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ORIGINAL PAPER

Dietary arsenic intake and subsequent risk of cancer: the Japan Public Health Center-based (JPHC) Prospective Study

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Abstract
Purpose Arsenic is a known human carcinogen and has been linked to adverse health outcomes, including cancer. However, the effects of arsenic exposure from food on health are still unknown. We researched to examine the association between arsenic exposure from food and incidence of cancer in a Japanese population.
Methods We conducted a population-based prospective study in 90,378 Japanese men and women aged 45–74 years. Participants responded to a validated questionnaire that included 138 food items. We estimated dietary arsenic intake from 12 food groups (75 items) based on the questionnaire data. During 11 years of follow-up, 7,002 cancer cases were identified. Hazard ratios (HRs) and 95 % confidence intervals (CIs) for cancer were calculated by Cox proportional hazards modeling.
Results Total arsenic and inorganic arsenic showed no association with the risk of total cancer in both men and women. Total arsenic and inorganic arsenic intake tended to be associated with an increased risk of lung cancer in men. In particular, these positive associations were strengthened in currently smoking men, with HRs (95 % CI) in the highest categories of arsenic and inorganic arsenic intake compared with the lowest of 1.29 (95 % CI = 1.03–1.61) and 1.36 (95 % CI = 1.09–1.70), respectively. We also detected an interaction between arsenic and inorganic arsenic intake and smoking status in men ($p_{\text{interaction}} < 0.01$ and 0.07, respectively).
Conclusion A significant dose–response trend was seen in the association of arsenic and inorganic intake with lung cancer risk in currently smoking men.

Keywords Arsenic intake · Cancer · Lung cancer · Prospective study

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Introduction

Arsenic is widely distributed in nature, and the general population is exposed to arsenic through air, drinking water, food, and beverages [1]. The International Agency for Research on Cancer documented that arsenic is a group 1 human carcinogen, and there is sufficient evidence to establish that arsenic in drinking water causes cancers of the urinary bladder, lung, and skin in humans [2]. However, most previous studies were conducted among highly exposed populations, namely workers with occupational exposure or drinkers of contaminated well water in Taiwan [3–9], Japan [10–12], Chile [13, 14], Argentina [15–17], and Bangladesh [18].

Although the Japanese Water Supply Law and Ordinance presently restricts arsenic concentration in drinking water to less than 0.01 mg/L, Japanese people commonly consume various seafood and seaweeds which accumulate arsenic [1]. In one study, mean arsenic levels in foods commonly consumed by Japanese were two times higher than those in Western countries, for example, the USA, Canada, and Sweden [19]. Although seafood and seaweeds

generally contain almost completely nontoxic organic arsenic, for example, arsenosugars [20], arsenosugars detected in seaweeds are metabolized to dimethylarsinic acid in humans, which is more toxic than arsenosugars [21]. Additionally, the edible seaweed *hijiki* (Hizikia fusiforme), which is often consumed by Japanese people, contains toxic inorganic arsenic [22–24]. However, the effects of arsenic and inorganic arsenic exposure from food on health are still unknown. The possible effects of arsenic and inorganic arsenic on cancer risk are therefore an important public health issue among Japanese, who have relatively high arsenic exposure from food.

Here, we investigated the association between arsenic intake and subsequent cancer in a large prospective cohort study in Japan.

Materials and methods

Study population

The Japan Public Health Center-based (JPHC) Prospective Study was launched from 1990 for Cohort I and from 1993 for Cohort II. The study design has been described in detail previously [25]. The participants were recruited in five Public Health Center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo) for Cohort I, and in six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka) for Cohort II. In the present analysis, Tokyo subjects were not included in data analyses because incidence data for them were not available. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

The cohort participants responded to a self-administered questionnaire at baseline in 1990 (Cohort I) and 1993 (Cohort II). A five-year follow-up survey was conducted in 1995 (Cohort I) and 1998 (Cohort II). The five-year follow-up survey included more comprehensive information on food intake frequency than the baseline survey and accordingly was used as baseline (starting point) for the present study. The questionnaire also included information on medical history and lifestyle factors, such as smoking, alcohol drinking, and others. After exclusion of 11,933 persons who had died, moved out of a study area, or were lost to follow-up before the starting point, the remaining 121,143 subjects were eligible for participation. Of these, 98,513 subjects responded (46,028 men, 52,485 women; response rate 81.3 %) and were included in the present study.

Assessment of arsenic intake

A self-administered food frequency questionnaire (FFQ) in the 5-year follow-up survey had 138 food and beverage items with standard portions/units and nine frequency categories. A standard portion size was specified for each food item, and respondents were asked to choose their usual portion size from three options (less than half the standard portion size, standard portion size, or more than 1.5 times the standard portion size).

