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Research Article

Dose-Response Relationship between Cooking Fumes Exposures and Lung Cancer among Chinese Nonsmoking Women

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Abstract

The high incidence of lung cancer among Chinese females, despite a low smoking prevalence, remains poorly explained. Cooking fume exposure during frying could be an important risk factor. We carried out a population-based case-control study in Hong Kong. Cases were Chinese female nonsmokers with newly diagnosed primary lung cancer. Controls were female nonsmokers randomly sampled from the community, frequency matched by age groups. Face-to-face interviews were conducted using a standardized questionnaire. The "total cooking dish-years," categorized by increments of 50, was used as a surrogate of cooking fumes exposure. Multiple unconditional logistic regression was used to estimate the odds ratios (OR) for different levels of exposure after adjusting for various potential confounding factors. We interviewed 200 cases and 285 controls. The ORs of lung cancer across increasing levels of cooking dish-years were 1, 1.17, 1.92, 2.26, and 6.15. After adjusting for age and other potential confounding factors, the increasing trend of ORs with increasing exposure categories became clearer, being 1, 1.31, 4.12, 4.68, and 34. The OR of lung cancer was highest for deep-frying (2.56 per 10 dish-years) followed by that of frying (1.47), and stir-frying had the lowest OR (1.12) among the three methods. Cumulative exposure to cooking by means of any form of frying could increase the risk of lung cancer in Hong Kong nonsmoking women. Practical means to reduce exposures to cooking fumes should be given top priority in future research. (Cancer Res 2006; 66(9): 4961-7)

Introduction

Chinese women in Hong Kong have one of the highest incidence rates of lung cancer in the world despite a decreasing trend since 1990 (1). Unusually high rates were also observed among women in other cities of China (2, 3) as well as women of Chinese origin living in Singapore, Malaysia, Hawaii, and Japan (4–7).

Although cigarette smoking is well established as the prime cause of lung cancer in men (8), only ~36% of new cases of female lung cancer in Hong Kong and 24% in Shanghai could be attributed to smoking (9, 10). Besides active smoking, environmental tobacco smoke (ETS) has been linked to excess risk of lung cancer in epidemiologic studies (11–13). However, the overall evidence indicates that this association is weak (in terms of relative risk) and varied widely according to the study design and the population under study (14, 15).

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Epidemiologic studies conducted among Chinese women in China (16–21), Taiwan (22), and Singapore (23) found excess risk of lung cancer among subjects who cooked more. However, various exposure indices were used, and none considered intensity and duration of exposure simultaneously. Furthermore, most previous studies did not adequately address the influence of potential confounding factors, such as dietary habits and residential radon exposure (RRE).

In the present study, we investigated the association between lung cancer and fumes emitted from Chinese-style cooking among Hong Kong Chinese women using a composite index for lifetime cumulative exposure and taking into account the influence of various potential confounding factors.

Materials and Methods

Study population. The study population for the present case-control study was a restricted set of cases and controls from a larger study that also included active smokers. Original eligible cases were Chinese females ages 30 to 79 years with newly diagnosed primary carcinomas of the lung (*International Classification of Diseases, Ninth Revision* code 162) in the largest oncology center in Hong Kong from July 1, 2002 to June 30, 2004 (case identification and interviews were totally suspended between April 1, 2003 and October 30, 2003 because of the epidemic of severe acute respiratory syndrome and its aftermath in Hong Kong). All cases were histologically or cytologically confirmed according to the WHO histologic typing of lung tumors (24). Among a total of 291 eligible cases, 279 were interviewed with a participation rate of 96%. Two patients could not respond to the interview due to poor medical condition and the other 10 refused. Sixty-seven of those interviewed were smokers, leaving 212 nonsmoking lung cancer cases. Twelve subjects had missing data in some variables, and only 200 cases were used in the data analysis.

Control subjects were randomly sampled from residents of districts where the cases came from using the residential telephone directory. They were frequency matched by 10-year age groups according to the age distribution of incident female lung cancer cases. All controls must have no history of physician-diagnosed cancer in any site. We identified 661 eligible control subjects, and 322 (48.7%) subjects were successfully interviewed. We excluded 30 smokers, leaving 292 controls. Seven subjects had missing data in some variables, and only 285 controls were used in the data analysis.

