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# Joint Effects of Environmental Exposures and Familial Susceptibility to Lung Cancer in Chinese Never Smoking Men and Women

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## Abstract

**Objectives:** Previous epidemiological studies had limited power to investigate the joint effects of individual environmental risk factors and familial susceptibility to lung cancer. This study aimed to address this shortcoming.

**Methods:** We recruited 345 never smoking lung cancer cases and 828 community referents. We developed a collective environmental exposure index by assigning a value of 1 to subjects at high risks regarding environmental risk factors and 0 otherwise, and then summed over using weights equivalent to the excess odds ratio. Potential additive and multiplicative interactions between environmental exposure index and family cancer history were examined.

**Results:** Compared with "low environmental exposure and without family cancer history", the odds ratio was 6.80 (95% confidence interval = 3.31–13.98) for males who had high environmental exposures but without family cancer history, whereas it increased to 30.61 (95% confidence interval = 9.38–99.87) if they also had a positive family history. The corresponding associations became weaker in never smoking females. No multiplicative interaction was observed for both genders and an additive interaction was restricted among males.

**Conclusions:** This study developed a novel environmental exposure index that offers sufficient interest deserving further studies on the interactions between environmental exposures and familial susceptibility to lung cancer risk.

### Keywords

Environmental risk factors; Lung neoplasm; Familial susceptibility; Interaction

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Lung cancer is the global leading cause of neoplasm for both men and women, and tobacco smoking in any form is the major determinant.[1] Other environmental risk factors potentially contributing to the etiology of lung cancer were occupational lung carcinogens, residential radon, cooking emissions, atmospheric pollution, and less consumption of vegetables.[2–7] Familial aggregation of cancer in first-degree relatives was reported to be associated with a 70% excess risk of lung cancer in both men and women.[8] Besides shared environmental factors by family members, this increased risk is also thought to be linked to genetic variations such as *P53* gene mutations, homozygous deletion of *GSTM1* gene, and three regions on chromosomes 5 (5p15.33), 6 (6p21.33), and 15 (15q25);[9–12] however, these genetically determined susceptibility alone contributed little to the development of lung cancer, and a majority fraction of lung cancer etiology is attributable to environmental risk factors and the interactions with genetics.[10]

Tobacco smoking is the most important environmental risk factor for lung cancer and its presence makes researchers difficult to look into the effects of other environmental exposures with low to moderate carcinogenic potency. Restricting study subjects to never smokers provides the best approach in this way but power is limited by too few lung cancer cases in never smokers, particularly for the males.[13] We addressed this shortcoming by developing a new environmental exposure index by considering all environmental risk factors collectively rather than individually under an additive assumption[14,15] so that power is largely increased. This study aimed at examining the joint effects of collective environmental exposures and familial susceptibility to lung cancer among Chinese never smoking men and women in Hong Kong.

## METHODS

Participants of this study were never smoking cases and community referents who were derived from two case-referent studies between 2002–2004 (female lung cancer study) and 2004–2006 (male lung cancer study) that also included smokers.[16,17] Briefly, eligible cases were Hong Kong Chinese who were the new cases of primary carcinoma of the lung confirmed by histology and were consecutively recruited from the largest oncology center in Hong Kong. We interviewed all cases in person in outpatient department or ward, and the interval between the date of interview and date of diagnosis of lung cancer was 14 days (median). All the referents were randomly selected from the same districts as the cases using the residential telephone directory, and >90% of community referents were interviewed through telephone; however, most of the community referents were not willing to provide their exact residential addresses, which made us unable to assess the differences in residential proximity of cases and controls. We matched community referents in 5-year age groups to the cases by frequency and excluded those who had history of physician-diagnosed cancer at any site. As a result, a total of 1487 lung cancer cases (1208 males and 279 females) and 1391 community referents (1069 males and 322 females) agreed to participate with a response rate of 96% for the cases and 48% for referents. We excluded 1143 ever smoking cases and 563 referents, and the data included in this study were the subgroup of 1173 never smokers (cases: 132 males and 213 females; referents: 536 males and 292 females) defined by subjects who had never smoked as many as 20 packs of

cigarettes or 12 oz (342 g) of tobacco in lifetime or one cigarette a day or one cigarette a week for 1 year.[18]

