A Case–Control Study of Smoking and Bladder Cancer Risk: Emergent Patterns Over Time

Dalsu Baris, Margaret R. Karagas, Castine Verrill, Alison Johnson, Angeline S. Andrew, Carmen J. Marsit, Molly Schwenn, Joanne S. Colt, Sai Cherala, Claudine Samanic, Richard Waddell, Kenneth P. Cantor, Alan Schned, Nathaniel Rothman, Jay Lubin, Joseph F. Fraumeni Jr, Robert N. Hoover, Karl T. Kelsey, Debra T. Silverman

Background Cigarette smoking is a well-established risk factor for bladder cancer. The effects of smoking duration, intensity (cigarettes per day), and total exposure (pack-years); smoking cessation; exposure to environmental tobacco smoke; and changes in the composition of tobacco and cigarette design over time on risk of bladder cancer are unclear.

Methods We examined bladder cancer risk in relation to smoking practices based on interview data from a large, population-based case–control study conducted in Maine, New Hampshire, and Vermont from 2001 to 2004 (N = 1170 urothelial carcinoma case patients and 1413 control subjects). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. To examine changes in smoking-induced bladder cancer risk over time, we compared odds ratios from New Hampshire residents in this study (305 case patients and 335 control subjects) with those from two case–control studies conducted in New Hampshire in 1994–1998 and in 1998–2001 (843 case patients and 1183 control subjects).

Results Regular and current cigarette smokers had higher risks of bladder cancer than never-smokers (for regular smokers, OR = 3.0, 95% CI = 2.4 to 3.6; for current smokers, OR = 5.2, 95% CI = 4.0 to 6.6). In New Hampshire, there was a statistically significant increasing trend in smoking-related bladder cancer risk over three consecutive periods (1994–1998, 1998–2001, and 2002–2004) among former smokers (OR = 1.4, 95% CI = 1.0 to 2.0; OR = 2.0, 95% CI = 1.4 to 2.9; and OR = 2.6, 95% CI = 1.7 to 4.0, respectively) and current smokers (OR = 2.9, 95% CI = 2.0 to 4.2; OR = 4.2, 95% CI = 2.8 to 6.3; OR = 5.5, 95% CI = 3.5 to 8.9, respectively) (P for homogeneity of trends over time periods = .04). We also observed that within categories of intensity, odds ratios increased approximately linearly with increasing pack-years smoked, but the slope of the increasing trend declined with increasing intensity.

Conclusions Smoking-related risks of bladder cancer appear to have increased in New Hampshire since the mid-1990s. Based on our modeling of pack-years and intensity, smoking fewer cigarettes over a long time appears more harmful than smoking more cigarettes over a shorter time, for equal total pack-years of cigarettes smoked.

J Natl Cancer Inst 2009;101:1553–1561

Cigarette smoking accounts for about 65% of bladder cancer risk in men and 20%–30% in women (1). Studies have consistently shown a two- to threefold risk of bladder cancer among regular cigarette smokers, defined as those who smoked at least one cigarette per day for at least 6 months, compared with those who never smoked (1). Experimental evidence has suggested that 2-naphthylamine and 4-aminobiphenyl may be the bladder carcinogens in cigarette smoke (1–8).

Numerous studies have demonstrated that bladder cancer risk increases with increasing duration and intensity (cigarettes per day) of smoking, although risk levels off at higher intensity but not at higher duration (1,9). Bladder cancer risk decreases as time since quitting increases (10–12), but it is unclear whether risk eventually returns to that of never-smokers (1). Moreover, previous bladder cancer studies (8,13–17) have yielded equivocal results on the risk associated with exposure to environmental tobacco smoke (ETS).

Changes over time in the composition of tobacco and design of cigarettes have altered the constituents of mainstream cigarette

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (DB, JSC, KPC, NR, CS, JL, JFF, RNH, DTS); Department of Community and Family Medicine, Dartmouth Medical School, Hanover, NH (MRK, ASA, RW, AS); Department of Community Health and Pathology and Laboratory Medicine, Brown University, Providence, Rhode Island (CJM, KTK); Maine Cancer Registry, Augusta, ME (CV, MS); New Hampshire Cancer Registry, Concord, NH (SC); Vermont Cancer Registry, Burlington, VT (AJ).

Correspondence to: Dalsu Baris, MD, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, 6120 Executive Blvd, EPS Rm 8008, North Bethesda, MD 20852 (e-mail: barisd@mail.nih.gov).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp361

Published by Oxford University Press 2009.

Advance Access publication on November 13, 2009.

CONTEXT AND CAVEATS

Prior knowledge

Although it is well established that cigarette smoking is associated with risk of bladder cancer, the influence of various parameters of smoking history as well as secular trends in the smoking/bladder cancer relationship were unclear.

Study design

Odds ratios for bladder cancer risk were calculated in relation to smoking practices learned from interviews among 1170 bladder cancer patients and 1413 control subjects from Maine, New Hampshire, and Vermont in 2001–2004. Odds ratios for the New Hampshire participants of this study were compared with those from two similar case–control studies conducted in 1994–1998 and 1998–2001 in New Hampshire.

Contribution

Overall, current smokers, compared with never-smokers, had more than a five fold higher risk of bladder cancer. Among New Hampshire residents, there was a statistically significant progressive increase over each time period in bladder cancer risk among both former and current smokers compared with never-smokers.

Implications

The smoking-related risks of bladder cancer appear to have increased over time, at least among New Hampshire residents.

Limitations

Time-trend data were unavailable from Maine and Vermont, and there was a 65% participation rate among both cases patients and control subjects, which may have led to an underestimation of estimates of risk.

From the Editors

smoke. Although the sales-weighted average nicotine yield of cigarettes in the United States decreased gradually from the 1950s to 1990s (18), limited data suggests that the presence of lung and bladder carcinogens in cigarette smoke may have increased during the same period (19,20).

