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Original Contribution

Tobacco Smoking, Smoking Cessation, and Cumulative Risk of Upper Aerodigestive Tract Cancers

Cristina Bosetti[1], Silvano Gallus[1], Richard Peto[2], Eva Negri[1], Renato Talamini[3], Alessandra Tavani[1], Silvia Franceschi[4], and Carlo La Vecchia[1,5]

[1] Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy.
[2] Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom.
[3] Unità di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico di Aviano, Aviano, Italy.
[4] International Agency for Research on Cancer, Lyon, France.
[5] Istituto di Statistica Medica e Biometria "G. A. Maccacaro," Università degli Studi di Milano, Milan, Italy.

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Upper aerodigestive tract cancers are strongly related to smoking, and their incidence is substantially lower in former smokers than in continuing smokers. To estimate the effect of smoking cessation on the cumulative incidence of these cancers by age 75 years (in the absence of competing causes of death), the authors combined odds ratios for males from a network of Italian hospital-based case-control studies (1984–2000) with 1993–1997 incidence data for Italian men. The studies included 961 cases with oral/pharyngeal cancer, 618 cases with esophageal cancer, and 613 cases with laryngeal cancer, plus 3,781 controls. For all upper aerodigestive tract cancers, the cumulative risks by 75 years of age were 6.3% for men who continued to smoke any type of tobacco, 3.1% and 1.2% for men who stopped smoking at around 50 and 30 years of age, respectively, and 0.8% among lifelong nonsmokers. Corresponding figures were 3.3%, 1.4%, 0.5%, and 0.2% for oral/pharyngeal cancer; 1.0%, 0.5%, 0.4%, and 0.2% for esophageal cancer; and 2.1%, 1.1%, 0.2%, and 0.2% for laryngeal cancer. In this Italian population, men who stopped smoking before age 50 years avoided more than half of the excess risk of upper aerodigestive tract cancer as men who did not, and men who stopped smoking before age 30 years avoided more than 90% of the risk.

head and neck neoplasms; risk factors; smoking; smoking cessation; tobacco

Abbreviations: CI, confidence interval; OR, odds ratio.

In many populations, persistent tobacco smoking is the cause of most cancers of the upper aerodigestive tract (1). Several studies have shown that although former smokers have higher risks than never smokers, they also have substantially lower risks than persons who continue to smoke, the difference in risk being greater the longer ago smoking stopped (1–3). Some favorable effect of stopping smoking is evident within just a few years after cessation, although the main absolute benefit comes later.

Although case-control studies of cancer are often used to estimate only the odds ratios in various categories of smoking, ex-smoking, and nonsmoking, the corresponding absolute risks can be estimated from these odds ratios by combining them with the prevalence of various smoking categories in controls and with the overall incidence rate (irrespective of smoking) in a population similar to that in which the study took place. In populations where many persons in later middle age who smoke have done so for several decades but many who used to smoke stopped some decades previously, these methods can be usefully informative about the eventual absolute benefits of cessation. In Europe around 1990, this was generally true for men (who were experiencing

Correspondence to Dr. Cristina Bosetti, Istituto di Ricerche Farmacologiche "Mario Negri," Via La Masa, 19, 20156 Milano, Italy (e-mail: bosetti@marionegri.it).

high incidence rates of lung and upper aerodigestive tract cancer from tobacco smoking) but not for women (among whom most of those who smoked had not yet done so for long enough for the full eventual hazard to be seen).

For men in the United Kingdom in 1990, such methods indicated that the cumulative risk of death from lung cancer by age 75 years (in the hypothetical absence of earlier death from another cause) was 16 percent for those who continued to smoke and 6 percent and 2 percent for those who stopped smoking at ages 50 and 30 years, respectively (4). Similar absolute risks of death from male lung cancer were found in a study from Germany, Italy, and Sweden (5) and in another study from Central Europe (6).

No similar estimates of absolute risk are yet available for cancers of the upper aerodigestive tract. Thus, to measure the absolute risks of developing cancers of the oral cavity and pharynx, esophagus, and larynx for various tobacco smoking categories and ages at stopping smoking, we combined the odds ratios from a network of case-control studies conducted in Italy between 1984 and 2000 with incidence data for Italian men, using the method already adopted for lung cancer (4, 5).