We selected items containing arsenic based on items common to our FFQ and reports from the Ministry of Agriculture, Forestry and Fisheries of Japan [26] and from Ishizaki et al. [27]. Average concentrations reported in these studies were from at least five items in each food. The following 12 food groups (75 items) were then selected: rice (3 items: "boiled rice," "boiled rice cooked with millet or barley," and "rice cake"); wheat (6 items: "bread," "noodle (in Okinawa)," "wheat noodle," "Chinese noodle," "biscuit," and "cake"); soybeans (7 items: "*tofu*," "*yushidofu* [predrained tofu]," "*koyadofu* [freeze-dried tofu]," "*aburaage* [deep-fried tofu]," "*natto* [fermented soybean]," "miso [fermented soybean paste]," and "soy milk"); potatoes (3 items: "potato," "sweet potato," and "taro"); vegetables, including mushrooms (19 items: "Chinese radish," "pickled Chinese radish," "carrot," "cabbage," "broccoli," "Chinese cabbage," "lettuce," "spinach," "onion," "cucumber," "pickled cucumber," "pickled eggplant," "tomato," "tomato juice," "sweet pepper," "shiitake mushroom," "garland chrysanthemum," "pumpkin," and "shimeji mushroom and enoki mushroom"); fruits (12 items: "strawberry," "apple," "orange," "persimmon," "kiwifruit," "melon," "banana," "pear," "grapes," "pineapple," "apple juice," and "orange juice"); seafood (13 items: "bonito," "tuna," "sea bream," "horse mackerel," "saury," "squid," "prawn," "crab shell," "canned tuna," "*chikuwa*, fish paste product," "*kamaboko*, fish paste product," "flatfish," and "mackerel"); seaweeds (2 items: "*wakame*, brown seaweed; and *kombu*, kelp" and "*Nori*, dried laver seaweed"); *hijiki* (1 item: *hijiki*); meats (5 items: "chicken," "pork," "beef," "chicken liver," and "pork liver"); eggs (1 item: egg); and dairy products (3 items: "milk," "cheese," and "butter"). Arsenic intake was calculated by multiplying the average arsenic concentration in each item by the quantity of each item. We used average arsenic concentrations based on reports from the Ministry of Agriculture, Forestry and Fisheries of Japan [26] and from Ishizaki et al. [27]. The amount of each food consumed (grams/day) was calculated from responses in the FFQ, and total arsenic intake from food was calculated by summing arsenic intake from each item. None of the regions in which our cohorts resided are reported to be arsenic-contaminated areas, other than Niigata Prefecture. However, the Japanese Water Supply Law and Ordinance concerning water limits arsenic in drinking water to less than 0.01 mg/L. Further, wells are not generally used, and the diffusion rate of municipal water supply is more than 99.9 % in the cohort area in

Niigata (both data from the cohort area in Niigata) [28]. We therefore excluded arsenic in drinking water from consideration. Additionally, we calculated inorganic arsenic intake using reports from the Food Safety Commission of the Cabinet Office [29]. The proportion of inorganic arsenic to total arsenic among food groups is as follows: 86 % in rice, 73 % in *hijiki*, 10 % in seaweeds other than *hijiki*, and 5 % in seafood. The proportion of inorganic arsenic to total arsenic among other food groups is assumed to be 100 %, because these are unknown [29].

Of the 98,513 subjects who completed the questionnaire, we exclude those with a history of cancer ($n = 2,228$) and those who reported extreme total energy intake (lower and upper 2.5 percentiles: 990 and 4,204 kcal/day in men and 837 and 3,685 kcal/day in women, respectively), leaving 90,378 subjects for final analysis, including 7,002 with cancer. Energy intake was calculated using the Fifth Revised Edition of the Standard Tables of Food Composition in Japan [30].

To evaluate the validity of energy-adjusted arsenic intake, we compared estimates from the FFQ with 28-day (or 14-day for the Okinawa PHC area) dietary records from a subsample of the cohort. Spearman's rank correlation coefficients for arsenic and inorganic arsenic were 0.30 and 0.33 in men and 0.15 and 0.19 in women, respectively.

Follow-up and identification of cancer cases

We followed up all registered cohort subjects from the starting point until 31 December 2008. Residency registration and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are thought to be complete. During the follow-up period in the present study, 9,370 subjects died, 2,951 moved out of the study area, and 298 (0.3 %) were lost to follow-up.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and from data linkage with population-based cancer registries, with permission from each of the local governments responsible for the cancer registries. Information on the cause of death was supplemented by death certificate information, with permission. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The proportion of cases ascertained by death certificate only (DCO) was 6.1 %. These ratios were considered satisfactory for the present study. For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers diagnosed at different times.

Statistical analysis

Person-years of follow-up were calculated for each subject from the date of the starting point to the date of cancer diagnosis, date of relocation from the study area, date of death, or end of the study period (31 December 2008), whichever occurred first. For subjects who were lost to follow-up, the last confirmed date of presence in the study area was used as the date of censor.

The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) of cancer by energy-adjusted arsenic intake using the SAS program (PROC PHREG) (SAS Institute Inc., Cary, NC, USA). Arsenic is included in a lot of foods, and thus increasing intake of various foods is speculated as increasing arsenic and energy intake. Thus, energy adjustment of arsenic intake was done using the residual method [31].