In a large, population-based case–control study in northern New England, we examined bladder cancer risk in relation to 1) cigarette smoking as measured by duration, intensity, and total exposure (pack-years); 2) years since smoking cessation; and 3) exposure to ETS. We also compared the odds ratios (ORs) from our study with those from two earlier studies of comparable design to evaluate the trend in smoking-related bladder cancer risk over time.

Subjects and Methods

The case series included all patients with a histologically confirmed carcinoma of the urinary bladder (including carcinoma in situ) newly diagnosed between September 1, 2001, and October 31, 2004 (Maine and Vermont) or between January 1, 2002, and July 31, 2004 (New Hampshire) among residents of these three states aged 30–79 years. Patient ascertainment in each state during the study period was conducted through hospital pathology departments, hospital cancer registries, and the state cancer registries. We pretested each state's plan to locate patients and closely monitored and audited the progress and completeness of this effort in all three states throughout the course of the study.

We interviewed 1213 bladder cancer patients (65% of 1878 eligible patients). Of eligible patients who did not participate, 50% refused, 22% were deceased, 12% were too ill, 5.5% did not speak English fluently, 5% had a physician who refused, and 5% were not able to be located. The study's expert pathologist (A. Schned) carried out a blind review of the initial diagnostic slides to confirm diagnosis, histological classification, and tumor stage and grade. Based on the expert pathology review, 20 patients who did not have cancer and 22 who did not have urothelial carcinomas were excluded, leaving 1171 patients eligible for the smoking analysis.

Control subjects aged 30–64 years were selected randomly from Department of Motor Vehicle (DMV) records in each state, and control subjects aged 65–79 years were selected from beneficiary records of the Centers for Medicare and Medicaid Services (CMS). It is possible that some potential control subjects may not have been included in the DMV or CMS databases (eg, younger control subjects who did not have a driver's license). To evaluate this issue, bladder cancer patients were asked about possession of either a Medicare card or driver's license (depending on age) on their reference date. The restriction of key analyses to only those patients with a driver's license or Medicare card did not change the results, however.

Control subjects were frequency matched to case patients by state, sex, and within 5 years of age at diagnosis of patients. We interviewed 1418 (594 DMV and 824 CMS) control subjects (65% of eligible DMV and 65% of eligible CMS control subjects). Of control subjects who did not participate, 70% of DMV and 65% of CMS control subjects refused, 24% of DMV and 11% of CMS control subjects were not able to be located, 3% of DMV and 10% of CMS control subjects did not speak English fluently, 1% of DMV and 7% of CMS control subjects were too ill, and 1% of DMV and 7% of CMS control subjects were deceased.

Individuals who agreed to participate were interviewed at home by a trained interviewer using a detailed computer-assisted personal interview. The interviewer obtained detailed information on demographics, use of tobacco products, occupational and residential histories, fluid intake, use of hair coloring products, family history of cancer, medication use, and dietary factors.

Our smoking analyses included 1170 urothelial carcinoma patients and 1413 control subjects who provided data on smoking (ie, one case and five controls were excluded because of missing smoking data). We defined "never-smokers" as subjects who had smoked less than 100 cigarettes over their lifetime. "Occasional smokers" were subjects who had smoked more than 100 cigarettes overall but never consumed cigarettes regularly (ie, at least one cigarette per day for at least 6 months). "Regular smokers" were subjects who consumed more than occasional smokers (ie, at least one cigarette per day for at least 6 months). Regular smokers were further categorized as "former smokers" (ie, those who quit smoking 1 year or more before the diagnosis date for case patients or selection date for control subjects) or "current smokers" (ie, those who were still smoking regularly at the time of their interview or had quit within 1 year of the reference date).

Among never-smokers, we assessed exposure to ETS by asking participants about the number of people who smoked around them everywhere they lived for at least 2 years duration since the age of 10 years and at the longest job they held for at least 6 months since the age of 16 years. We computed a series of ETS metrics: duration

of time spent living with one or more smokers in childhood (at or before age 18 years) and in adulthood, the cumulative residential ETS exposure (ie, the sum of the total number of smokers in each residence multiplied by the time spent in each residence over the person's lifetime), and the cumulative occupational ETS exposure. To measure cumulative occupational ETS exposure, we used the same approach for the longest jobs that a subject held as we did for each residence that he or she lived in for at least 2 years duration.

Statistical Analysis

We computed odds ratios and 95% confidence intervals (CIs) for smoking-related variables using unconditional logistic regression models, adjusting for age (<55, 55–64, 65–74, and ≥75 years), sex, race or ethnicity (white only, mixed race, or other race), Hispanic status (yes or no), and state (Maine, New Hampshire, or Vermont). Adjustment for employment in a high-risk occupation had no impact on the odds ratios and was not included in the final models. We used the Wald test to test for linear trend, treating categorical variables as continuous by using the median value for each category among control subjects. All statistical tests were two-sided, with $P < .05$ taken as a measure of statistical significance.

To clarify the effects of smoking dose as measured by smoking intensity (ie, cigarettes per day), smoking duration (ie, number of years of exposure), and pack-years, we evaluated the effects of the delivery rate of exposure (ie, how increasing cigarettes per day and decreasing duration of smoking affects risk of bladder cancer for a given total number of pack-years of exposure). This analysis used a recently described three-parameter model to estimate the excess odds ratio (EOR) (21,22), the details of which are presented in the Appendix.

To examine trends in smoking-related bladder cancer risk over time, we included data from two previous population-based case–control studies of bladder cancer that were carried out in New Hampshire and were virtually identical in design to the current study (23,24). These studies included cases from July 1, 1994, to June 30, 1998, and from July 1, 1998, to December 31, 2001, and totaled 843 case patients and 1183 control subjects who provided data on smoking. We used the likelihood-ratio test to evaluate homogeneity over time in trends in the odds ratios for smoking-related bladder cancer risk.

