Cancer Causes and Control **16**: 75–81, 2005.

Interaction between environmental tobacco smoke and arsenic methylation ability on the risk of bladder cancer

Yen-Ching Chen[1,2,*], Huey-Jen Jenny Su[3], Yu-Liang Leon Guo[3], E. Andres Houseman[4] & David C. Christiani[2]
[1]*Department of Medicine, Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [2]*Occupational Health Program, Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA;* [3]*Department of Environmental and Occupational Health, Medical College, National Cheng-Kung University, Tainan, Taiwan;* [4]*Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA*

Received 9 March 2004; accepted in revised form 17 August 2004

Key words: arsenic methylation ability, bladder cancer, environmental tobacco smoke, Taiwan.

Abstract

Objective: Arsenic exposure and environmental tobacco smoke (ETS) have been suspected to be associated with bladder cancer risk. We hypothesize that interaction between ETS and the ability to methylate arsenic, a detoxification pathway, modifies the risk of bladder cancer.
Methods: From January 1996 to December 1999, we identified 41 newly diagnosed bladder cancer patients and 202 fracture and cataract patients at the National Cheng-Kung University (NCKU) Medical Center. The levels of urinary arsenic species [As(III), As(V), MMA(V), and DMA(V)] were determined in all subjects.
Results: We found significant interaction between ETS and secondary methylation index (SMI) on the risk of bladder cancer ($p = 0.02$). Among non-smokers with a high primary methylation index (PMI), the risk of bladder cancer was lower in subjects exposed to ETS (OR, 0.37; 95% CI, 0.14–0.96) than in subjects without exposure to ETS. Among non-smokers without ETS, the risk of bladder cancer was 4.7 times higher in subjects with a low SMI (95% CI, 1.30–16.81) than in subjects with a high SMI.
Conclusions: Ability to methylate arsenic plays an important role in reducing the risk of bladder cancer attributable to the continuation of arsenic exposure from drinking water and from ETS exposure.

Abbreviations: Environmental tobacco smoke, (ETS); Arsenite, As(III); arsenate, As(V); monomethylarsonic acid, MMA(V); monomethylarsonous acid, MMA(III); dimethylarsinic acid, DMA(V); cumulative arsenic exposure, CAE; primary arsenic methylation index, PMI; secondary arsenic methylation index, SMI.

Introduction

Previous studies have shown that arsenic exposure may lead to cancers of the liver, kidney, bladder, prostate, lymphoid tissue, skin, lung, colon, and nasal cavity; blackfoot disease (BFD); ischemic heart disease; hyperpigmentation, hyperkeratosis; diabetes; meningioma; and other health effects [1, 2]. Several epidemiologic studies [2–8] have related mortality, prevalence, and lifetime risk of bladder cancer to arsenic exposure.

Groundwater supplies in Bangladesh, India (West Bengal), China (Inner Mongolia), and parts of the United States (California, Nevada, Alaska, and Utah) have high levels of arsenic. The US Environmental Protection Agent (EPA) has estimated that about 350,000 people in the US drink water containing >50 μg/l of arsenic and about 2.5 million people drink water containing >25 μg/l [9]. On January 22, 2001, the EPA lowered the standard for arsenic in drinking water to 10 μg/l.

* Address correspondence to: Yen-Ching Chen, Channing Laboratory, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School, Boston, MA, USA. Ph.: (617) 510-2105; Fax: (617) 510-2008; E-mail: karen.chen@channing.harvard.edu

Tobacco smoke has been related to an elevated risk of bladder cancer [10–12]. For non-smokers, environmental tobacco smoke (ETS) is a source of arsenic exposure, *i.e.*, arsenic is a constituent of tobacco smoke [13]. Little research has been done assessing the relationship between ETS and bladder cancer [14–16], and findings to date show that ETS contributes little to the risk of bladder cancer.

