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Potential effect modifiers of the arsenic-bladder cancer risk relationship

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Abstract

Populations exposed to arsenic in drinking water have an increased bladder cancer risk and evidence suggests that several factors may modify arsenic metabolism, influencing disease risk. We evaluated whether the association between cumulative lifetime arsenic exposure from drinking water and bladder cancer risk was modified by factors that may impact arsenic metabolism in a population-based case-control study of 1,213 cases and 1,418 controls. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between cumulative arsenic intake and bladder cancer stratified by age, sex, smoking status, body mass index (BMI), alcohol consumption, and folate intake. P-values for interaction were computed using a likelihood ratio test. We observed no statistically significant multiplicative interactions although some variations in associations were notable across risk factors, particularly for smoking and BMI. Among former smokers and current smokers, those with the highest cumulative arsenic intake had elevated risks of bladder cancer (OR=1.4, 95%CI:0.96–2.0 and OR=1.6, 95% CI:0.91–3.0, respectively; while the OR among never smokers was 1.1, 95%CI:0.6–1.9, p-interaction=0.49). Among those classified as normal or overweight based on usual adult BMI, the highest level of cumulative arsenic intake was associated with elevated risks of bladder cancer (OR=1.3, 95%CI:0.89–2.0 and OR=1.6, 95% CI:1.1–2.4, respectively), while risk was not elevated among those who were obese (OR=0.9, 95%CI: 0.4–1.8) (p-interaction=0.14). Our study provides some limited evidence of modifying roles of age, sex, smoking, BMI, folate, and alcohol on arsenic-related bladder cancer risk that requires confirmation in other, larger studies.

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INTRODUCTION

For several decades, exposure to high levels of arsenic in drinking water has been studied across regions of the world, leading to the classification of inorganic arsenic (InAs) as an established bladder carcinogen.[1] Subsequent studies of populations with low-to-moderate levels of exposure have also suggested associations between arsenic exposure and bladder cancer. [2–6] Most recently, in a large, population-based case-control study in New England, we reported a positive exposure-response relationship between cumulative arsenic intake from drinking water and bladder cancer risk (Odds Ratio (OR) for highest exposed vs. lowest unlagged exposure =1.6, 95% Confidence Interval (CI): 0.9, 2.9 and OR=2.2, 95%CI: 1.3, 3.9 for exposure lagged 40 years).[2]

Once ingested, InAs undergoes stepwise methylation in the liver where a large portion is converted to monomethylarsenate (MMA) and subsequently to dimethylarsenate (DMA), passed through the kidneys and excreted in urine.[1] InAs, MMA, and DMA, as well the relative proportions of these compounds in urine have been linked to bladder cancer risk. [7, 8] A growing body of epidemiologic evidence suggests that several biological and behavioral factors have the potential to modify arsenic metabolism or methylation capacity potentially influencing disease risk.[9] For example, increased age and smoking have been linked to reduced arsenic methylation [7, 10], and arsenic methylation may be more efficient in women compared with men in both high and low arsenic exposure settings .[11] Some studies observed impaired arsenic metabolism among alcohol drinkers[4], while others have not.[12, 13] Two recent studies have found inverse associations between body mass index (BMI) and urinary arsenic biomarkers.[14, 15] Intake of folate and related nutrients has been shown to impact arsenic metabolism based on cohort studies and randomized trials showing enhanced methylation capacity with folate supplementation in a folate deficient population with high drinking water arsenic exposure [16, 17]; however, the possible modifying effect of folate on arsenic-related bladder cancer risk is unclear, particularly in a population that is relatively folate replete.

Much of the literature evaluating potential modifiers of arsenic metabolism has been conducted in the setting of high arsenic exposure. Here, we evaluated whether the association between lifetime cumulative arsenic ingestion from drinking water and bladder cancer risk is modified by factors that have the potential to influence arsenic metabolism among participants in the New England Bladder Cancer Study (NEBCS), a population with low to moderate levels of arsenic in drinking water.