Results

Effects of Cigarette Smoking

Regular cigarette smokers had a higher risk of bladder cancer than never-smokers (OR = 3.0, 95% CI = 2.4 to 3.6) (Table 1). Among these regular smokers, risk estimates of bladder cancer were statistically significantly higher for both current (OR = 5.2, 95% CI = 4.0 to 6.6) and former (OR = 2.3, 95% CI = 1.9 to 2.8) smokers compared with never-smokers. Risk estimates were similar for men and women. We observed statistically significant trends in risk estimates with smoking duration, intensity, and pack-years ($P_{trend} < .001$ for each metric) (Table 1). Risks of bladder cancer that were estimated by intensity and pack-years, but not by duration, reached a plateau at the higher levels of smoking exposure. Similar patterns were observed for men and women, although fewer women were heavy smokers, leading to greater variability in the risk estimates.

Table 2 shows risk of developing bladder cancer cross-classified by both duration and intensity smoked among regular smokers only. We observed a statistically significant consistent trend in risk of bladder cancer with increasing smoking duration after adjustment for smoking intensity ($P_{trend} < .001$). There was, however, no consistent trend in bladder cancer risk either with increasing smoking intensity within each smoking duration category or overall by intensity after adjustment for duration ($P_{trend} = .898$).

We observed an inverse association in risk of bladder cancer with years since smoking cessation. However, the entire risk reduction was observed within the first 5 years after quitting. Compared with current smokers, the odds ratios were 0.6, 0.6, 0.7, and 0.7 for the categories of less than 5, 5–9, 10–19. After 20 or more years since quitting, risk still remains higher than that for never smokers.

Temporal Variations

We compared odds ratios for developing bladder cancer among the New Hampshire subjects in our study with odds ratios observed in two previous population-based case–control studies conducted in New Hampshire. Figure 1 shows the odds ratios for former and current smokers relative to never-smokers for three consecutive periods (1994–1998, 1998–2001, and 2002–2004) from data restricted to New Hampshire. There was a statistically significant increasing trend in smoking-related bladder cancer risk over three consecutive periods among former smokers (OR = 1.4, 95% CI = 1.0 to 2.0; OR = 2.0, 95% CI = 1.4 to 2.9; and OR = 2.6, 95% CI = 1.7 to 4.0 for 1994–1998, 1998–2001, and 2002–2004, respectively) and current smokers (OR = 2.9, 95% CI = 2.0 to 4.2; OR = 4.2, 95% CI = 2.8 to 6.3; OR = 5.5, 95% CI = 3.5 to 8.9 for 1994–1998, 1998–2001, and 2002–2004, respectively) (P for homogeneity of trends over time period = .04). This trend was similar for both men and women (data are not shown). Among former smokers, the mean numbers of cigarettes smoked per day were 22, 21, and 22 for the three periods, respectively, and the mean smoking durations were 30, 24, and 22 years. For current smokers, the corresponding values were 21, 20, and 23 cigarettes per day, and 41, 40, and 41 years. The similarity of the mean values of duration smoked and of cigarettes smoked per day across the three periods makes it unlikely that the differences across the three study populations with respect to duration of smoking and cigarettes smoked per day are the source of the observed time trend.

Effects of Rate of Delivery of Exposure

To evaluate effects of the rate of delivery of exposure, we first computed odds ratios for bladder cancer by categories of pack-years and intensity among current smokers relative to never-smokers (Figure 2). Within each level of intensity, an increasing trend in odds ratios with increasing pack-years was apparent. When we fitted a linear model for odds ratios by continuous pack-years within each intensity category, all trends were consistent with linearity, except for the 5–9 cigarettes per day category ($P = .03$). Estimates of the linear slope parameter (ie, the EOR per pack-year) varied with intensity. This variation defines the relative effects of exposure delivery (ie, increasing intensity and decreasing duration) for a fixed total pack-years of exposure. For example, in an individual who has smoked 40 pack-years, the odds ratio would

Table 1. Number of case patients and control subjects, odds ratio (OR), and 95% confidence intervals (95% CIs) for bladder cancer according to smoking status, duration smoked, intensity smoked, and pack-years

	All subjects				Men				Women			
	Case patients (N = 1170)	Control subjects (N = 1413)	OR* (95% CI)	P_{trend}†	Case patients (n = 897)	Control subjects (n = 1034)	OR* (95% CI)	P_{trend}†	Case patients (n = 273)	Control subjects (n = 379)	OR* (95% CI)	P_{trend}†
Smoking status												
Never smoked	171	470	1.0		114	305	1.0		57	165	1.0	
Occasional smokers‡	22	40	1.5 (0.9 to 2.6)		19	24	2.1 (1.1 to 4.0)		3	16	0.5 (0.1 to 1.9)	
Regular smokers	977	903	3.0 (2.4 to 3.6)		764	705	3.0 (2.3 to 3.8)		213	198	3.1 (2.2 to 4.5)	
Former smokers	602	698	2.3 (1.9 to 2.8)		484	557	2.3 (1.8 to 3.0)		118	141	2.3 (1.6 to 3.4)	
Current smokers§	374	204	5.2 (4.0 to 6.6)		279	147	5.2 (3.9 to 7.0)		95	57	5.5 (3.5 to 8.7)	
Duration smoked, y				<.001				<.001				<.001
Never smoked	171	470	1.0		114	305	1.0		57	165	1.0	
<10	54	103	1.4 (1.0 to 2.1)		36	82	1.2 (0.8 to 1.9)		18	21	2.4 (1.2 to 4.9)	
10–19	115	194	1.6 (1.2 to 2.1)		99	150	1.8 (1.3 to 2.5)		16	44	1.0 (0.5 to 2.0)	
20–29	182	217	2.3 (1.8 to 3.0)		146	171	2.3 (1.7 to 3.2)		36	46	2.4 (1.4 to 4.1)	
30–39	241	158	4.2 (3.2 to 5.5)		185	122	4.2 (3.0 to 5.7)		56	36	4.5 (2.7 to 7.6)	
40–49	230	136	4.8 (3.6 to 6.3)		183	101	5.2 (3.7 to 7.2)		47	35	3.9 (2.3 to 6.8)	
≥50	149	86	5.1 (3.7 to 7.1)		110	71	4.7 (3.2 to 6.8)		39	15	7.9 (3.9 to 15.7)	
Intensity smoked (packs per day				<.001				<.001				<.001
Never smoked	171	470	1.0		114	305	1.0		57	165	1.0	
<1 pack	226	270	2.3 (1.8 to 2.9)		146	176	2.3 (1.7 to 3.1)		80	94	2.4 (1.6 to 3.7)	
≥1 to <2 packs	559	463	3.3 (2.7 to 4.2)		441	378	3.2 (2.4 to 4.1)		118	85	4.3 (2.8 to 6.5)	
≥2 to <3 packs	157	129	3.4 (2.5 to 4.5)		146	112	3.5 (2.5 to 4.9)	]	14	18	2.1 (1.0 to 4.5)	
≥3 packs	33	37	2.5 (1.5 to 4.2)		30	36	2.3 (1.4 to 3.9)					
Pack-years				<.001				<.001				<.001
Never smoked	171	470	1.0		114	305	1.0		57	165	1.0	
<20	210	345	1.7 (1.3 to 2.1)		148	247	1.6 (1.2 to 2.2)		62	98	1.8 (1.2 to 2.9)	
20–39	288	251	3.2 (2.5 to 4.1)		216	195	3.0 (2.2 to 4.0)		72	56	3.8 (2.4 to 6.2)	
40–49	153	90	4.9 (3.5 to 6.7)		124	73	4.8 (3.3 to 6.9)		29	17	5.1 (2.6 to 10.0)	
50–59	102	59	5.0 (3.4 to 7.2)		77	52	4.2 (2.8 to 6.4)		25	7	11.1 (4.5 to 27.5)	
≥60	216	146	4.2 (3.2 to 5.6)		193	128	4.2 (3.1 to 5.8)		23	18	3.7 (1.8 to 7.4)	

