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Non-Occupational Cadmium Exposure is Emerging as a Major Cause of Cancer, Vascular Disorders, and Other Pathologies - A Long-term Controlled Trial of Supplementation with High-Dose Zinc, a Cadmium Antagonist, is Needed

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Abstract

Epidemiological studies assessing cadmium (Cd) body burden by determining its creatinine-corrected level in urine strongly suggest that non-occupational Cd exposure can boost systemic oxidative stress and inflammation, and is a major mediating factor in the pathogenesis of various common cancers, vascular disease, and other health disorders. Cadmium's effects in this regard often appear to reflect competition with zinc for binding to regulatory proteins. Indeed, increased intakes of zinc counteract Cd toxicity in rodent models. Zinc's protective impact in this regard is mediated in part by induction of metallothionein; this sequesters Cd is such a way as to reduce its intestinal absorption and alleviate its pathogenic effects. Zinc's Cd antagonistic effects may rationalize epidemiology associating increased zinc intakes with lower cancer risks. The significant 27% decrease in total mortality noted in zinc-supplemented subjects (80 mg daily) in the AREDS1 study might also be partially attributable to Cd antagonism. In light of growing evidence that Cd is a major mediator of a number of life-threatening disorders throughout the world, and that zinc can notably lessen its pathogenicity, a large and long-term controlled trial of high-dose zinc supplementation in an older population, with mortality as its primary endpoint, can be strongly recommended. Targeting a population with relatively high Cd exposure, such as that of Japan, would be most appropriate in this regard.

Keywords: Cadmium; Zinc; Metallothionein; Oxidative stress; Inflammation; Cancer; Cardiovascular disease; Mortality; Japan

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Determinants of Cadmium Exposure

There is growing reason to suspect that, even in people not occupationally exposed to the toxic heavy metal cadmium (Cd), body Cd content – most reliably assessed by measuring urinary Cd levels corrected for creatinine - plays a pathogenic role not only in renal tubular dysfunction and osteopathy (commonly seen with high Cd exposure), but also in vascular disease, liver disease, and cancer [1,2]. Cd is a particularly pernicious problem, owing to the fact that there are no physiological mechanisms for excreting it; hence it persists in the body with a half-life estimated at 10-30 years [3]. Moreover, currently available chelating agents are only useful for treating recent acute exposure to Cd; in the absence of such exposure, the vast majority of the body's Cd pool is sequestered intracellularly, and pharmacological chelating agents are not cell permeable [4]. In those not exposed to it occupationally, the major sources of Cd exposure are tobacco smoke and food. Cd is found in shellfish and organ meats, but for most non-smokers, ingestion of plant products – green leafy vegetables, root vegetables, tubers, and grains – is the primary source of their Cd body burden. Indeed, a survey in the Slovakia found that vegans had higher Cd levels than omnivores [5]. Importantly, a recent

meta-analysis has concluded that organically-grown foods tend to have about half as much Cd as conventionally-grown foods, [6] likely reflecting the fact that phosphate fertilizers used in conventional agriculture are frequently contaminated with Cd [7-10]. Hence, avoiding tobacco smoke and choosing organic foods are practical strategies for moderating Cd exposure. In Japan, where rice consumption is the chief food source of Cd exposure, efforts are underway to develop genetically modified rice strains with an impaired capacity to assimilate Cd from the soil [11]. Phytoremediation strategies for decreasing the Cd content of agricultural soils are also being studied [12-14].

Iron deficiency increases the efficiency of intestinal Cd absorption, thus accounting for the fact that urinary Cd tends to be higher in women than in men [15]. Cd can "hitch a ride" on intestinal iron transporters up-regulated when iron stores are low; hence, avoiding or correcting iron deficiency is another practical way to moderate Cd body burden [16]. Rodent studies suggest that ample intakes of zinc or magnesium with meals can also lessen Cd absorption [4,17].

Urinary Cadmium as an Index of Cadmium Body Burden

There are now a great many studies showing positive correlations between creatinine-corrected urinary Cd and disease risks. Although such correlations evidently do not necessarily reflect causality, there is good reason to suspect that they do, at least in non-smokers, since metabolic states which predispose to disease, such as metabolic syndrome, are not known to influence Cd absorption or excretion, and the foods which supply the majority of dietary Cd are generally considered to be healthful – staples of vegan or "Mediterranean" diets. Moreover, rodent studies establish that Cd is carcinogenic, can exacerbate atherogenesis, and has pathogenic effects on a wide range of tissues [18-20].

