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

Lap Ah Tse, Ignatius Tak-sun Yu,* Nathaniel Rothman,† Bu-Tian Ji,† Hong Qiu,* Xiao-rong Wang,* Wei Hu,† Joseph Siu-kie Au,‡ and Qing Lan†*

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.

Key Words: Environmental risk factors, Lung neoplasm, Familial susceptibility, Interaction

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*Division of Occupational and Environmental Health, JC School of Public Health and Primary Care, The Chinese University of Hong Kong, HKSAR, China; †Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; and ‡Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, HKSAR, China.

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Address for correspondence: Ignatius Tak-Sun Yu, 4/F School of Public Health, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR, China. E-mail: iyu@cuhk.edu.hk

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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