MATERIALS AND METHODS

The present analysis was based on data from six hospital-based case-control studies of cancer (two of the oral cavity and pharynx, two of the esophagus, and two of the larynx) conducted in Italy around the same time period and using similar protocols. The methods of these studies have already been described (7–9). Only men were included in the present analysis, because in women cancers of the upper aerodigestive tract are rare and the proportion of former smokers is low.

Briefly, the studies on oral and pharyngeal cancer were conducted between 1984 and 1997 in major teaching and general hospitals in the Greater Milan area and in the provinces of Pordenone, Rome, and Latina. The studies included 961 male cases under age 75 years (median age, 58 years) with incident, histologically confirmed cancer and 2,824 controls (median age, 56 years) (7). The two studies on esophageal cancer were conducted between 1984 and 1998 in major teaching and general hospitals in the Greater Milan area and in the provinces of Pordenone and Padua. Those studies included 618 male cases aged 26–83 years (median age, 60 years) and 2,400 controls aged 25–83 years (median age, 57 years) (8, 10). The studies on laryngeal cancer were conducted between 1986 and 2000 in major teaching and general hospitals in Greater Milan and the province of Pordenone. These studies included 613 male cases aged 30–80 years (median age, 61 years) and 2,646 controls aged 30–80 years (median age, 58 years) (9, 11). There was some overlap between the controls in the different studies; thus, in total, there were 2,192 cases with upper aerodigestive tract cancer and 3,781 controls.

All controls were patients admitted to the same hospitals as the cases for a wide spectrum of acute nonneoplastic conditions that would not have been expected to be related to tobacco smoking, alcohol consumption, or diet. Overall, 27 percent of the controls were admitted for trauma, 28 percent for nontraumatic orthopedic disorders, 28 percent for acute surgical conditions, and 17 percent for miscellaneous other illnesses, including eye, ear, nose, throat, skin, and dental disorders. The response rate was over 95 percent for both cases and controls.

Cases and controls were interviewed during their hospital stay by trained interviewers using similar structured questionnaires. The questionnaires collected information on sociodemographic characteristics and lifestyle habits, such as tobacco smoking and alcohol drinking, before cancer diagnosis or (for controls) before hospital admission. The section on tobacco smoking included questions on smoking status (never, current, or ex-smoker), daily number of cigarettes, pipes, or cigars smoked in different periods of life, age at starting to smoke, duration of smoking, and, for ex-smokers, age at smoking cessation. Smokers were defined as men who had smoked any type of tobacco within the past 12 months. Ex-smokers were defined as those who had stopped smoking at least 12 months previously and before age 65 years.

Because national age-specific cancer incidence rates were not available, we used the incidence rates from the province of Varese, near Greater Milan, for the period 1993–1997 (12, 13)—that is, those from a cancer registry close to the main population source of our study patients.

Statistical analysis

Odds ratios and their corresponding 95 percent confidence intervals for each category of tobacco smoking were estimated using unconditional multiple logistic regression (14). The models included terms for age (in 5-year groups), study center, years of education (<7, 7–11, or ≥ 12 years), and alcohol consumption (<0.5, 0.5–<21, 21–<35, 35–<56, 56–<84, or ≥ 84 drinks/week).

The cumulative risks were estimated by multiplying the odds ratios for different tobacco smoking categories by a unique common factor, calculated so that the combination of these odds ratios with the prevalence of smoking among study controls resulted in the age-specific cancer incidence rate for that age group (see Appendix) (4, 5, 15). We assumed that within each age group, the smoking distribution of the local Italian male population was represented by our control distribution. Finally, we calculated the cumulative rate (C) per 100,000 males for the different categories of smoking by adding age-specific absolute rates (in 5-year age groups), and then calculated the cumulative risk incurred by age 75 years using the standard formula $100 \times [1 - \exp(-5C/10^5)]$ (16). This can be interpreted as the probability that an individual will develop the cancer of interest before 75 years of age, in the absence of competing causes of death. We calculated 95 percent confidence intervals for these cumulative risks by incorporating floating variances for log odds ratios (17) into a Taylor series expansion.