METHODS

Study Population

Cases in the NEBCS were all patients with histologically confirmed carcinoma of the urinary bladder (including carcinoma *in situ*) newly diagnosed between 2001 and 2004 among residents of Maine, New Hampshire, and Vermont, ages 30 to 79 years. A total of 1213 bladder cancer patients were ascertained through hospital pathology departments and hospital and state cancer registries and interviewed (65% of eligible cases). Control subjects were selected randomly from state Department of Motor Vehicle (DMV) records (age 30–64

years) and Centers for Medicare and Medicaid Services (CMS) beneficiary records (age 65–79 years), frequency matched to case patients by state, sex, and five-year age group at diagnosis. A total of 1418 (594 DMV, 824 CMS) control subjects (64.8% of eligible DMV and 64.7% of eligible CMS control subjects) were interviewed. All participants gave written consent. The study protocol was approved by all appropriate institutional review boards. For the current analysis, we excluded 44 case patients with missing information on arsenic exposure and 70 non-white case patients to be consistent with the previous analysis [2]; 1079 case patients remained. Similarly, we excluded 47 control subjects missing information on arsenic exposure and 84 non-white control subjects; 1287 control subjects remained.

Exposure Information and Statistical Analysis

The exposure assessment for cumulative arsenic intake has been described previously.[2, 18] Briefly, study participants provided lifetime residential and work locations, and identified the type of drinking water supply to each residence and workplace (e.g., public supply, private well). For each private well, information on well type and depth was collected. For public supplies, utility name for the current home was collected. The residence and workplace locations were geocoded. Yearly arsenic concentration in drinking water for each residence and workplace were estimated using two approaches: 1) measurement of arsenic in water samples collected at current homes, and at a limited number of former residences with private wells in the three study states, and 2) prediction modeling for the large proportion of past residences where water sampling was not feasible, and for each workplace.[18] The arsenic concentration information for residences and workplaces was combined with information provided by the participants on usual adult water intake, including water alone and water from beverages and foods made with water, as well as information on water source, to calculate cumulative arsenic intake.

Biological and behavioral factors evaluated as possible modifiers of the relationship between arsenic and bladder cancer were assessed via a detailed computer-assisted personal interview conducted by a trained interviewer at the participant's home and included known bladder cancer risk factors: age at diagnosis/interview (<55, 55–64, 65–74, 75+), smoking status (never, former, current), and sex. We also evaluated the modifying effect of BMI (usual adult BMI using the following categories, normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), obese (30.0+ kg/m^2)). Food intake over the previous five years was assessed with a modified version of the National Cancer Institute diet history questionnaire (DHQ), a self-administered 144 food item food frequency questionnaire, which included frequency and dietary supplement questions.[19, 20] The amount of alcohol consumed from beer, wine, and liquor was also assessed in the DHQ. The frequency and duration of folic acid from supplements were derived from the use of three types of multivitamins (Centrum-type, Therapeutic or Theragran type, and One-a-Day type), use as part of a B-complex vitamin, as well as use of folic acid or folate supplements. Nutrient values were estimated by the methods described by Subar et al.[19], using the USDA's survey nutrient database which provided both pre-and post-fortification folate contents for foods. In 1998, the United States implemented mandatory fortification of grain products with folic acid to prevent neural tube defects. For this analysis, we used pre-fortification dietary folate values as this best represented the relevant period of exposure prior to bladder cancer diagnosis/interview

among participants. We adjusted the dietary exposures, except alcohol use, for energy using the nutrient density method. Total folate intake was calculated as energy adjusted dietary intake plus unadjusted supplemental intake. Categories were split according to cut-points reflecting the RDA (recommended daily allowance) (>400 mcg/day and 0–400 mcg/day).

