Fumes from Meat Cooking and Lung Cancer Risk in Chinese Women[1]

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Abstract

Chinese women are recognized to have a high incidence of lung cancer despite a low smoking prevalence. Several studies have implicated domestic exposure to cooking fumes as a possible risk factor, although the exact carcinogens have yet to be identified. Heterocyclic amines are known carcinogens, which have been identified in cooked meat, and also in fumes generated during frying or grilling of meats. We conducted a case-control study of 303 Chinese women with pathologically confirmed, primary carcinomas of the lung and 765 controls to examine the association between exposure to meat cooking and lung cancer risk. Data on demographic background, smoking status, and domestic cooking exposure, including stir-frying of meat, were obtained by in-person interview while in hospital. The response rates among eligible cases and controls were 95.0 and 96.9%, respectively. The proportion of smokers (current or ex-smokers) among cases and controls was 41.7 and 13.1%, respectively. Adenocarcinomas comprised 31.5% of cancers among smokers and 71.6% among nonsmokers. When cases were compared with controls, the odds ratio (OR) for lung cancer (all subtypes) among ex-smokers was 4.3 [95% confidence interval (CI) 2.7–6.8] and that among current smokers was 5.0 (95% CI, 3.4–7.3). Among smokers, women who reported that they stir-fried daily in the past had a significantly increased risk of lung cancer (adjusted OR, 2.0; 95% CI, 1.0–3.8) and among these women, risk was enhanced for those who stir-fried meat daily (OR, 2.7; 95% CI, 1.3–5.5). Women who stir-fried daily but cooked meat less often than daily did not show an elevated risk (OR, 1.0. 95% CI, 0.5–2.4). Risk was further increased among women stir-frying meat daily who reported that their kitchen was filled with oily fumes during cooking (OR, 3.7; 95% CI, 1.8–7.5). These cooking practices on their own did not increase risk among nonsmokers in our study population. Our results suggest that inhalation of carcinogens, such as heterocyclic amines generated during frying of meat, may increase the risk of lung cancer among smokers. Further studies in different settings are warranted to examine this possibility, which may also help to explain the higher risk observed among women smokers compared with men.

Introduction

Lung cancer is a leading cause of death among women worldwide (1, 2). Although cigarette smoking is well-established as the predominant risk factor for the disease, it is also recognized that, especially among women, other factors play a significant role (3). Among the risk factors that have been identified are passive smoking (4), occupational exposures (5, 6), and previous lung disease (7, 8). The protective effects of fruit and vegetables have also been demonstrated (9, 10).

Heterocyclic amines are a group of compounds formed by pyrolysis of protein-containing foods, through a reaction between creatinine and amino acids and/or sugars (11). The occurrence of this group of compounds in cooked meat products has been well documented (12–15), and they are known to be potent mutagens on the Ames test and carcinogenic in animal studies (16–20). The role of these compounds in human carcinogenesis has yet to be confirmed, but recent epidemiological studies suggest that dietary intake of fried, well-done meat may be related to lung cancer (21) and breast cancer (22). In animal studies, heterocyclic amines have been shown to induce tumors in lung tissue, among other sites (17, 18).

Apart from being present on the meat surface, heterocyclic amines have been identified in smoke condensates from frying of beef, pork, and fish (23–25), and their formation is similarly temperature and time dependent (26). Higher levels are produced during frying and grilling than other cooking methods (11). These observations are consistent with findings that the volatile fraction produced by frying meat contributed a significant proportion of the total mutagenic activity in laboratory systems (23, 27). In addition, some but not all studies of occupational groups report an increased risk of respiratory tract cancers among cooks (5, 28). In contrast to dietary heterocyclic amines, the role of inhaled heterocyclic amines in cancer risk has not been examined.

Gender differences in smoking-related risk of lung cancer are increasingly being recognized. Women smokers appear to have a higher risk of lung cancer than male smokers in some but not all studies (2, 29–31). For example, the risk among smokers was 12.7 (95% CI 11.5–13.9) for females compared with 9.1 (8.3–10.0) for men from population-based data in Missouri (30). These differences persist after adjusting for lifetime dose (32) and years since quitting (29).

Compared with women of other ethnicities, Chinese

Received 4/26/00; revised 8/9/00; accepted 8/21/00.

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[1] This study was funded by Grant NMRC 1996/0155 from the National Medical Research Council. M. C. Y. is supported by the United States National Cancer Institute Grant R35 CA53890.

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women worldwide are known to have a high risk of lung cancer, despite a low smoking prevalence (9, 33–35). Domestic exposures, such as to fumes from cooking oils, have been implicated as a possible risk factor in studies among Chinese women in Asia (36–38), but the exact carcinogens have not been identified. Stir-frying, which involves heating of oil in a wok to high temperatures before ingredients are added, is frequently used in Chinese home cooking and some mutagens identified in heated oils, particularly Chinese rapeseed oil, include formaldehye, acrolein, 1,3-butadiene, and benzene (39, 40).

Lung cancer is the third most common cancer among women in Singapore (41), a small island republic with a population of 3.1 million, of which 78% are ethnic Chinese (42). Although the pattern of disease in this country is rapidly evolving toward that of the West (43), reflecting the changing lifestyle of the population, the smoking prevalence in females is relatively low, ~3% (44). Lung cancer comprises 17.8% of cancers diagnosed annually (41), and the incidence has been fairly stable over the last 25 years (45). It was in this context that we were interested to investigate the risks of lung cancer associated with cooking exposures among women with a hospital-based case-control study over a 30-month period from April 1, 1996 to September 30, 1998.

