MERCURY AND THE RISK OF CORONARY HEART DISEASE IN MEN

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ABSTRACT

Background A high dietary intake of mercury from consumption of fish has been hypothesized to increase the risk of coronary heart disease.

Methods Using a nested case–control design, we investigated the association between mercury levels in toenails and the risk of coronary heart disease among male health professionals with no previous history of cardiovascular disease or cancer who were 40 to 75 years of age in 1986. Toenail clippings were collected in 1987 from 33,737 cohort members, and during five years of follow-up, we documented 470 cases of coronary heart disease (coronary-artery surgery, nonfatal myocardial infarction, and fatal coronary heart disease). Each patient was matched according to age and smoking status with a randomly selected control subject.

Results The mercury level was significantly correlated with fish consumption (Spearman $r=0.42$, $P<0.001$), and the mean mercury level was higher in dentists than in nondentists (mean, 0.91 and 0.45 μg per gram, respectively; $P<0.001$). After age, smoking, and other risk factors for coronary heart disease had been controlled for, the mercury level was not significantly associated with the risk of coronary heart disease. When the highest and lowest quintiles of mercury level were compared, the relative risk of coronary heart disease was 0.97 in the highest level (95 percent confidence interval, 0.63 to 1.50; P value for trend=0.78). Adjustment for intake of n–3 fatty acids from fish did not appreciably change these results.

Conclusions Our findings do not support an association between total mercury exposure and the risk of coronary heart disease, but a weak relation cannot be ruled out. (N Engl J Med 2002;347:1755-60.)

SEVERAL lines of evidence suggest that oxidation of low-density lipoprotein (LDL) in the arterial intima has an important role in atherogenesis.[1-3] Mercuric chloride increased hydrogen peroxide formation and depleted glutathione in rats.[4] In a prospective cohort study in eastern Finland, fish consumption and the levels of mercury in the hair were positively associated with the risk of coronary heart disease and with serum titers of immune complexes containing oxidized LDL. The authors hypothesized that the associations were due to catalysis of lipid peroxidation by mercury, with which fish in the region are highly contaminated.[5]

Cadmium is also postulated to increase the risk of hypertension and coronary heart disease,[6,7] but the evidence is limited and inconsistent.[8] In studies in animals, the administration of mercury modifies the distribution and retention of injected cadmium in various organs,[9,10] a result that suggests an interaction between cadmium and mercury. Selenium is thought to antagonize some of the adverse effects of mercury.[11-16]

In this analysis, we assessed the association between base-line levels of mercury in the toenails and the subsequent risk of coronary heart disease among men in the Health Professionals Follow-up Study. Because the majority of participants are dentists, who have occupational as well as dietary exposures to mercury, the range of mercury burden was unusually wide. The assessment included the evaluation of possible interactions of mercury with cadmium and selenium.

METHODS

Study Population

The Health Professionals Follow-up Study is a prospective cohort study of the relation between diet and coronary heart disease and cancer among 51,529 men who were 40 to 75 years old in 1986. The population includes 29,683 dentists, 10,098 veterinarians, 485 pharmacists, 3745 optometrists, 2218 osteopathic physicians, and 1600 podiatrists. The study began in 1986, when all cohort members completed a mailed questionnaire about dietary intake, risk factors for heart disease, and medical history. Every two years, follow-up questionnaires were sent to obtain updated information on newly diagnosed heart disease during the previous two years. In 1987, the cohort members supplied 33,737 sets of toenail clippings; these were stored for subsequent analyses of trace elements in nested case–control studies. The analysis excluded 1595 men whose reported daily energy intake according to the 1986 semiquantitative food-frequency questionnaire was below 800 kcal per day or greater than 4200 kcal per day or who left 70 or more questions blank on the questionnaire. The men who reported a diagnosis of cancer (other than nonmelanoma skin cancer), myocardial infarction, angina, stroke, coronary-artery bypass surgery, or percutaneous transluminal coronary angioplasty on the 1986 questionnaire were also excluded. This study was approved by the Harvard School of Public Health committee for the protection of human subjects; after participants were informed in writing of the purpose of the study, return of nail specimens by mail was deemed to indicate consent.