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between cumulative arsenic exposure defined by unlagged quartiles among controls: 0–15.7 mg (quartile 1/Q1), >15.7–34.5 mg (quartile 2 /Q2), >34.5–77.0 mg (quartile 3/Q3), and >77.0 mg (quartile 4/Q4), as well as quartiles lagged 40-years among controls 0–3.52 mg (Q1), >3.52–8.77 mg (Q2), >8.77–22.42 mg (Q3), and >22.42mg (Q4) and bladder cancer risk. Among the group at the high end of exposure in our study, people in the top 25% of cumulative arsenic, or >77.04 mg, the mean average arsenic concentration is 5.51 ug/L (range 0.5–376.3 ug/L) and the mean average daily intake is 10.8 μg (range 2.8–172.0 μg), which represents low to moderate exposure (generally < 100 ug/L). Associations between arsenic and bladder cancer were stratified by age, sex, smoking status, BMI, alcohol consumption, and folate intake. Models were adjusted for age, sex, ethnicity, state of residence, smoking (including duration for smoking status strata), disinfection byproduct exposure in drinking water, and high-risk occupation, and were consistent with the adjustments used in the main analysis of cumulative arsenic exposure and bladder cancer risk.[2] The p-value for each interaction was computed by comparing nested models with and without the cross-product terms based on a likelihood ratio test. Evidence of effect modification was considered if the p-value for interaction was less than 0.05. All statistical analyses were performed using SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 shows the association between arsenic and bladder cancer by cumulative exposure and exposure lagged 40 years as well as the association between hypothesized effect modifiers and bladder cancer risk. In the current analysis, quartiles of cumulative arsenic were used to examine effect modification to have adequate power to detect interaction; ORs in the top quartile of exposure were (cumulative As unlagged $OR_{Q4vs.Q1}$=1.3, 95% CI 1.02, 1.7, p-trend=0.06 and lagged 40-yrs $OR_{Q4vs.Q1}$ = 1.4 (1.04, 95% CI: 1.04–1.8, p-trend =0.03). Former and current smoking was associated with significantly increased risks of bladder cancer, no other factors (aside from arsenic itself) were significantly associated with risk. Table 2 shows the association between unlagged cumulative arsenic and bladder cancer risk stratified by hypothesized effect modifiers. No evidence of effect modification was observed for any of the factors as all p-interaction values were in the range of 0.14 to 0.95 and thus all were greater than 0.05. Effect modification by age and by sex were not apparent (p-interaction =0.53 and 0.95, respectively). Both for former smokers and for current smokers, those in the highest quartile of cumulative arsenic (>77.04 mg) had elevated risks of bladder cancer (OR=1.4, 95% CI: 0.96, 2.0 and OR=1.6, 95% CI:0.91, 3.0, respectively); the OR among never smokers was 1.1 (95% CI: 0.6, 1.9). The test for interaction showed no difference among smoking status groups (p-interaction=0.49) or when never/ever smoking was considered (p-interaction=0.24, data not shown). Among those classified as normal and among those classified as overweight, the highest quartile of cumulative arsenic was

associated with elevated risks of bladder cancer (OR=1.3, 95% CI: 0.89, 2.0 and OR=1.6, 95% CI: 1.1, 2.4, respectively), while no increased risk was apparent among those who were obese (OR=0.9, 95% CI: 0.4, 1.8). The p-value for interaction, however, was not statistically significant (p-interaction=0.14). There was also no apparent effect modification by folate or by alcohol intake (p-interaction=0.55 and 0.23, respectively).

Table 3 shows the association between cumulative arsenic lagged 40-years and bladder cancer risk stratified by hypothesized effect modifiers. Similar to results for the unlagged metric, no statistically significant interactions (p-interaction ranged between 0.09 and 0.94) between cumulative arsenic lagged 40 years and bladder cancer risk by any of the factors were identified. Compared to the stratified results for the unlagged arsenic exposure metric, some differences among ORs within strata were evident, however. Among women, the association between cumulative arsenic lagged-40 years was null, regardless of exposure category, while a significantly increased risk was present with increasing exposure among men (OR=1.5, 95% CI: 1.1, 2.1). Analysis of those classified as normal, as overweight, or as obese showed no detectable differences in the ORs comparing the highest quartile of lagged cumulative arsenic to the lowest quartile (OR_{normal}=1.4, $OR_{overweight}$=1.4, OR_{obese}=1.4, p-interaction=0.56). Further, those in the highest quartile of cumulative arsenic lagged 40 years who never drank any alcohol had a significantly increased risk of bladder cancer (OR=2.5, 95% CI: 1.3, 4.8), while there was no such significant association between lagged cumulative arsenic and bladder cancer among drinkers (OR=1.1, 95% CI: 0.8, 1.6; p-interaction= 0.09). Examining ever drinkers by drinks/day also showed no significant increased risk (data not shown). Compared to those with both sufficient folate intake (>400 mcg/day) and low cumulative arsenic (0–3.52 mg), those with both insufficient folate intake (0–400 mcd/day) and high cumulative arsenic (>22.42 mg) had a 1.6 times higher risk of bladder cancer (95% CI: 1.04, 2.3) while those at the same level of cumulative arsenic (>22.42 mg) but with sufficient folate intake (>400 mcg/day) had a weaker association, (OR=1.3, 95% CI:0.86, 1.9) (data using common reference not shown).