A survey of the pertinent epidemiological literature quickly reveals that, whereas urinary Cd typically emerges as a risk factor for health disorders, estimates of dietary Cd usually do not. Most likely, this reflects the fact that estimates of dietary Cd intake based on food tables are highly dubious, as there is no characteristic Cd content of a given food – the Cd content of a food reflects the Cd content of the soil in which it is grown, and other soil factors which influence the efficiency with which plants assimilate Cd. (Plants absorb less Cd from alkaline than acidic soils). [2] In contrast, urinary Cd reflects kidney Cd content, and is thought to give a fairly accurate estimate of total Cd body burden – which has accumulated over the last several decades [1,2,21]. Hence, epidemiological studies focusing on urinary Cd should be much more meaningful than those which attempt estimates of Cd dietary intake. Indeed, a recent study evaluating over 1700 post-menopausal Danish women concluded that "Dietary-Cd intake estimated from food frequency questionnaires correlates only minimally with U-Cd biomarker, and its use as a Cd exposure indicator may be of limited utility in epidemiologic studies." [22]. Blood Cd tends to mirror recent Cd exposure, rather than lifelong exposure; [1] nonetheless, if Cd exposure is steady rather than episodic, blood Cd can be expected to correlate with Cd body burden.

Cadmium as a Mediator of Oxidative Stress and Inflammation

The broad pathogenicity of Cd likely reflects the fact that it gives rise to oxidative stress and inflammation. There are several studies showing that urinary cadmium correlates tightly with urinary levels of oxidatively damaged DNA bases (8-hydroxy-2-deoxyguanosine or 8-oxo-dG); 4 studies compare urinary 8-oxo-dG levels above and below the median Cd concentration [23-26]. In the upper half of the urinary Cd distribution, as compared to the lower half, the levels of 8-oxo-dG were 21%, 24%, 32%, and 39% higher. None of these studies involved workers exposed to exceptional levels of Cd, and the latter three surveyed only never-smokers. (In other words, elevated Cd is not just serving as a marker for exposure to the other oxidants in tobacco smoke.) In an additional study, urinary 8-oxo-dG was 27% higher in subjects in the upper 15% of urinary Cd, as compared to subjects in the bottom 15% [27].

The source of this increased oxidative stress is not yet clear. There are several studies showing that, in specific tissues or cells, Cd exposure boosts NADPH oxidase activity [28-34]. Diminished expression of certain antioxidant enzymes may also contribute to this effect [35].

Urinary Cd levels also correlate tightly with markers of systemic inflammation, most notably C-reactive protein (CRP) [36-38]. For example, in the Third National Health and Nutrition Examination Survey, risk for elevated CRP (>1.0 mg/dl) was approximately 2 or 3-fold greater in the upper tertile of urinary Cd relative to the lower tertile, in women and men, respectively [36]. Two more recent studies used multiple regression analysis to factor out the contribution of smoking to this phenomenon. In one of these, an interquartile increase in urinary Cd was associated with a 48% increase in CRP; in the other, risk for elevated CRP was 62% greater in the 4th than the 1st quartile of urinary Cd [37,38].

These findings suggest that ambient variations of Cd body stores are a major determinant of systemic oxidative stress and inflammation. This might explain why Cd body burden has been linked directly not only to cancer, [39-41] but vascular disease, [42-48] liver disease, [49] and other disorders.

Cadmium and Cancer Risk – Focus on Breast Cancer

While Cd can induce mutagenic oxidative stress, it can also promote tumorigenesis by inhibiting DNA mismatch repair, and by inducing epigenetic changes. [18,50-52]. These effects seem to reflect Cd's ability to mimic the structure of zinc, an essential component of "zinc finger" nuclear proteins that regulate DNA repair and gene expression [53]. By substituting for zinc in these proteins, Cd can cause alterations in their structure which impacts their function. *In vitro*, these effects of Cd are largely prevented by co-administration of zinc, suggesting that zinc and Cd are functional competitors in this regard [51] (Zinc-mediated induction of metallothionein, a Cd antagonist, may play a role in this effect as well, as discussed below.) Cadmium's inhibition of mismatch repair is associated with a failure of cells with DNA damage to stop cycling prior to S phase and undergo apoptosis; hence, Cd not only increases DNA damage (via oxidative stress

and disruption of repair mechanisms), but also increases the chances that damaged cells will survive to produce progeny.