Data collection. Trained interviewers conducted in-person interviews using a standardized structured questionnaire to collect information on cooking habits and potential confounding factors. Only six cases and six controls could not provide the information themselves, and their first-degree relatives were interviewed. Relevant medical information, medical diagnosis, International Classification of Diseases codes, histologic findings, etc. were abstracted from the hospital records. Approval to conduct this study was granted by the relevant ethics committees of both the Chinese University of Hong Kong (Shatin, New Territories, Hong Kong Special Administrative Region, China) and the Queen Elizabeth Hospital (Kowloon, Hong Kong Special Administrative Region, China). Informed consent was obtained before each interview.

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Assessment of Cooking Fumes Exposure

We collected information on regular cooking habits at each residence since childhood, including the number of years of cooking, the frequencies of stir-frying, frying, and deep-frying, the types of cooking oils used, the use of fume extractor or exhaust fan, and the habit of heating up a wok (Chinese pan) to high temperatures.

To take into account both the frequency and the duration of cooking, we constructed a new composite index, the cooking dish-years. The cooking dish-years for three cooking methods (stir-frying, frying, and deep-frying) were calculated separately. The concept of cooking dish-years is similar to the smoking pack-years widely used for measuring cigarette smoking in epidemiologic studies. One stir-frying dish-year means cooking one stir-fried dish daily for a year. The dish-years for each cooking methods was computed:

$$\text{Cooking dish} - \text{years} = \sum_{i=1}^{k} d_i y_i$$

where k = number of residences lived, d_i = average number of dishes cooked daily by that method at the ith residence, and y_i = years of cooking at the ith residence.

The total cooking dish-years was calculated by summing up the stir-frying dish-years, frying dish-years, and deep-frying dish-years.

Potential Confounding Variables

We collected information on several potential confounding factors, including ETS exposure, RRE, other sources of indoor air pollutants (cooking fuel used, incense burning, and use of mosquito coils), dietary habits, preexisting lung diseases, family history of cancer, and sociodemographic factors. ETS exposure was defined as ever lived or worked with a smoker for at least 1 year and was regularly exposed to tobacco smoke (12). RRE was assessed based on detailed information about the lifetime residences (floor level, building material and wall surface covering materials, building age, and window opening practices) of all subjects, using information available from a territory-wide indoor radon survey in Hong Kong (details given in Appendix A; ref. 25) A reduced version of the Diet History Questionnaire designed by the National Cancer Institute was used to collect the information on diet (26).

Statistical analysis. All data were double keyed into a database using EpiData version 2.0 (27). χ^2 tests or t tests were used to test differences of sociodemographic factors between the cases and controls. The total cooking dish-years was categorized into five groups using intervals of 50 dish-years, and unconditional logistic regression was used to estimate the odds ratio (OR) of each category using the lowest category as reference. The relationship between the exposure index (total cooking dish-years in five categories) and the risk of lung cancer was further examined after adjusting for age and various groups of potential confounding factors using multiple logistic regression models. Model 1 included age and four personal/familial variables (education, employment status, past history of lung diseases, and history of lung cancer in first-degree relatives). Model 2 included age and six indoor pollutant exposure variables (ETS, RRE, kerosene use, firewood use, incense burning, and mosquito coil use). Model 3 included age and nine dietary factors (intakes of orange/yellow vegetables, dark green vegetables, meats, citrus fruits, salted fish, pickled vegetables, and multivitamins, and coffee and tea drinking). All 20 potential confounding variables were then included in a final model (model 4).

To further explore associations between cooking habits and lung cancer, ORs for the habit of heating a wok to high temperatures, use of fume extractor or exhaust fan, and habits of using three types of cooking oil were estimated among those who had ever cooked by logistic regression models controlling for age, total cooking dish-years (in five categories), and potential confounding factors that were statistically significant in the model 4.

ORs for stir-frying dish-years, frying dish-years, and deep-frying dish-years (in multiples of 10) were computed, adjusting for age and potential confounding factors that were statistically significant in the model 4 for the purpose of comparing the magnitude of association between these three traditional Chinese-style cooking methods and lung cancer. The total cooking dish-year was not included in these regressions as it was compiled from the three subtypes of frying dish-years.