HRs were adjusted for the following potential confounding factors: age at the starting point (five-year groups), PHC area, smoking status (never, former, and current: <20, 21–40, or ≥41 cigarettes/d), alcohol intake (almost never, less than 3–4 times/week, and more than 5–6 times/week), body mass index (<21, 21–23, 23–25, and ≥25), and sports in leisure time (almost none, less than 1–2 times/week, and more than 3–4 times/week) in the analysis of the association between arsenic and cancer. Moreover, women were further adjusted for menopausal status (premenopausal and postmenopausal) and use of exogenous female hormones (yes or no). These variables, obtained from the questionnaire, are either known or suspected risk factors for cancer that have been identified in the previous studies. Furthermore, we adjusted for screening examination (chest radiograph, gastric radiograph, gastrointestinal endoscopy, fecal occult blood test, barium enema, colonoscopy for men and women, mammography, and Papanicolaou smear for women) and nuclear family (father, mother, brothers, and sisters) history of any cancer, but the results did not substantially change. Therefore, we did not adjust for screening examination or family history of cancer in the final model.

Because of potential synergistic effects between arsenic and smoking on lung cancer [6, 11, 18, 32], we then tested effect modification by smoking status (never and ever) through the addition of cross-product terms into the multivariate model. Trends were assessed by assignment of the ordinal value. All p values were two-sided, and statistical significance was determined at the $p < 0.05$ level.

Results

The average estimated energy-adjusted arsenic intake in the cohort was 170.0 μg/d. Seafood, *hijiki*, seaweeds, rice, and vegetables contributed 32, 28, 20, 16, and 1 % of total arsenic intake, respectively. Other food groups contributed less than 1 % of arsenic intake. *Hijiki*, rice, seaweeds,

Table 1 Subject characteristics by quartile of arsenic intake

	Men (n = 42,029)				Women (n = 48,349)			
	Lowest	Second	Third	Highest	Lowest	Second	Third	Highest
Arsenic intake (median, μg)	88.3	127.8	166.1	247.5	93.7	132.2	171.5	253.2
Inorganic arsenic (median, μg)	40.5	54.7	63.5	99.1	40.6	53.7	62.6	105.7
No. of subjects	10,507	10,507	10,508	10,507	12,087	12,088	12,087	12,087
Age, years ± SD	55.7 ± 7.9	56.0 ± 7.6	56.9 ± 7.6	58.2 ± 7.8	56.3 ± 8.2	56.4 ± 7.8	57.2 ± 7.7	58.3 ± 7.8
Body mass index, ±SD (kg/m^2)	23.7 ± 3.0	23.5 ± 2.9	23.6 ± 2.8	23.5 ± 2.8	23.5 ± 3.2	23.4 ± 3.2	23.5 ± 3.2	23.6 ± 3.1
Never smoker (%)	31.1	32.2	34.3	35.8	86.0	88.0	88.8	86.7
Alcohol intake (≥5 times/week) (%)	56.0	50.9	46.7	42.2	6.7	5.1	4.2	3.5
Leisure time physical activity (≥3 times/week) (%)	9.3	9.8	10.7	12.7	8.6	9.4	11.0	13.3
Postmenopausal (%)	–	–	–	–	74.6	76.3	79.3	83.3
Use of exogenous female hormones (%)	–	–	–	–	2.8	2.6	2.5	2.3
Energy, ±SD (kcal/day)	2,170.5 ± 675.4	2,152.0 ± 608.3	2,148.2 ± 627.3	2,181.6 ± 651.5	1,872.9 ± 604.7	1,838.6 ± 534.4	1,851.1 ± 546.2	1,866.2 ± 561.3
Rice, ±SD (g/day)	190.7 ± 73.7	205.6 ± 71.8	202.5 ± 68.6	185.5 ± 66.4	159.8 ± 60.3	166.9 ± 54.4	162.6 ± 52.5	150.4 ± 52.7
Wheat, ±SD (g/day)	43.3 ± 42.1	40.6 ± 30.7	39.5 ± 28.6	40.3 ± 28.6	47.5 ± 40.3	41.2 ± 29.1	38.9 ± 26.7	38.0 ± 27.5
Soybean, ±SD (g/day)	27.0 ± 27.1	30.4 ± 21.9	33.4 ± 23.0	37.4 ± 26.6	27.3 ± 24.8	30.5 ± 21.2	33.1 ± 21.7	37.3 ± 26.8
Potatoes, ±SD (g/day)	16.3 ± 20.1	20.8 ± 19.7	25.2 ± 22.3	32.2 ± 27.4	24.1 ± 26.3	29.0 ± 23.5	32.8 ± 24.0	39.6 ± 30.2
Vegetables, ±SD (g/day)	159.4 ± 130.2	188.5 ± 120.7	211.7 ± 121.0	244.4 ± 134.0	204.1 ± 141.8	224.6 ± 125.8	243.1 ± 123.8	269.2 ± 138.5
Seafood, ±SD (g/day)	57.2 ± 36.1	81.3 ± 38.9	102.5 ± 43.6	132.6 ± 68.6	59.1 ± 38.6	80.4 ± 37.5	98.7 ± 41.9	117.6 ± 59.9
Seaweed, ±SD (g/day)	2.5 ± 3.1	5.8 ± 4.5	8.8 ± 6.3	14.5 ± 15.3	4.5 ± 3.6	7.3 ± 5.0	10.4 ± 6.6	16.3 ± 15.4
Hijiki, ±SD (g/day)	1.0 ± 0.4	1.3 ± 0.5	1.8 ± 1.0	5.0 ± 5.8	1.1 ± 0.4	1.4 ± 0.6	2.0 ± 1.1	5.8 ± 7.1
Meat, ±SD (g/day)	68.7 ± 50.4	65.9 ± 40.8	64.8 ± 39.0	62.4 ± 38.9	65.0 ± 46.6	59.3 ± 35.1	56.2 ± 33.0	53.2 ± 34.8
Dairy, ±SD (g/day)	189.8 ± 244.4	166.4 ± 175.1	164.8 ± 164.8	166.0 ± 162.5	242.4 ± 238.3	207.8 ± 177.4	194.4 ± 162.0	198.0 ± 168.5