Ascertainment of Cases

The participants in the Health Professionals Follow-up Study receive a mailed questionnaire every two years. We searched the Na-

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tional Death Index for deaths among those who did not respond to the questionnaires. Through January 31, 1992, we had received questionnaires from, or confirmed the deaths of, more than 94 percent of eligible participants.[17,18]

Men who had fatal coronary heart disease, nonfatal myocardial infarction, coronary-artery bypass surgery, or percutaneous transluminal coronary angioplasty between the return of toenail clippings in 1987 and January 31, 1992, were considered case patients. A letter was sent to all men who reported a newly diagnosed myocardial infarction on the 1988, 1990, or 1992 follow-up questionnaire to confirm the report and to ask for permission to review their medical records.

A myocardial infarction was confirmed by a study physician using World Health Organization criteria[19] or autopsy reports. Fatal coronary heart disease was considered confirmed if it was listed on the death certificate as the underlying cause and a new diagnosis of coronary heart disease was confirmed by records or interviews. Myocardial infarction was considered the probable cause of death if the medical records could not be obtained but the patient required hospital admission and the diagnosis was corroborated by correspondence or telephone interview of a family member or personal physician. Confirmation of coronary-artery bypass surgery or percutaneous transluminal coronary angioplasty was based on self-report only; hospital records obtained for a sample of 102 men confirmed the procedure for 96 percent of them. Sudden death was considered to be due to coronary heart disease, because most sudden deaths in men are due to myocardial infarction.[17,18] During five years of follow-up between 1987 and January 1992, coronary heart disease developed in 470 participants eligible for this analysis (234 had nonfatal myocardial infarctions; 109 died of coronary heart disease, including 45 who died suddenly; and 127 underwent coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty). For the main analyses, we used the first end point for men with more than one coronary heart disease outcome during follow-up.

For each patient with coronary heart disease, a control subject without coronary heart disease, who was alive at the time the patient received his diagnosis, was chosen randomly from the cohort participants who returned toenail clippings. The patient and the control were matched according to age (within one calendar year), smoking status (current smoker; former smoker, matched according to the number of years since stopping; or nonsmoker [i.e., never smoked]), and the date on which the clippings were returned (within one month). In this analysis we included 442 matched pairs, as well as an additional 28 patients and 22 controls for whom the matched participant had missing data on nail trace-element values or other variables.

Assessment of Exposure

The levels of mercury, selenium, and cadmium in the toenails were analyzed by instrumental neutron-activation analysis at the University of Missouri Research Reactor.[20,21] Before analysis, the toenail clippings were washed in a sonicator with deionized water. Case and control specimens were analyzed together, but in random order, with the case status of the toenail specimens unknown to the laboratory personnel.[21,22] In a quality-control study, the average coefficient of variation was 3.0 percent for selenium, 6.2 percent for mercury, and 14.2 percent for cadmium. Because toenails incorporate mercury during formation but are of different lengths, nail clippings taken from all toes at the same time reflect the incorporation of mercury that has occurred over approximately one year. In a study of nurses, the correlation between mercury levels in nails from the same women collected at an interval of six years was 0.58.[21]

Nutrient intakes were calculated from the 1986 dietary questionnaire.[23] In a food-based validation of the 1986 questionnaire, correlations corrected for week-to-week variation were 0.73 for canned tuna fish and 0.58 for dark-meat fish.[24]

Statistical Analysis

Because the distribution of cadmium levels was skewed to the right, the values were log-transformed to improve normality. The Pearson correlation coefficient for the log-transformed cadmium level and the sample weight was −0.48 ($P<0.001$). Therefore, the cadmium level was adjusted for the weight of the toenail sample with the use of residuals from the regression of log cadmium values on the specimen weight. A constant, the predicted log cadmium level for the mean of sample weight, was added back to the residuals, and the antilog values were then calculated.

Differences in means between patients and controls were tested by paired t-tests after log transformation or by Wilcoxon signed-rank tests. Spearman correlation coefficients were calculated to assess associations between the levels of the metals in the toenails and the consumption of specific foods.