* Adjusted for age, race, Hispanic status, and state of residence. Results for all subjects are also adjusted for sex.

† P_{trend} values were calculated by using a two-sided Wald test.

‡ An occasional smoker is one who reported smoking at least 100 cigarettes during his/her lifetime, but who did not smoke regularly (at least one cigarette per day for 6 months or longer). No further information was available for occasional smokers, and they are excluded from all subsequent analyses.

§ Subjects were defined as current smokers if they still smoked or had quit within 1 year of the reference date.

Table 2. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of bladder cancer according to duration smoked and number of cigarettes smoked per day, among smokers only

	Smoking intensity (among smokers)						All subjects	
	Less than 1 pack per day		1–2 packs per day		2 or more packs per day			
Duration smoked, y	Case patients/ control subjects	OR* (95% CI)	Case patients/ control subjects	OR* (95% CI)	Case patients/ control subjects	OR* (95% CI)	Case patients/ control subjects	OR*† (95% CI)
<20	81/120	1.0	66/138	0.7 (0.5 to 1.1)	22/38	0.9 (0.5 to 1.6)	169/296	1.0
20–29	41/65	0.9 (0.6 to 1.5)	108/112	1.4 (1.0 to 2.1)	33/40	1.3 (0.7 to 2.2)	182/217	1.5 (1.1 to 1.9)
30–39	35/31	1.7 (1.0 to 3.0)	145/82	2.7 (1.8 to 4.0)	61/44	2.1 (1.3 to 3.4)	241/157	2.7 (2.0 to 3.6)
40–49	40/31	2.1 (1.2 to 3.6)	143/73	3.0 (2.0 to 4.6)	46/31	2.3 (1.3 to 3.9)	229/135	3.1 (2.3 to 4.1)
≥50	27/19	2.3 (1.2 to 4.5)	94/54	2.9 (1.9 to 4.5)	27/13	3.4 (1.6 to 7.0)	148/86	3.3 (2.3 to 4.6)
All subjects‡	224/266	1.0	556/459	1.2 (0.9 to 1.5)	189/166	1.1 (0.8 to 1.4)		

* Odds ratios relative to smokers of <1 pack per day for duration of less than 20 years; adjusted for age, sex, race, Hispanic status, and state of residence.

† Odds ratios for duration smoked relative to <20 years duration smoked (P_{trend} < .001), adjusted for intensity smoked. P_{trend} values were calculated by using a two-sided Wald test.

‡ Odds ratios for intensity smoked relative to <1 pack pesr day smoked (P_{trend} = .898), adjusted for duration smoked. P_{trend} values were calculated by using a two-sided Wald test.

Figure 1. Trend in smoking-induced bladder cancer in New Hampshire from 1994 to 2004. Odds ratios (ORs) and 95% confidence intervals for bladder cancer are shown for former and current smokers relative to never-smokers during three consecutive time intervals: from July 1, 1994, to June 30, 1998 (372 case patients and 456 control subjects) (**white bars**); from July 1, 1998, to December 31, 2001 (324 case patients and 328 control subjects) (**light gray bars**); and from January 1, 2002, to December 31, 2004 (253 case patients and 199 control subjects) (**dark gray bars**).

be approximately 6.4, 6.0, 5.5, 2.3, 5.1, or 3.3 depending on the intensity of smoking being 10–14, 15–19, 20–24, 25–29, 30–39, or 40 or more cigarettes per day, respectively (Figure 2). These changing odds ratios correspond to the effects of exposure delivery, that is, the combination of increasing intensity and decreasing duration of smoking.

We plotted the estimated EOR per pack-year and 95% confidence interval by the mean number of cigarettes per day within each intensity category and fitted a smooth model using continuous data (Figure 3). The category-specific EOR per pack-year estimates declined with increasing number of cigarettes per day, with the fitted line corresponding closely to the estimates (Figure 3, solid line). At low intensity, the range of pack-years was necessarily limited, and thus, estimates of the EOR per pack-year (plotted as mean cigarettes per day) were highly variable. We therefore refitted the model after excluding smokers who consumed less than 10 cigarettes per day (17 cases and 13 control subjects) and again observed a close correspondence between the fitted model and the EOR per pack-year estimates (Figure 3, dashed line). Finally, with all parameters in Equation 1 (Appendix 1) except β fixed at previously determined summary values as described in Lubin et al. (21), the model (Figure 3, dotted line) provided an excellent fit to the observed data. A test of homogeneity with two *df* indicated that the patterns of EOR per pack-year in the 10-study data were consistent with the current data (P = .55) and that the declining exposure rate patterns were quantitatively similar.

