Lung Cancer Decreased Sharply in First 5 Years After Smoking Cessation in Chinese Men

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Background: The rate of decline in lung cancer risk after smoking cessation among male population and the importance of the magnitude of the early decline were not sufficiently defined in the earlier studies. We evaluated the detailed duration-response relationship between years since smoking cessation and lung cancer risk across major histological types in a population-based case-referent study.

Methods: We recruited 1208 consecutive incident cases of primary lung cancer among Chinese males from the largest oncology center in Hong Kong during 2004–2006, and 1069 male community referents frequency-matched in 5-year age groups. We performed unconditional multiple logistic regression and generalized additive model incorporating smoothing spline to model the potential nonlinear effect of years since cessation on lung cancer.

Results: All histological types of lung cancer were strongly associated with current smoking. We observed a rapidly decreasing odds ratio of lung cancer (>50%) across all major histological types of lung cancer (except for the large cell type) within the first 5 years of quitting; the odds ratio continued to decrease but at a slower rate in the subsequent years.

Conclusion: The substantial benefits obtainable within a short period of 5 years' abstinence should convey an encouraging message to chronic smokers, clinicians, and public health workers.

Key Words: Lung neoplasm, Histology, Smoking cessation.

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Lung cancer remains a leading lethal cancer worldwide, including Hong Kong.[1] About 60% of lung cancer among Chinese males and more than 80% among Western males could be attributable to cigarette smoking.[2] Many studies examined the duration-response relationship between years since smoking cessation and lung cancer risk and observed a greater decline in the risk estimate for squamous cell carcinoma (SQCC) and small cell carcinoma (SCC) than adenocarcinoma (ADC).[3] The rate of decline after smoking cessation had been examined in the Nurse's Health Study among women, but the results may not be generalized to the male population as a gender difference in lung cancer etiology may exist[4]; in addition, the importance of the magnitude of the early decline was not sufficiently addressed in the earlier studies.

Most previous studies estimated the association with lung cancer by either categorizing the years since smoking cessation or using conventional parametric general linear models. The former uses "artificial" cut-points that may not have biological basis and the latter imposes an a priori simple linear relationship that could deviate from reality. These shortcomings can be overcome by using the smoothing spline modeling approach, which is more flexible, informative, and accurate in analyzing an exposure-response relationship, and allows the data to speak for itself.[5] Being one of the largest population-based case-referent lung cancer studies in Asian men, this study aimed at examining the detailed duration-response relationship between years since smoking cessation and the risk of lung cancer across major histological types, using both the conventional ordinal categorical analysis and the more flexible smoothing spline modeling.

METHODS

Recruitment of Study Subjects

Eligible cases were Chinese males aged 35 to 79 years with newly diagnosed primary carcinomas of the lung (International Classification of Disease [ICD], Revision 9, code 162) that were histologically confirmed according to the World Health Organization histological typing of lung tumors.[6] Cases were recruited consecutively from the largest oncology center in Hong Kong from February 1, 2004, to September 30, 2006, and were interviewed within 3 months after diagnosis. Among 1259 eligible cases, 1208 were interviewed with a response rate of 96%, 35 cases could not respond due to poor medical condition, and 16 refused because of lack of interest.

Referents with no history of physician-diagnosed cancer in any site were randomly selected from residents of districts where the cases came from, using residential telephone directories, and were frequency-matched in 5-year age groups according to the age distribution of incident lung

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cancer cases. We replaced the referent who refused to participate by another similar referent from the same district of the case. We finally recruited 1069 community referents with a response rate of 48%, which was considered to be not low compared with other similar population-based case-referent studies. The main reasons for nonparticipation were lack of time or no interest. This research was approved by the ethical committees of both the Chinese University of Hong Kong and the Queen Elizabeth Hospital.

Data Collection and Interviews

Trained interviewers conducted personal interviews immediately after informed consents were obtained. A standardized structured questionnaire was used to obtain information on lifetime consumption of tobacco and most known potential confounding factors. Relevant medical information of cases including medical diagnosis, ICD codes, and histological findings was abstracted from hospital records.