Table 2 Hazard ratios for total cancer incidence by quartile of arsenic and inorganic arsenic intake

	Intake by quartile				p_{trend}
	Lowest	Second	Third	Highest	
Arsenic					
Men					
Median intake (μg/day)	88.8	127.8	166.1	247.5	
Number of cases	1,002	1,038	1,116	1,167	
Person-years of follow-up	112,502	112,696	112,003	109,158	
Age–area-adjusted HR (95 % CI)	1.00	1.00 (0.92–1.09)	0.99 (0.91–1.08)	0.98 (0.89–1.06)	0.56
Multivariate HR (95 % CI)	1.00	1.01 (0.92–1.11)	1.04 (0.94–1.14)	1.03 (0.94–1.13)	0.50
Women					
Median intake (μg/day)	93.7	132.2	171.5	25.3	
Number of cases	635	646	715	683	
Person-years of follow-up	133,894	135,104	134,924	132,963	
Age–area-adjusted HR (95 % CI)	1.00	0.99 (0.89–1.10)	1.05 (0.95–1.18)	0.98 (0.88–1.10)	0.96
Multivariate HR (95 % CI)	1.00	0.99 (0.88–1.12)	1.07 (0.96–1.21)	0.98 (0.87–1.10)	0.94
Inorganic arsenic					
Men					
Median intake (μg/day)	36.5	51.4	64.7	102.2	
Number of cases	1,084	1,072	1,042	1,125	
Person-years of follow-up	111,399	112,541	112,403	110,017	
Age–area-adjusted HR (95 % CI)	1.00	0.96 (0.88–1.05)	0.91 (0.83–0.99)	0.94 (0.86–1.02)	0.09
Multivariate HR (95 % CI)	1.00	0.98 (0.89–1.07)	0.95 (0.87–1.05)	1.00 (0.91–1.10)	0.92
Women					
Median intake (μg/day)	37.1	51.2	64.1	107.6	
Number of cases	634	649	722	674	
Person-years of follow-up	134,833	134,486	134,491	133,075	
Age–area-adjusted HR (95 % CI)	1.00	1.02 (0.91–1.14)	1.10 (0.99–1.23)	1.02 (0.91–1.14)	0.51
Multivariate HR (95 % CI)	1.00	1.00 (0.89–1.12)	1.08 (0.96–1.22)	0.99 (0.87–1.11)	0.85

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, and leisure time physical activity. They were further adjusted for menopausal status and use of exogenous female hormones in women

seafood, vegetables, and fruits contributed 50, 35, 5, 4, 3, and 2 % of inorganic arsenic intake, respectively. Other food groups contributed less than 1 % of inorganic arsenic intake.

During 983,245 person-years of follow-up (average follow-up period 10.9 years) for 90,378 subjects (42,029 men and 48,349 women), there were 7,002 newly diagnosed cases of cancer (4,323 in men and 2,679 in women). In men, gastric cancer was the most common ($n = 781$, 18 %), followed by cancers of the lung ($n = 685$, 16 %), colorectum ($n = 681$, 16 %), and prostate ($n = 595$, 14 %). In women, the most common cancers were colorectal cancer ($n = 481$, 18 %), followed by cancers of the breast ($n = 470$, 18 %), stomach ($n = 328$, 12 %), and lung ($n = 290$, 11 %).

The characteristics of participants according to arsenic intake are shown in Table 1. Men and women with higher arsenic intake tended to be older, smoke less, drink less alcohol, and consume less rice, wheat, meat, and dairy products and consume more soybeans, potatoes, vegetables, seaweeds, seafood, and *hijiki*. In women with higher arsenic intake, the proportion of postmenopausal women was high and use of exogenous female hormones was low.

Table 2 shows the association of arsenic and inorganic arsenic intake with total cancer incidence. No relationship was observed between arsenic and total cancer, with HRs for the highest versus lowest quartile of 1.03 (95 % CI = 0.94–1.13) for men and 0.98 (0.87–1.10) for women. Furthermore, no association was also shown between inorganic arsenic and total cancer, with HRs for the highest versus lowest quartile of 1.00 (95 % CI = 0.91 to 1.10) for men and 0.99 (0.87 to 1.11) for women.