Mercury values were categorized into quintiles on the basis of their distribution among the controls. The association between the level of mercury in the toenails and the risk of coronary heart disease was expressed as the relative risk, estimated as an odds ratio, with the 95 percent confidence interval, when the lowest quintile was used as the reference category. Multiple logistic-regression analysis was used to control for known and potential risk factors. The intake of nutrients and the body-mass index were also grouped into quintiles. Alcohol intake was grouped into four categories: 0.0, 0.1 to 5.0, 5.1 to 30.0, and 30.1 or more grams per day. Age was grouped into six categories: less than or equal to 50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and 71 or more years. Smoking status was grouped into three categories (never smoked, former smoker, and current smoker), and the current smokers were further grouped into two categories (1 to 24 and 25 or more cigarettes per day).

Conditional and unconditional logistic regression gave similar overall results; therefore, in this paper only the results from the latter method are given, to increase power in the subgroups by using the data from all patients and controls. Tests for trend were conducted by assigning the median value for each quintile to all persons in that group and using these values as a continuous, five-level variable. Interactions between mercury and selenium or cadmium were assessed by stratified analysis and the use of a cross-product term, with both elements as continuous variables. In the stratified analysis, the association between mercury levels and coronary heart disease was assessed separately within three levels of cadmium or selenium. In the evaluation of joint classification, nine categories were generated by grouping the amounts of each trace element into three levels.

RESULTS

The range of mercury levels among the control participants was 0.03 to 14.56 μg per gram. Table 1 shows the proportion of dentists, the level of fish consumption, and potential confounding factors according to the level of mercury in the toenails. The mean (±SD) mercury level was 0.91±1.47 μg per gram in dentists, as compared with 0.45±0.40 μg per gram among nondentists ($P<0.001$ by nonparametric unpaired test). Fish consumption among all participants was higher with higher mercury levels. The median toenail mercury levels were 0.29, 0.34, 0.44, 0.62, and 0.75 μg per gram for increasing quintiles of fish consumption (median intake, 20.7, 26.1, 30.4, 37.2, and 51.0 g per day) (Spearman $r=0.42$, $P<0.001$).

The mean mercury level was similar in the patients and the controls, both among matched pairs (mean, 0.74±1.21 μg per gram for patients and 0.72±1.40

TABLE 1. BASE-LINE (1986) CHARACTERISTICS OF THE CONTROLS ACCORDING TO QUINTILE OF MERCURY LEVEL IN THE TOENAILS.*

CHARACTERISTIC	MEDIAN MERCURY LEVEL IN TOENAILS†					P VALUE‡
	0.15 (0.03–0.21)	0.28 (0.22–0.35)	0.45 (0.36–0.54)	0.67 (0.55–0.86)	1.34 (0.87–14.56)	
	range (median)					
No. of men	85	94	97	97	91	
Median age — yr	61	64	62	60	62	0.22
Median body-mass index§	26.2	24.9	25.8	25.0	24.7	0.02
Dentist — no. (%)	34 (40)	57 (61)	60 (62)	68 (70)	76 (84)	<0.001
Family history of coronary heart disease — no. (%)	3 (4)	10 (11)	12 (12)	4 (4)	6 (7)	0.96
Hypertension — no. (%)	22 (26)	28 (30)	21 (22)	23 (24)	20 (22)	0.37
Hypercholesterolemia — no. (%)	6 (7)	8 (9)	10 (10)	12 (12)	12 (13)	0.15
Diabetes mellitus — no. (%)	3 (4)	2 (2)	2 (2)	4 (4)	7 (8)	0.12
Smoking status — no. (%)						
Never smoked	36 (42)	39 (41)	33 (34)	36 (37)	33 (36)	0.44
Former smoker	33 (39)	45 (48)	48 (49)	45 (46)	45 (49)	0.28
Current smoker	14 (16)	8 (9)	14 (14)	11 (11)	9 (10)	0.65
Unknown	2 (2)	2 (2)	2 (2)	5 (5)	4 (4)	
Median daily intake of food or nutrient						
Fish — g	20.7	26.1	30.4	37.2	51.0	<0.001
Red meat — no. of servings	1.1	0.9	0.9	0.8	0.5	<0.001
Poultry — no. of servings	0.21	0.3	0.3	0.3	0.4	0.02
Fruits and vegetables — no. of servings	4.7	4.8	4.6	5.1	6.0	0.01
Alcohol — g	4.7	6.5	7.5	9.2	10.9	0.006
Vitamin E, including supplements — IU	13.3	14.5	13.7	11.8	18.6	0.76
Dietary fiber — g	19.9	20.5	20.8	19.2	23.0	0.04
Folate, including supplements — μg	391	402	397	386	416	0.75
Median toenail selenium level — μg/g	0.85	0.88	0.85	0.84	0.87	0.88
Median toenail cadmium level — μg/g	0.60	0.60	0.63	0.63	0.69	0.03