Assessment of Tobacco Smoking

We asked the respondents about their lifetime consumptions of various types of tobacco products, including cigarettes, Chinese prepared tobacco, and cigars. One who had ever smoked more than 20 packs of cigarettes (one pack = 20 cigarettes) or 12 oz of tobacco in his lifetime, or more than 1 cigarette a day or more than 1 cigar a week for 1 year was defined as an ever smoker.[7] Otherwise, a subject was classified as a never smoker. Ever smokers were asked to report the amount of each type of tobacco consumed during lifetime, the age at smoking initiation, and the age at smoking cessation. Less than 5% cases and referents reported ever use of Chinese prepared tobacco or cigar smoking.

Indices of cigarette smoking used in the analysis included smoking status (never, former, and current) and smoking cessation (age at smoking cessation and years since smoking cessation). Other variables related to cigarette smoking were age at smoking initiation, intensity (average number of cigarettes smoked per day), years of smoking, and pack-years.

Potential Confounding Factors

Most known potential confounding factors were collected,[9] including residential radon exposure, lifetime environmental tobacco smoke exposure (workplace and household exposures), other sources of indoor air pollutants (years of cooking by frying, type of fuel use, incense burning, and use of mosquito coils), dietary habits, alcohol drinking habits, history of lung diseases, cancer history in first-degree relatives, education level, place of birth, and exposures to known or suspected occupational lung carcinogens. Exposure to known and suspected occupational lung carcinogens was defined as ever regularly exposed to any of these agents: silica, asbestos, arsenic, nickel, chromium, tars, asphalts, painting, pesticide, diesel, cooking fume, and welding fume in the workplace. A reduced version of the Diet History Questionnaire designed by the National Cancer Institute (USA) was used to collect the information on diet.[10]

Test-Retest Reliability

We invited 30% of the cases and referents to participate in a second interview 2 months later after the initial interview to evaluate the reliability of the recall of lifetime tobacco use; 276 lung cancer cases and 286 community referents responded to the second interview.

Statistical Analysis

Two-tailed χ^2 tests or independent t tests were used to compare various indices of cigarette smoking and other major risk factors between the cases and referents. Cohen's kappa and intraclass correlation coefficient were used to estimate the reliability of categorical variables and ordinal or continuous variables, respectively. Unconditional multiple logistic regression models were applied to calculate the odds ratio (OR) and the 95% confidence interval (95% CI) of various indices of cigarette smoking after adjusting for age only or age and other known potential confounders, and the duration-response relationship with years since smoking cessation in six categories (1–1.9, 2–4.9, 5–9.9, 10–14.9, 15–19.9, ≥20) was examined by trend test. We treated a variable (e.g., education level) as a potential confounder if inclusion of such variable made a 5% change (a more conservative criterion) in the smoking OR, even if it was not statistically significant. All potential confounding factors were included in the final model to estimate the adjusted OR of smoking for the risk of all lung cancers. We used the same strategies to identify specific confounding factors for major histological types of lung cancer: SQCC, ADC, SCC, and large cell carcinoma (LCC). In addition, we used generalized additive models incorporating cubic regression smoothing spline to model nonlinear effects of years since smoking cessation on all lung cancers and the major histological types after controlling for most known potential confounding factors and other smoking indices (i.e., number of cigarettes per day and years of smoking). Analysis was conducted in R2.10.0 after loading mgcv package (a library package that is installed in the R2.10.0 to fit the generalized additive model).[11] The minimum Akaike's information criterion (a measure of the goodness of fit of a statistical model) value was used as a guide for selection of best model fit with different degrees of freedom. We further performed two-stage fractional polynomial models to estimate the effect of years since smoking cessation according to the approaches proposed by Royston et al.[12] and compared the model fit with the smoothing spline, and the Akaike's information criterion was very similar (Supplement 1, http://links.lww.com/JTO/A93). We chose the generalized additive model with smoothing spline because it is a nonparametric approach with a more flexible form to reflect the data itself. All the models were repeated by replacing the "number of cigarettes per day" and "years of smoking" by "smoking pack-years." Models with the former items showed significantly better fits ($p < 0.05$) and are reported here.