DISCUSSION

In this analysis, we evaluated factors previously found to impact arsenic metabolism as possible modifiers of the observed association between cumulative arsenic intake and bladder cancer risk. While none of the factors were statistically significant modifiers of the effect of arsenic, several observed associations from the current analysis are noteworthy.

We observed differences in the point estimates for cumulative arsenic intake and bladder cancer risk by cigarette smoking status. Although inorganic arsenic compounds are not considered mutagenic [1], experimental evidence suggests that they can act as co-mutagens.[21, 22] Co-mutagenesis may occur by interference with DNA repair pathways that are critical in the repair of damage associated with tobacco carcinogens.[21, 23, 24] Further, prior studies of both lung and bladder cancer, two tobacco-driven cancers, suggest that co-exposure with arsenic may further increase risk.[5, 25, 26] Like our study, neither the study by Ferreccio *et al.* [26], nor those summarized by Tsuji *et al.*[27] provide support for a statistically significant interaction between smoking and arsenic exposure and bladder cancer risk. This could be because no such relationship exists or there may be insufficient power to detect this

relationship in these studies. Exploration of the potential synergistic effects of low-to-moderate levels of arsenic exposure and cigarette smoking on bladder cancer risk are needed in larger or pooled studies.

The biochemical pathway responsible for the methylation of arsenic is dependent on folate and studies have shown that folic acid supplementation to participants with low plasma folate enhances arsenic methylation and enhanced excretion which may reduce arsenic toxicity.[17] Thus, there is interest in the possible modifying role of folate on the relationship between arsenic and bladder cancer, among other outcomes.[1] In our study, we did not observe a consistent role for folate in modifying the arsenic-bladder cancer relationship. This may be because our population, unlike those previously reported to show an effect modifying role of folate, was folate sufficient or because additional consideration of metabolic differences, including genetic variation and urinary output of specific methylated metabolites, also play a role in how folate impacts arsenic metabolism to affect cancer risk.

We also observed no increased bladder cancer risk associated with high unlagged cumulative arsenic exposure among individuals who were obese for most of their adult lives, while increased risks were observed for normal and overweight individuals. This observation is in line with recent studies reporting lower levels of toenail arsenic with higher BMI [28] and lower urine %MMA concentrations with increasing BMI. [14, 29, 30] The mechanism by which BMI or adiposity might modify the observed cancer relationship is unclear; however, some studies suggest that this may be due to differential metabolic function in obese individuals [28] or to differential ingestion of co-factors that might influence arsenic metabolism [14, 29], including intake of nutrients that contribute to one-carbon metabolism (e.g. folate). There was no relationship between usual BMI and folate intake in our study. Only about 15% of participants were obese for most of their adult lives, limiting our power to detect a modifying role of BMI. Also, results considering cumulative arsenic lagged 40-years did not suggest a similar heterogeneity in risk, possibly since data on BMI were representative of usual adult life rather than time-dependent as was the exposure assessment of cumulative arsenic. Given the consistent line of evidence in recent epidemiologic studies linking body composition and arsenic metabolism, further work on this topic will be of interest. The incorporation of additional information on gut microbiome phenotypes might also be important given the observed gut microbiome alterations induced by exposure to arsenic.[31]