Exposure to ETS

Table 3 shows bladder cancer risk by type of ETS exposure among never-smokers of cigarettes, cigars, and pipes. Compared with subjects with no ETS exposure, we observed no statistically significant increase in bladder cancer risk with ETS exposure when subjects

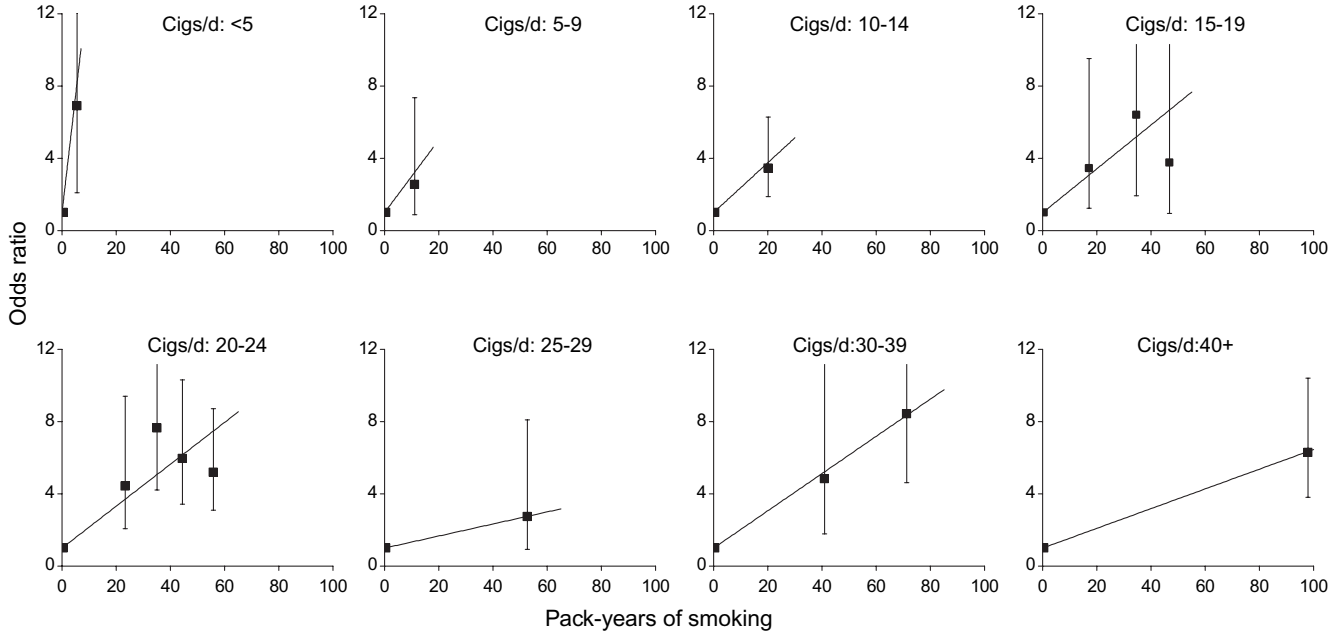

Figure 2. Odds ratios (ORs) and 95% confidence intervals for bladder cancer among smokers, relative to never-smokers, by categories of total pack-years of exposure and cigarettes smoked per day (cigs/d), and fitted linear models for the odds ratios by pack-years (**square symbols**).

were exposed to ETS at home either as children or as adults, at the workplace, or at the home and workplace combined.

Discussion

This population-based study from New England suggests that risk estimates for bladder cancer related to cigarette smoking have increased over time. When we compared the odds ratios from our study of New Hampshire subjects from 2001 to 2004 with those from two previous studies in that state, we observed a positive trend in risk among former and current cigarette smokers during the period from 1994 to 2004. Our findings are consistent with those from a recent case–control study from the Roswell Park Cancer Institute that suggested that risk of smoking-related bladder cancer increased from the late 1950s to the late 1990s (25). The upward trend in smoking-related bladder cancer may explain why the increased risk observed among current smokers in our study exceeds that observed among current smokers in the National Bladder Cancer Study, a large, population-based case–control study of 2982 bladder cancer cases and 5782 control subjects conducted by National Cancer Institute in 1978 in 10 areas of the United States (10). Long-term smokers (those who had smoked for 60 years or more) in the National Bladder Cancer Study had an odds ratio for bladder cancer of 3.2 (95% CI = 2.4 to 4.2), whereas long-term smokers (those who had smoked for 50 years or more) in our study had an odds ratio of 5.1 (95% CI = 3.7 to 7.1).