RESULTS

Sociodemographic Characteristics

The distributions of main sociodemographic information for cases and referents are summarized in Table 1. Cases were

TABLE 1. Sociodemographic Information and Smoking History of Lung Cancer Cases and Community Referents in Hong Kong Males During 2004–2006

	Major Types of Lung Cancer						
Characteristics	Squamous Cell	Adenocarcinoma	Small Cell	Large Cell	All Cases	Referents	p^a
Total	272 (22.5)	440 (36.4)	118 (9.8)	25 (2.1)	1208 (100)	1069	
Age (yr)[b]	68.0 ± 8.7	65.0 ± 9.7	67.2 ± 8.1	63.2 ± 10.6	65.8 ± 9.5	66.2 ± 9.9	0.326
Place of birth[b]							
Hong Kong	35 (12.9)	114 (25.9)	20 (16.9)	8 (32.0)	266 (22.0)	397 (37.1)	<0.001
Outside Hong Kong	237 (87.1)	325 (73.9)	98 (83.1)	17 (68.0)	941 (77.9)	672 (62.9)	
Education level[b]							
Primary (6–11 yr)	80 (29.4)	97 (22.0)	39 (33.1)	6 (24.0)	298 (24.7)	142 (13.3)	<0.001
High School (12–18 yr)	125 (46.0)	171 (38.9)	53 (44.9)	7 (28.0)	525 (43.5)	383 (35.8)	
College (≥19 yr)	65 (23.9)	165 (37.5)	24 (20.3)	11 (44.0)	366 (30.3)	528 (49.4)	
Alcohol drinking							
No	91 (33.5)	150 (34.1)	49 (41.5)	10 (40.0)	445 (36.8)	541 (50.6)	<0.001
Yes	181 (66.5)	287 (65.2)	68 (57.6)	15 (60.0)	756 (62.6)	518 (48.5)	
Environmental tobacco smoke							
Never	49 (18.0)	79 (18.0)	19 (16.1)	8 (32.0)	230 (19.0)	281 (26.3)	<0.001
Ever	223 (82.0)	361 (82.0)	99 (83.9)	17 (68.0)	977 (80.9)	788 (73.7)	
Status of smoking[b]							
Never	5 (1.8)	89 (20.2)	0	2 (8.0)	132 (10.9)	536 (50.1)	<0.001
Ever	267 (98.2)	351 (79.8)	118 (100.0)	23 (92.0)	1076 (89.1)	533 (49.9)	
Former[c]	85 (31.2)	124 (28.2)	26 (22.0)	5 (20.0)	340 (28.1)	357 (33.4)	
Current[d]	182 (66.9)	227 (51.6)	92 (78.0)	18 (72.0)	736 (60.9)	176 (16.5)	
Years since cessation[b]	4.63 ± 9.47	6.07 ± 11.46	3.06 ± 7.18	1.75 ± 4.33	4.63 ± 9.47	12.98 ± 14.32	
Never quitters[e]	170 (62.5)	219 (49.8)	83 (70.3)	17 (68.0)	691 (57.2)	169 (15.8)	<0.001
1–1.9	12 (4.4)	8 (1.8)	9 (7.6)	1 (4.0)	45 (3.7)	7 (0.7)	
2–2.9	9 (3.3)	13 (3.0)	2 (1.7)	2 (8.0)	33 (2.7)	19 (1.8)	
3–3.9	8 (2.9)	8 (1.8)	1 (0.8)	0	25 (2.1)	13 (1.2)	
4–4.9	4 (1.5)	9 (2.0)	1 (0.8)	1 (4.0)	23 (1.9)	13 (1.2)	
5–9.9	17 (6.3)	16 (3.6)	7 (5.9)	0	65 (5.4)	55 (5.1)	
10–14.9	14 (5.1)	14 (3.2)	5 (4.2)	1 (4.0)	54 (4.5)	53 (5.0)	
15–19.9	10 (3.7)	16 (3.6)	4 (3.4)	1 (4.0)	44 (3.6)	47 (4.4)	
≥20	22 (8.1)	44 (10.0)	4 (3.4)	0	87 (7.2)	145 (13.6)	
Never smoker	5 (1.8)	89 (20.2)	0	2 (8.0)	132 (10.9)	536 (50.1)	