Those in the highest quartile of cumulative arsenic, lagged 40 years, who never drank any alcohol had an increased risk of bladder cancer, while ever drinkers did not. This pattern in risk was not consistent when evaluating unlagged cumulative arsenic, suggesting a lack of effect modifying role for alcohol, and contrasts with the literature describing a possible modifying role for intake of alcohol (rather than never drinking) on arsenic methylation capacity.[4, 9] A recent meta-analysis showed that InAs% was 0.16-fold higher, MMA% was 0.17-fold higher among drinkers than among non-drinkers, while DMA% was 0.24-fold lower among drinkers compared to non-drinkers [9]; significant heterogeneity in the studies reporting these summary estimates was also indicated, suggesting that there is still uncertainty about the role of alcohol on the metabolism of arsenic.

Strengths of our study include its large size, population-based design, and use of histologically confirmed incident bladder cancer cases. In addition, detailed high-quality exposure assessment for current and historical arsenic exposure, as well as a range of possible confounding variables, was collected. Our study also has limitations. In some instances, the numbers of subjects in certain strata were small (never smokers, women, obese individuals), which may have limited our ability to detect interactions. In addition, all participants in the current study were white because there were too few non-whites for analysis, limiting the generalizability of the results to other racial/ethnic groups.

In summary, our evaluation of the observed association between cumulative arsenic exposure and bladder cancer risk provided some limited evidence of effect modification by factors reported to impact arsenic metabolism. Studies with similar exposure information should be combined to increase the power to detect interactions to further our understanding of the mechanisms and eventual prevention of arsenic-induced bladder cancer.

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Novelty and Impact:

In this large case-control study, we explored whether the association between lifetime arsenic exposure in a population with low-to-moderate levels of exposure in drinking water and bladder cancer risk may be modified by several biological and lifestyle factors reported to influence the metabolism of arsenic. These data provide insights into factors influencing arsenic-induced bladder cancer that merit further study.

Table 1.

Odds ratios (OR) and 95% confidence intervals (CI) for bladder cancer by factors affecting arsenic metabolism.

Factors	Cases	Controls	OR* (95% CI)
Cumulative Arsenic (mg)**			
0–15.7	228	327	1.0 (ref)
>15.7–34.5	288	321	1.2 (0.92–1.5)
>34.5–77.0	263	321	1.1 (0.87–1.5)
>77.0–291.0	235	257	1.3 (1.00 to 1.7)
>291.0–483.6	33	32	1.3 (0.7 to 2.3)
>483.6	32	29	1.6 (0.90 to 2.9)
Cumulative Arsenic lagged 40-yrs (mg)**			
0–3.52	233	313	1.0 (ref)
>3.52–8.77	269	308	1.1 (0.87–1.5)
>8.77–22.42	260	311	1.2 (0.92–1.6)
>22.4–83.5	213	247	1.3 (0.95 to 1.7)
>83.5–124.8	34	29	1.7 (0.96 to 3.1)
>124.8	47	29	2.2 (1.3 to 3.9)
Smoking Status			
Never	164	430	1.0 (ref)
Former	550	638	2.4 (1.2–4.6)
Current	343	181	5.3 (4.0–6.9)
Usual Body Mass Index (kg/m^2)			
Normal weight	437	530	1.0 (ref)
Overweight	424	557	0.9 (0.8–1.4)
Obese	192	176	1.3 (0.99–1.7)
Folate (mcg/day)			
>400	480	629	1.0 (ref)
0–400	511	565	1.1 (0.91–1.3)
Alcohol			
Any Alcohol			
Ever	722	885	1.0 (ref)
Never	249	276	1.1 (0.88–1.4)
Beer			
Ever	578	698	1.0 (ref)
Never	403	472	1.0 (0.8–1.3)
Wine			
Ever	471	639	1.0 (ref)
Never	510	529	1.1 (0.94–1.4)
Liquor			
Ever	509	629	1.0 (ref)

Factors	Cases	Controls	OR* (95% CI)
Never	463	534	1.1 (0.92–1.3)

* Adjusted for age, sex, ethnicity, state of residence, smoking, disinfection by products, and high-risk occupation.