The role of Cd as a human carcinogen first came to attention when workers with occupational exposure to Cd were found to be at higher risk for lung cancer [18,54,55]. The Cd content of tobacco smoke is also thought to contribute to lung cancer risk in smokers [56,57]. But it is now recognized that more modest levels of Cd exposure common in the general population may increase cancer risk not only in the lung, but in a number of other organs as well. In particular, recent epidemiology has focused on Cd's likely role in the induction of breast cancer.

There have now been 5 case-control studies published correlating urinary Cd levels with breast cancer risk [58-61]. (The Gallagher paper analyzes two separate cohorts [59]) On the assumption that Cd exposure mediates zero breast cancer risk in the lowest quartile (or tertile) of Cd exposure, the proportion of total breast cancer risk attributable to Cd in each of the studies, using the odds ratio calculations most fully adjusted for covariates in each study, is as follows: (Attributable risk is the proportion of breast cancer cases observed that would not be expected to occur if all subjects had urinary Cd in the lowest quartile or tertile. For example, if there were 10 cases of cancer in the first tertile, 20 in the second, and 30 in the third, the total number of cases would be 60, but only 30 cases would have been expected if all subjects had had Cd levels in the first tertile. So the calculated attributable risk for Cd exposure in this instance would be 50%) (Table 1).

It is notable that the risk for breast cancer associated with Cd exposure increases linearly as the level of average Cd exposure increases in the cohorts. Cd exposure in the Japanese cohort is exceptionally high. The Strumylaite study is from Lithuania, and those of McElroy and Gallagher assess U.S. cohorts.

Note that these calculations represent an *underestimate* of Cd-mediated risk, as it is hardly likely that Cd caused *no* cases of breast cancer in the lowest quartiles/tertiles. The high Cd-mediated attributable risk in the Japanese study is particularly notable.

Several studies have correlated urinary Cd with total cancer mortality, using multivariate models that corrected for smoking status. A Belgian study found that a doubling of urinary Cd was associated with a 29% increase in cancer mortality (HR = 1.29; 95% CI:1.01-1.65) [40]. In an analysis of the 3rd NHANES cohort, a doubling of urinary Cd was associated with a 26% increase in cancer mortality in men (95% CI:1.07-1.48) in men, and a 21% increase (95% CI:1.04-1.42) in women [62]. In another analysis within the same cohort, the multivariate-adjusted risks for cancer mortality in men across tertiles of urinary Cd were 1.00, 2.16 (1.11-4.21), and 4.29 (2.31-7.96) – suggesting that Cd exposure may have been responsible for about 60% of their cancer mortality [36]. (Oddly, urinary Cd did not correlate with cancer mortality among the women in this study.) And in the Strong Heart Study cohort, comprised of Native Americans, 35% of total cancer mortality could be ascribed to Cd exposure ($p<0.001$) [63].

In sub-analyses, lung and pancreatic cancer mortality correlate strongly with urinary Cd in these studies. The only case-control study to date to focus on cadmium and pancreatic cancer was conducted in a south Louisiana population with relatively high Cd exposure for the U.S. (38% with a urinary Cd in excess of 1 µg/g creatinine). Multivariate-adjusted odds ratios for pancreatic cancer incidence across quartiles of urinary Cd were found to be 1.00, 3.34, 5.58, and 7.70, implying an attributable risk of at least 77% [64]. (By contrast, the impact of past or present smoking on this risk failed to achieve statistical significance.) Cadmium may also play a role in induction of bladder cancer, the ninth leading cause of cancer mortality [65-67]. In a Belgian case-control study, which assessed Cd status by measuring whole blood Cd, the odds ratios over tertiles of blood Cd were 1.00, 1.83, and 5.73, following multivariate adjustments for smoking habits, age, sex, and occupational exposure to bladder carcinogens; this corresponds to an attributable risk for Cd of at least 65% [65].