Values are given as *N* (%) or mean ± SD.
[a] Compare all lung cancer cases with community referents.
[b] Significant heterogeneities among histological subtypes ($p < 0.05$).
[c] "Former smokers" referred to those who had quit smoking for 2 yr or more.
[d] "Current smokers" referred to those who had never quit smoking or quit smoking for less than 2 yr.
[e] "Never quitters" referred to those who had never quit smoking or quit smoking for less than 1 yr.

more likely ever smokers (with the majority being current smokers), alcohol drinkers, and born outside Hong Kong. They had lower education attainment, more exposures to environmental tobacco smoke, and shorter duration of smoking cessation among former smokers. Among the histological subgroups, a higher proportion of ADC cases were never smokers. On the other hand, all cases of SCC were ever-smokers, hindering the proper quantification of the association with smoking. There was no missing data for smoking status, and the missing data for years since smoking cessation were very low in the cases (0.75%) and referents (1.12%).

Cigarette Smoking and Lung Cancer Risk by Histological Types

Table 2 presents the ORs for four major histological types of lung cancer by smoking status. We observed much higher crude ORs (only adjusted for age) of lung cancer for current smokers than former smokers in all histological types, and the strongest association was with SQCC (except for SCC with no never smokers), followed by LCC, and then ADC. Multiple logistic regression analyses showed that all the adjusted ORs (except for the former smoking OR with LCC) were lower than the crude ORs by 6 to 36%, indicating that confounding effects of other risk factors were not negligible.

Effect of Smoking Cessation

Except for ADC, we observed an increased OR of lung cancer for men who had quit smoking for less than 2 years when compared with never quitters (Table 3). However, a significantly negative gradient ($p < 0.001$ for trend test) of lung cancer risk was observed with increasing years since smoking cessation (ordinal categorical scale) after 2 years.

TABLE 2. Odds Ratios (OR, 95% CI) for all Lung Cancers and the Major Histological Subtypes According to Smoking Status in Hong Kong Males During 2004–2006

Levels of Exposure	All Cases (N = 1208)	Squamous Cell (N = 272)	Adenocarcinoma (N = 440)	Small Cell[a] (N = 118)	Large Cell (N = 25)
Smoking status (adjusted for age)[b]					
Never	1.00	1.00	1.00	1.00	1.00
Ever	9.13 (7.29–11.43)	54.72 (22.34–134.03)	4.49 (3.42–5.89)	—	14.78 (3.41–64.16)
Former[c]	4.08 (3.17–5.25)	22.42 (8.96–56.05)	2.30 (1.68–3.16)	—	4.43 (0.83–23.59)
Current[d]	17.17 (13.34–22.10)	110.67 (44.76–273.65)	7.90 (5.85–10.66)	—	27.70 (6.36–120.66)
Smoking status (adjusted for most known potential confounding factors)					
Never	1.00[e]	1.00[f]	1.00[g]	1.00	1.00[h]
Ever	6.65 (5.25–8.42)	37.50 (15.21–92.51)	3.85 (2.91–5.09)	—	13.85 (3.08–62.15)
Former[c]	3.11 (2.38–4.07)	15.31 (6.06–38.68)	2.08 (1.50–2.88)	—	4.53 (0.82–24.96)
Current[d]	12.16 (9.34–15.84)	74.21 (29.78–184.96)	6.46 (4.75–8.79)	—	23.42 (5.21–105.25)

Values are given as OR (95% CI).
[a] All cases with small cell were ever smokers.
[b] The model was only adjusted for the age at interview.
[c] "Former smokers" referred to those who had quit smoking for 2 yr or more.
[d] "Current smokers" referred to those who had never quit smoking or quit smoking for less than 2 yr.
[e] The model (all lung cancers) was adjusted for age, place of birth, education level, intake of meat, history of lung diseases, and exposure to occupational carcinogens.
[f] The model (squamous cell carcinoma) was adjusted for age, place of birth, education level, intake of meat, and history of lung diseases.
[g] The model (adenocarcinoma) was adjusted for age, education level, alcohol drinking, and history of lung diseases.
[h] The model (large cell carcinoma) was adjusted for age, education level, exposure to environmental tobacco smoke, history of lung diseases, any cancer in first-degree relatives, consumption of fried food, and exposure to occupational carcinogens.