On additional analysis that used specific cancers as endpoints, higher consumption of arsenic was associated with a higher risk of lung cancer in men (Table 3), although the linear trend was not significant (multivariable HR in the third and highest categories (HR = 1.35, 95 % CI = 1.06–1.72; and HR = 1.23, 95 % CI = 0.96–1.57, respectively)). In contrast, no association was shown

Table 3 Hazard ratios for incidence of cancer at specific sites by quartile of arsenic intake in men

	Intake by quartile				p_{trend}
	Lowest	Second	Third	Highest	
Men					
Stomach					
Number of cases	141	188	171	186	
Multivariate HR (95 % CI)	1.00	1.18 (0.94–1.47)	1.00 (0.80–1.25)	1.09 (0.87–1.37)	0.86
Colorectal					
Number of cases	150	142	150	159	
Multivariate HR (95 % CI)	1.00	0.94 (0.75–1.19)	0.96 (0.76–1.21)	1.01 (0.80–1.28)	0.88
Liver					
Number of cases	61	57	82	85	
Multivariate HR (95 % CI)	1.00	0.79 (0.55–1.13)	1.01 (0.72–1.42)	0.93 (0.66–1.32)	0.89
Pancreas					
Number of cases	29	44	39	30	
Multivariate HR (95 % CI)	1.00	1.33 (0.83–2.13)	1.10 (0.67–1.80)	0.84 (0.50–1.43)	0.35
Lung					
Number of cases	119	144	174	162	
Multivariate HR (95 % CI)	1.00	1.18 (0.92–1.51)	1.35 (1.06–1.72)	1.23 (0.96–1.57)	0.07
Prostate					
Number of cases	111	119	142	148	
Multivariate HR (95 % CI)	1.00	0.99 (0.76–1.28)	1.06 (0.82–1.37)	1.08 (0.83–1.39)	0.47
Bladder					
Number of cases	33	36	35	37	
Multivariate HR (95 % CI)	1.00	1.01 (0.62–1.62)	0.90 (0.55–1.47)	0.95 (0.58–1.55)	0.74
Kidney					
Number of cases	17	20	23	23	
Multivariate HR (95 % CI)	1.00	1.22 (0.64–2.35)	1.41 (0.74–2.67)	1.44 (0.75–2.75)	0.25

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, and leisure time physical activity

between arsenic intake and any specific cancer in women (Table 4), including lung cancer.

Additionally, we observed a positive association between inorganic arsenic intake and lung and kidney cancer risk in men (Table 5). The multivariate HRs of lung cancer across increasing quartiles of inorganic arsenic were 1.00, 1.15, 1.19, and 1.28 (95 % CI = 1.00–1.62; p_{trend} = 0.05). For kidney cancer, the multivariate HRs across increasing quartiles of inorganic arsenic were 1.00, 1.72, 1.66, and 2.05 (95 % CI = 1.05–4.03; p_{trend} = 0.06). Similar findings in lung cancer were observed in women, albeit without statistical significance (Table 6). Multivariable HR for the highest versus lowest quartile of inorganic arsenic was 1.37 (95 % CI = 0.95–1.98, p_{trend} = 0.08).

No substantial changes in results were seen after stratifying by age and body mass index; on analysis by decile of arsenic and inorganic intake; or after further adjustment for additional nutrition factors, such as fiber and calcium intake (data not shown). Furthermore, our analyses did not change when restricted to cases that occurred after the first 3 years of follow-up (data not shown).

To evaluate potential synergistic effects between arsenic and smoking on lung cancer, we also assessed the effect of arsenic and inorganic arsenic intake on lung cancer according to smoking status (Table 7). Arsenic intake was inversely associated with lung cancer risk in never smokers (highest tertile compared with lowest, multivariate HR = 0.49 (95 % CI = 0.27–0.86), p for trend = 0.01). In contrast, we observed that HRs increased as arsenic intake increased among current smokers (highest tertile compared with lowest, multivariate HR = 1.37 (95 % CI = 1.06–1.77), p for trend = 0.03) and detected an interaction between arsenic intake and smoking status ($p_{interaction} < 0.01$). Similarly, we detected an increased risk among current smokers who had a high intake of inorganic arsenic (highest tertile compared with lowest, multivariate HR = 1.38 (95 % CI = 1.07–1.77), p for trend = 0.01) and an interaction between inorganic arsenic intake and smoking status ($p_{interaction}$ = 0.07). In never-smoking women, inorganic arsenic was positively associated with lung cancer risk (HR for the highest versus lowest tertile was 1.57 (95 % CI = 1.12–2.20)) and arsenic intake slightly increased the risk of lung cancer (HR for the

Table 4 Hazard ratios for incidence of cancer at specific sites by quartile of arsenic intake in women

	Intake by quartile				p_{trend}
	Lowest	Second	Third	Highest	
Women					
Stomach					
Number of cases	63	71	64	75	
Multivariate HR (95 % CI)	1.00	0.99 (0.70–1.39)	0.84 (0.59–1.19)	0.96 (0.68–1.36)	0.64
Colorectal					
Number of cases	97	97	117	107	
Multivariate HR (95 % CI)	1.00	0.98 (0.74–1.30)	1.15 (0.97–1.51)	1.05 (0.79–1.39)	0.51
Liver					
Number of cases	21	33	34	29	
Multivariate HR (95 % CI)	1.00	1.36 (0.78–2.37)	1.28 (0.74–2.23)	1.05 (0.59–1.87)	0.95
Pancreas					
Number of cases	26	21	34	24	
Multivariate HR (95 % CI)	1.00	0.80 (0.44–1.39)	1.17 (0.69–1.99)	0.81 (0.45–1.43)	0.81
Lung					
Number of cases	60	54	66	74	
Multivariate HR (95 % CI)	1.00	0.89 (0.61–1.29)	1.05 (0.74–1.51)	1.16 (0.81–1.65)	0.28
Breast					
Number of cases	102	100	124	105	
Multivariate HR (95 % CI)	1.00	0.95 (0.72–1.26)	1.19 (0.91–1.56)	1.06 (0.80–1.41)	0.35
Endometrial					
Number of cases	18	21	19	20	
Multivariate HR (95 % CI)	1.00	1.13 (0.60–2.14)	1.08 (0.56–2.08)	1.23 (0.64–2.37)	0.58
Bladder					
Number of cases	7	9	10	7	
Multivariate HR (95 % CI)	1.00	1.37 (0.50–3.73)	1.61 (0.60–4.34)	1.17 (0.40–3.44)	0.70
Kidney					
Number of cases	8	9	13	4	
Multivariate HR (95 % CI)	1.00	1.03 (0.39–2.71)	1.53 (0.62–3.78)	0.48 (0.14–1.64)	0.50