No published studies have assessed the arsenic exposure from these two sources, tobacco smoke and drinking water, together. Arsenic methylation is the main pathway to detoxicify arsenic in drinking water or in inhaled tobacco smoke. In earlier studies [17, 18], we found an elevated risk of bladder and skin cancer among persons with lower arsenic methylation ability and higher cumulative arsenic exposure (CAE). These two studies were conducted in southwestern Taiwan, an area formerly endemic for arsenic-related black-foot disease. Study subjects were exposed to arsenic in drinking water 30 years ago. We hypothesize that there is an interaction between ETS and arsenic methylation ability affecting the risk of bladder cancer among people exposed to arsenic via drinking water. We also assess the role of arsenic methylation on the risk of bladder cancer.

Materials and methods

Study design

The research protocol was approved by the Institutional Review Boards of the Harvard School of Public Health and National Cheng-Kung University (NCKU). From January 1996 to December 1999, a hospital-based case-control study was conducted in southwestern Taiwan. Forty-one patients with newly diagnosed bladder cancer and 202 controls (fracture and cataract patients) were recruited from the NCKU Medical Center. Since this population included few young subjects and older people tend to smoke more than younger people, we excluded 8 cases and 22 controls younger than 50. The NCKU Medical Center is the main medical referral center for cancer diagnosis and treatment for residents of Tainan City and surrounding rural communities. Patients with long-bone fractures or cataracts were chosen because these conditions are not known to be associated with arsenic exposure.

Of the patients with newly diagnosed bladder cancer recruited in our study, 80% had confirmed transitional cell carcinoma (TCC) (80%) and 20% were missing information on specific cell-type. The pathologic diagnosis was performed at the NCKU Pathology Department using the International Classification of Diseases, version 9 (ICD-9; code 188) [19].

Primary and secondary methylation indexes were defined as the ratios of urinary MMA(V)/inorganic arsenic and DMA(V)/MMA(V), respectively. Since most arsenic exposure was through the consumption of drinking water, we needed to estimate arsenic exposure over time. We defined the cumulative arsenic exposure index (CAE) (2) as $\mathrm{CAE} = \Sigma[(\text{Average arsenic concentration of artesian well water in mg/l})_i \times (\text{Duration of consuming artesian well water in years})_{\text{i:unit of village}}]$. We estimated the average concentration of arsenic in artesian well water from questionnaire data based on the village of the subject's residence 30 years previously and the average arsenic level in well water for each village obtained from the Taiwan Provincial Institute of Environmental Sanitation survey of 83,656 wells between 1974 and 1976 [20].

At the time of urine collection, each subject was administered a questionnaire by trained interviewers, all of whom were blinded to exposure status and study hypotheses. Subjects' smoking status and ETS exposure were obtained from the questionnaire. Smoking status was validated by another question, *e.g.*, the age they started to smoke. ETS exposure was validated by smoking status obtained from questionnaire, *i.e.*, a person who had ETS exposure could only be a non-smoker. The questionnaire also included questions on demographics (gender, age, ethnicity, height, body weight, education, and working experience), personal habits (cigarette smoking, consumption of alcohol, tea, and coffee; and use of hair dye), disease history, other relevant questions (history and duration of each residence, sources of drinking water, medication usage, and occupations), and diet recalled over the past year. Persons who did not complete or refused to answer the questionnaire were excluded. Completed questionnaires were obtained from 74% of eligible subjects. Parts of the questionnaire were verified from lists of names and addresses of residents in the study area obtained from local household registration offices that register and update sociodemographic characteristics (*e.g.*, gender, age, educational level, marital status, and occupation) of all residents annually.

Laboratory analysis

A spot urine sample was collected from each subject and stored in a −20 °C freezer at the NCKU Medical Center. The urinary levels of four arsenic species [As(III), As(V), MMA(V), and DMA(V)] were determined for all subjects. We described our laboratory procedures in detail in our previous study [17].

Statistical analysis

We used two multiple logistic regression models, one for men and the other for women, to estimate the multivariate odds ratios (and 95% confidence intervals) of bladder cancer associated with ETS by smoking status. The same models were used to assess the association between arsenic methylation ability and the risk of bladder cancer. The interaction between PMI and ETS was analyzed in two models, one for smokers and the other for nonsmokers. The same methods were applied for the interaction between SMI and ETS. The *p*-values indicating interaction are also reported. Statistical software, SAS 8.1, was used throughout the analysis [21]. To control for potential confounding, we adjusted for the following risk factors in the multivariate models: age, gender, body-mass index (BMI), CAE, cigarette smoking, use of hair dye, and education.