The risk of SCC and SQCC decreased by around 83% and 78% within 5 years from smoking cessation and was the most rapid among histological types. The OR of ADC decreased less abruptly in the first 5 years (by 52%) but caught up quickly in the next 5 years to 80%. A further decreased OR (0.04) for SCC was observed after 20 years, but it was not substantial for SQCC and ADC. Overall, the OR of SCC decreased by 96% (95% CI: 83–99%) after a smoker continued to abstain from cigarette smoking for 20 years or more, and the corresponding figures for SQCC and ADC were 85% (95% CI: 67–93%) and 80% (95% CI: 65–89%), respectively. In general, the risk could not revert back to that of never smokers. A notable decreasing risk of LCC with increasing years since smoking cessation was also observed after 5 years of cessation, despite the less stable results due to small number of cases. The changing risk of lung cancer with increasing years of smoking cessation was better depicted using smoothing spline analyses, which allowed the quantification of the impact over a full range of years since cessation on a continuous scale (Figure 1). We observed an early rapid decrease in OR and an almost linear trend of the decreased OR in the first 5 years after smoking cessation across major histological types, whereas the estimates afterward were less stable.

Our study did not suggest an interaction between intensity and years of smoking on the risk of all lung cancers ($OR_{interaction}$ = 0.99, 95% CI: 0.93–1.06) and the major histological types, and there was also no evidence for an interaction between age of initiation and age of cessation for smoking. Sensitivity analyses showed that the main results did not change much after inclusion of other types of tobacco consumption in the analyses (results omitted).

Reliability of Measurement

The test-retest reliability for smoking status, age at smoking initiation and quitting, the amount, and years since smoking cessation was excellent for both the cases (kappa or intraclass coefficient ranged from 0.77 to 0.95) and the referents (kappa or intraclass coefficient ranged from 0.83 to 0.95).

DISCUSSION

This study demonstrates a rapidly decreasing OR of lung cancers across all major histological types in the first 2 to 5 years after smoking cessation. Each type of lung cancer was strongly associated with current smoking but the OR decreased substantially after smoking cessation. Overall, the OR reduced by more than half (54%) in the first 2 to 5 years of quitting, being 52%, 78%, and 83% for ADC, SQCC, and SCC, respectively, and continued to decrease, at a slower rate, in the subsequent years. The overall OR after smoking cessation decreased up to 96% for SCC, 85% for SQCC, and 80% for ADC; however, it did not reduce down to that of never smokers in general.

There is little doubt on a beneficial effect of reducing lung cancer risk after quitting smoking,[3,13] but the magnitude of risk reduction may differ among different histological types and vary among different populations. A meta-analysis published in 2001 combined results of 14 studies from Western populations (including both genders) and found that the greatest reduction in OR in the first 5 years of cessation was seen in SCC (19%, 95% CI: 10–27%), which was followed by SQCC (16%, 95% CI: 10–22%), LCC (14%, 95% CI: 9–19%), and ADC (12%, 95% CI: 10–17%).[3]

TABLE 3. Odds Ratios (OR, 95% CI) for all Lung Cancers and the Major Histological Subtypes According to Years Since Cessation in Hong Kong Males During 2004–2006