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, leisure time physical activity, menopausal status, and use of exogenous female hormones

highest versus lowest tertile was 1.25 (95 % CI = 0.90–1.75)), although no interaction was detected in women ($p_{interaction}$ for arsenic and inorganic arsenic 0.14 and 0.31, respectively).

With regard to *hijiki*, which had the highest ratio of inorganic arsenic, although *hijiki* intake showed a slight positive association with lung cancer in ever-smoking men (highest tertile compared with lowest, multivariate HR = 1.22 (95 % CI = 0.995–1.51), p for trend = 0.05), we did not detect an interaction between *hijiki* intake and smoking status ($p_{interaction} = 0.54$). In women, although *hijiki* intake was positively associated with lung cancer risk in never-smoking women (HR for the highest versus lowest tertile 1.46 (95 % CI = 1.06–2.01)), we did not detect an interaction between *hijiki* intake and smoking status ($p_{interaction} = 0.12$) (data not shown).

Discussion

Here, we investigated the association between arsenic intake and the risk of cancer in a population-based prospective study in Japan. Although we saw no overall association between arsenic and inorganic arsenic intake and total cancer, results showed an increased risk of lung cancer in men with a higher consumption of arsenic and inorganic arsenic, especially among currently smoking men. Of particular note, we showed that cigarette smoking had a modifying effect on the association between arsenic intake and lung cancer.

Many studies have reported that arsenic intake through drinking water is positively associated with the risk of cancers of the lung [5–7, 9–14, 16, 18, 32, 33], bladder [5, 7–9, 13–15, 17, 33, 34], kidney [13, 16, 33], and liver [5, 9,

Table 5 Hazard ratios for incidence of cancer at specific sites by quartile of inorganic arsenic intake in men

	Intake by quartile				p_{trend}
	Lowest	Second	Third	Highest	
Men					
Stomach					
Number of cases	164	188	166	168	
Multivariate HR (95 % CI)	1.00	1.02 (0.83–1.26)	0.88 (0.70–1.10)	0.89 (0.71–1.11)	0.16
Colorectal					
Number of cases	152	161	133	155	
Multivariate HR (95 % CI)	1.00	1.09 (0.87–1.37)	0.91 (0.72–1.16)	1.05 (0.83–1.32)	0.93
Liver					
Number of cases	68	49	78	90	
Multivariate HR (95 % CI)	1.00	0.62 (0.43–0.90)	0.87 (0.62–1.22)	0.94 (0.67–1.31)	0.67
Pancreas					
Number of cases	34	31	46	31	
Multivariate HR (95 % CI)	1.00	0.80 (0.49–1.32)	1.14 (0.72–1.80)	0.78 (0.47–1.29)	0.66
Lung					
Number of cases	131	147	153	168	
Multivariate HR (95 % CI)	1.00	1.15 (0.91–1.47)	1.19 (0.93–1.52)	1.28 (1.00–1.62)	0.05
Prostate					
Number of cases	134	128	122	136	
Multivariate HR (95 % CI)	1.00	0.83 (0.73–1.19)	0.85 (0.65–1.10)	0.92 (0.71–1.18)	0.42
Bladder					
Number of cases	28	41	26	46	
Multivariate HR (95 % CI)	1.00	1.45 (0.89–2.37)	0.89 (0.51–1.55)	1.56 (0.95–2.55)	0.24
Kidney					
Number of cases	14	22	21	26	
Multivariate HR (95 % CI)	1.00	1.72 (0.87–3.39)	1.66 (0.83–3.35)	2.05 (1.05–4.03)	0.06

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, and leisure time physical activity

16, 33]. Currently, the mechanisms of arsenic toxicity are considered to involve the role of oxidative stress, enhanced cell proliferation, and modulation of gene expression. In humans, inorganic arsenic ingested through drinking water is taken up through the blood and distributed primarily to the liver, kidneys, lungs, and other organs [35, 36]. Additionally, recent studies have shown that arsenic exposure decreases DNA repair capacity [37, 38].