Both male and female lung cancer studies used similar methods to collect participant's information on socio-demographics, dietary habits, lifetime tobacco smoking, indoor air pollution (residential radon exposure,[5] environmental tobacco smoke (ETS), incense burning, mosquito coil burning, and cooking fumes), lifetime occupational exposures to known or suspected lung carcinogens, previous history of lung diseases (1 year before the interview), and family cancer history that was defined if one of participant's biological parents or siblings had developed cancer in any sites.[16,19] We collected dietary intakes in terms of different types of vegetables and meat in both frequency and amount. We defined exposure to confirmed or suspected occupational carcinogens as ever regularly exposed (i.e., at least once a week for at least 6 months) to any of these agents: silica, asbestos, arsenic, nickel, chromium, tars, asphalts, painting, pesticide, diesel exhaust, cooking fume, and welding fume in the workplace.[16] We semiquantitatively estimated cumulative residential radon exposure based on detailed information about each participant's lifetime residences (e.g., building age, window opening practices, floor level) according to an established formula recommended by Hong Kong Government.[20] A higher score indicated a higher level of exposure to residential radon.

We performed unconditional multiple logistic regression models (backward stepwise method) to identify significant risk factors of lung cancer among never smokers. We only presented main effect models because no multiplicative interaction (i.e., likelihood ratio test for interaction by introducing a product term at $p$ level of 0.05) between individual environmental exposure of interest and family cancer history was detected. We developed a new exposure index to document the joint effects of collective environmental exposures for males and females separately according to an approach introduced by Katsouyanni et al.[14] We assigned a value of 1 to subjects at high risks of lung cancer regarding environmental risk factors and 0 otherwise. We then summed over all these identified factors using weights equivalent to the excess odds ratio (OR; defined as OR-1) derived from this study, whereas a weight of "0" was assigned otherwise. We quantified the potential additive interactions (i.e., risk difference modifications) between environmental exposure index and family cancer history on lung cancer risk using the synergy index after an approach proposed by Hosmer and Lemeshow.[21] An additive interaction is indicated if the synergy index was significantly above one.[15,16] A subgroup analysis was only restricted to 233 adenocarcinoma cases (67.5% of all 345 cases) because of very few never smokers in other histologic subtypes. We examined the exposure-response relationships between environmental exposure index and lung cancer separately for subjects with and without family history at an alpha level of 0.05.

## RESULTS

A total of 93 never smoking lung cancer cases (39 males and 54 females) and 120 never smoking referents (74 males and 46 females) reported having history of cancer in first-degree relatives. There were 25 never smoking lung cancer cases (13 males and 12 females) and 44 never smoking community referents (30 males and 14 females) with family history of lung carcinoma. The OR for family cancer history derived from a main effect multivariate

model was 2.80 (95% confidence interval [CI] = 1.68–4.66) and 2.20 (95% CI = 1.32–3.67) for never smoking males and females, and the corresponding ORs for family history of lung carcinoma was 2.57 (95% CI = 1.15–5.73) and 1.52 (95% CI = 0.–3.76). As summarized in Table 1, the statistically significant environmental risk factors for lung cancer among never smoking males were high residential radon exposure, exposure to known or suspected occupational lung carcinogens, lack of hazard control in the workplace, less intake of orange vegetable, and high intake of meat. The magnitude of ORs for the studied environmental risk factors varied slightly between the adenocarcinoma and all lung cancers, with an exception of exposure to high level of ETS. High ETS exposure was associated with a significantly increased risk of adenocarcinoma among our never smoking males (OR = 2.51, 95% CI = 1.24–5.08).