Levels of Exposure	All Cases (*N* = 1208)	Squamous Cell (*N* = 272)	Adenocarcinoma (*N* = 440)	Small Cell[a] (*N* = 118)	Large Cell (*N* = 25)
Years since cessation (adjusted for age only)[b]					
Never quitters[c]	1.00	1.00	1.00	1.00	1.00
1–1.99	1.58 (0.70–3.57)	1.65 (0.63–4.31)	0.86 (0.30–2.42)	2.67 (0.96–7.46)	1.38 (0.16–11.98)
2–2.99	0.44 (0.24–0.79)	0.42 (0.18–0.96)	0.56 (0.27–1.18)	0.19 (0.04–0.85)	1.20 (0.25–5.76)
3–3.99	0.48 (0.24–0.96)	0.56 (0.23–1.41)	0.48 (0.19–1.19)	0.15 (0.02–1.14)	—
4–4.99	0.44 (0.22–0.90)	0.29 (0.09–0.91)	0.57 (0.24–1.37)	0.15 (0.02–1.14)	0.84 (0.10–6.88)
5–9.99	0.30 (0.20–0.45)	0.27 (0.15–0.48)	0.24 (0.13–0.44)	0.23 (0.10–0.53)	—
10–14.99	0.26 (0.17–0.39)	0.23 (0.12–0.44)	0.22 (0.12–0.41)	0.17 (0.07–0.45)	0.21 (0.03–1.66)
15–19.99	0.24 (0.15–0.37)	0.18 (0.09–0.38)	0.29 (0.16–0.52)	0.15 (0.05–0.44)	0.25 (0.03–1.95)
≥20	0.15 (0.11–0.21)	0.13 (0.08–0.22)	0.26 (0.17–0.38)	0.05 (0.02–0.14)	—
Never smoker	0.06 (0.05–0.08)	0.01 (0.00–0.02)	0.13 (0.09–0.17)	—	0.04 (0.01–0.16)
Years since cessation (adjusted for most known potential confounding factors)					
Never quitters[c]	1.00[d]	1.00[e]	1.00[f]	1.00[g]	1.00[h]
1–1.99	1.74 (0.74–4.05)	1.71 (0.60–4.88)	0.84 (0.28–2.54)	2.87 (0.89–9.23)	1.39 (0.13–15.33)
2–2.99	0.43 (0.23–0.80)	0.34 (0.14–0.82)	0.57 (0.26–1.24)	0.19 (0.04–0.87)	1.56 (0.25–9.90)
3–3.99	0.51 (0.24–1.08)	0.62 (0.22–1.75)	0.43 (0.17–1.12)	0.19 (0.02–1.63)	—
4–4.99	0.46 (0.21–0.97)	0.22 (0.06–0.78)	0.48 (0.19–1.24)	0.17 (0.02–1.39)	1.40 (0.15–12.70)
5–9.99	0.28 (0.18–0.43)	0.22 (0.11–0.45)	0.20 (0.10–0.38)	0.19 (0.08–0.50)	—
10–14.99	0.29 (0.18–0.48)	0.20 (0.09–0.44)	0.20 (0.10–0.40)	0.17 (0.06–0.52)	0.16 (0.02–1.45)
15–19.99	0.26 (0.16–0.44)	0.16 (0.07–0.38)	0.24 (0.12–0.47)	0.12 (0.04–0.42)	0.15 (0.02–1.45)
≥20	0.17 (0.11–0.28)	0.15 (0.07–0.33)	0.20 (0.11–0.35)	0.04 (0.01–0.17)	—
Never smoker	0.13 (0.07–0.26)	0.02 (0.01–0.09)	0.14 (0.06–0.31)	—	0.02 (0.00–0.28)

Values are given as OR (95% CI).
[a] All cases with small cell were ever smokers.
[b] The model was only adjusted for the age at interview.
[c] "Never quitters" referred to those who had never quit smoking or quit smoking for less than 1 yr.
[d] The model (all lung cancers) was adjusted for age, place of birth, education level, intake of meat, history of lung diseases, exposure to occupational carcinogens, and intensity (number of cigarettes smoked per day).
[e] The model (squamous cell carcinoma) was adjusted for age, place of birth, education level, intake of meat, history of lung diseases, intensity (number of cigarettes smoked per day), and years of smoking.
[f] The model (adenocarcinoma) was adjusted for age, education level, alcohol drinking, history of lung diseases, intensity (number of cigarettes smoked per day), and years of smoking.
[g] The model (small cell carcinoma) was adjusted for age, place of birth, education level, intake of meat, history of lung diseases, exposure to occupational carcinogens, and intensity (number of cigarettes smoked per day).
[h] The model (large cell carcinoma) was adjusted for age, education level, exposure to environmental tobacco smoke, history of lung diseases, any cancer in first-degree relatives, consumption of fried food, exposure to occupational carcinogens, intensity (number of cigarettes smoked per day), and years of smoking.