Results

As expected, among the subjects with bladder cancer, more were men ($p = 0.003$), the BMI was lower ($p = 0.043$), and more were heavy smokers ($p = 0.024$) than in the control group (Table 1). The patients with bladder cancer and controls were similar with regard to age, hair dye usage, education status, CAE, and arsenic methylation ability (PMI and SMI).

Among male non-smokers, the risk of bladder cancer was markedly higher (seven-fold) in subjects with ETS exposure (95% CI, 1.87–27.4) than in subjects without ETS exposure (Table 2). This was not the case among female non-smokers. Because of the few female smokers in this population ($n = 2$), we could not assess this association for women.

Among non-smokers with high PMI, the risk of bladder cancer was lower in subjects exposed to ETS (OR = 0.37; 95% CI, 0.14–0.96) than in subjects not exposed to ETS (Table 3). Overall, no interaction was found between ETS, PMI, and the risk of bladder cancer. However, we observed a statistically significant interaction ($p = 0.02$) between ETS, SMI, and the risk of bladder cancer. Among non-smokers without ETS, the risk of bladder cancer was 4.6 times higher in subjects with low SMI (95% CI, 1.30–16.81) than in subjects with high SMI. Finally, among smokers, no interaction was found between ETS, SMI, and bladder cancer.

Discussion

To our knowledge, this is the first study to assess the association between ETS and arsenic methylation ability (PMI and SMI) and the risk of bladder cancer among people exposed to arsenic from drinking water. We found a significant interaction between ETS and SMI on the risk of bladder cancer. Among non-smokers with high PMI, after adjustment for cumulative arsenic exposure and other risk factors, subjects with ETS exposure had about one third the risk of bladder cancer than did subjects without ETS exposure (0.37 *versus* 1.00). Among non-smokers without ETS exposure, subjects with low SMI had more than four times the risk of bladder cancer than did those with high SMI (4.68 *versus* 1.00). Therefore, arsenic methylation ability appears to play an important role in reducing the risk of

Table 1. Characteristics of subjects with bladder cancer and control subjects

Variable	Bladder cancer (n = 41)		Controls subjects (n = 202)		p-value
	n	%	n	%	
Age					
> 50–60	6	14.6	34	16.8	
> 60–70	22	53.7	89	44.1	
> 70	13	31.7	79	39.1	0.24[e]
Gender					
Male	35	85.4	120	59.4	
Female	6	14.6	82	40.6	< 0.01[a,e]
BMI					
< 18.5	1	2.6	11	5.4	
18.5–23	22	57.9	72	35.6	
> 23	15	39.5	109	54.0	0.04[a,e]
Smoking (pack-years)					
Never	13	31.7	117	58.2	
> 0–10	3	7.3	15	7.5	
> 10–20	4	9.8	13	6.5	
> 20	21	51.2	56	27.9	0.02[a,e]
Hair dye					
Yes	13	31.7	68	33.7	
No	28	68.3	134	66.2	0.52[e]
Education					
Illiterate	10	24.4	59	29.2	
Elementary	17	41.5	96	47.5	
High school and above	14	34.2	47	23.3	0.07[e]
Average CAE[b] (mg/l-year)	7.9		8.2		0.90[f]
PMI[c]	3.7		4.2		0.72[f]
SMI[d]	8.4		10.6		0.30[f]

[a] p – value < 0.05.

[b] CAE denotes the cumulative arsenic exposure, and these data were collected from a questionnaire.

[c] PMI denotes primary methylation index calculated from urinary MMA(V)/inorganic arsenic.

[d] SMI denotes secondary methylation index calculated from urinary DMA(V)/MMA(V).

[e] Chi – square test.

[f] t–test.