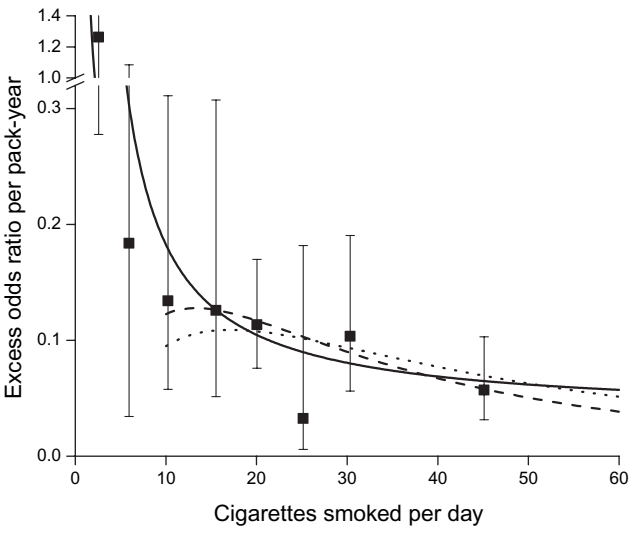

Figure 3. Estimates of the excess odds ratio (EOR) per pack-year for categories of intensity (<5, 5–9, 10–14, 15–19, 20–24, 25–29, 30–39, ≥40 cigarettes per day). The EOR per pack-year and 95% confidence intervals were plotted at the mean numbers of cigarettes per day within each category (**square symbols**). The three models shown are fitted to all data (**solid line**), to all data excluding smokers who consumed less than 10 cigarette per day (**dashed line**), and to all data excluding smokers who consumed less than 10 cigarettes per day with intensity effects fixed at $\varphi_1 = 2.72$ and $\varphi_2 = -0.479$ (Equation 1 in Appendix 1) determined from a previous analysis of multiple smoking-related cancer studies (**dotted line**) (21).

The upward trend in the risk of smoking-related bladder cancer may be due in part to changes over time in the composition of tobacco and design of cigarettes, which may have led to increased levels of bladder carcinogens in cigarette smoke (18,20). Based on limited data, 2-naphthylamine, a known bladder carcinogen found in amounts ranging from 1 to 22 ng per cigarette smoked, according to earlier reports (26,27), increased to 35 ng by 1985 (18). Production of low–nicotine yield cigarettes may also have led to increased depth and frequency of inhalation to satisfy the need for nicotine (28,29), further increasing exposure to bladder carcinogens. Interestingly, the rising incidence of lung adenocarcinoma has been associated with deeper inhalation of low–nicotine yield cigarettes coupled with increases in nitrosamine levels in cigarette smoke (30–34). Although the changes in tobacco composition and cigarette design first began

in the 1950s, the reformulated cigarettes were not marketed heavily until the 1960s and 1970s (35). Thus, the increases in smoking-related risk over the past decade are consistent with the 20- to 30-year latent period for aromatic amine-induced bladder cancer (36).

We observed statistically significant dose–response relationships in bladder cancer risk for smoking duration, intensity, and pack-years ($P < .001$). In contrast to consistent increases in risk with increasing duration of smoking, risk appeared to reach a plateau at high levels of smoking intensity. This phenomenon has been observed in previous studies of smoking-related bladder cancer (1,9), as well as in studies of smoking-related lung, pancreas, esophagus and oral cavity cancers (21). Our findings further suggest that, for an equal total exposure (in pack-years), smoking at a lower intensity for a longer duration is more harmful than smoking at a higher intensity for a shorter duration. This observation is consistent with previously reported patterns for several smoking-related cancers, including three bladder cancer studies (21,22,37).

The inverse delivery rate effect for cigarette smoke may reflect different inhalation patterns associated with smoking intensity (1,9,38–40). If heavy smokers inhale less vigorously and are thus exposed to fewer carcinogens with each additional cigarette, an observation that has been reported for lung cancer (41), the relative impact of an additional cigarette would be expected to decline at higher intensities (9). Although modified inhalation patterns may explain some plateauing of risk with intensity, a simulation study based on the relationship of urinary cotinine and cigarettes per day suggests that it is unlikely to fully account for the observed pattern (42). Alternatively, the intensity effect may have been influenced by misclassification of the amount smoked per day, with increasing underreporting by heavy smokers. This explanation seems unlikely, however, because this type of misclassification would induce greater curvilinearity on the disease to pack-year association with increasing intensity, patterns which were not observed.

We observed an inverse association in bladder cancer risk with length of time since quitting, with an immediate reduction in risk within the first 5 years, underscoring the public health importance of smoking cessation. There was no additional risk reduction with further increases in the time since quitting. Our findings support the hypothesis that cigarette smoke may act as a late-stage carcinogen (1,8,43). Yet, our results are also consistent with previous studies indicating that bladder cancer risk among people who quit smoking for at least 20 years remains higher than that for never-smokers, suggesting an early-stage irreversible effect of cigarette smoke (1,8,44).

The well-established association between smoking and bladder cancer offers grounds to suspect that exposure to ETS may increase bladder cancer risk. Only a few studies have examined ETS as a risk factor for bladder cancer, with some reporting positive associations (13,14,45) and others reporting null results (8,17,46,47) including a recent meta-analysis (48). We observed no statistically significant association between ETS exposure and bladder cancer risk. It is possible, however, that ETS may be a weak bladder carcinogen (47) that may have eluded epidemiological detection of small risks because of low levels of exposure. Additionally, there may have been some nondifferential misclassification of exposure that would bias our results toward the null.

The strengths of this study include large sample size, the population-based study design, and the ascertainment of a detailed smoking history from participants, including information on ETS. The main weakness of our study is the lack of time trend data from the two other participating states, Maine and Vermont, which limits the ability of our results to be generalized beyond the New Hampshire population. Another limitation is the 65% participation rate among both case patients and controls. The nondifferential nonresponse rate of 35% may have led to underestimation of some our estimates of risk.

In summary, our findings suggest that the odds ratios for smoking-related bladder cancer have increased in New Hampshire over time. This trend may be related to changes in the 1960s and 1970s in the composition of tobacco and cigarette design coupled with modifications in inhalation patterns resulting in

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) of bladder cancer by cumulative residential and occupational exposure to environmental tobacco smoke (ETS) among nonsmokers*