We reviewed the 14 original studies cited in the meta-analysis and found that only 8 studies in fact provided the risk estimates by years of smoking cessation for lung cancer,[14–21] and 7 of them presented results by histological types.[14–19,21] All seven were case-referent studies but only three[15,17,19] of them identified the referents from the general population. The study in Germany (869 male cases, 165 female cases) showed a very high OR of lung cancer (all lung cancers: 6.86; SQCC: 6.84; SCC: 4.03; ADC: 10.24) in the first year of smoking cessation compared with current smokers.[19] The OR (1.18–1.81) was still significantly increased 2 to 5 years after smoking cessation, it became borderline in the next 5 years, and then started to decrease from the 10th year, with an overall decrease in OR of 75% after 20 or more years of cessation.[19] Age at interview and smoking pack-years were adjusted, but age at smoking initiation and other important confounding factors (e.g., family cancer history and occupational exposures) were not considered.[19] The study in Canada (403 male cases, 442 female cases) assumed a linear relationship between OR and years since smoking cessation but only presented results at 10 years: overall OR decreased by 35% in males and 48% in females, with effects being slightly strong for SCC. Smoking pack-year was the only variable being adjusted in the analysis.[17] The population-based study in Sweden included only 210 female cases with 30 ex-smokers, the overall OR decreased by 40% for the period 3 to 10 years after cessation, and 70% after 10 years, while the risk estimates by histology were very unstable because of small numbers.[15]

In an article published after the 2001 meta-analysis, Rachet et al.[22] used smoking data from a large population-based case-referent study (640 lung cancer cases) conducted in Montreal in the 1980s to show a likely linear trend in a decreased OR of all lung cancers with an annual percentage change of −7.3% (95% CI: −10.0 to −4.6%) after quitting

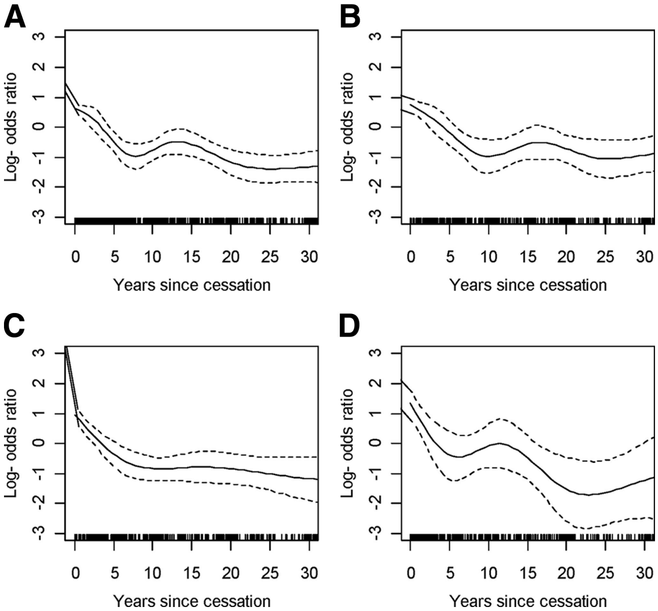

FIGURE 1. Duration-response relationships of years since smoking cessation for major histological types of lung cancer: (*A*) all lung cancers, (*B*) adenocarcinoma; (*C*) squamous cell carcinoma; (*D*) small cell carcinoma. The curves were estimated in generalized additive models using cubic regression spline with degree of freedom of 6, 6, 4, and 5 for all lung cancers, adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, respectively.

smoking, regardless of the amount or the duration of smoking. Smoothing spline approach was incorporated in the modeling of the effects of daily cigarette consumption, but no further analysis was carried out according to different histological types of lung cancer.

Among three Asian studies evaluating the associations between smoking cessation and lung cancer risk by histological types among males,[23–25] only two of them (conducted in Japan and Taiwan) investigated years since smoking cessation and the risks of major histological types of lung cancer (SQCC and SCC combined; ADC) and showed a negative trend, but no statistical significance was achieved due to few cases of former smokers (Japan: 67; Taiwan: 39).[24,25] In addition, the Japan cohort study showed that the risks of lung cancer reached almost the same level as that of never smokers after 20 years of smoking cessation[24]; however, adjustment was only made for age. A recently published cohort study among 45,900 Singapore Chinese (with 463 lung cancers) showed a 28% (95% CI: 2–47%) risk reduction after smoking cessation for an average of 5.8 years and a larger reduction (58%, 95% CI: 44–68%) was observed for those quitting smoking longer; however, the relatively short period of follow-up (5.8 years) for ascertainment of adequate incidence cases precluded a more detailed analysis by histological subtypes.[26]