RESULTS

Table 1 gives the odds among ex-smokers relative to those among continuing smokers (of any type of tobacco) for cancers of the oral cavity (including pharynx), esophagus, and larynx and for all upper aerodigestive tract sites

TABLE 1. Odds ratio for upper aerodigestive tract cancer according to tobacco smoking, time since stopping smoking, and age at stopping smoking among men, Italy, 1984–2000

	All upper aerodigestive tract sites				Oral cavity and pharynx				Esophagus				Larynx			
	No. of cases	No. of controls	OR*,†	95% CI*	No. of cases	No. of controls	OR†	95% CI	No. of cases	No. of controls	OR†	95% CI	No. of cases	No. of controls	OR†	95% CI
Never smokers	87	943	0.12	0.09, 0.15	24	701	0.07	0.05, 0.11	39	577	0.20	0.14, 0.30	24	656	0.09	0.06, 0.14
Current smokers‡	1,514	1,476	1.00		712	1,176	1.00		400	1,032	1.00		402	1,092	1.00	
Ex-smokers																
Time since cessation (years)																
<10	338	478	0.70	0.56, 0.88	144	383	0.51	0.40, 0.65	90	309	0.78	0.59, 1.05	104	331	0.83	0.63, 1.09
10–19	155	489	0.58	0.47, 0.73	56	330	0.20	0.14, 0.28	49	270	0.40	0.28, 0.58	50	292	0.33	0.23, 0.47
≥20	95	391	0.27	0.22, 0.34	23	232	0.12	0.08, 0.20	39	210	0.36	0.24, 0.55	33	273	0.18	0.12, 0.27
Age at cessation (years)																
<35	40	248	0.19	0.13, 0.27	13	162	0.14	0.08, 0.26	18	137	0.40	0.23, 0.69	9	160	0.11	0.06, 0.23
35–44	105	391	0.26	0.21, 0.34	45	279	0.20	0.14, 0.29	27	222	0.33	0.21, 0.53	33	250	0.28	0.19, 0.42
45–54	215	426	0.44	0.36, 0.53	90	301	0.36	0.27, 0.48	61	258	0.50	0.36, 0.70	64	286	0.46	0.33, 0.64
55–64	228	293	0.69	0.56, 0.86	75	203	0.48	0.34, 0.66	72	172	0.89	0.63, 1.27	81	200	0.85	0.62, 1.18

* OR, odds ratio; CI, confidence interval.
† Estimated from unconditional logistic regression with adjustment for age, study center, education, and alcohol drinking.
‡ Reference category. Includes smokers of any type of tobacco and ex-smokers who stopped smoking at age 65 years or later.

combined, according to time since stopping smoking and age at stopping smoking. For the aggregate of all of these cancer sites, comparing ex-smokers with current smokers, the odds ratio was lower after smoking cessation, and this difference in odds ratio became more extreme with increasing time since cessation. Twenty or more years after smoking cessation, the odds ratios for oral and pharyngeal cancer (odds ratio (OR) = 0.12), esophageal cancer (OR = 0.36), laryngeal cancer (OR = 0.18), and all upper aerodigestive tract cancers combined (OR = 0.27) were much lower than 1, but they were still approximately twice those of never smokers. Likewise, as compared with current smokers, men who had stopped smoking before age 35 years had odds ratios of 0.14 for oral and pharyngeal cancer, 0.40 for esophageal cancer, 0.11 for laryngeal cancer, and 0.19 for all upper aerodigestive tract cancers.

Since some ex-smokers who had stopped only a few years previously may have stopped partly because of early symptoms of the disease (2, 3), we also analyzed those who had stopped less than 5 years previously and 5–9 years previously. These odds ratios were, respectively, 0.54 and 0.48 for cancers of the oral cavity and pharynx, 0.95 and 0.67 for cancer of the esophagus, 0.88 and 0.73 for cancer of the larynx, and 0.70 and 0.58 for all upper aerodigestive tract cancers combined.

Figure 1 shows the age-specific cumulative risks of all upper aerodigestive tract cancers in the absence of any competing causes of death, according to age at stopping smoking. The cumulative risks by 75 years of age were 6.3 percent (95 percent confidence interval (CI): 5.9, 6.8) for men who continued to smoke, 5.1 percent (95 percent CI: 4.2, 5.9), 3.1 percent (95 percent CI: 2.6, 3.6), 1.7 percent (95 percent CI: 1.3, 2.1), and 1.2 percent (95 percent CI: 0.8, 1.7) for men who stopped smoking at around 60, 50, 40, and 30 years of age, respectively, and 0.8 percent (95 percent CI: 0.6, 0.9) for lifelong nonsmokers.

