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 smoke and the types and amounts of carcinogens that are released. As the smoking population changed over time, smoking practices and tobacco products also changed. This made it more difficult to understand changes in the risk over time.

Subjected through hospital pathology departments, hospital cancer registries and the state 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.

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 < .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 < .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 = .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

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case patients</td>
<td>Control subjects</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>171 (N = 1170)</td>
<td>470 (N = 1413)</td>
<td>1.0</td>
</tr>
<tr>
<td>Occasional smokers‡</td>
<td>22 (N = 1170)</td>
<td>40 (N = 1413)</td>
<td>1.5 (0.9 to 2.6)</td>
</tr>
<tr>
<td>Regular smokers</td>
<td>977 (N = 1170)</td>
<td>903 (N = 1413)</td>
<td>3.0 (2.4 to 3.6)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>602 (N = 1170)</td>
<td>698 (N = 1413)</td>
<td>2.3 (1.9 to 2.8)</td>
</tr>
<tr>
<td>Current smokers§</td>
<td>374 (N = 1170)</td>
<td>204 (N = 1413)</td>
<td>5.2 (4.0 to 6.6)</td>
</tr>
<tr>
<td>Duration smoked, y</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>171 (N = 1170)</td>
<td>470 (N = 1413)</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;10</td>
<td>54 (N = 1170)</td>
<td>103 (N = 1413)</td>
<td>1.4 (1.0 to 2.1)</td>
</tr>
<tr>
<td>10–19</td>
<td>115 (N = 1170)</td>
<td>194 (N = 1413)</td>
<td>1.6 (1.2 to 2.1)</td>
</tr>
<tr>
<td>20–29</td>
<td>182 (N = 1170)</td>
<td>217 (N = 1413)</td>
<td>2.3 (1.8 to 3.0)</td>
</tr>
<tr>
<td>30–39</td>
<td>241 (N = 1170)</td>
<td>158 (N = 1413)</td>
<td>4.2 (3.2 to 5.5)</td>
</tr>
<tr>
<td>40–49</td>
<td>230 (N = 1170)</td>
<td>136 (N = 1413)</td>
<td>4.8 (3.6 to 6.3)</td>
</tr>
<tr>
<td>≥50</td>
<td>149 (N = 1170)</td>
<td>86 (N = 1413)</td>
<td>5.1 (3.7 to 7.1)</td>
</tr>
<tr>
<td>Intensity smoked (packs per day)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>171 (N = 1170)</td>
<td>470 (N = 1413)</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;1 pack</td>
<td>226 (N = 1170)</td>
<td>270 (N = 1413)</td>
<td>2.3 (1.8 to 2.9)</td>
</tr>
<tr>
<td>≥1 to &lt;2 packs</td>
<td>559 (N = 1170)</td>
<td>463 (N = 1413)</td>
<td>3.3 (2.7 to 4.2)</td>
</tr>
<tr>
<td>≥2 to &lt;3 packs</td>
<td>157 (N = 1170)</td>
<td>129 (N = 1413)</td>
<td>3.4 (2.5 to 4.5)</td>
</tr>
<tr>
<td>≥3 packs</td>
<td>33 (N = 1170)</td>
<td>37 (N = 1413)</td>
<td>2.5 (1.5 to 4.2)</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>171 (N = 1170)</td>
<td>470 (N = 1413)</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;20</td>
<td>210 (N = 1170)</td>
<td>345 (N = 1413)</td>
<td>1.7 (1.3 to 2.1)</td>
</tr>
<tr>
<td>20–39</td>
<td>288 (N = 1170)</td>
<td>251 (N = 1413)</td>
<td>3.2 (2.5 to 4.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>153 (N = 1170)</td>
<td>90 (N = 1413)</td>
<td>4.9 (3.5 to 6.7)</td>
</tr>
<tr>
<td>50–59</td>
<td>102 (N = 1170)</td>
<td>59 (N = 1413)</td>
<td>5.0 (3.4 to 7.2)</td>
</tr>
<tr>
<td>≥60</td>
<td>216 (N = 1170)</td>
<td>146 (N = 1413)</td>
<td>4.2 (3.2 to 5.6)</td>
</tr>
</tbody>
</table>

* Adjusted for age, race, Hispanic status, and state of residence. Results for all subjects are also adjusted for sex.
† P<sub>adj</sub> 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.

<table>
<thead>
<tr>
<th>Duration smoked, y</th>
<th>&lt;20</th>
<th>20 – 29</th>
<th>30 – 39</th>
<th>40 – 49</th>
<th>≥50</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>81/120 (0.5 to 1.0)</td>
<td>108/112 (1.0 to 2.1)</td>
<td>145/82 (1.8 to 4.0)</td>
<td>143/73 (2.0 to 4.6)</td>
<td>94/54 (1.9 to 4.5)</td>
<td>224/266 (1.0)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>41/65 (0.6 to 1.5)</td>
<td>108/112 (1.0 to 2.1)</td>
<td>145/82 (1.8 to 4.0)</td>
<td>143/73 (2.0 to 4.6)</td>
<td>94/54 (1.9 to 4.5)</td>
<td>182/217 (1.5)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>35/31 (1.0 to 3.0)</td>
<td>108/112 (1.0 to 2.1)</td>
<td>145/82 (1.8 to 4.0)</td>
<td>143/73 (2.0 to 4.6)</td>
<td>94/54 (1.9 to 4.5)</td>
<td>241/157 (2.7)</td>
</tr>
<tr>
<td>40 – 49</td>
<td>40/31 (1.2 to 3.6)</td>
<td>108/112 (1.0 to 2.1)</td>
<td>145/82 (1.8 to 4.0)</td>
<td>143/73 (2.0 to 4.6)</td>
<td>94/54 (1.9 to 4.5)</td>
<td>229/135 (3.1)</td>
</tr>
<tr>
<td>≥50</td>
<td>27/19 (1.2 to 4.5)</td>
<td>108/112 (1.0 to 2.1)</td>
<td>145/82 (1.8 to 4.0)</td>
<td>143/73 (2.0 to 4.6)</td>
<td>94/54 (1.9 to 4.5)</td>
<td>148/86 (3.3)</td>
</tr>
<tr>
<td>All subjects†</td>
<td>224/266 (1.0)</td>
<td>189/166 (1.1)</td>
<td>189/166 (1.1)</td>
<td>189/166 (1.1)</td>
<td>189/166 (1.1)</td>
<td>189/166 (1.1)</td>
</tr>
</tbody>
</table>

* 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 per day smoked (P_trend = .898), adjusted for duration smoked. P_trend values were calculated by using a two-sided Wald test.
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).

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
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) \((21,22)\):

\[
\text{OR}(d) = 1 + \beta \frac{d}{g(n)} \tag{1}
\]

where \(d\) = total pack-years and \(n\) = cigarettes per day. The parameter \(\beta\) represents the slope (EOR per pack-year) of a simple linear relationship at \(g(n) = 1\), whereas \(g(n)\) represents the modifying effect of intensity on \(\beta\). For each fixed intensity, \(\beta(n)\) thus defines 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 \(\varphi_1\) and \(\varphi_2\) parameters of \(g(n)\) define the relative impact of intensity on the EOR per pack-year.

References


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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.

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