Cadmium's Links to Vascular Disorders and Total Mortality

Since oxidative stress and inflammation are key drivers of cardiovascular disease, it would be logical to expect Cd exposure to impact risk for vascular disorders. Moreover, Cd exposure markedly amplifies atherogenesis in ApoE knockout mice, and also impairs vascular endothelial function in rodents [32,68]. In the 1988-1994 NHANES cohort, after correction for numerous covariates including several indices of smoking intensity (such as serum cotinine), subjects at the 80th percentile of urinary Cd, in comparison to those at the 20th percentile, had a hazard ratio of 1.74 (95% CI 1.07-2.83) for cardiovascular mortality [69]. The association between urinary Cd and peripheral artery disease (PAD) is well documented. In the prospective Strong Heart Study, subjects in the third tertile of urinary Cd, as compared to those in the first, were about twice as likely to develop PAD (HR=1.96; 95% CI 1.32-2.81) [70]. An association of similar magnitude was observed in the 1999-2000 NHANES cohort [71]. Positive associations between urinary Cd and prevalent stroke or heart failure have also been reported [72,73]. Urinary Cd predicted the rate of growth of atherosclerotic lesions of the carotid arteries in 64-year-old women, and in young women was associated with higher prevalence of early atherosclerosis [44,74].

Not surprisingly – given its links to risks for both cancer and vascular disease – urinary Cd has also been reported to correlate prospectively with total mortality. In the 1988-1994 NHANES cohort, subjects at the 80th percentile of urinary Cd, in comparison to those at the 20th percentile, had a multivariate-corrected hazard ratio of 1.52 (95% CI 1.00-2.29) for total mortality[69]. More recently, in a Japanese prospective cohort study focusing on regions of Japan not known to have experienced industrial Cd exposure, the multivariate adjusted hazard ratios for total mortality in the 4th quartile of urinary Cd were found in be 1.50 (95% CI 1.11-2.02) and 1.50 (95% CI 1.08-2.09) in men and women, respectively [75].

Now a meta-analysis incorporating nine prospective cohort studies has examined the association of baseline urinary Cd with subsequent mortality [76]. Comparing the highest and lowest

Table 1 Proportion of breast cancer risk attributable to Cd exposure in case-control studies correlating urinary Cd levels with breast cancer risk

Strumylaite et al. [62]	27%	[Quartile 4 >0.40 µg/g Cd]
McElroy et al. [59]	36%	[Quartile 4 >0.58 µg/g Cd]
Gallagher et al. [60]	41% and 46%	[Quartile 4 >0.60 µg/g Cd]
Nagata et al. [61]	68%	[Tertile 3 >2.62 µg/g Cd]

categories of urinary Cd, hazard rates for all-cause, cancer, and cardiovascular mortality were found to be 1.44 (95% CI 1.25-1.64), 1.39 (95% CI 0.96-1.99), and 1.57 (95% CI 1.27-1.95). Similar findings were observed when the analysis was restricted to populations with relatively moderate Cd exposure (mean urinary Cd < 1 µg/g creatinine, typical of the U.S.). The authors conclude that even "low-level" exposure to Cd may be broadly pathogenic.

Additional Disorders Linked to Cadmium Exposure

Common levels of Cd exposure have also been linked to increased risk for osteoporosis, renal disorders, and non-alcoholic fatty liver disease. Human Cd toxicity first came to prominent attention in the 1960s after the "itai itai" disease afflicting Toyama prefecture in Japan – characterized by renal tubulopathy, hypercalciuria, osteomalacia, fractures, and anemia – was linked to severe industrial Cd pollution [77-79]. A number of subsequent epidemiological studies have associated less substantial levels of Cd exposure to increased risk for osteoporosis and osteopenia; this appears to reflect both a direct stimulation of osteoclastic activity in bone, as well as an elevation of renal calcium loss stemming from tubulopathy [2,79-85]. For example, a cross-sectional analysis of NHANES cohorts found that, in women over 50 years of age, osteoporosis was 43% more likely (OR= 1.43; 95% CI 1.02-2.00) in women with urinary Cd in the range 0.50-1.00 mcg/g creatinine, than in women with lower urinary Cd [82]. Another analysis in an NHANES cohort, examining both sexes, found that, as compared to subjects with urinary Cd below 1.0 mcg/g, those with urinary Cd of 1.00-1.99 mcg/g or of 2.00 mcg/g and over had significantly increased risks for osteoporosis of 78% and 280%, respectively [85]. In men exposed occupationally to Cd (mean urinary Cd 1.02 mcg/g), urinary Cd correlated directly with urinary calcium and inversely with bone mineral density [84].