ETS exposure	Case patients (n = 145)	Control subjects (n = 402)	OR (95% CI)	P_{trend}†
Childhood residential‡				.797
No lifetime ETS exposure	12	37	1.0	
No childhood ETS exposure	25	70	1.0 (0.5 to 2.4)	
≤18	66	183	1.1 (0.5 to 2.3)	
>18	42	112	1.1 (0.5 to 2.4)	
Adult residential§				.700
No lifetime ETS exposure	12	37	1.0	
No adult ETS exposure	20	57	1.0 (0.4 to 2.3)	
>0 to ≤7	42	106	1.2 (0.5 to 2.5)	
>7 to ≤30.5	33	103	1.0 (0.5 to 2.2)	
>30.5	38	99	1.2 (0.5 to 2.6)	
Occupational‖				.571
No lifetime ETS exposure	12	37	1.0	
No occupational ETS exposure	61	184	1.0 (0.5 to 2.1)	
>0 to ≤105	31	68	1.5 (0.7 to 3.3)	
>105 to ≤170	24	53	1.4 (0.6 to 3.3)	
>170	16	60	0.7 (0.3 to 1.7)	
Combined (residential and occupational)				.726
No lifetime ETS exposure	12	37	1.0	
>0 to ≤45.3	42	122	1.0 (0.5 to 2.2)	
>45.3 to ≤143.5	53	130	1.3 (0.6 to 2.8)	
>143.5	38	113	0.9 (0.4 to 2.0)	

* Adjusted for age, race, sex, Hispanic status, and state of residence. Includes only nonsmokers of cigarettes, cigars, and pipes.

† P_{trend} values were calculated by using a two-sided Wald test.

‡ Sum of the years spent at each childhood residence (up to age 18 years) multiplied by the number of smokers in each residence and categorized above and below median in controls.

§ Sum of the years spent at each adult residence multiplied by the number of smokers in each residence and categorized according to tertiles in controls.

‖ Sum of the years spent at the longest job multiplied by the number of smokers and categorized according to tertiles in control subjects.

increased exposure to bladder carcinogens. The observed relationship between smoking and bladder cancer risk was stronger than that reported in earlier studies, with statistically significant trends in risk with increasing duration, intensity, and pack-years for both men and women. Additional modeling of the rate of delivery of cigarette smoke supports previous observations, suggesting a greater risk for total exposure delivered at a lower intensity (and for longer duration) than for an equivalent exposure delivered at a higher intensity (and for shorter duration).

Appendix

We fitted the following three-parameter model for the excess odds ratio (EOR) (21,22):

$$\mathrm{OR}(d) = 1+\beta\, d\, g(n) \qquad [1]$$

where d = total pack-years and n = cigarettes per day. The parameter β represents the slope (EOR per pack-year) of a simple linear relationship at $g(n) = 1$, whereas g(.) represents the modifying effect of intensity on β. For each fixed intensity, $\beta g(n)$ thus defined the slope of a linear relationship for the odds ratios of bladder cancer by total pack-years. As in previous analyses (21,22,47), we set $g(n) = \exp\{\varphi_1 \ln(n) + \varphi_2 \ln(n)^2\}$ where φ_1 and φ_2 parameters of g(.) define the relative impact of intensity on the EOR per pack-year.

References

1. Silverman DT, Devesa SS, Moore LL, Rothman N. Bladder cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. New York, NY: Oxford University Press; 2006:1101–1127.
2. Jones PA, Ross RK. Prevention of bladder cancer. *N Engl J Med.* 1999; 340(18):1424–1426.
3. Stabbert R, Schafer KH, Biefel C, et al. Analysis of aromatic amines in cigarette smoke. *Rapid Commun Mass Spectrom.* 2003;17(18):2125–2132.
4. Riedel K, Scherer G, Engl J, et al. Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. *J Anal Toxicol.* 2006; 30(3):187–195.
5. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem Res Toxicol.* 1998;11(6):559–603.
6. Vineis P, Pirastu R. Aromatic amines and cancer. *Cancer Causes Control.* 1997;8(3):346–355.
7. Skipper PL, Tannenbaum SR, Ross RK, et al. Nonsmoking-related arylamine exposure and bladder cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2003;12(6):503–507.
8. Samanic C, Kogevinas M, Dosemeci M, et al. Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev.* 2006;15(7):1348–1354.
9. Vineis P, Kogevinas M, Simonato L, et al. Levelling-off of the risk of lung and bladder cancer in heavy smokers: an analysis based on multicentric case-control studies and a metabolic interpretation. *Mutat Res.* 2000;463(1): 103–110.
10. Hartge P, Silverman D, Hoover R, et al. Changing cigarette habits and bladder cancer risk: a case-control study. *J Natl Cancer Inst.* 1987;78(6): 1119–1125.
11. Castelao JE, Yuan JM, Skipper PL, et al. Gender- and smoking-related bladder cancer risk. *J Natl Cancer Inst.* 2001;93(7):538–545.
12. Sorahan T, Lancashire RJ, Sole G. Urothelial cancer and cigarette smoking: findings from a regional case-controlled study. *Br J Urol.* 1994; 74(6):753–756.
13. Jiang X, Yuan JM, Skipper PL, et al. Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res.* 2007;67(15):7540–7545.
14. Alberg AJ, Kouzis A, Genkinger JM, et al. A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol.* 2007;165(6): 660–666.
15. Bjerregaard BK, Raaschou-Nielsen O, Sorensen M, et al. The effect of occasional smoking on smoking-related cancers: in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control.* 2006;17(10):1305–1309.
16. Zeegers MP, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control.* 2002;13(1):83–90.
17. Kabat GC, Dieck GS, Wynder EL. Bladder cancer in nonsmokers. *Cancer.* 1986;57(2):362–367.
18. Hoffmann D, Hoffmann I. The changing cigarettes: chemical studies and bioassays. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, eds. *Risk Associated With Smoking Cigarettes With Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. NIH, National Cancer Institute, NIH Publication No. 02-5074; 2001:159–19.
19. Hoffmann D, Djordjevic MV, Hoffmann I. The changing cigarette. *Prev Med.* 1997;26(4):427–434.
20. Hoffmann D, Hoffmann I, El Bayoumy K. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. *Chem Res Toxicol.* 2001; 14(7):767–790.
21. Lubin JH, Alavanja MC, Caporaso N, et al. Cigarette smoking and cancer risk: modeling total exposure and intensity. *Am J Epidemiol.* 2007;166(4) :479–489.
22. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(3):517–523.
23. Karagas MR, Tosteson TD, Morris JS, et al. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes Control.* 2004;15(5):465–472.
24. Fortuny J, Kogevinas M, Zens MS, et al. Analgesic and anti-inflammatory drug use and risk of bladder cancer: a population based case control study. *BMC Urol.* 2007;7(13).
25. Peppone LJ, Hayland A, O'Connor JO. Cigarette smoking, bladder cancer and change in risk over 40 years. In: *Frontiers in Cancer Prevention Research Conference Proceedings*; November 12–15, 2006; Boston, MA.
26. Patrianakos C, Hoffmann D. Chemical studies on tobacco smoke LXIV. On the analyses of aromatic amines in cigarettes smoke. *J Anal Toxicol.* 1979;3(4):150–154.
27. Masuda Y, Hoffmann D. Quantitative determination of 1-naphthylamine and 2-naphthylamine in cigarette smoke. *Anal Chem.* 1969;41(4):650–652.
28. Benowitz NL. Compensatory smoking of low yields cigarettes. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, eds. *Risk Associated With Smoking Cigarettes With Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. NIH, National Cancer Institute, NIH Publication No. 02-5074, 2001:39–63.
29. Scherer G. Smoking behaviour and compensation: a review of the literature. *Psychopharmacology (Berl).* 1999;145(1):1–20.
30. Brooks DR, Austin JH, Heelan RT, et al. Influence of type of cigarette on peripheral versus central lung cancer. *Cancer Epidemiol Biomarkers Prev.* 2005;14(3):576–581.
31. Devesa SS, Bray F, Vizcaino AP, et al. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer.* 2005;117(2):294–299.
32. Jemal A, Travis WD, Tarone RE, et al. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer.* 2003;105(1):101–107.
33. Wynder EL, Hoffmann D. Re: Cigarette smoking and the histopathology of lung cancer. *J Natl Cancer Inst.* 1998;90(19):1486–1488.
34. Stellman SD, Muscat JE, Thompson S, et al. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. *Cancer.* 1997;80(3):382–388.
35. Burns DM, Major JM, Shanks TG, Thun MJ, Samet JM. Smoking lower yield cigarettes and disease risk. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, eds. *Risk Associated With Smoking Cigarettes With Low Machine-Measured Yields of Tar and Nicotine*. Bethesda, MD: U.S. NIH, National Cancer Institute, NIH Publication No. 02-5074; 2001:65–158.