In 2004 and 2010, the Food Standards Agency (FSA) of the United Kingdom advised against the consumption of *hijiki* [39] owing to its high levels of inorganic arsenic, which is a suspected carcinogen. In response, the Japanese Ministry of Health, Labor, and Welfare (MHLW) announced that *hijiki* consumption does not confer an adverse effect on health, on the basis of its estimation that inorganic arsenic intake through *hijiki* does not exceed the Provisional Tolerable Weekly Intake (PTWI) of 15 μg/kg/week, as defined by the WHO [40]. In 2010, however, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reported that the lower limit on the benchmark dose of inorganic arsenic causing a 0.5 % increase in the incidence of lung cancer (BMDL0.5) was determined from epidemiological studies to be 3.0 μg/kg bw per day (2–7 μg/kg bw per day based on the range of estimated total dietary exposure), using a range of assumptions to estimate total dietary exposure to inorganic arsenic from drinking water and food. The Committee noted that the PTWI (15 μg/kg bw is equivalent to 2.1 μg/kg bw per day) is in the region of the BMDL0.5 and was therefore no longer appropriate [41]. Thus, studies on the association between arsenic intake and cancer have been sought. Despite the fact that Japanese people consume seaweeds, including *hijiki*, on a daily basis, no research on the association between arsenic intake through food and cancer has appeared, albeit that a few papers have investigated the association between drinking water and mortality in a contaminated area. In those studies, drinking water contaminated with arsenic from a factory in the town of Nakajo in Niigata Prefecture, Japan, was associated with a significantly elevated ratio of observed to expected deaths

Table 6 Hazard ratios for incidence of cancer at specific sites by quartile of inorganic arsenic intake in women

	Intake by quartile				p_{trend}
	Lowest	Second	Third	Highest	
Women					
Stomach					
Number of cases	65	61	74	73	
Multivariate HR (95 % CI)	1.00	0.82 (0.57–1.16)	0.93 (0.66–1.30)	0.92 (0.65–1.29)	0.86
Colorectal					
Number of cases	109	89	113	107	
Multivariate HR (95 % CI)	1.00	0.83 (0.62–1.10)	1.02 (0.78–1.34)	0.97 (0.73–1.28)	0.80
Liver					
Number of cases	21	32	36	28	
Multivariate HR (95 % CI)	1.00	1.36 (0.78–2.38)	1.41 (0.81–2.46)	1.10 (0.61–1.97)	0.83
Pancreas					
Number of cases	20	31	27	27	
Multivariate HR (95 % CI)	1.00	1.62 (0.91–2.88)	1.38 (0.76–2.51)	1.37 (0.75–2.49)	0.49
Lung					
Number of cases	53	61	68	72	
Multivariate HR (95 % CI)	1.00	1.18 (0.81–1.71)	1.29 (0.89–1.87)	1.37 (0.95–1.98)	0.08
Breast					
Number of cases	101	114	116	100	
Multivariate HR (95 % CI)	1.00	1.12 (0.86–1.48)	1.16 (0.88–1.52)	1.02 (0.77–1.36)	0.84
Endometrial					
Number of cases	23	17	19	19	
Multivariate HR (95 % CI)	1.00	0.73 (0.39–1.37)	0.81 (0.44–1.51)	0.86 (0.46–1.60)	0.71
Bladder					
Number of cases	6	10	10	7	
Multivariate HR (95 % CI)	1.00	1.96 (0.70–5.53)	2.06 (0.72–5.87)	1.54 (0.50–4.73)	0.47
Kidney					
Number of cases	13	7	5	9	
Multivariate HR (95 % CI)	1.00	0.48 (0.19–1.23)	0.34 (0.12–0.96)	0.64 (0.27–1.53)	0.24

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, leisure time physical activity, menopausal status, and use of exogenous female hormones

from lung cancer [10–12]. Our present study also showed that a higher intake of arsenic increased the risk of lung cancer and is the first prospective study to observe a positive association between lung cancer and arsenic intake through food in a general population.

Additionally, several studies have suggested an apparent synergistic effect between a high level of arsenic exposure and cigarette smoking in men [6, 11, 18, 32, 34, 42–44]. A meta-analysis of studies on occupational arsenic exposure from inhalation found a synergistic effect of cigarette smoking and arsenic on lung cancer, with 30 to 54 % of lung cancer cases attributable to both exposures [45]. Consistent with these previous papers, our study also provided evidence of synergism between arsenic intake and smoking in the development of lung cancer. A previous study showed that metabolism of arsenic related to glutathione S-transferase M1 and T1 [46]. Hays et al. [47] showed that combined exposure to arsenic and cigarette smoke leads to the depletion of total glutathione stores in the lung. Additionally, they also suggested that arsenic and cigarette smoke increased DNA oxidation. These findings indicate that smokers might be more susceptible than nonsmokers to arsenic exposure.

Seaweed is consumed on a daily basis in a traditional Japanese diet. Seaweeds are rich in minerals and dietary fiber [48–50], and dietary seaweeds have been reported to have antioxidant and antimutagenic effects in experimental studies [51, 52]. A case–control study showed an inverse association between seaweed intake and breast cancer risk [53]. Although our study showed no association between arsenic intake and breast cancer, intake was inversely associated with lung cancer among never-smoking men.