All analyses were carried out using the Statistical Package for the Social Sciences software version 13.0 for windows.

Results

Adenocarcinoma was the most frequent histologic type (137 cases, 68.5%). Squamous cell and large cell carcinoma each comprised 4.5% (9 cases) of all lung cancers. Non–small cell lung carcinoma without further classification and unspecified carcinoma accounted for the remaining 22.5% (45 cases).

The distributions of matching and major risk factors among cases and controls are shown in Table 1. More cases than controls had never been employed (19% versus 11.9%; $P = 0.043$ for χ^2 test). There were no significant differences between the cases and controls in mean age at interview and current residence district as well as for the other six sociodemographic factors: marital status, educational level, place of birth, current monthly household income, current average living area, and type of current living quarter. The mean total cooking dish-years was 90 among the cases and 65 among the controls, the difference being highly statistically significant ($P < 0.001$, t test). Significant associations were also found between lung cancer and the following variables: past history of lung diseases, lung cancer in first-degree relatives, RRE (only for linear-by-linear association), intakes of dark green vegetables, yellow orange vegetables, meat, and multivitamins, and coffee drinking. The association with ETS was not statistically significant.

The crude OR of all lung cancers increased with higher categories of total cooking dish-years, from 1.17 in the second category to 6.15 in the fifth category (Table 2). ORs of the three higher categories were all statistically significant. A similar trend was seen when analysis was restricted to adenocarcinomas, but the 95% confidence intervals (95% CI) were wider. For nonadenocarcinomas, the trend was less obvious. After adjustment for the potential confounding factors in the multivariate models, the ORs for each category of cooking dish-year increased, and their CIs became wider, but the general dose-response trend was maintained (Table 3). Six cases and 6 controls could not provide the information themselves, and their first-degree relatives were interviewed. After excluding these 12 subjects, the ORs in model 4 were pretty much preserved, being 1, 1.16, 3.83, 4.52, and 25.93 from the lowest category to the highest category.

We also compiled two indices indicating frequency and duration of cooking fumes exposure (i.e., meals cooked weekly and total years of cooking) and examined their relationships with the risk of lung cancer. The OR for meals cooked weekly adjusting for all potential confounders was 1.14 (95% CI, 1.06-1.23) and for total cooking dish-years was 1.01 (95% CI, 0.98-1.03). The model fit was best for the model using total cooking dish-years as the exposure variable. We also used a stepwise approach to examine the three indicators of cooking fumes exposure, and only total cooking dish-years could enter the final model with the other two indices becoming nonsignificant afterwards.

As shown in Table 4, more cases (67.9%) always heated a wok to high temperatures than controls (46.6%). The ORs for subjects who sometimes and always heated a wok to high temperatures were 1.22 and 2.72 compared with those who never or seldom did so. Very few subjects never used fume extractor and/or exhaust fan (6.2% and 5.8% for cases and controls, respectively). Subjects who

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Table 1. Comparisons of major risk factors between cases and controls