*Quintiles of toenail mercury were calculated on the basis of data from the 464 controls. Family history of coronary heart disease was defined as a maternal or paternal history of myocardial infarction before 65 years of age. Data on hypertension, hypercholesterolemia, and diabetes mellitus are from self-reports of diagnosis by a physician.

†Quintile values are medians, expressed in micrograms per gram, with the range in parentheses.

‡P values were calculated by a nonparametric test based on Spearman correlation.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

μg per gram for controls; P=0.76 by the nonparametric paired test) and among all patients and controls (mean, 0.72±1.40 μg per gram for the 470 patients and 0.74±1.21 μg per gram for the 464 controls; P=0.36 by the nonparametric unpaired test). The relative risks of coronary heart disease according to quintile of toenail mercury level are shown in Table 2. After adjusting for age, smoking, and other risk factors for coronary heart disease, we found no evidence of an increased risk of coronary heart disease with higher mercury levels. Furthermore, inclusion of n−3 fatty acid intake from fish in the multivariate model did not change the relative risks appreciably.

Toenail cadmium levels were not associated with the risk of coronary heart disease (P for trend=0.18) after adjustment for age, smoking, alcohol intake, presence or absence of a family history of coronary heart disease, high blood pressure, hypercholesterolemia, and diabetes, and body-mass index (the relative risks [and 95 percent confidence intervals] for increasing quintiles of cadmium were 1.00, 0.95 [0.62 to 1.45], 1.11 [0.72 to 1.71], 0.98 [0.64 to 1.52], and 1.31 [0.85 to 2.03]). For men in the highest category of both mercury and cadmium levels (in which the risk was hypothesized to be the greatest), the relative risk, as compared with those who were in the lowest categories of both, was 1.18 (95 percent confidence interval, 0.68 to 2.04). The interaction was not significant (P=0.87).

Table 3 shows the relative risks of coronary heart disease according to toenail mercury levels within three roughly equal categories of toenail selenium level (low, medium, and high). The toenail mercury levels within the low and medium selenium categories were not significantly associated with the risk of coronary heart disease. Within the highest nail selenium category,

TABLE 2. RELATIVE RISK OF CORONARY HEART DISEASE DURING THREE YEARS OF FOLLOW-UP ACCORDING TO TOENAIL MERCURY LEVELS IN 934 SUBJECTS.

MEASURE*	QUINTILE OF MERCURY LEVEL					P FOR TREND†
	1	2	3	4	5	
Mercury level in toenails — μg/g						
Median	0.15	0.28	0.45	0.67	1.34	
Range	0.03–0.21	0.22–0.35	0.36–0.54	0.55–0.86	0.87–14.56	
No. of patients (n=470)	101	93	90	90	96	
No. of controls (n=464)	85	94	97	97	91	
Age- and smoking-adjusted RR (95% CI)‡§	1.00	0.83 (0.55–1.25)	0.77 (0.51–1.16)	0.77 (0.51–1.16)	0.87 (0.57–1.31)	0.83
Multivariate RR (95% CI)‡¶	1.00	0.92 (0.60–1.41)	0.80 (0.52–1.24)	0.92 (0.60–1.41)	0.97 (0.63–1.50)	0.78
Multivariate RR (95% CI)‡‖	1.00	0.93 (0.60–1.43)	0.83 (0.53–1.30)	0.96 (0.62–1.51)	1.03 (0.65–1.65)	0.55

*RR denotes relative risk, and CI confidence interval.