With respect to kidney disorders, an analysis of NHANES 1999-2006 linked urinary Cd > 1 mcg/g with increased risk for albuminuria (OR=1.63, 95% CI 1.23, 2.16) [86]. This study also found increased risk for both albuminuria and chronic kidney disease in subjects with blood Cd over 1 mcg/L. A subsequent analysis of the same cohort by the same group found an increased risk for renal stone formation in women with urinary Cd over 1 mcg/g (OR=1.40; 95% CI 1.06, 1.86.); this association did not achieve statistical significance in males [87]. Not unlikely, increased calciuria contributed to Cd's impact on renal stone risk.

Nor is the liver immune from Cd's pro-inflammatory impact. A very recent analysis of NHANES III found that for men in the top quartile of urinary Cd, as contrasted with the bottom quartile, multivariate-adjusted odds ratios for hepatic necroinflammation, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and liver-related mortality were 2.21, 1.30, 1.95, and 3.42, respectively; all of these associations were statistically significant [49,88]. In the top quartile urinary Cd in women, hepatic necroinflammation and liver-related mortality were significantly more common.

It should not surprise us if common levels of Cd exposure are linked to other pathologies in the future. As this essay was being written, another analysis of an NHANES cohort has found a strong trend toward increased risk of age-related macular degeneration (AMD) – the chief cause of partial blindness in the elderly – in the top quartile of urinary Cd, that just misses statistical significance after correction for pack years of smoking (OR=2.18; 95% CI 0.70, 6.83). Adding to the credibility of this association are previous reports that smokers with AMD have higher urinary Cd than those who don't, and that Cd levels of the retina are elevated in subjects with AMD [87,89].

Zinc – Cadmium Antagonist and Antioxidant

While measures which can lessen Cd exposure or absorption are clearly worthwhile, each of us carries a pathogenic Cd body burden which would persist for decades even if further Cd absorption were minimal, and which is resistant to current chelation therapies. Hence, strategies for opposing the pathogenic impact of the Cd already in the body are clearly needed.

In this regard, it is particularly intriguing that numerous rodent studies have demonstrated that ample dietary intakes of zinc mitigate Cd toxicity [90-94]. In part, this may reflect the fact that zinc and Cd compete for binding sites in zinc finger and other zinc-binding proteins that play key regulatory roles. However, zinc also promotes induction of metallothioinein, which can bind and sequester Cd, thereby limiting its toxic impact [95-97]. Intakes of supplemental zinc in the range of 15-50 mg daily have been shown to markedly boost the protein or mRNA of metallothionein in the monocytes and erythrocytes of healthy young men [98-100]. Metallothionein binding of Cd in intestinal epithelial cells can also decrease dietary absorption of Cd, since this metallothionein-bound Cd is often sloughed off into the intestinal contents when these epithelial cells are exfoliated [101]. (A similar mechanism is responsible for supplemental zinc's inhibitory impact on absorption of copper – also bound by metallothionein – when zinc is used to treat Wilson's disease [102]) In this regard, a recent analysis of the NHANES 2003-2012 cohort, which estimated total daily zinc intake (from diet plus supplements) and measured serum levels of zinc and Cd, as well as urinary Cd, found that both dietary and serum zinc correlated inversely with both measures of Cd status – likely reflecting the ability of dietary zinc to suppress absorption of dietary Cd [103].

Howard and colleagues studied a group of non-smoking workers who were exposed to significant amounts of tobacco smoke in their work environment; tobacco smoke is a major source of Cd pollution [104]. As compared to a comparable group of workers not exposed to tobacco smoke, their whole blood levels of 8-oxo-dG were 63% higher. When these smoke-exposed workers were given an antioxidant supplement for 60 days, their 8-oxo-dG level dropped by 62%. This antioxidant supplement was distinguished by the fact that it provided 40 of zinc per daily dose; other antioxidants were provided in modest nutritional doses (3 mg beta carotene, 60 mg vitamin C, 30 IU of alpha-tocopherol, 40 µg of selenium, 2 mg copper) that would seem unlikely to have much impact in normally nourished subjects. Hence, the high zinc content of this supplement may have been primarily responsible for the marked decline in 8-oxo-dG reported. A placebo-controlled study by Prasad and colleagues, in which normal volunteers received 45 mg of zinc daily (as gluconate) or matching placebo

for 8 weeks, analogously demonstrated a significant 37% decline in plasma 8-oxo-dG in those supplemented with zinc, whereas this parameter did not change in the placebo group [105].