Like the German study,[19] our results showed a phenomenon of "quitting ill effect" (a higher risk) in the first years of smoking cessation, which might have resulted from smokers quitting smoking due to early symptoms related to lung cancer before diagnosis. Nevertheless, our results indicated a more rapidly decreased OR for all types of lung cancer during the period 2 to 5 years after smoking cessation, with the sharpest decrease for SCC. The discrepancy might be due to our male smokers having longer smoking history (37.0 years) and smoking heavier than other study populations (44.1 pack-years); however, no relevant information was provided in the German study for a meaningful comparison. Compared with previous population-based case-referent studies with subgroup analyses according to histological subtype, our study had the advantages of being the largest (>1200 cases) and with adequate adjustments for most known potential confounding factors; hence, we believe that our results were more reliable and valid than the previous studies. Barnoya and Clantz demonstrated an accelerated reduction in lung cancer incidence 2 years after the California Tobacco Control Program was launched, providing supportive evidence on a 2-year window from the start of smoking cessation (quitting ill effect) at a population level.[27]

Except for the two Canadian studies mentioned above,[17,22] previous studies using traditional "step function" analysis, by grouping continuous years since quitting smoking into distinct categories, provided insufficient flexibility in evaluating the impact of smoking cessation. The cutoff points used to categorize the continuous variable were usually artificial and might not have biological basis, thus useful information might be lost within broad categories. On the other hand, simple parametric regression analysis might result in inaccurate estimation of the duration-response relationship when the true effect was nonlinear. By performing flexible smoothing spline modeling and incorporating other smoking parameters (i.e., age at start of smoking, the amount, and years of smoking) and most known potential confounding factors in the analyses, results from our study regarding the impact of smoking cessation should be more accurate and informative in reflecting the true duration-response relationship between smoking cessation and lung cancer. Our results using both approaches consistently showed that the decreased OR of lung cancer was dependent on the time since smoking cessation.

The rapidly decreased OR (56% for all lung cancers) observed in the first 5 years after smoking cessation has important clinical and public health implications (especially for the cell types of SCC and SQCC) and provides a very encouraging message to chronic smokers who are worried about their high risk of lung cancer. This information would be very useful for clinicians in coercing their chronic smoking patients to quit smoking. Additional benefits are also achievable by maintaining abstinence for longer periods. On the other hand, the fact that the risk could not revert to that among never smokers would act as a deterrent for young people attempting to take up smoking.

Results of this large population-based case-referent lung cancer study are valid and reliable and have been discussed in detail elsewhere.[28] The cases (96%) and referents (48%) had different participant rates, raising the possibility of selection bias; nevertheless, major selection bias was unlikely because the distributions of lung cancer histology in our lung cancer cases and the smoking status of our community referents were fairly similar to the general male population in Hong Kong.[2,29] Interviewer bias and potential differential misclassification on smoking status were also less likely because data from a special group of 64 subjects (who had to undergo surgical operations for suspected lung cancer and were handled as lung cancer cases during the interviews but eventually were diagnosed as not suffering from lung cancer) showed that the proportion of ever smokers and smoking amount were different from the 228 surgically confirmed lung cancer cases—part of the 1208 cases—but similar to the community referents. However, we did not obtain complete information on the use of filtered cigarettes, characteristics of inhalation, and the brands, which might limit further interpretations on the association with lung cancer risks. Our estimates of the risk of LCC were imprecise because of the small number of cases.

In conclusion, our study found that all histological types of lung cancer were strongly associated with current cigarette smoking, but the OR decreased substantially with increasing years of abstinence from smoking, with the greatest decline for SCC. We found a sharp decrease in OR of more than 50% in the first 5 years of quitting for all major histological types of lung cancer (except for LCC), and the benefits obtainable within such a short period of abstinence should convey an encouraging message to chronic smokers, as well as clinicians and public health workers.

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