For oral and pharyngeal cancers, the cumulative risks by 75 years of age were 3.3 percent (95 percent CI: 3.0, 3.6) for men who continued to smoke, 2.1 percent (95 percent CI: 1.7, 2.6), 1.4 percent (95 percent CI: 1.1, 1.7), 0.7 percent (95 percent CI: 0.5, 0.9), and 0.5 percent (95 percent CI: 0.2, 0.8) for men who stopped smoking at around 60, 50, 40, and 30 years of age, respectively, and 0.2 percent (95 percent CI: 0.1, 0.3) for lifelong nonsmokers (figure 2, part *A*). The corresponding figures for esophageal cancer were 1.0 percent (95 percent CI: 0.9, 1.1), 0.9 percent (95 percent CI: 0.7, 1.2), 0.5 percent (95 percent CI: 0.4, 0.7), 0.3 percent (95 percent CI: 0.2, 0.5), 0.4 percent (95 percent CI: 0.2, 0.6), and 0.2 percent (95 percent CI: 0.1, 0.3) (figure 2, part *B*). The figures for laryngeal cancer were 2.1 percent (95 percent CI: 1.9, 2.4), 1.9 percent (95 percent CI: 1.4, 2.5), 1.1 percent (95 percent CI: 0.8, 1.4), 0.6 percent (95 percent CI: 0.3, 0.9), 0.2 percent (95 percent CI: 0.1, 0.4), and 0.2 percent (95 percent CI: 0.1, 0.3), respectively (figure 2, part *C*).

DISCUSSION

Our study provides a quantitative description of the extent to which stopping smoking at various ages limits the

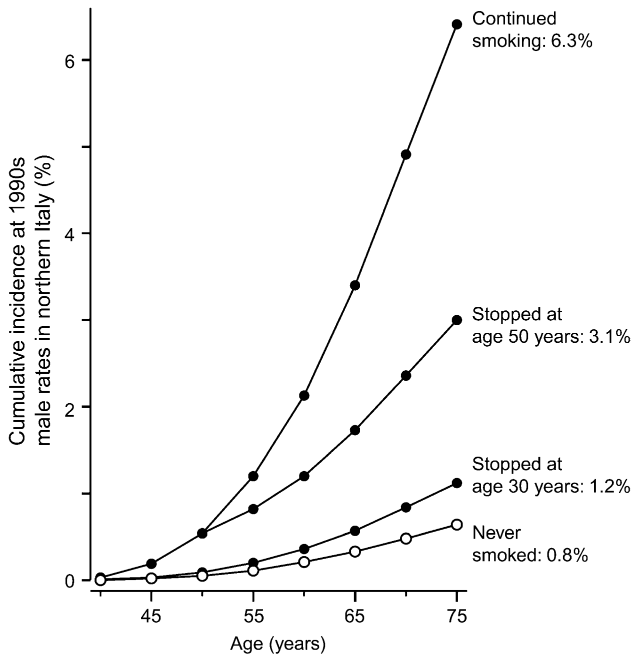

FIGURE 1. Effect of stopping smoking at various ages on the cumulative risk (%) of all upper aerodigestive tract cancers (oral/pharyngeal, esophageal, and laryngeal) up to the age of 75 years, estimated using 1990s incidence rates for Italian men.

cumulative incidence of cancer of the upper aerodigestive tract. In the current analysis, men who stopped smoking at around 40 years of age avoided approximately 80 percent of the excess risk of those who continued to smoke, and men who stopped at around 30 years of age avoided about 90 percent of the risk. Even in ex-smokers who had stopped smoking at around 50 years of age, the excess risk by age 75 years (as compared with never smoking) was approximately halved in comparison with continuing to smoke.

Some differences were observed across various cancer sites. For oral and pharyngeal cancers, the beneficial effect of stopping smoking was evident even in men who stopped at around age 60 years. For esophageal cancer, the cumulative risks among smokers were low because of the low incidence rates in Italy and because smoking is not as strong a risk factor for esophageal cancer as it is for other cancers of the upper aerodigestive tract (18, 19). The slightly greater reduction in esophageal cancer among men who had stopped smoking at around age 40 years as compared with those who had stopped at around age 30 years can most plausibly be explained by random variation. In absolute terms, however, the main benefits of cessation come not in the first few years but many years later (figure 2), and these late benefits are not materially affected by such biases.