Factor	Level	Control, *n* (%)	Case, *n* (%)	*P**
Age	Mean (y)	64.1	63.3	0.41
Cooking experience	Mean (dish-years)	65.2	89.9	<0.001
District of residence	New Territories	39 (13.7)	30 (15)	0.38
	Kwai Tsing	82 (28.8)	52 (26)	
	Wong Tan Sin	49 (17.2)	37 (18.5)	
	Kowloon City	46 (16.1)	24 (12)	
	Yau Tsim Mong	26 (9.1)	25 (12.5)	
	Sham Shui Po	43 (14.7)	28 (14)	
	Others	1 (0.4)	4 (2)	
Employment	Never	34 (11.9)	38 (19)	0.04
	Ever	251 (88.1)	162 (81)	
Past history of lung diseases	No	260 (91.2)	170 (85)	0.04
	Yes	25 (8.8)	30 (15)	
Lung cancer in first-degree relatives	No	249 (87.4)	146 (73)	<0.01
	Yes	13 (4.6)	12 (6)	
	Unsure	23 (8.1)	42 (21)	
ETS exposure	Nil	45 (15.8)	24 (12)	0.49
	Home or workplace	159 (55.8)	118 (59)	
	Home and workplace	81 (28.4)	58 (29)	
Radon exposure (in quintile)	1st	61 (21.4)	41 (20.5)	0.28 (P_{trend} = 0.03)
	2nd	63 (22.1)	32 (16)	
	3rd	64 (22.5)	42 (21)	
	4th	54 (18.9)	43 (21.5)	
	5th	43 (15.1)	42 (21)	
Dark green vegetables (servings daily)	<1	46 (16.1)	67 (33.5)	<0.01
	1	56 (19.6)	35 (17.5)	
	2-3	133 (46.7)	59 (29.5)	
	>4	50 (17.5)	39 (19.5)	
Yellow orange vegetables (servings daily)	<1	75 (26.3)	100 (50)	<0.01
	1	104 (36.5)	57 (28.5)	
	2-3	52 (18.2)	22 (11)	
	>4	54 (18.9)	21 (10.5)	
Meat (servings daily)	<1	20 (7)	13 (6.5)	<0.01
	1	60 (21.1)	20 (10)	
	>2	205 (71.9)	167 (83.5)	
Multivitamins	Never	234 (82.1)	179 (89.5)	<0.01
	Irregular	19 (6.7)	14 (7)	
	Regular	32 (11.2)	7 (3.5)	

*χ^2 test for categorical variables and *t* test for continuous variables.

ever used fume extractor and/or exhaust fan had a nonsignificant lower risk of lung cancer (OR, 0.94; 95% CI, 0.43-2.02). Those who always used peanut oil seemed to have a higher risk (OR, 1.45) but not statistically significant. Few cases and controls always used corn oil and canola oil, and no significant associations with lung cancer risk were found. Adjusting for total cooking dish-years and potential confounding factors did not materially change the associations. The ORs for the five categories of total cooking dish-years did not change much in the regression models with these variables on cooking habits, and the dose-response relationship seen in the earlier analysis was preserved.

Deep-frying was associated with the highest risk (per 10 dish-year) with an OR of 2.56 (95% CI, 1.31-5). This was followed by frying (OR, 1.47; 95% CI, 1.27-1.69) and stir-frying (OR, 1.12; 95% CI, 1.07-1.18).

A group of eligible cases in the present study came from inpatients who had to undergo surgical operations for suspected lung cancer. A total of 114 inpatients were interviewed before the operation, and they were handled as cases when interviews were conducted. Thirty-nine of them did not have primary lung cancer after the diagnostic workup, and they reported much less exposures than the 75 confirmed cases (mean of 46 versus 87 total dish-years; $P < 0.005$, *t* test).

Discussion

This is the first study linking cooking fumes exposure and lung cancer among Chinese females using a quantitative indicator for cumulative exposure, the cooking dish-year. Compared with nonsmoking Chinese females who never cooked or cooked 50 dish-years or less, the OR of lung cancer was ~3 to 4 for those with >100 total cooking dish-years (e.g., cooking five dishes daily for a period of 20 years or cooking four dishes daily for a period of 25 years or cooking two dishes daily for a period of 50 years) and

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increased to >8 among those with >200 total cooking dish-years (indicating quite intensive regular cooking). A nice dose-response relationship between the cumulative exposure to cooking fumes and lung cancer risk was shown even after adjusting for major potential confounding factors. We further found that different methods of frying were associated with different levels of risks, with deep-frying having the highest risk and stir-frying the lowest. This comparison among different frying methods using the same denominator (10 cumulative dish-years) has not been reported before.

Most past studies on cooking fume exposure and lung cancer used the usual cooking practices before the diagnosis of lung cancer to compile the exposure index without consideration of the possible changes with time. Subjective exposure indices used included "smokiness" and "eye irritation," and the associations with lung cancer were quite consistent (16, 18, 20, 23, 28), but these indicators were more subjected to recall bias. The duration (years) of cooking was positively associated with lung cancer risk in some earlier studies (17), but more recent studies reported no significant associations (21, 28). The frequency of cooking, including different types of frying, was also used to indicate exposure. The number of meals cooked daily did not have a consistent association with lung cancer risk (19, 21, 28). The frequency (intensity) of stir-frying (16, 20–23), frying (20, 22), and deep-frying (16, 18, 20) seemed to be positively associated with lung cancer risk, but a clear dose-response relationship could not be adequately documented in any of the past studies. The total cooking dish-years used in the current study measured both the frequency (intensity) and the duration of cooking and was therefore superior to exposure indices used in previous studies in reflecting the total dose of exposure. This was supported by our analyses, indicating that the total cooking dish-years provided the best model fit among the three indicators used (frequency, duration, and cumulative) and that the total cooking dish-years was the only exposure indicator selected into the final model using a stepwise approach. Due to the retrospective nature of the study, direct measurements of the cooking fume exposures could not be done.