†The P value was calculated from a test for trend across quintiles.

‡The lowest quintile of toenail mercury level served as the reference category.

§Values have been adjusted for age (six categories: ≤50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and >70 years) and smoking status (four categories: never smoked, former smoker, 1–24 cigarettes daily, and >24 cigarettes daily).

¶Values have been adjusted for age (six categories: ≤50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and >70 years), smoking status (four categories: never smoked, former smoker, 1 to 24 cigarettes daily, and >24 cigarettes daily), alcohol intake (four categories: 0, 1.0 to 5.0, 5.1 to 30.0, and >30.0 g per day), family history of coronary heart disease (binary), high blood pressure (binary), hypercholesterolemia (binary,) diabetes (binary), body-mass index (five categories) at the 1986 base line, and quintile of toenail sample weight.

‖Values have been adjusted for the covariates listed above and also for quintiles of intake of n−3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid).

men with the highest mercury level had a higher risk of coronary heart disease than those with the lowest mercury level; however, the result of the test for trend did not attain statistical significance. The subjects were also divided into three groups according to levels of mercury, as well as according to selenium levels. For men in the highest category for mercury and the lowest category for selenium, in which the risk was hypothesized to be the greatest, the multivariate relative risk, as compared with those in the lowest category for mercury and the highest category for selenium, was 0.99 (95 percent confidence interval, 0.57 to 1.72), after age and other risk factors were controlled for (P for interaction=0.89).

In separate multivariate analyses, the relative risk of nonfatal myocardial infarction or fatal coronary heart disease for men in the highest versus the lowest quintile of mercury level was 1.04 (95 percent confidence interval, 0.65 to 1.68; P for trend=0.68), and for coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty, the relative risk was 0.96 (95 percent confidence interval, 0.48 to 1.90; P for trend=0.65).

The form of mercury in fish is primarily methylmercury, and that to which dentists are occupationally exposed is elemental mercury. Because it is possible that different forms of mercury may have different effects on cardiovascular risk, we repeated our analyses after excluding dentists. Although the statistical power was substantially reduced (220 cases), we observed a nonsignificant association with the toenail mercury level. The multivariate relative risk for the highest (0.84 μg per gram) versus the lowest (0.13 μg per gram) quintile of mercury was 1.27 (95 percent confidence interval, 0.62 to 2.59; P for trend=0.43); with additional control for intake of eicosapentaenoic acid plus docosahexaenoic acid, the relative risk was 1.70 (95 percent confidence interval, 0.78 to 3.73; P for trend=0.41).

DISCUSSION

Among the participants in this study, dentists and those who ate more fish had significantly higher levels of mercury in their toenails. However, our data do not support an association between mercury levels and an increased risk of coronary heart disease, as has been reported previously[5] and also in a study reported in this issue of the *Journal*.[25] The absence of any clear association is probably not due to methodologic bias, because this study used a nested case–control design within a large prospective cohort, and because the toenail specimens were collected prospectively before the

TABLE 3. RELATIVE RISK OF CORONARY HEART DISEASE DURING THREE YEARS OF FOLLOW-UP ACCORDING TO TOENAIL MERCURY AND SELENIUM LEVELS AMONG PATIENTS AND CONTROLS.

MEASURE*	QUINTILE OF MERCURY LEVEL					P FOR TREND†
	1	2	3	4	5	
Low selenium (range, 0.49–0.81 μg/g)‡						
No. of controls (n=159)	28	27	37	37	30	
No. of patients (n=153)	37	29	23	33	31	
Multivariate RR (95% CI)§¶	1.00	0.99 (0.45–2.16)	0.51 (0.23–1.12)	0.78 (0.37–1.63)	1.00 (0.46–2.20)	0.70
Medium selenium (range, 0.81–0.94 μg/g)‡						
No. of controls (n=157)	26	33	32	31	35	
No. of patients (n=153)	33	28	31	31	30	
Multivariate RR (95% CI)§¶	1.00	0.65 (0.30–1.43)	0.72 (0.33–1.56)	0.96 (0.45–2.08)	0.65 (0.30–1.44)	0.50
High selenium (range, 0.94–5.00 μg/g)‡						
No. of controls (n=148)	31	34	28	29	26	
No. of patients (n=164)	31	36	36	26	35	
Multivariate RR (95% CI)§¶	1.00	1.58 (0.73–3.46)	1.82 (0.81–4.12)	1.69 (0.71–4.03)	2.47 (1.01–6.04)	0.12

*RR denotes relative risk, and CI confidence interval.

