body burden of cadmium in nonsmokers is generally higher among women [14, 37, 38] because of a relative iron depletion in reproductive stage of life. In spite of the fact that the urinary cadmium concentration in women is higher than in men, the hazard rates per unit increase in urinary cadmium of total cancer [10, 12, 14] and lung cancer [10] tended to be larger in men.

Our meta-analysis should be interpreted within the context of its inherent limitations. Meta-analytical evidence might be biased due to the predicament of publication bias and the fact that only studies with positive results are published. Although the number of included studies was small ($n = 3$), they comprised a large number of participants ($n = 20{,}459$) from the general population and consisted all of prospective data based on urinary cadmium as biomarker of cadmium exposure reflecting lifetime individual exposure. The forest plots showed that the majority of the studies reported a significant increase in total cancer and lung cancer risk associated with environmental cadmium exposure. Despite the limited number of studies and the variation in magnitude of the association between the different studies, our combined estimate was robust and not driven by a single study as substantiated by the sensitivity analyses. All studies applied adjustment for smoking, and we ran an additional sensitivity analysis in which we calculated the combined

effect based on the stratified analysis in the studies of García-Esquinas et al. [12] and Adams et al. [10] for non-smokers only. Although weaker than in the main analysis, this subgroup analysis still revealed increased risks which remained significant for lung cancer but not for total cancer. A sensitivity analysis including only fatal cancer cases did not alter the reported associations of the main analysis. Finally, we explored the impact of the different NHANES III studies on the combined risk. The study with the longest follow-up and minimal restrictions was included in the main analysis, and the findings did hold when the estimates of total cancer of Adams et al. [10] (average follow-up of 13.6 years) were changed by those of Menke et al. [14] (average follow-up of 9.0 years). The NHANES III study published by Cheung et al. [11] did not take the prospective nature of the data into account and was therefore not considered in the sensitivity analysis. An additional study within the NHANES III study population specifically addressed the question whether cadmium–zinc interactions might modify the risk of cadmium-induced cancers. Lin et al. [13] reported increased cancer mortality related to urinary cadmium but with a significant effect modification associated with dietary zinc intake (higher relative risk for cadmium, in those with lower zinc status).

In conclusion, our meta-analysis based on published prospective studies with individual cadmium exposure measurements provides important and reliable input for the discussion on the etiological role of environmental long-term low-level exposure to cadmium in the development of cancer (total and lung) in the population at large.

Acknowledgments This study is supported by grants from the European Research Council (ERC-2012-StG 310898) and Flemish Research Council (FWO G073315N/G.0880.13). We thank Dr. García-Esquinas and Dr. Navas-Ancien for providing necessary input of their study to make comparison on a continuous scale possible.?>

References

1. Jaworowski Z, Barbalat F, Blain C, Peyre E (1985) Heavy metals in human and animal bones from ancient and contemporary France. Sci Total Environ 43:103–126
2. Bernhard D, Rossmann A, Henderson B, Kind M, Seubert A, Wick G (2006) Increased serum cadmium and strontium levels in young smokers: effects on arterial endothelial cell gene transcription. Arterioscler Thromb Vasc Biol 26:833–838
3. Nawrot TS, Staessen JA, Roels HA, Munters E, Cuypers A, Richart T, Ruttens A, Smeets K, Clijsters H, Vangronsveld J (2010) Cadmium exposure in the population: from health risks to strategies of prevention. Biometals 23:769–782
4. Nordberg GF, Kido T, Roels HA (2008) Cadmium-induced renal effects. In: De Broe ME, Porter GA (eds) Clinical nephrotoxins, 3rd edn. Springer Science, New York, pp 785–810
5. Elder A, Nordberg GF, Kleinman M (2015) Routes of exposure, dose, and toxicokinetics of metals. In: Nordberg GF, Fowler BA, Nordberg M (eds) Handbook on toxicology of metals, 4th edn. Academic Press, London, pp 45–74
6. Nawrot TS, Kuenzli N, Sunyer J, Shi T, Moreno T, Viana M, Heinrich J, Forsberg B, Kelly FJ, Sughis M, Nemery B, Borm P (2009) Oxidative properties of ambient PM2.5 and elemental composition: heterogeneous associations in 19 European cities. Atmos Environ 43:4595–4602
7. IARC (1993) Beryllium, cadmium, mercury and exposure in the glass manufacturing industry. Monographs on the evaluation of carcinogenic risks in humans, vol 58. International Agency for Research on Cancer, Lyon
8. Nordberg GF, Herber RFM, Allessio G (1992) Cadmium in the human environment: toxicity and carcinogenicity. IARC scientific publications, Lyon
9. Nawrot T, Plusquin M, Hogervorst J, Roels HA, Celis H, Thijs L, Vangronsveld J, Van Hecke E, Staessen JA (2006) Environmental exposure to cadmium and risk of cancer: a prospective population-based study. Lancet Oncol 7:119–126
10. Adams SV, Passarelli MN, Newcomb PA (2012) Cadmium exposure and cancer mortality in the third national health and nutrition examination survey cohort. Occup Environ Med 69:153–156
11. Cheung MR, Kang J, Ouyang D, Yeung V (2014) Association between urinary cadmium and all cause, all cancer and prostate cancer specific mortalities for men: an analysis of national health and nutrition examination survey (NHANES III) data. Asian Pac J Cancer Prev 15:483–488
12. Garcia-Esquinas E, Pollan M, Tellez-Plaza M, Francesconi KA, Goessler W, Guallar E, Umans JG, Yeh J, Best LG, Navas-Acien A (2014) Cadmium exposure and cancer mortality in a prospective cohort: the strong heart study. Environ Health Perspect 122:363–370
13. Lin YS, Caffrey JL, Lin JW, Bayliss D, Faramawi MF, Bateson TF, Sonawane B (2013) Increased risk of cancer mortality associated with cadmium exposures in older Americans with low zinc intake. J Toxicol Environ Health A 76:1–15
14. Menke A, Muntner P, Silbergeld EK, Platz EA, Guallar E (2009) Cadmium levels in urine and mortality among U.S. adults. Environ Health Perspect 117:190–196
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283:2008–2012
16. Nawrot TS, Van Hecke E, Thijs L, Richart T, Kuznetsova T, Jin Y, Vangronsveld J, Roels HA, Staessen JA (2008) Cadmium-related mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. Environ Health Perspect 116:1620–1628
17. Verougstraete V, Lison D, Hotz P (2003) Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data. J Toxicol Environ Health B Crit Rev 6:227–255
18. Jarup L, Bellander T, Hogstedt C, Spang G (1998) Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occup Environ Med 55:755–759
19. Kazantzis G, Blanks RG, Sullivan KR (1992) Is cadmium a human carcinogen? IARC Sci Publ 118:435–446
20. Sorahan T, Lancashire RJ (1997) Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. Occup Environ Med 54:194–201
21. Sorahan T, Waterhouse JA (1983) Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Br J Ind Med 40:293–300
22. Sorahan T, Lister A, Gilthorpe MS, Harrington JM (1995) Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946–92. Occup Environ Med 52:804–812