** p-trend for cumulative As= 0.12 and for cumulative As lagged 40-yrs =0.004.

Table 2.

Association between unlagged cumulative arsenic and bladder cancer risk stratified by demographic and lifestyle factors

	Cumulative Arsenic (mg)							
	0–15.70		>15.70–34.50		>34.50–77.04		>77.04	
	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)
Age								
<55	48/73	1.0 (ref)	48/55	1.3 (0.7, 2.3)	33/58	0.8 (0.4, 1.5)	37/48	1.1 (0.6, 2.1)
55–64	57/85	1.0 (ref)	78/78	1.5 (0.91, 2.5)	80/66	1.7 (0.99, 2.8)	76/74	1.6 (0.95, 2.8)
65–74	82/112	1.0 (ref)	106/115	1.1 (0.7, 1.7)	93/134	0.9 (0.6, 1.4)	119/132	1.1 (0.7, 1.7)
75+	41/57	1.0 (ref)	56/73	1.0 (0.6, 1.8)	57/63	1.3 (0.7, 2.3)	68/64	1.7 (0.96, 3.0)
							p-interaction=0.53	
Sex								
Female	54/84	1.0 (ref)	71/83	1.2 (0.7, 1.9)	71/91	1.1 (0.6, 1.8)	62/83	1.2 (0.7, 2.0)
Male	174/243	1.0 (ref)	217/238	1.2 (0.88, 1.6)	192/230	1.2 (0.85, 1.5)	238/235	1.4 (1.02, 1.9)
							p-interaction=0.95	
Smoking								
Never smokers	50/122	1.0 (ref)	41/90	1.2 (0.7, 2.1)	36/113	0.9 (0.5, 1.5)	37/105	1.1 (0.6, 1.9)
Former smokers	108/146	1.0 (ref)	151/178	1.1 (0.8, 1.6)	139/152	1.3 (0.89, 1.8)	152/162	1.4 (0.96, 2.0)
Current smokers	64/47	1.0 (ref)	89/46	1.5 (0.8, 2.6)	86/46	1.3 (0.7, 2.3)	104/42	1.6 (0.91, 3.0)
							p-interaction=0.49	
Usual BMI (kg/m^2)								
Normal Weight	97/142	1.0 (ref)	105/133	0.9 (0.6, 1.4)	111/136	1.1 (0.7, 1.6)	124/119	1.3 (0.89, 2.0)
Overweight	91/140	1.0 (ref)	123/136	1.5 (0.99, 2.2)	93/147	1.1 (0.7, 1.7)	117/134	1.6 (1.1, 2.4)
Obese	33/33	1.0 (ref)	55/45	1.2 (0.6, 2.3)	49/36	1.2 (0.6, 2.4)	55/62	0.9 (0.4, 1.8)
							p-interaction=0.14	
Folate (mcg/day)								
>400	97/159	1.0 (ref)	127/146	1.4 (0.97, 2.1)	111/160	1.2 (0.8, 1.8)	131/141	1.6 (1.1, 2.4)
0–400	104/132	1.0 (ref)	135/143	1.1 (0.7, 1.5)	126/128	1.1 (0.8, 1.7)	126/142	1.1 (0.7, 1.7)
							p-interaction=0.55	
Any Alcohol								
Ever	160/235	1.0 (ref)	212/222	1.3 (0.98, 1.8)	173/223	1.1 (0.8, 1.5)	177/205	1.3 (0.92, 1.7)

	Cumulative Arsenic (mg)							
	0–15.70		>15.70–34.50		>34.50–77.04		>77.04	
Never	46/56	1.0 (ref)	54/72	0.7 (0.4, 1.3)	66/66	1.2 (0.7, 2.1)	83/82	1.4 (0.8, 2.4)
							p-interaction=0.23	

*ORs are adjusted for age, sex, ethnicity, state of residence, smoking (including duration for smoking strata), disinfection by products, and high-risk occupation. ¶ p-interaction for ever/never smokers = 0.24.

Table 3.