Table 2. Association between environmental tobacco smoke (ETS) and bladder cancer, stratified by gender and smoking status

Variable	Number of cases	Number of controls	Multivariate adjusted odds ratio (95% CI)[d]	*p*-value[c]
Male				
Non-smoker				
ETS[b] exposure (no)	4	22	1.00	
ETS[b] exposure (yes)	2	11	7.16 (1.87–27.4)	< 0.01[a]
Smoker				
ETS[b] exposure (no)	16	24	7.58 (0.62–92.97)	0.113
ETS[b] exposure (yes)	13	60	28.56 (2.82–289.00)	< 0.01[a]
Female				
Non-smoker				
ETS[b] exposure (no)	2	43	1.00	
ETS[b] exposure (yes)	4	38	1.09 (0.42–2.80)	0.89
Smoker				
ETS[b] exposure (no)	–	1	–	–
ETS[b] exposure (yes)	–	2	–	–

[a] p-value < 0.05.
[b] ETS denotes environmental tobacco smoke.
[c] Chi-square test for a score test having null hypothesis that log OR $= 0$.
[d] Two multiple logistic regression models, one for men and the other for women, were used to estimate the multivariate odds ratios (and 95% confidence intervals) of bladder cancer associated with ETS by smoking status. All models adjusted for age, body mass index, cumulative arsenic, hair dye usage, and education.

bladder cancer attributable to arsenic exposure from drinking water and ETS.

Our results are consistent with previous studies documenting the association between tobacco smoke and the risk of bladder cancer [10–12]. However, limited research evaluating the relationship between ETS and bladder cancer showed that ETS contributed little to the risk of bladder cancer [14–16]. Our study found that ETS significantly elevated the risk of bladder cancer among men (Table 2) in a population with known exposure to arsenic in drinking water.

For non-smokers without ETS exposure, the main source of arsenic exposure is drinking water, and consistent with our previous findings [17], those with a low SMI had a significantly higher risk of bladder cancer than those with a high SMI. Among non-smokers with arsenic exposure from both drinking water and ETS, a high PMI significantly lowered the risk of bladder cancer.

The effect of tobacco smoke (active and passive) on the risk of bladder cancer would not expected to be less than the effect of arsenic from drinking water because this population had low cumulative exposure to arsenic for the past 30 years. For smokers, the effect of active smoking on the risk of bladder cancer was greater than that of arsenic from drinking water, and additional ETS exposure further elevated the risk. We found that ETS exposure also significantly elevated the risk of bladder cancer among male non-smokers. ETS exposure did not affect the risk of bladder cancer among female non-smokers, probably because our study included too few women with bladder cancer. Because this population included many more male than female smokers, we observed the significantly elevated risk of bladder cancer among men. Our findings are consistent with those of a previous study [22] and with cancer surveillance statistics for 2003 from the American Cancer Society, which reported that the bladder cancer rate is two to three times higher among men than among women [23].

The updated rank order of arsenical toxicity, defined by carcinogenesis and vascular disorders, is MMA(III) > As(III) > As(V) > MMA(V) = DMA(V) [24]. Presumed arsenic detoxification pathways include (1) methylation of arsenic in the liver (major) or kidneys (minor) and (2) the pulmonary ciliary escalator clearance system. Arsenic is one of the constituents of tobacco smoke. Because the particles from ETS are smaller than those from active tobacco smoke, they reach deeply into the lung's pulmonary alveolar region [25].

In humans, inorganic arsenic from ingested water is taken up readily by red blood cells and then distributed primarily to the liver, kidneys, spleen, lungs, intestines, and skin [26–28]. The target systems of arsenic exposure comprise the respiratory, gastrointestinal, cardiovascular, nervous, and hematopoietic systems [26]. As(V) is reduced to As(III) in blood and then methylated to MMA(V) and DMA(V), which are less toxic than inorganic arsenic and have a lower tissue affinity. Therefore, methylation of inorganic arsenic, mainly in the liver, is considered a detoxification procedure and differs from most other phase-II

Table 3. Interaction between environmental tobacco smoke (ETS), arsenic methylation ability, and the risk of bladder cancer