Major risk factors of lung cancer in never smoking females differed from those in never smoking males (Table 2). Women in this study were considered to be at high risk of lung cancer if she had been exposed to high level of cooking emissions, relatively high intake of meat, less intake of vegetable (dark green, yellow, or orange), without regular intake of multiple vitamins, and current employed; whereas intake of dark green vegetables and occupational history were not identified as the significant risk factors for the adenocarcinoma.

Significant environmental risk factors obtained from Tables 1 and 2 were then used to develop the collective environmental exposure index for males and females separately. Overall, the environmental exposure index ranged from 0 to 8.99 (median = 3.44) for males and from 0 to 11.58 (median = 5.72) for women. We classified the exposure index score into three categories by tertile of the lung cancer cases for males (<3.83, 3.83–5.48, and >5.48) and females (5.79, 5.79–7.51, and >7.51), respectively. We then evaluated the joint effects of collective environmental exposure index and family cancer history using “no family cancer history and low environmental exposures” as the reference (Table 3). Among males without family cancer history, we found a positive association between environmental exposure index and lung cancer ($p < 0.001$, test for trend). Among males with family cancer history, there was an even strong positive gradient of associations with the environmental index ($p < 0.001$, test for trend), with the highest OR of 30.61 (95% CI = 9.38–99.87) in males who had high levels of environmental exposures. We detected a statistically significant synergy index of 3.98 (95% CI = 1.14–13.92) between family cancer history and the environmental index (i.e., the highest category of exposure), which indicated that the joint effect was about threefold greater than the sum of independent effects of the exposures of interest. Table 3 presents a similar pattern of ORs when analyses were restricted to the adenocarcinoma, although there was a relatively lower OR in those who had a positive family history and high environmental exposure scores; the synergy index for environmental exposure index (i.e., the highest category of exposure) and family history for adenocarcinoma was 1.83 (95% CI = 0.48–6.88) in never smoking males.

Despite a positive gradient of the association between environmental index and family cancer history was also indicated in never smoking females ($p < 0.001$, test for trend), there was some indications that, in the subgroup of absence of family history, women who had high environmental exposures were at higher risks of lung cancer than that of the males

(Table 4); nevertheless, the association became less strong if women who had high environmental exposures had also a positive family history. The synergy index between environmental exposure index (i.e., the highest category of exposure) and family history was 1.21 (95% CI = 0.45–3.60) for all female lung cancers and it was 1.28 (95% CI = 0.45–3.60) for the adenocarcinoma (Table 4). Results were similar when the same categories of environmental exposures as those of the males were applied to the females (Supplemental Digital Content, http://links.lww.com/JTO/A581). There was no multiplicative interaction between environmental exposure index and family history on the risk of all lung cancers and the adenocarcinoma for both males ($p$ value: 0.226 and 0.489) and females ($p$ value: 0.576 and 0.632), and these results had no statistically significant difference in different gender subgroups ($p$ value: 0.628 and 0.643). Further analyses for the association between environmental exposure index and family history of lung carcinoma were hindered by the small number of cases with family history of lung carcinoma, particularly for the female subgroup.

## DISCUSSION

Results from this case-referent study regarding the associations between individual environmental risk factors and lung cancer among never smokers were consistent with those reported elsewhere.[3,4,6,22] We further discovered a statistically significant additive interaction between a collective environmental exposure index and family cancer history in never smoking males. Despite a positive gradient of the association between environmental exposure index and lung cancer was also indicated in never smoking females, there was lack of a multiplicative and additive interaction between environmental exposure index and family cancer history.