Association between cumulative arsenic, lagged 40 years and bladder cancer risk stratified by demographic and lifestyle factors

	Cumulative Arsenic lagged 40-yrs (mg)							
	0–3.52		>3.52–8.77		>8.77–22.42		>22.42	
	Ca/Co	OR * (95% CI)	Ca/Co	OR * (95% CI)	Ca/Co	OR * (95% CI)	Ca/Co	OR * (95% CI)
Age								
<55	90/121	1.0 (ref)	36/38	1.1 (0.6, 2.0)	15/28	0.7 (0.3, 1.4)	11/11	1.0 (0.4, 3.0)
55–64	73/91	1.0 (ref)	75/90	1.1 (0.7, 1.8)	73/63	1.8 (1.1, 3.0)	65/47	1.7 (0.99, 3.0)
65–74	55/69	1.0 (ref)	108/124	1.0 (0.6, 1.6)	101/144	0.9 (0.6, 1.5)	133/154	1.1 (0.7, 1.8)
75+	15/32	1.0 (ref)	50/56	1.9 (0.89, 4.2)	71/76	1.9 (0.86, 4.2)	85/93	2.4 (1.1, 5.2)
							p-interaction=0.36	
Sex								
Female	52/71	1.0 (ref)	63/70	1.0 (0.6, 1.8)	61/84	1.0 (0.6, 1.8)	74/92	1.1 (0.6, 1.9)
Male	181/242	1.0 (ref)	206/238	1.2 (0.86, 1.6)	199/227	1.3 (0.91, 1.7)	220/213	1.5 (1.1, 2.1)
							p-interaction=0.59	
Smoking								
Never smokers	48/119	1.0 (ref)	33/91	1.0 (0.5, 1.7)	40/91	1.3 (0.7, 2.3)	37/104	1.1 (0.6, 2.0)
Former smokers	94/128	1.0 (ref)	149/172	1.1 (0.8, 1.6)	140/171	1.2 (0.8, 1.7)	162/153	1.6 (1.1, 2.4)
Current smokers	83/57	1.0 (ref)	83/36	1.7 (0.96, 3.0)	75/42	1.3 (0.7, 2.3)	91/36	1.6 (0.85, 3.0)
							p-interaction=0.50	
Usual BMI (kg/m^2)								
Normal Weight	90/122	1.0 (ref)	101/133	0.9 (0.6, 1.4)	105/129	1.1 (0.7, 1.6)	128/125	1.4 (0.87, 2.3)
Overweight	97/142	1.0 (ref)	112/131	1.3 (0.86, 2.0)	105/131	1.5 (0.96, 2.3)	105/133	1.4 (0.89, 2.3)
Obese	38/39	1.0 (ref)	53/38	1.4 (0.7, 2.8)	43/49	0.9 (0.4, 1.8)	56/44	1.4 (0.7, 3.1)
							p-interaction=0.56	
Folate (mcg/day)								
>400	96/134	1.0 (ref)	128/161	1.2 (0.8, 1.7)	107/139	1.2 (0.8, 1.9)	128/155	1.3 (0.87, 2.1)
0–400	108/134	1.0 (ref)	118/125	1.2 (0.8, 1.8)	125/137	1.2 (0.8, 1.8)	129/126	1.5 (0.97, 2.3)
							p-interaction=0.94	
Any Alcohol								
Ever	172/222	1.0 (ref)	190/223	1.1 (0.8, 1.5)	175/193	1.2 (0.88, 1.7)	167/210	1.1 (0.8, 1.6)

	Cumulative Arsenic lagged 40-yrs (mg)							
	0–3.52		>3.52–8.77		>8.77–22.42		>22.42	
Never	34/47	1.0 (ref)	58/63	1.5 (0.8, 2.9)	64/87	1.3 (0.7, 2.4)	93/74	2.5 (1.3, 4.8)
							p-interaction=0.09	

*ORs are adjusted for age, sex, ethnicity, state of residence, smoking (including duration for smoking strata), disinfection by products, and high-risk occupation. ¶ p-interaction for ever/never smokers = 0.39.