Variable	Number of cases	Number of controls	Multivariate adjusted OR (95%CI)[e]	*p*-value (interaction)
Non-smoker				
ETS[b] exposure (no)				
High PMI[c] (≤0.9)	6	42	1.00	
Low PMI[c] (>0.9)	1	17	0.51 (0.16–1.68)	
ETS[b] exposure (yes)				
High PMI[c] (≤0.9)	3	35	0.37 (0.14–0.96)[a]	
Low PMI[c] (>0.9)	3	10	1.02 (0.28–3.71)	0.11
Smoker				
ETS[b] exposure (no)				
High PMI[c] (≤0.9)	11	20	1.00	
Low PMI[c] (>0.9)	4	5	2.17 (0.44–10.71)	
ETS[b] exposure (yes)				
High PMI[c] (≤0.9)	11	50	0.49 (0.21–1.19)	
Low PMI[c] (>0.9)	2	9	0.31 (0.07–1.36)	0.13
Non-Smoker				
ETS[b] exposure (no)				
High SMI[d] (≤4.8)	2	43	1.00	
Low SMI[d] (>4.8)	4	13	4.68 (1.30–16.81)[a]	
ETS[b] exposure (yes)				
High SMI[d] (≤4.8)	4	29	1.22 (0.48–3.13)	
Low SMI[d] (>04.8)	2	15	0.52 (0.16–1.68)	0.02[a]
Smoker				
ETS[b] exposure (no)				
High SMI[d] (≤4.8)	8	15	1.00	
Low SMI[d] (>4.8)	8	8	3.42 (0.84–13.97)	
ETS[b] exposure (yes)				
High SMI[d] (≤4.8)	9	37	0.50 (0.18–1.37)	
Low SMI[d] (>4.8)	4	23	0.62 (0.20–1.94)	0.28

[a] p-value < 0.05.
[b] ETS denotes environmental tobacco smoke.
[c] PMI denotes primary methylation index calculated from urinary MMA(V)/inorganic arsenic.
[d] SMI denotes secondary methylation index calculated from urinary DMA(V)/MMA(V).
[e] Interaction between PMI and ETS was analyzed in two multiple logistic regression models: one for smokers and the other for nonsmokers. Same method was applied for the interaction between SMI and ETS. All models adjusted for age, gender, body mass index (BMI), cumulative arsenic exposure (CAE), hair dye usage, and education.

reactions because it generally decreases solubility in water and masks functional groups that might otherwise be conjugated by the phase-II enzymes [29]. Factors with important roles in arsenic methylation ability include dose, forms of arsenic administered and routes of administration, lifestyle (*e.g.*, diet, smoking, and alcohol consumption), genetic polymorphisms in metabolism, and probably other sources of inter-individual variability. Arsenic not methylated is deposited in skin, hair, bone, epididymis, testis, and thyroid, and other parts of the body [30, 31].

Bladder cancer is rare in young persons. About 80% of newly diagnosed cases of bladder cancer, for both genders, are in people 60 years and older [32]. Since more older people than younger people smoke and we had few young subjects, we tested our hypothesis by analyzing data on subjects 50 years and older. Some significant associations and the interaction between ETS and SMI on the risk of bladder cancer were observed only among subjects older than 50. Similarly low CAE was observed among cases and controls, indicating that factors other than arsenic from drinking water, in this case tobacco smoke, play more important roles in the risk of bladder cancer.

ETS status (ETS exposure among non-smokers) was validated by other questions in the questionnaire (*e.g.*, age when subject started to smoke, whether the subject had ever quit smoking). Only subjects who confirmed their non-smoking status from their answers to these validation questions who reported that people smoked in their presence most of the time were treated as having true ETS exposure, minimizing misclassification of ETS exposure status.