Although the absolute risks of cancer of the upper aerodigestive tract are lower than the risks of lung cancer (4–6), the odds ratios show similar patterns with smoking and with cessation at various ages, demonstrating that for all of these tobacco-related neoplasms, stopping smoking in or

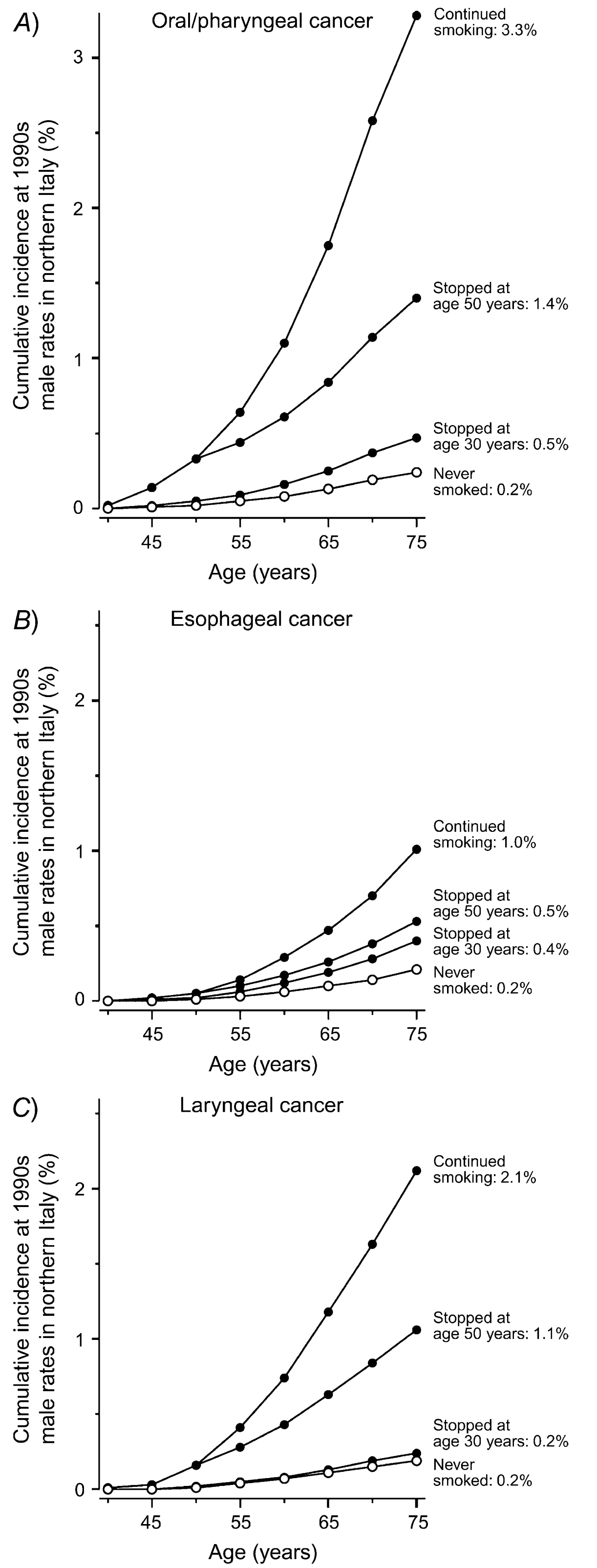

FIGURE 2. Effect of stopping smoking at various ages on the cumulative risk (%) of cancers of the oral cavity and pharynx (part *A*), esophagus (part *B*), and larynx (part *C*) up to the age of 75 years, estimated using 1990s incidence rates for Italian men.

before middle age has a substantial impact on the absolute risk.

The men enrolled in our studies were around age 60 years in the 1990s, so they had typically been born in the 1930s. This generation of Italian men was severely exposed to the adverse effects of smoking, with over two thirds of them taking up the habit, mostly at an early age, but with appreciable numbers later stopping (20). Consequently, we were able to estimate both the hazards of prolonged smoking and the effects of prolonged cessation. In the 1990s, incidence and mortality for cancers of the oral cavity, pharynx, esophagus, and larynx in Italy were intermediate on a European scale (21). Thus, the eventual benefits of stopping smoking at 30 or 40 years of age in this study could probably be extended to European men in general, and to most other male populations in which smokers aged 30 or 40 years have been smoking since early adulthood. The same probably applies to women (22–25), although in these studies we could not reliably assess the eventual effects of prolonged smoking or smoking cessation among women.