36. Decarli A, Peto J, Piolatto G, et al. Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. *Br J Cancer.* 1985;51(5):707–712.
37. Lubin JH, Virtamo J, Weinstein SJ, et al. Cigarette smoking and cancer: intensity patterns in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study in Finnish men. *Am J Epidemiol.* 2008;167(8): 970–975.
38. Lubin JH, Kogevinas M, Silverman D, et al. Evidence for an intensity-dependent interaction of NAT2 acetylation genotype and cigarette smoking in the Spanish Bladder Cancer Study. *Int J Epidemiol.* 2007;36(1): 236–241.
39. Sak SC, Barrett JH, Paul AB, et al. DNA repair gene XRCC1 polymorphisms and bladder cancer risk. *BMC Genet.* 2007;8(13).
40. Vineis P, Marinelli D, Autrup H, et al. Current smoking, occupation, N-acetyltransferase-2 and bladder cancer: a pooled analysis of genotype-based studies. *Cancer Epidemiol Biomarkers Prev.* 2001;10(12): 1249–1252.
41. Law MR, Morris JK, Watt HC, et al. The dose-response relationship between cigarette consumption, biochemical markers and risk of lung cancer. *Br J Cancer.* 1997;75(11):1690–1693.
42. Lubin JH, Caporaso N, Wichmann HE, et al. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. *Epidemiology.* 2007;18(5):639–648.
43. Day NE, Brown CC. Multistage models and primary prevention of cancer. *J Natl Cancer Inst.* 1980;64(4):977–989.
44. Brennan P, Bogillot O, Cordier S, et al. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer.* 2000;86(2):289–294.
45. Bjerregaard BK, Raaschou-Nielsen O, Sorensen M, et al. Tobacco smoke and bladder cancer–in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2006;119(10):2412–2416.
46. Zeegers MP, Kellen E, Buntinx F, et al. The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. *World J Urol.* 2004;21(6):392–401.
47. Burch JD, Rohan TE, Howe GR, et al. Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer.* 1989; 44(4):622–628.
48. Van Hemelrijck MJ, Michaud DS, Connolly GN, et al. Secondhand smoking, 4-aminobiphenyl, and bladder cancer: two meta-analyses. *Cancer Epidemiol Biomarkers Prev.* 2009;18(4):1312–1320.

Funding

Intramural Research Program of the National Institute of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics (contract number N02-CP-01037). The earlier phases of the New Hampshire component of the study were funded by National Institutes of Health grants, P42 ES007373 from the National Institute of Environmental Health Sciences and R01 CA57494 and CA121147 from the National Cancer Institute.

Notes

None of the authors have conflicts of interest that are relevant to the subject matter or materials discussed in the manuscript. The authors had full responsibility for the design of the study, collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

We thank Anna McIntosh, Paul Hurwitz, Patricia Clark and Vanessa Olivo (Westat, Rockville, MD) for their support in study and data management, and Anne Taylor and Mary McAdams (Information Management Services, Silver Spring, MD) for their programming help. We would like to acknowledge Dr Michael Jones (Maine Medical Center), Sue Ledoux and Dawn Nicolaides (Maine Cancer Registry), Kimberley Walsh and Christina Robinson (Dartmouth Medical School), Dr Masatoshi Kida (University of Vermont), William Apao and Carolyn Greene (Vermont Cancer Registry) for their contributions during the fieldwork and data collection phases. We also thank all fieldwork staff, interviewers, and data abstractors for their dedicated work, and our study participants for agreeing to be part of this study. We thank Dr Dietrich Hoffmann for his thoughtful suggestions.

Manuscript received November 19, 2008; revised August 19, 2009; accepted September 17, 2009.