Limitations to our study should be acknowledged when interpreting these results: we collected arsenic exposure information from questionnaires by area of

residence and used the average arsenic level of well water in each village. This estimation does not permit evaluation of individual dose-response relationships between arsenic exposure and the risk of bladder cancer. Hence, our exposure estimation might lead to non-differential misclassification of exposure, resulting in an underestimation of the association between CAE and risk of bladder cancer. However, having found a statistically significant association between ETS, SMI, and bladder cancer, our odds ratios are likely underestimates. In addition, because arsenic exposure from drinking water is low in this population and our focus is on ETS, this issue is negligible. Selection bias in this study is unlikely because the NCKU Medical Center, a referral center, covers 80% of all patients requiring specialists in the region and our cases are likely to be representative of bladder cancers affecting the general community. Recall bias is a potential confounder for all case-control studies. Therefore, we validated most of the information obtained from questionnaires (*e.g.*, gender, age, occupation, and residence) from the household registration (*i.e.*, census) office. Because smoking by Asian women is rarer (3–4%) than among Western women (22–26%) [33–35], we need an adequate sample size to assess ETS. However, because the relatively small sample size resulted in the inclusion of few women with bladder cancer who were smokers, we were unable to assess the association between ETS and bladder cancer among female smokers.

We found that arsenic methylation abilities (PMI and SMI) play an important role in reducing the risk of bladder cancer for both non-smokers and smokers exposed to ETS. Therefore, this study provides important information on the role of arsenic methylation ability on the risk of bladder cancer among persons exposed to arsenic from both drinking water and ETS. Pooled analyses or large-scale studies among subjects of different ethnicities are encouraged to confirm our findings.

Acknowledgement

The authors are grateful to Miss Lia Shimada for her assistance. Funding for the study was provided by National Institute of Health Grants ES 05947 and ES 00002.

References

1. Chan PC, Huff J. (1997) Arsenic carcinogenesis in animals and in humans: mechanistic, experimental, and epidemiological evidence. *Environ Carcino Ecotox Revs* **C15**(2): 83–122.
2. Chiou HY, Hsueh YM, Liaw KF, Horng SF, Chiang MH, Pu YS, *et al.* (1995) Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. *Cancer Res* **55**: 1296–1300.
3. Brown KG, Guo HR, Kuo TL, Greene HL. (1997) Skin cancer and inorganic arsenic : uncertainty -status of risk. *Risk Anal* **17**(1): 37–42.
4. Chiang HS, Hong CL, Guo HR, Lee EF, Chen TY. (1988) Comparative study on the high prevalence of bladder cancer in the blackfoot disease area in Taiwan. *J Formosan Med Assoc* **87**(11): 1074–1079.
5. Chiang HS, Guo HR, Hong CL, Lin SM, Lee EF. (1993) The incidence of bladder cancer in the black foot disease endemic area in Taiwan. *Br J Urol* **71**: 274–278.
6. Chen CJ, Chuang YC, You SL, Lin TM, Wu HY (1986) A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br J Cancer* **53**: 399–405.
7. Lien HC, Tsai TF, Lee YY, Hsiao CH. (1999) Merkel cell carcinoma and chronic arsenicism. *J Am Acad Dermatol* **41**(4): 641–643.
8. Chen CJ, Chen CW, Wu MM, Kuo TL (1992) Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* **66**: 888–892.
9. IARC. (1987) Monographs on the Evaluation of Carcinogenic Risks to Humans. *Lyon: International Agency for Res on Cancer*.
10. Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK (2002) Arylamine exposures and bladder cancer risk. *Mutat Res* **506–507**: 21–28.
11. Tripathi A, Folsom AR, Anderson KE, Iowa Women's Health S. (2002) Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. *Cancer* **95**(11): 2316–2323.
12. Castelao JE, Yuan JM, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, *et al.* (2001) Gender- and smoking-related bladder cancer risk.[comment]. *J Nat Cancer Ins* **93**(7): 538–545.
13. Landsberger S, Wu D. (1995) The impact of heavy metals from environmental tobacco smoke on indoor air quality as determined by Compton suppression neutron activation analysis. *Sci Total Environ* **173–174**: 323–337.
14. Grimmer G, Dettbarn G, Seidel A, Jacob J (2000) Detection of carcinogenic aromatic amines in the urine of non-smokers. *Sci Total Environ* **247**(1): 81–90.
15. Vineis P, Pirastu R. (1997) Aromatic amines and cancer. *Cancer Causes Control* **8**(3): 346–355.
16. Tredaniel J, Boffetta P, Saracci R, Hirsch A (1993) Environmental tobacco smoke and the risk of cancer in adults. *Euro J Cancer* **29A**(14): 2058–2068.
17. Chen YC, Su HJ, Guo YL, Hsueh YM, Smith TJ, Ryan LM, *et al.* (2003) Arsenic methylation and bladder cancer risk in Taiwan. *Cancer Causes Control* **14**(4): 303–310.
18. Chen YC, Guo YL, Su HJ, Hsueh YM, Smith TJ, Ryan LM, *et al.* (2003) Arsenic methylation and skin cancer risk in southwestern Taiwan. J Occup Environ Med **45**(3): 241–248.
19. Percy C, Van Holten V. (1998) Conversion of neoplasms by topography and morphology from the international classification of diseases for oncology, 2nd edn (ICD-O-2) to international classification of diseases, 9th revision (ICD-9) and the international classification of diseases, 9th revision, clinical modification (ICD-9-CM). 4th ed. National Institutes of Health (NIH) publication; pp. 98–2007.
20. Chen CJ. (1990) Blackfoot disease. *Lancet* **336:** 442.