Our study demonstrated sex differences in components of environmental exposure index between never smoking males and females. In Hong Kong, popular occupations of male predominance that are potentially exposed to confirmed or suspected lung carcinogens are the construction and renovation work, shipyard and car repairing services, professional drivers, and operators of engine machines.[23] These job tasks are frequently linked to a variety of confirmed or suspected occupational lung carcinogens, in particular, asbestos, diesel motor exhaust, painting work, and silica dust.[24–26] Meanwhile, we observed a reduced lung cancer risk among those having adopted controls of hazard (e.g., wet process, dust control) in the workplace, and this encouraging message enhances employers and employees confidence that better worker protection deserves rewards of health. Chinese women in Hong Kong had different job opportunities from those of men, and the cleaner is the popular occupation in Hong Kong women that accounted for 22.2% of female lung cancer cases locally.[27] The elevated risk of lung cancer among female cleaners might be associated with prolonged exposures to certain organic solvents that have carcinogenetic effects.[27]

Radon is a confirmed human lung carcinogen and radon exposure in homes of Hong Kong is mainly released from concrete materials of the buildings.[28] A territory-wide indoor radon survey conducted by Environmental Protection Department demonstrated that radon levels of 5% of the residential buildings in Hong Kong were above the World Health Organization’s safety guideline level of 200 Becquerel per cubic meter ($Bq/m^3$).[29] Hong

Kong holds one of the most densely populated areas in the world, given a land mass of 1104 $km^2$ and a population of 7.07 million people. Poor ventilation in most Hong Kong home may lead the high radon exposures indoors hard to being diluted. Overall, exposures to confirmed or suspected occupational lung carcinogens and residential radon were the major components of environmental exposure index among Hong Kong never smoking males, and these factors taking together had played important roles in lung cancer etiology.

Dietary intakes had played an important role in lung cancer etiology for never smoking males and females in Hong Kong. We observed that the lung cancer risk was inversely associated with vegetables and multivitamins intakes (for females only) and these findings were consistent with other studies.[30,31] We further found that high meat intake was associated with an increased risk of lung cancer and this finding was consistent for males and females. There are some indications that ETS (adjusted OR = 1.34, 95% CI = 0.73–2.46) and high residential radon exposure (adjusted OR by quartile: 1.00, 0.95 [95% CI = 0.53–1.70], 0.98 [95% CI = 0.55–1.75], 1.27 [95% CI = 0.72–2.26]) were also positively associated lung cancer in females, whereas these variables were not included in the collective environmental exposure index because these associations were not statistical significance. The positive association between ETS exposure and the male lung adenocarcinoma (Table 1) was mainly attributable to the workplace exposures.[19]

Exposure to cooking emissions had a strong association with an elevated risk of lung cancer among Chinese never smoking women.[5] In Chinese tradition, women are supposed to undertake most homework (especially for cooking) regardless of their employment statuses, while frying or even deep-frying is a very popular cooking practice in most Chinese families. Females long-term exposed to various carcinogens and mutagens (e.g., 1,3-butadiene, acrolein) identified from heated oil may put them at a high risk of lung cancer.[5,32] To the best of our knowledge, very few Chinese males in Hong Kong (<5%) have regular cooking at home, and thus this study does not have power to examine the association between domestic cooking and lung cancer risk among male population.

Several studies reported that family history of lung carcinoma in first-degree family members was associated with an increased risk of lung cancer in never smokers and for the adenocarcinoma and squamous cell carcinoma subtypes.[6,8,33,34] Our study also showed some indications of an increased risk of lung cancer among never smoking males (adjusted OR = 2.57, 95% CI = 1.15–5.73) and females (adjusted OR = 1.52, 95% CI = 0.61–3.76) who had a family history of lung carcinoma; however, the small number of cases particularly for the females prevented us from performing meaningful interaction analyses with environmental exposure index. We are aware that family history of lung carcinoma or any cancer may not completely represent shared genetic susceptibility but be a reflection of shared environmental exposure of family members; this speculation, however, tends not to be supported by this study given a weak correlation between environmental risk factors and family history of lung carcinoma ($r = -0.15$ to 0.061) or any cancer ($r = -0.044$ to 0.046). In our study, an adjustment of ETS exposure did not substantially affect the association between family cancer history and lung cancer risk.