Table 7 Hazard ratios for incidence of lung cancer by quartile of arsenic and inorganic arsenic intake in men by smoking status

	Men			p_{trend}	$p_{interaction}$	WOMEN			p_{trend}	$p_{interaction}$
	Intake by tertile					Intake by tertile				
	Lowest	Middle	Highest			Lowest	Middle	Highest		
Arsenic										
Never smoker										
Number of cases	37	21	19			65	70	89		
Multivariate HR (95 % CI)	1.00	0.57 (0.33–0.99)	0.49 (0.27–0.86)	0.01		1.00	1.03 (0.73–1.46)	1.25 (0.90–1.75)	0.17	
Ever smoker										
Number of cases	135	180	207			10	12	8		
Multivariate HR (95 % CI)	1.00	1.24 (0.99–1.56)	1.29 (1.03–1.61)	0.03	<0.01	1.00	0.95 (0.40–2.24)	0.67 (0.26–1.76)	0.42	0.14
Past										
Number of cases	27	32	45			0	1	3		
Multivariate HR (95 % CI)	1.00	1.04 (0.62–1.72)	1.16 (0.71–1.87)	0.54		1.00	–	–		
Current										
Number of cases	101	153	164			10	11	5		
Multivariate HR (95 % CI)	1.00	1.41 (1.09–1.82)	1.37 (1.06–1.77)	0.03		1.00	0.78 (0.32–1.89)	0.40 (0.13–1.20)	0.10	
Inorganic arsenic										
Never smoker										
Number of cases	32	23	22			58	74	92		
Multivariate HR (95 % CI)	1.00	0.81 (0.46–1.42)	0.72 (0.41–1.29)	0.27		1.00	1.31 (0.92–1.86)	1.57 (1.12–2.20)	<0.01	
Ever smoker										
Number of cases	149	158	215			10	11	9		
Multivariate HR (95 % CI)	1.00	1.07 (0.85–1.34)	1.36 (1.09–1.70)	<0.01	0.07	1.00	0.92 (0.38–2.25)	0.67 (0.27–1.72)	0.40	0.31
Past										
Number of cases	34	20	50			0	1	3		
Multivariate HR (95 % CI)	1.00	0.56 (0.32–0.98)	1.22 (0.77–1.94)	0.26		1.00	–	–		
Current										
Number of cases	115	137	166			10	10	6		
Multivariate HR (95 % CI)	1.00	1.20 (0.93–1.55)	1.38 (1.07–1.77)	0.01		1.00	0.89 (0.35–2.23)	0.45 (0.16–1.29)	0.13	

Multivariate HRs were adjusted for age, area, body mass index, smoking status, frequency of alcohol intake, and leisure time physical activity. They were further adjusted for menopausal status and use of exogenous female hormones in women

In past-smoking women, we could not calculate HRs due to small sample size

The results might be due to antioxidant effects of seaweeds without smoking.

In contrast, we observed a positive association between inorganic arsenic intake, *hijiki* intake, and lung cancer among never-smoking women. Lung adenocarcinoma in adult female mice exposed to arsenic showed higher ERα expression than lung tissue cells of unexposed animals [54]. Given that many studies have suggested an association between female hormonal factors and the risk of lung cancer in women, and the high proportion of lung adenocarcinoma in never-smoking women in our study (71 %), it is possible that arsenic increases the risk of lung cancer through a mechanism associated with female hormones. However, given the low validity between arsenic intake by FFQ and DR in women, we cannot rule out the possibility that this result occurred by chance.

Average dietary arsenic exposure was higher in our study (170 μg/day) than that reported in other countries, where mean daily adult intake of arsenic in food is estimated to range from 16.7 to 129 μg [55]. Further, arsenic intake in our study was similar to that calculated by a duplicate-portion estimation (178 μg/day) [29], indicating the accuracy of our assessment of dietary arsenic exposure. Although duplicate-portion collection provides precise measurement, it is disadvantaged by its heavy burden on sample donors, which hampers sampling of large populations and accordingly limits case numbers and analysis of specific cancer sites. Arsenic intake as evaluated by FFQ is a reasonable way of estimating arsenic exposure in large cohort studies.

The major strengths of our study are its prospective design, high response rate (80 %), and negligible proportion of loss to follow-up (0.3 %). Other strengths were that information on arsenic intake was collected before the subsequent diagnosis of cancer, thereby diminishing the probability of the recall bias that is inherent to case–control studies. Further, the quality of our cancer registry system was satisfactory over the study period.

Several potential limitations of this analysis warrant mention. First, misclassification of exposure due to changes in arsenic intake during the study period might have occurred, because information on consumption was obtained at one point only. The main sources of inorganic arsenic in the Japanese diet are *hijiki* and rice, but few Japanese have any clear understanding of this. Thus, such misclassification would probably be nondifferential and may underestimate the true relative risk. On the other hand, misclassification due to low Spearman's rank correlation coefficient might also have occurred, particularly in women. It is possible that we did not precisely evaluate the association between arsenic intake and cancer among women and may be accordingly unable to conclude that there is no association between arsenic intake and cancer in women. Second, analyses by site of cancer are limited by the low number of cases and restricted statistical power, leading to somewhat imprecise estimates, albeit that the study cohort is large. A larger sample size might have detected the positive effects of arsenic on some cancers with greater precision, particularly in women. Moreover, we could not analyze the association between arsenic intake and rare cancers. Finally, the positive association between arsenic intake and lung cancer in current-smoking men might have occurred by chance, because of multiple testing. This is unlikely, however, because previous papers and mechanism support our results.

In conclusion, this study found a significant dose–response trend for the association of arsenic intake with lung cancer risk in men, which was prominent among smokers. Appropriate public health interventions such as cigarette smoking cessation programs are warranted.

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