21. SAS software release 8.1. In: SAS Institute Inc.; 1999–2000.
22. Castelao JE, Yuan JM, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, *et al.* (2001) Gender- and smoking-related bladder cancer risk. *J Nat Cancer Inst* **93**(7): 538–545.
23. What Are the Risk Factors for Bladder Cancer? Atlanta, GA: American Cancer Society; (2003).
24. Aaltonen LA, Salovaara R, Kristo P, Canzlan F, Hemminki A, Peltomarkl P, *et al.* (1998) Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* **338**: 1481–1487.
25. Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H (1997) The increasing incidence of lung adenocarcinoma: reality or artifact? A review of the epidemiology of lung adenocarcinoma. *Int J Epidemiol* **26**: 14–23.
26. Hsueh YM, Huang YL, Huang CC, Wu WL, Chen HM, Yang MH, *et al.* (1998) Urinary levels of inorganic and organic arsenic metabolites among residents in an arseniasis-hyperendemic area in Taiwan. *J Toxicol Environ Health*, Part A **54**: 431–444.
27. Yamato N. (1988) Concentrations and chemical species of arsenic in human urine and hair. *Bull Environ Contam Toxicol* **40**: 633–640.
28. Yamauchi H, Fowler BA (1994) Ch.3: Toxicity and Metabolism of Inorganic and Methylated Arsenicals. In: Nriagu JO, ed. Arsenic in the environment. Part II: Human health and ecosystem effects. New York: Wiley, Inc.; p. 35–53.
29. Parkinson A. (1996) Ch.6 Biotransformation of Xenobiotics. In: Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's Toxicology-The Basic Science of Poisons*. 5th ed. New York: McGraw-Hill, pp. 113–186.
30. Vahter M, Marafante E. (1988) In Vivo Methylation and Detoxification of Arsenic. In, Craig PJ, Glockling F, eds. *The Biological Alkylation of Heavy Elements*. London: Royal Society of Chemistry, pp. 105–119.
31. Mann S, Droz PO, Vahter M. (1996) A physiologically based pharmacokinetic model for arsenic exposure: II Validation and application in humans. *Toxicol Appl Pharmacol* **140**: 471–486.
32. Cancer Facts and Figures (2002) Atlanta, GA: American Cancer Society.
33. Koo LC, Ho JHC (1990) Worldwide epidemiological patterns of lung cancer in nonsmokers. *Int J Epidemiol* **19**(Suppl 1): S14–23.
34. Ko YC, Cheng LSC, Lee CH, Huang JJ, Huang MS, Kao EL, *et al.* (2000) Chinese food cooking and lung cancer in women nonsmokers. *Am J Epidemiol* **151**(2): 140–147.
35. Group GYTSC. (2003) Differences in Worldwide Tobacco Use by Gender: Findings from the Global Youth Tobacco Survey. *J School Health* **73**(6): 207–215.