Hong Kong is a modern metropolis with heavy traffic and presence of various industries. According to the statistics of the $PM_{2.5}$ Speciation Study in Hong Kong, the annual average $PM_{2.5}$ mass ranged from 28 to 53 $\mu g/m^3$ during 2004–2005 based on a total of 61 samples, and all these far exceeded the USEPA annual 24-hour $PM_{2.5}$ standard of 15 $\mu g/m^3$.[35] Recent findings from an extended follow-up of the Harvard Six Cities study revealed that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration was associated with 37% (95% CI = 7–75%) increase in lung cancer mortality for the entire cohort and 25% (95% CI = −46% to 189%) for the never smokers.[7] This association, however, could not be examined in the current study because we did not collect the $PM_{2.5}$ concentration data.

We detected a possible difference in the joint effects between familial susceptibility and the collective environmental exposure index between males and females. Despite this new finding has never been reported by previous studies, it has to be mentioned that cross gender may not be entirely comparable because the included components (individual risk factors) of the environmental exposure index are different for males and females. However, given the fact that males and females are likely to be exposed to different risk factors and thus have different lung cancer etiology, it is not common in a population-based study that the components of environmental index in different gender subgroups are necessarily comparable. Adopting a collective exposure index score may dilute the overall impact from various environmental risk factors, but it deems valuable in improving statistical power, as is the case of our study. Selection bias is a concern because the cases and referents differed in response rate (95% versus 48%); we made efforts to recruit referents from the same residing areas as the cases that may reduce the potential selection bias and also improved comparability between cases and references regarding environmental exposures (e.g., ambient air pollution, residential radon, and consumption of vegetables); however, this matching approach might have resulted in a dilution of the actual associations between these environmental exposures and lung cancer risk, which subsequently may lead to an underestimation of the effect of environmental exposure scores on the risk of lung cancer.

Recall bias is a major concern for most case-referent studies but it may not present a serious issue in our study. The median interval between the date of interview and date of diagnosis of lung cancer was 14 days. However, it was less likely that the patients were not aware that they were suspected to have cancer despite some of them may not have known about the actual diagnosis before the date of interview. Even for the subgroup undergoing surgical operations for confirmation, they were probably told of the possibility of cancer. Hence, recall bias could be present, but results from a special group of our study subjects (103 inpatients 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 having lung cancer) showed that the exposures (e.g., ETS and cooking fume exposure) among those eventually diagnosed to have cancer approximated the other cases, whereas exposures among those eventually diagnosed as not having cancer were different from the cases but approximated the control group.[5,19] These differential exposures noted between these two subgroups support that the recall bias might not be a serious concern of this study. We recognized that using 20 packs of cigarettes or equivalent as the cutoff for ever smokers may open the possibility of misclassification of light and never smokers, hence residual confounding effect from light smoking may not be totally ruled out from our study.

Differential misclassifications of exposures may possibly be present in this study because of the different magnitude of potential misclassifications of exposures between gender groups, as the awareness of exposure for males and females may differ from each other. Despite we did not perform objective testing on the measures regarding occupational exposures to ascertain whether the respondents had been exposed, good reliabilities between the initial and second survey regarding occupational exposures suggested that the data quality tended to be reliable.[23] We are currently performing job-exposure-matrix for some major exposures (e.g., silica, diesel motor exhausts, and radon) and this will provide us an opportunity to test the validity of self-reported occupational exposures in the future. We made efforts to introduce to both the cases and controls as “the general men or women health” study, and thus, the misclassification bias, if it is present, would have led to a dilution of true associations. Moreover, we invited approximately 30% of participants to respond a second interview two months later after the initial interview to evaluate the reliability of the recall of several important exposures (e.g., smoking, exposures to ETS and cooking fumes, lifetime occupational exposures). Results from test-retest reliability suggested a good repeatability of the collected exposure data.[5,19,36] Different cell types of lung cancer may represent different disease entities in which different environmental and genetic factors may be involved in the etiology; however, the data only allowed us carrying out analyses for the adenocarcinoma and further analyses by histology were hindered by limited cases of squamous cell and other histologic subtypes.