The approach adopted to estimate the cumulative risk of upper aerodigestive tract cancer does not involve data from a prospective cohort. Instead, it requires only population data on disease incidence, control data on the prevalence of exposure, and unbiased odds ratio estimates. The estimates of cumulative risk obtained in our study may have been affected by various limitations, because of the lack of age-specific national data on cancer incidence, the case-control design of the studies used to estimate the odds ratios, and the prevalence of tobacco smoking. In these studies, however, the information on tobacco smoking was reproducible and valid (26, 27), and the analyses allowed for possible confounding by alcohol consumption and education, which are important risk factors for these neoplasms. The prevalence of smoking in our control group was comparable to that of the general Italian male population aged 15 years or more (approximately 39 percent at that time) (28), although the prevalence of smoking cessation was somewhat higher (36 percent vs. 28 percent) because our controls included a higher proportion of older men, who would be more likely to have stopped smoking.

In this population of Italian men, stopping tobacco smoking in or before early middle age enabled an individual to avoid most of the eventual risk of developing cancer of the upper aerodigestive tract, and even stopping in later middle age had some beneficial effect. Because of the decrease in smoking prevalence that has occurred among Italian men since the early 1960s (29), together with the decrease in alcohol drinking (30), male mortality from cancers of the upper aerodigestive tract has decreased over the last few decades (31–33). Still, among men in the early 2000s, upper aerodigestive tract cancers caused more than 5,000 deaths per year in Italy and more than 40,000 deaths per year in the European Union (12, 13). Helping current smokers who want to stop smoking carry out their intention would substantially reduce the future number of deaths from upper aerodigestive tract cancers, as well as from other diseases.

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APPENDIX

The cumulative risk was calculated using methods similar to those described by Peto et al. (4). Briefly, to estimate the cumulative risk, we need first to calculate the odds ratios in the various smoking categories (step 1). In our study, the odds ratios for upper aerodigestive tract cancer were estimated by means of unconditional logistic regression models, using lifelong nonsmokers as the reference category.

$$r_i \text{ is the odds ratio in the } i_i\text{th smoking category,} \quad \text{(Step 1)}$$

where the i smoking categories are: 1 = never smokers; 2 = ex-smokers, subdivided by age at smoking cessation (<35, 35–44, 45–54, or 55–64 years); and 3 = current smokers.

The second step was to calculate the percentage of controls in each smoking category and for each age group (step 2), using the assumption that within each country, the smoking distribution of the population was represented by the smoking distribution observed among the study controls.

$$p_{ij} \text{ is the percentage of controls in the } j\text{th age group and the } i\text{th smoking category,} \quad \text{(Step 2)}$$

where the age categories are: <35, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74 years.

The third step was the estimation of common factors combining the odds ratios (step 1) for the different smoking categories with the age-specific prevalences of such smoking habits among study controls (step 2), thus obtaining the quantities denoted by step 3.

$$S_j = r_1 p_{1j} + \cdots + r_i p_{ij}. \quad \text{(Step 3)}$$

Combining the age-specific cancer incidence rates (step 4) with the common factors (step 3), we obtained the proportions given in step 5.

$$h_j \text{ is the age-specific incidence rate.} \quad \text{(Step 4)}$$

$$f_j = h_j / S_j. \quad \text{(Step 5)}$$

Multiplying these proportions with the odds ratios for the different smoking categories produced the age-specific absolute risks in the different smoking categories (step 6).

$$a_{ij} = f_j \times r_i \text{ is the absolute rate in the } (i,j)\text{th cell.} \quad \text{(Step 6)}$$

Next, we calculated the cumulative rates for the different categories of smoking by adding age-specific absolute rates (step 7).

$$C_i \text{ is the cumulative rate, and } C_i = \sum_j \mathrm{R}_j \times a_{ij}, \quad \text{(Step 7)}$$

where R_j is the width of the jth age category in years.

Finally, the cumulative risks by age 75 years were estimated using the standard formula (step 8).

$$\text{Cumulative risk } (\%) = 100 \times [1 - \exp(-C_i)]. \quad \text{(Step 8)}$$

The cumulative risk may be interpreted as the probability that an individual will develop lung cancer before age 75 years in the absence of competing causes of death.