In light of Cd's up-regulatory impact on CRP, it is intriguing to note that a supplemental intake of 45 mg zinc daily was found to reduce plasma CRP by a significant 23% in elderly subjects [106]. Conceivably, Cd antagonism contributes to zinc's efficacy in this regard; in any case, it exerts a countervailing effect on the pro-inflammatory impact of Cd.

The ability of ample zinc intakes to limit oxidative damage to DNA – possibly in part by opposing Cd's toxic impact – as well as zinc's capacity to counteract Cd's interference with DNA repair *in vitro*, suggests that it may have potential for cancer prevention, particularly in the context of significant Cd exposure. A Canadian prospective cohort study has found that breast cancer risk was approximately 50% lower (HR = 0.47; CI: 0.28-0.78) in postmenopausal women who had taken zinc supplements for at least the 10 years previous years [107]. There is also a recent report that the ratio of estimated dietary zinc intake to urinary Cd correlates inversely with total cancer mortality in both men and women [108]. In an ecologic analysis of cancer rates in the U.S., regional zinc intakes determined in the NHANES-III study were found to vary inversely with risks for 12 types of cancer; this paper also cites 8 previous observational studies in which increased dietary zinc intakes correlated significantly with decreased risk for various cancers [109]. A recent meta-analysis of studies correlating dietary zinc intake with risk for all cancers of the digestive tract – incorporating 19 studies with 400,000 participants – calculated a relative risk of 0.82 (95% CI: 0.70-0.96) for upper vs. lower category of zinc intake [110].

Other epidemiological studies suggest an interaction between dietary zinc and Cd body burden in the induction of pathology. Among men with a dietary intake of zinc below the median, urinary Cd correlated positively with serum levels of prostate-specific antigen (PSA); no correlation between Cd and PSA was noted among men with higher zinc intake [111]. Although the association of Cd with risk for benign prostatic hyperplasia (BPH) has not been studied, Indian researchers recently reported that the Cd content of hypertrophied prostates correlated directly with PSA and inversely with maximum urinary flow rate [112]. Also, Cd administration can induce a BPH-like syndrome in rats [113]. In the Atherosclerosis Risk Factors in Young Females study, serum Cd levels correlated directly with the intima-media thickness of the carotid arteries, but only in those subjects whose serum zinc was in the lower two tertiles [75]. With respect to risk for obstructive lung disorders (COPD), data from the Third NHANES cohort indicate that dietary zinc intake correlates inversely, and urinary Cd levels correlate directly, with this risk [114]. Those in the lower tertile of zinc intake were approximately twice as likely to experience COPD; after statistical adjustments for smoking habit, those in the upper tertile of urinary Cd, relative to those in the lower tertile, had an odds ratio of 3.48 (95% CI:2.54-4.76) for COPD. The log-transformed zinc-to-cadmium ratio was highly predictive of COPD risk. An analogous analysis by the same group, examining risk for nephropathy in the 2011-2012 NHANES, found that multivariate-adjusted risks for reduction in estimated glomerular filtration rate and for albuminuria were elevated in the 4th quartile of blood cadmium relative to the 1st quartile – OR= 2.21 (1.09-4.40) and 2.04 (1.13-3.69), respectively; moreover, risk for nephropathy was greater at lower serum zinc levels, and the log-transformed ratio of serum zinc to blood cadmium correlated inversely with odds ratio for nephropathy assessed by either measure [115].

Perhaps the most provocative clinical finding with supplemental zinc has emerged from an analysis of the AREDS1 study. Subjects randomized to receive 80 mg zinc daily (plus 2 mg copper, to prevent zinc-induced copper deficiency) for the 6.5 years of the study experienced a significantly lower total mortality rate (adjusted RR=0.73, 95% CI 0.61-0.89) than those not supplementing with zinc [116]. Reductions of cancer mortality and of cardiovascular mortality did not achieve statistical significance (RR=0.78, 95% CI 0.56-1.09, and R=0.77, 95% CI 0.57-1.05, respectively) but trended toward protection, as would be expected if zinc were antagonizing Cd's pathogenicity. These findings are consistent with the thesis that Cd exposure is a major cause of mortality, and that high-dose zinc provides meaningful protection in this regard.