In conclusion, this study developed a novel environmental exposure index that improves power to examine the interactions between environmental exposures and familial susceptibility to lung cancer. Males had different environmental risk factors from those of the females, and there is a gender differences in joint effects between respective environmental exposure index and familial susceptibility to lung cancer risk among never smoking population. Our findings are sufficiently interesting to deserve further separate studies on the interactions of environmental exposures and familial susceptibility to lung cancer risk in male and female population. This study conveys important messages that people with family cancer history may obtain greater benefits from removal of environmental exposures, particularly for the males.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**TABLE 1.**

Distribution of Selected Environmental Risk Factors, the Corresponding Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) Among 132 Never Smoking Lung Cancer Cases and 536 Community Referents in Hong Kong Males

| | References | All Lung Cancers | | Adenocarcinoma | |
|---|---|---|---|---|---|
| **Environmental Risk Factors** | **(n = 536)** | **(n = 132)** | **OR (95% CI)*** | **(n = 89)** | **OR (95% CI)*** |
| Residential radon exposure | | | | | |
| First quartile | 146 (27.2) | 16 (12.1) | 1.00 | 12 (13.5) | 1.00 |
| Second quartile | 130 (24.3) | 33 (25.0) | **2.46 (1.20–5.03)** | 22 (24.7) | 1.95 (0.87–4.36) |
| Third quartile | 129 (24.1) | 33 (25.0) | 2.07 (0.99–4.31) | 21 (23.6) | 1.36 (0.59–3.14) |
| Fourth quartile | 121 (22.6) | 43 (32.6) | **3.72 (1.80–7.67)** | 31 (34.8) | **3.04 (1.36–6.81)** |
| Occupational carcinogens† | | | | | |
| No | 344 (64.2) | 61 (46.2) | 1.00 | 41 (46.1) | 1.00 |
| Yes | 192 (35.8) | 71 (53.8) | **1.76 (1.13–2.73)** | 48 (53.9) | **1.82 (1.08–3.06)** |
| Control of hazards in workplace | | | | | |
| No | 24 (4.5) | 17 (12.9) | **2.52 (1.18–5.40)** | 11 (12.4) | **2.46 (1.01–6.00)** |
| Yes | 512 (95.5) | 115 (87.1) | 1.00 | 78 (87.6) | 1.00 |
| Intake of orange vegetable | | | | | |
| <1/wk | 111 (20.9) | 62 (48.1) | **3.38 (2.15–5.29)** | 38 (42.7) | **2.98 (1.75–5.08)** |
| ≥1/wk | 419 (79.1) | 67(51.9) | 1.00 | 50 (57.3) | 1.00 |
| Intake of meat | | | | | |
| <1/day | 102 (19.2) | 12 (9.3) | 1.00 | 6 (6.7) | 1.00 |
| ≥1/day | 428 (80.8) | 117 (90.7) | **2.62 (1.28–5.36)** | 81 (91.0) | **3.54 (1.39–9.00)** |
| Lifetime exposure to environmental tobacco smoke (smoker-years)‡ | | | | | |
| 0 | 183 (34.1) | | | 21 (23.6) | 1.00 |
| 1–69 | 98 (18.3) | | | 18 (20.2) | 1.55 (0.73–3.29) |
| ≥70 | 94 (17.5) | | | 26 (29.2) | **2.51 (1.24–5.08)** |

The bold values represent *P* values less than 0.05.

*ORs were adjusted for age at interview, place of birth, history of benign lung diseases, and variables included in the table.

†Ever regularly exposed (i.e., at least once a week for at least 6 months) to any of these agents: silica, asbestos, arsenic, nickel, chromium, tars, asphalts, painting, pesticide, diesel exhaust, cooking fume, and welding fume in the workplace.

[‡]The indicated subgroups were categorized by the median of smoker-years in the cases; smoker-years of environmental tobacco smoke exposure was the summation of smoker-years at household and workplace (here, smoker-years at household were the product of the number of smokers smoking inside the house and the years of exposure to such behavior, whereas smoker-years at workplace were the number of coworkers smoking in the presence of the study subjects and the years of exposure to such behavior).