23. Hartwig A (2010) Mechanisms in cadmium-induced carcinogenicity: recent insights. Biometals 23:951–960
24. Thevenod F, Lee WK (2013) Toxicology of cadmium and its damage to mammalian organs. Met Ions Life Sci 11:415–490
25. Watkin RD, Nawrot T, Potts RJ, Hart BA (2003) Mechanisms regulating the cadmium-mediated suppression of Sp1 transcription factor activity in alveolar epithelial cells. Toxicology 184:157–178
26. Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, Resnick MA, Gordenin DA (2003) Cadmium is a mutagen that acts by inhibiting mismatch repair. Nat Genet 34:326–329
27. Martinez-Zamudio R, Ha HC (2011) Environmental epigenetics in metal exposure. Epigenetics 6:820–827
28. Arisawa K, Nakano A, Saito H, Liu XJ, Yokoo M, Soda M, Koba T, Takahashi T, Kinoshita K (2001) Mortality and cancer incidence among a population previously exposed to environmental cadmium. Int Arch Occup Environ Health 74:255–262
29. Arisawa K, Uemura H, Hiyoshi M, Dakeshita S, Kitayama A, Saito H, Soda M (2007) Cause-specific mortality and cancer incidence rates in relation to urinary beta2-microglobulin: 23-year follow-up study in a cadmium-polluted area. Toxicol Lett 173:168–174
30. Li Q, Nishijo M, Nakagawa H, Morikawa Y, Sakurai M, Nakamura K, Kido T, Nogawa K, Dai M (2011) Relationship between urinary cadmium and mortality in habitants of a cadmium-polluted area: a 22-year follow-up study in Japan. Chin Med J (Engl) 124:3504–3509
31. Nakagawa H, Nishijo M, Morikawa Y, Miura K, Tawara K, Kuriwaki J, Kido T, Ikawa A, Kobayashi E, Nogawa K (2006) Urinary cadmium and mortality among inhabitants of a cadmium-polluted area in Japan. Environ Res 100:323–329
32. Nishijo M, Morikawa Y, Nakagawa H, Tawara K, Miura K, Kido T, Ikawa A, Kobayashi E, Nogawa K (2006) Causes of death and renal tubular dysfunction in residents exposed to cadmium in the environment. Occup Environ Med 63:545–550
33. Jarup L, Berglund M, Elinder CG, 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):1–51
34. Axelson O, Steenland K (1988) Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 13:105–118
35. Blair A, Hoar SK, Walrath J (1985) Comparison of crude and smoking-adjusted standardized mortality ratios. J Occup Med 27:881–884
36. Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L (1988) Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. J Occup Med 30:617–625
37. Staessen J, Amery A, Bernard A, Bruaux P, Buchet JP, Bulpitt CJ, Claeys F, De Plaen P, Ducoffre G, Fagard R, et al (1991) Blood pressure, the prevalence of cardiovascular diseases, and exposure to cadmium: a population study. Am J Epidemiol 134:257-267
38. Vahter M, Akesson A, Liden C, Ceccatelli S, Berglund M (2007) Gender differences in the disposition and toxicity of metals. Environ Res 104:85–95