Consistent with previous studies (20, 28), the habit of heating the wok to high temperatures increased the risk of lung cancer. Over 50 volatile organic compounds have been identified from heated oil as well as cooked foods, and some of these agents in emissions of cooking oils are mutagens and human carcinogens, such as 1,3-butadiene, benzene, benzo(*a*)pyrene, dibenzo(*a,h*)anthracene, acrolein, and formaldehyde (29–34). It has been found in experimental studies that temperature is the most important factor for mutagen formation (35, 36). The use of fume extractor or exhaust fan did not confer benefit as found in a previous study (22). The type of cooking oil did not have a significant influence on lung cancer risk, and rapeseed oil was not used in Hong Kong.

We collected information on all major risk factors of lung cancer and examined their potential confounding effects on the association between cooking fume exposure and lung cancer, including RRE and dietary factors, which were frequently neglected in past studies. Our statistical analysis did not support important confounding effects from radon exposure and ETS, though they might have independent effects on the risk of lung cancer. In fact, in our final model, both types of exposures did increase the risk of lung cancer, but their effects were not statistically significant in our regression models. Nonsmoking women exposed to ETS at home and/or at work had an OR of ~1.35 ($P = 0.67$) in the final model, and this level of risk is compatible with results from previous epidemiologic studies (37–39). The effect of ETS on lung cancer risk might become statistically significant if we had a larger sample size. We have tried other quantitative indicators for ETS exposure, including number of smokers at home and years of workplace exposure, but the associations with lung cancer were still not significant, and the effects on the estimated ORs for the categories of total cooking dish-years were minimum. Our exposure assessment for RRE was based on weighing variables of residential buildings that had been found to influence indoor radon levels in a prior territory wide survey (25) and might be inaccurate and imprecise, but the semiquantitative ranking used indicated a possible dose-response relationship with lung cancer risk (with greater ORs for higher quintiles ranging from 1.8 to 2.5), though the association was not statistically significant (see Appendix A).

As in most population-based case control studies, the selection of appropriate controls might be a concern. A participation rate of ~50% was not high but not too low for this type of control. We managed to obtain some brief information from a group of the nonparticipating controls (n = 191). Comparisons with the participating controls showed that they were similar in age distribution, martial status, type of current housing, district of current residence, cooking history, and smoking history, suggesting that nonrespondent bias should not be serious. A lower proportion of the control subjects had never been employed. As individuals who had never been employed might cook more, the crude OR for cooking fumes exposure could be overestimated. However, the ~7% difference in employment status between cases and controls could not entirely account for the 300% to >700% increase in risk associated with moderate to high levels of cooking. In fact, adjustment for employment status did not change the results substantially. On the other hand, the high comparability in other sociodemographic factors between cases and controls indicated that selection bias would be minor in our study (40, 41).

Table 2. Crude ORs for lung cancer related to total cooking dish-years

Total dish-years	Controls (n = 285)	All lung cancers (n = 200)		Adenocarcinomas (n = 137)		Nonadenocarcinomas (n = 63)	
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
≤50	123 (43.2)	64 (32)	1	43 (31.4)	1	21 (33.3)	1
51-100	102 (35.8)	62 (31)	1.17 (0.76-1.81)	40 (29.2)	1.12 (0.68-1.86)	22 (34.9)	1.26 (0.66-2.43)
101-150	38 (13.3)	38 (19)	1.92 (1.12-3.30)	27 (19.7)	2.03 (1.11-3.72)	11 (17.5)	1.70 (0.75-3.83)
151-200	17 (6)	20 (10)	2.26 (1.11-4.62)	12 (8.8)	2.02 (0.89-4.57)	8 (12.7)	2.76 (1.06-7.19)
>200	5 (1.8)	16 (8)	6.15 (2.16-17.55)	15 (10.9)	8.58 (2.94-25.02)	1 (1.6)	1.17 (0.13-10.53)
χ^2 test for trend			$P < 0.001$		$P < 0.001$		$P = 0.052$