**TABLE 2.**

Distribution of Selected Environmental Risk Factors, the Corresponding Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) Among 213 Never Smoking Lung Cancer Cases and 292 Community Referents in Hong Kong Females

| | Referents | Lung Cancers | | Adenocarcinoma | |
|---|---|---|---|---|---|
| **Risk Factors** | **(n = 292)** | **(n = 213)** | **OR (95% CI)*** | **(n = 144)** | **OR (95% CI)*** |
| Exposure to cooking emissions (dish-years)† | | | | | |
| ≤50 | 125 (42.8) | 66 (31.0) | 1.00 | 44 (30.6) | 1.00 |
| 51–100 | 104 (35.6) | 65 (31.5) | 1.27 (0.77–2.10) | 41 (28.5) | 1.20 (0.67–2.12) |
| 101–150 | 38 (13.0) | 38 (17.8) | **2.70 (1.41–5.17)** | 27 (18.8) | **2.91 (1.43–5.93)** |
| >1 50 | 24 (8.2) | 39 (18.3) | **4.68 (2.29–9.58)** | 28 (19.4) | **4.49 (2.06–9.74)** |
| Intake of meat‡ | | | | | |
| <1 serving/day | 59 (20.2) | 28 (13.1) | 1.00 | 14 (9.7) | 1.00 |
| 1–1.99 servings/day | 138 (47.3) | 124 (58.2) | **2.10 (1.16–3.80)** | 86 (59.7) | **2.51 (1.24–5.11)** |
| ≥2 servings/day | 94 (32.2) | 59 (27.7) | 1.52 (0.80–2.92) | 43 (29.9) | 1.82 (0.85–3.88) |
| Intake of dark green vegetables‡ | | | | | |
| <1 serving/day | 33 (11.3) | 46 (21.6) | **2.02 (1.13–3.61)** | | |
| 1–1.99 servings/day | 64 (21.9) | 59 (27.7) | 1.62 (0.99–2.65) | | |
| >2 servings/day | 195 (66.8) | 105 (49.3) | 1.00 | | |
| Intake of yellow/orange vegetables‡ | | | | | |
| <1 serving/week | 81 (27.7) | 106 (49.8) | **3.49 (2.07–5.90)** | 72 (50.0) | **3.97 (2.26–7.00)** |
| 1–1.99 servings/week | 102 (34.9) | 61 (28.6) | 1.52 (0.89–0.60) | 41 (28.5) | 1.74 (0.95–3.18) |
| ≥2 servings/week | 107 (36.6) | 44 (20.7) | 1.00 | 30 (20.8) | 1.00 |
| Intake of multiple vitamins‡ | | | | | |
| No | 241 (82.5) | 189 (88.7) | **4.30 (1.75–10.55)** | 130 (90.3) | **3.82 (1.44–10.12)** |
| Irregularly | 14 (4.8) | 9 (4.2) | **3.62 (1.00–13.14)** | 6 (4.2) | 3.16 (0.76–13.12) |
| Regularly | 32 (11.0) | 8 (3.8) | 1.00 | 6 (4.2) | 1.00 |
| Occupational history | | | | | |
| Never employed | 37 (12.7) | 41 (19.2) | 1.00 | | |
| Retired | 224 (76.7) | 129 (60.6) | 0.61 (0.35–1.06) | | |
| Currently employed | 31 (10.6) | 43 (20.2) | **2.32 (1.05–5.15)** | | |

The bold values represent *P* values less than 0.05.

* ORs for overall lung cancers were adjusted for age and history of asthma whereas ORs for the adenocarcinoma were adjusted for age in addition to variables included in the table.

† One dish-year was defined as cooking one frying dish (i.e., stir-frying, deep-frying) daily for a year.

‡ One serving = 80 g.