In light of suggestive evidence that Cd may play a role in the induction of AMD, it is pertinent to note that subjects in AREDS1 randomized to receive zinc plus antioxidants were at decreased risk for progression to advanced AMD (OR=0.72, 95% CI 0.52, 0.98); a strong trend toward protection was also seen in those randomized to zinc alone (OR=0.75, 95% CI 0.55, 1.03) [117]. Arguably, zinc's antagonism of Cd toxicity contributed importantly to the successful outcome of the AREDS1 study.

A Japanese Trial of Long-Term High-Dose Zinc Supplementation is Needed

In summary, non-occupational Cd exposure is emerging as a major cause of a number of types of cancer, as well as of vascular disorders and other pathologies. Induction of oxidative stress and inflammation, as well as impairment of mechanisms which repair DNA or route genetically damaged cells to apoptosis, seem likely to mediate much of Cd's impact in this regard. These pathogenic effects of Cd may often reflect competition with zinc for binding to key regulatory proteins; this implies that increased tissue levels of zinc should provide protection from these effects. Moreover, zinc-mediated induction of metallothionein can sequester tissue Cd, decreasing its dietary absorption and lessening the pathogenicity of the body's Cd pool. These considerations rationalize the protective effects of dietary zinc in rodent models of Cd toxicity. High-dose supplemental zinc exerts antioxidant and anti-inflammatory effects that may be mediated in part by Cd antagonism, as well as additional mechanisms. Epidemiologically, higher dietary zinc intakes are being associated with lower cancer risk.

The substantial and highly significant reduction of total mortality associated with high-dose zinc supplementation in the AREDS1 study – the only large and long-term controlled study to evaluate high-dose zinc to date - has received little attention, possibly because the mechanism behind this effect was not understood; hence, many may have suspected this finding to be an irreproducible statistical fluke. However, in light of our developing understanding of the pathogenic risk posed by Cd exposure, and the role which zinc can play in mitigating Cd toxicity, this finding gains considerably in credibility. Indeed, an effort to repeat this finding, comparing high-dose zinc with placebo in an older population, and focusing on overall health and mortality rather

than macular degeneration, appears to be warranted. It would be logical to conduct such a study in a population in which Cd exposure is relatively high.

Cadmium exposure is notably high in Japan. Whereas the CDC reports that urinary Cd averages 0.18 µg/g creatine in the U.S. population (95th percentile: 0.79 µg/g), a 2000/2001 survey of over 10,000 Japanese women without known occupational exposure to Cd residing in 10 prefectures throughout Japan, found a geometrical mean urinary Cd of 2.97 µg/g [118]. High Cd exposure in Japan presumably reflects relatively high soil Cd levels and the fact that the Japanese staple food, rice, assimilates this Cd efficiently; as noted, efforts to develop rice strains with a lesser propensity to concentrate Cd are underway [11]. Epidemiological surveys conducted in Cd-polluted regions of Japan confirm that increased urinary levels of Cd and of markers for Cd-mediated renal toxicity correlated with increased risk for mortality from cancer, ischemic heart disease, and renal failure [45,119-121]. The increased risk for total mortality associated with urinary Cd in Cd non-polluted regions of Japan was cited above [70]. Hence, it would be especially appropriate to evaluate the long-term health impacts of high-dose zinc supplementation in a Japanese population.

As a caution, it should be noted that Cd is a component of many zinc ores, and, as a result, commercial zinc supplements contain detectible amounts of Cd. One survey found that this amount varied, per 15 mg dose of zinc, from 0.039 µg to 1.46 µg [121]. Zinc gluconate supplements consistently contained the lowest amounts of Cd. Evidently, it is desirable to choose zinc supplements that contain minimal Cd. In addition, high-dose zinc supplementation should be accompanied by a small dose of copper – as it was in the AREDS1 study – to avoid zinc-induced copper deficiency. A zinc dose in the range of 40-80 mg daily, with 1-2 mg copper, could be envisioned for such a study.

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