†The P value was calculated by a test for trend across quintiles.

‡The range includes both the patients and controls.

§The lowest quintile of toenail mercury level served as the reference category.

¶Values have been adjusted for age (six categories: ≤50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, and >70 years), smoking status (four categories: never smoked, former smoker, 1 to 24 cigarettes daily, and >24 cigarettes daily), alcohol intake (four categories: 0, 1.0 to 5.0, 5.1 to 30.0, and >30.0 g/day), family history of coronary heart disease (binary), high blood pressure (binary), hypercholesterolemia (binary), diabetes (binary), body-mass index (five categories) at the 1986 base line, and continuous toenail sample weight.

coronary heart disease events occurred. The absence of an association between mercury levels and coronary heart disease could be due to a limited range of mercury exposure. It is also possible that mercury levels in nails are not a good indicator of long-term mercury intake. However, the strong relation between mercury levels in nails and the intake of fish, as measured by a food-frequency questionnaire, and the much higher levels in dentists than nondentists support the validity of mercury levels in nails as a measure of exposure. Because of the occupational exposure of dentists, the range of mercury levels was greater than would be seen in the general U.S. population. Toenail mercury levels have previously been demonstrated to be a valid measure of dietary mercury exposure.[26] Nail mercury levels also provided an indicator of the long-term body burden of mercury among women in the Nurses' Health Study.[21]

We speculated that there might be some beneficial effects of n−3 fatty acids in fish that could counterbalance the effect of mercury. However, the multivariate analysis that controlled for n−3 fatty acid intake did not change the relative risks appreciably. Furthermore, in the same Health Professionals Follow-up Study cohort, increasing fish intake (from one to two servings per week to five to six servings per week) was not associated with the overall incidence of coronary heart disease, although an inverse trend was seen with the small number of sudden deaths.[27] The positive association between fish consumption and the risk of coronary heart disease in the Finnish study[5,28] could be due to differences in the nutrient composition of the fish, unique contaminants, or different risk-factor characteristics among fish eaters. The concentrations of mercury in hair from subjects in the Finnish study and in toenails from the recent European study[25] are similar to or lower than those reported in our study.

The form of mercury consumed in fish is primarily methylmercury, and that due to the occupational exposure of dentists is primarily elemental mercury. As indicated by the strong associations with toenail mercury concentrations in our study, both forms of mercury are absorbed, and both can have serious neurologic toxic effects.[29] However, there are some differences in the clinical and pathological manifestations of neurologic toxicity from these two forms of mercury, so the possibility exists that they might influence the risk of cardiovascular disease differently. We found a positive but nonsignificant association between mercury levels and the risk of coronary heart disease in an analysis excluding dentists.

The marginally significant increased risk of coronary heart disease associated with higher mercury levels among men in the highest third of the group with re-

spect to selenium level was probably due to chance, because the combination of high mercury and low selenium levels was not associated with excess risk. The higher proportion of current smokers in the lowest mercury-level category in this study is probably due to the participants' lifestyles, because health-oriented men may eat more fish in addition to not smoking.

In conclusion, toenail mercury levels measured by neutron activation reflect occupational exposure of dentists and intake of fish. However, we found no evidence, over a wide range of mercury exposures, that the overall levels were associated with any substantial increase in the risk of coronary heart disease. Furthermore, we found no increase in risk of coronary heart disease associated with higher mercury levels in combination with low selenium or high cadmium levels. However, a weak relation between mercury exposure, particularly from fish consumption, and the risk of coronary heart disease cannot be excluded.

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