**TABLE 3.**

Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) According to Family Cancer History and Environmental Exposure Index Score Among 132 Never Smoking Lung Cancer Cases and 536 Never Smoking Community Referents in Hong Kong Males

| | | Without Family Cancer History | | With Family Cancer History | |
|---|---|---|---|---|---|
| **Environmental Exposure Index*** | **Synergy Index†** | **No. of Cases/Controls** | **OR (95% CI)‡** | **No. of Cases/Controls** | **OR (95% CI)‡** |
| All lung cancers | | | | | |
| Low | | 20/220 | 1.00 | 10/41 | **2.64 (1.12–6.23)** |
| Intermediate | | 25/126 | **2.37 (1.24–4.52)** | 15/24 | **7.73 (3.34–17.86)** |
| High | | 23/36 | **6.80 (3.31–13.98)** | 13/5 | **30.61 (9.38–99.87)** |
| *p* value (test for trend) | | | <**0.001** | | <**0.001** |
| | **3.98 (1.14–13.92)** | | | | |
| Adenocarcinoma | | | | | |
| Low | | 15/218 | 1.00 | 3/36 | 1.03 (0.27–4.00) |
| Intermediate | | 14/127 | 1.69 (0.77–3.70) | 11/24 | **7.21 (2.83–18.39)** |
| High | | 17/37 | **8.05 (3.53–18.36)** | 7/10 | **13.92 (4.29–45.16)** |
| *p* value (test for trend) | | | <**0.001** | | <**0.001** |
| | 1.83 (0.48–6.88) | | | | |

The bold values represent *P* values less than 0.05.

*Using the tertile score of environmental exposure index as the cutpoint for all never smoking male lung cancer cases (<3.83, 3.83–5.48, and >5.48) and the adenocarcinoma (<4.05, 4.05–5.98, and >5.98), respectively.

†The synergy index for family cancer history and high environmental exposure index (i.e., third tertile or more) only.

‡ORs were adjusted for age, place of birth, and history of benign lung disease

**TABLE 4.**

Odds ratios (ORs) and 95% confidence intervals (95% CIs) according to family cancer history and environmental exposure index score among 213 never smoking lung cancer cases and 292 never smoking community referents in Hong Kong females

| | | Without Family Cancer History | | With Family Cancer History | |
|---|---|---|---|---|---|
| **Environmental Exposure Index*** | **Synergy Index†** | **No. of Cases/Controls** | **OR (95% CI)‡** | **No. of Cases/Controls** | **OR (95% CI) ‡** |
| All lung cancers | | | | | |
| Low | | 35/151 | 1.00‡ | 16/28 | **2.51 (1.22–5.18)** |
| Intermediate | | 34/44 | **3.54 (1.96–6.38)** | 16/10 | **7.12 (2.96–17.15)** |
| High | | 43/21 | **9.59 (5.00–18.40)** | 21/7 | **13.22 (5.15–33.97)** |
| *p* value (test for trend) | | | **<0.001** | | **<0.001** |
| | 1.21 (0.41–3.53) | | | | |
| Adenocarcinoma | | | | | |
| Low | | 22/153 | 1.00‡ | 10/29 | **2.37 (1.01–5.52)** |
| Intermediate | | 24/32 | **5.22 (2.61–10.45)** | 8/7 | **7.58 (2.49–23.08)** |
| High | | 36/31 | **8.28 (4.28–16.01)** | 15/9 | **12.05 (4.68–31.00)** |
| *p* value (test for trend) | | | **<0.001** | | **<0.001** |
| | 1.28 (0.45–3.60) | | | | |

The bold values represent *P* values less than 0.05.

*Using the tertile score of environmental exposure index as the cutpoint for all never smoking female lung cancer cases (<5.79, 5.79–7.51, and >7.51) and the adenocarcinoma (<5.34, 5.34–7.30, and >7.30), respectively.

†The synergy index for family cancer history and high environmental exposure index (i.e., third tertile or more) only.

‡ORs for overall lung cancers were adjusted for age and history of asthma, although ORs for the adenocarcinoma were adjusted for age only.