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Table 3. ORs for lung cancer related to total cooking dish-years after adjusting for potential confounding factors

Total dish-years	Adjusted OR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
≤50	1	1	1	1
51-100	1.31 (0.81-2.11)	1.43 (0.87-2.34)	1.23 (0.73-2.07)	1.31 (0.73-2.33)
101-150	2.80 (1.52-5.18)	2.65 (1.42-4.97)	2.89 (1.47-5.70)	4.12 (1.90-8.94)
151-200	3.09 (1.41-6.79)	3.10 (1.37-7)	3.63 (1.57-8.40)	4.68 (1.80-12.18)
>200	8.09 (2.57-25.45)	10.02 (3.21-31.26)	20.66 (5.26-81.11)	34 (7.16-161.39)

NOTE: Model 1: adjusting for *age*, education, employment status, previous lung diseases, and *history of lung cancer in first-degree relatives*; Model 2: adjusting for age, radon exposure index, ETS exposure, kerosene use, firewood use, incense burning, and mosquito coil use; Model 3: adjusting for *age*, intakes of *dark green vegetables, yellow orange vegetables, meat*, citrus fruit, salted fish, pickled vegetables and *multivitamin*, and *coffee* and tea drinking; Model 4: adjusting for all the above potential confounding factors with statistical significance for *history of lung cancer in first-degree relatives, dark green vegetables, yellow orange vegetables, meat, multivitamin*, and *coffee* (italicized variables were significant at 0.05 level in the respective models).

Recall bias should not distort our results to a great extent. We tried to minimize this bias by introducing the study to both the cases and the controls as a general "women health" study. Furthermore, the purported link between cooking fumes and lung cancer was not common knowledge, and subjects were asked to report the average number of dishes they cooked daily rather than their subjective feeling of smokiness during cooking. Thus, it was unlikely that cases would recall better, or overreport, their cooking practices than the controls. Inaccuracies in recall and reporting were possible and, as they were likely nondifferential, could cause dilution of a true association. We reinterviewed a subgroup of subjects (45 cases and 156 controls) after an interval of several weeks on their reported history of cooking practices in the most recent three residences, and good reproducibility was observed especially among the controls. κ for cooking status ranged between 0.7 and 1 for cases and between 0.98 and 1 for controls. κ for the use of exhaust fan/fume extractor was 0.88, 0.81, and 0.19 for cases in reverse chronological order and 0.92, 0.96, and 0.86 for controls. The Spearman rank correlation coefficient for meals cooked weekly, stir-frying dish-years, frying dish-years, and deep-frying dish-years, ranged between 0.61 and 0.9 for cases and between 0.85 and 0.96 for controls. To the best of our knowledge, this is the first study evaluating the reliability of measurement for cooking fumes exposure.

It was difficult to estimate to what extent the association was distorted by interviewer bias; however, data from a special group of our study subjects (inpatients who had to undergo surgical operations for suspected lung cancer) suggested that this bias

Table 4. ORs of lung cancer related to cooking habits

	n (%)*		OR (95% CI)	
	Cases	Controls	Crude OR	Adjusted OR†
Heating a wok to high temperatures				
Never/seldom	25 (13)	67 (24.2)	1	1
Sometimes	37 (19.2)	81 (29.2)	1.22 (0.67-2.24)	1.02 (0.51-2.06)
Always	131 (67.9)	129 (46.6)	2.72 (1.62-4.58)	1.97 (1.06-3.65)
Use of fume extractor				
Never	12 (6.2)	16 (5.8)	1	1
Ever	183 (93.8)	261 (94.2)	0.94 (0.43-2.02)	0.73 (0.29-1.87)
Use of peanut oil				
Seldom/sometimes	70 (35.9)	124 (44.8)	1	1
Always	125 (64.1)	153 (55.2)	1.45 (0.99-2.11)	1.36 (0.87-2.15)
Use of corn oil				
Seldom/sometimes	146 (74.9)	208 (75.1)	1	1
Always	49 (25.1)	69 (24.9)	1.01 (0.66-1.54)	1.27 (0.76-2.10)
Use of canola oil				
Seldom/sometimes	181 (92.8)	258 (93.1)	1	1
Always	14 (7.2)	19 (6.9)	1.05 (0.51-2.15)	1.40 (0.59-3.30)

*Five cases and eight controls who never cooked were excluded from the analysis.
†ORs adjusted for age, history of lung cancer in first-degree relatives, intakes of dark green vegetables, yellow orange vegetables, meat, and multivitamin, coffee drinking, and total cooking dish-years.

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should not be serious. They were all handled as lung cancer cases during the interviews. The 39 subjects who eventually did not have primary lung cancer after the diagnostic workup reported much less exposures than the 75 confirmed cases. The reported mean cooking dish-years in these two subgroups closely approximated the means for controls and cases in the whole study. The differential exposure reported in these two subgroups did not support the presence of interviewer bias and recall bias and, hence, provided further support for a positive association between cooking fumes exposure and lung cancer.

There might also be misclassification of disease status. The control subjects could include patients with undiagnosed lung cancer. Such misclassification, if present, would dilute the true association between cooking fumes exposure and lung cancer. On the other hand, all cases were histologically or cytologically confirmed and misclassification would be unlikely.

We observed a 3- to 4-fold increased risk related to moderate levels of cooking (101-150 total cooking dish-years). This risk estimate was compatible with those reported in seven case-control studies conducted elsewhere among Chinese women, with ORs ranging from 1.9 to 2.6 for the group with the highest frequency of stir-frying, frying, or deep-frying (16, 18, 20–23, 28). Together with a nice dose-response relationship, our study provides further support to the hypothesis that carcinogens in cooking fumes play an important role in the occurrence of lung cancer among Chinese women in Hong Kong.

In conclusion, we found strong evidence that cumulative exposure to cooking by means of any form of frying could increase the risk of lung cancer in Hong Kong nonsmoking women. Practical means to reduce exposures to cooking fumes should be given top priority in future research.

Appendix A. Residential Radon Exposure

RRE was assessed based on detailed information about the lifetime residences of all subjects. For each residence, in which the subject lived for >1 year, the subject was asked to give details on the duration of stay at the residence, the floor level (<4th floor, 4th-9th floor, and >9th floor), building materials (wood/iron/soil block, brick, concrete, and stone), wall surface covering materials (wall paper, plaster, water-based paint, and oil-based paint), building age (>30, 20 to 30, 11-20, 6-10, and ≤5 years), and window opening practices (most windows fully open all the time, most windows fully open only when family member(s) were at home, some windows open all the time, some windows open only when family member(s) were at home, and all windows closed tight all the time). Each exposure variable was scored using a three-point (floor level), four-point (building material and wall surface covering materials), or five-point scale (building age and window opening practices) according to the results of a territory-wide indoor radon survey in Hong Kong. The RRE index that measured lifetime RRE was generated from such information. A higher score indicated a higher level of RRE.

A lifetime weighed RRE index was calculated by the cumulative scores for all reported residences divided by the total number of years lived in those residences.

$$\text{RRE index} = \frac{\sum_{i}^{k}(S_{i1} + S_{i2} + S_{i3} + S_{i4} + S_{i5}) \times Y_i}{\sum_{i}^{k} Y_i}$$

where k = number of residences lived, S_{i1}, S_{i2}, S_{i3}, S_{i4}, and S_{i5} = score for each of the five factors at the ith residence, and y_i = number of years at the ith residence.

For subjects who had missing values in one or more residences, the scores of other residences with valid data were contributed to the calculation of RRE index. If a subject provided complete information on all residences since birth, the denominator of the above formula would be the age of the subject.

The RRE was categorized into quintiles for examining its effect on lung cancer risk. A significant linear-by-linear association with lung cancer was found on univariate analysis with χ^2 test (P = 0.03), and a nonsignificant dose-response relationship was present on multiple logistic regression controlling for all potential confounding factors in the current study, with greater ORs for higher quintiles of RRE index (ranging from 1.8 to 2.5).

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