Materials and Methods

Selection of Cases. Eligible cases were Chinese females with primary carcinoma of the lung diagnosed in one of three major hospitals (Singapore General Hospital, Tan Tock Seng Hospital, and National University Hospital), which together account for 75% of incident lung cancers among Singapore Chinese women.[3] All cases were <90 years of age, mentally alert and coherent, and were interviewed within 3 months of diagnosis of the disease. Pathology slides from all cases with biopsy or operative specimens were retrieved. Each of these was reviewed and subtyped independently by two study pathologists. Where the results differed, the final diagnosis was obtained by consensus on simultaneous examination. The medical records of all cases were reviewed at the end of the study period to exclude any subsequent diagnosis of a remote primary cancer.

During the study period, a total of 418 lung cancer patients were identified in the three hospitals. We excluded 38 cases (9.1%) who were too ill or who otherwise did not satisfy the eligibility criteria, leaving 380 women. Of these, 361 (95.0%) consented to the interview. Forty-four (12.2%) of these patients were diagnosed on clinical or radiological grounds and were excluded from the final analysis. We also excluded 2 (0.6%) patients with carcinoid tumors of the lung and 12 (3.3%) patients where pathological material was not available for review. Thus, in all a total of 303 microscopically confirmed lung cancer cases were included in this analysis. Both cases and controls gave written, informed consent for the interview and the tracing of their medical records.

Selection of Controls. Controls were selected from hospital patients, frequency matched by 10-year age group, the hospital to which they were admitted, and date of admission (within 2 months). For each stratum, two to three controls were recruited per case. Patients who had a history of malignant or chronic respiratory disease were excluded. We also excluded women with long-standing illnesses that would preclude carrying out usual activities, such as severe ischemic heart disease or renal failure.

A total of 789 eligible controls were approached, and of these, 765 (96.9%) consented to be interviewed. Control patients represented a wide range of conditions, of which 32.3% were diseases of the bones, joints, and connective tissue, 20.5% were admissions for acute traumatic injuries, and 12.4% were related to the gastrointestinal tract. An additional 8 and 6% of controls had illnesses of the cardiovascular and neurological systems, respectively.

Study Instrument. All subjects were interviewed in-person using a standardized questionnaire. Over the study period, a total of six research nurses were responsible for data collection, and each interviewed both cases and controls. Training and supervision were carried out by the same investigator throughout. Interviewers were not blinded to case or control status, but possible observer bias was monitored by recording and reviewing at random a sample of interviews conducted by each nurse. None of the interviews were carried out solely with next-of-kin, but where necessary, relatives present with the subject at the time of interview were allowed to give information that was corroborated by the subject.

The study instrument elicited information on demographic variables, occupational history, personal and passive tobacco smoking history, past domestic cooking exposure, dietary intake of fruits and vegetables, family history of cancer, and preexisting lung disease among others. Because the only form of tobacco use reported among the subjects in this study was cigarette smoking, a smoker was defined as someone who had ever smoked at least one cigarette a day (either manufactured, hand-rolled cigarettes, or both) for a year or more. This group includes ex-smokers, defined as smokers who had stopped smoking for 1 year at the time of interview. Passive smoke exposure was defined as a positive answer to the question "Did any of your household members smoke (including spouse, parents, children, or any other relative/friend living with you) in your presence more often than once a week?" Intake of fruit and vegetables was measured as the average number of standardized servings per week, over the last 3 years, of 12 fruit items and 19 vegetables widely available and commonly eaten locally. For cooking exposure, patients were asked about the frequency of using various cooking methods, particularly stir-frying (*e.g.*, "How often did you stir-fry food? How often did you stir-fry meat?") and types of oils (*e.g.*, "How often did you use peanut oil for frying?") as their usual practice 20–30 years before diagnosis. Subjects were also asked "How often did the air in your kitchen become filled with oily 'smoke' during frying?" For each of these cooking exposures, there were six possible responses ranging from "never/less than yearly," "less than monthly," to "daily" and "more than once a day."

Statistical Analysis. ORs[4] and 95% CIs were calculated for risk of lung cancer for smokers and nonsmokers separately. Analysis of the association between cooking exposure and lung cancer risk was carried out using unconditional logistic regression (46) adjusting for age, fruit and vegetable intake (as continuous variables), formal education (dichotomous; none/one year or more), and place of birth (dichotomous; local-born/China-born). Among ever smokers, duration of smoking (in years) and intensity of smoking (number of cigarettes per day in two groups: 1–5 sticks and 6+ sticks) were found on stepwise logistic regression analysis to adequately explain the variation in risk attributable to smoking. These were therefore entered as covariates into the logistic regression model for

[3] Singapore Cancer Registry, unpublished data.

[4] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Sociodemographic characteristics of lung cancer and controls among Singapore Chinese women

	Cases (n = 303)		Controls (n = 764)	
	No.	%[a]	No.	%[a]
Age at interview (yr)				
20–39	9	3.0	24	3.1
40–59	83	27.4	249	32.6
60–79	179	59.1	431	56.4
80–89	32	10.6	60	7.9
Mean (SD)	69.2 (8.9)		65.1 (12.8)	
Dialect group				
Hokkien	118	38.9	324	42.4
Teochew	72	23.8	149	19.5
Cantonese	76	25.1	160	20.9
Other	37	12.2	131	17.2
Education (yr)				
Nil	181	59.7	357	46.7
≤6 years	74	24.4	228	29.8
7 years or more	48	15.8	179	23.4
Dwelling				
1–3-room flat	128	42.2	341	44.6
4-room flat or larger	134	44.2	350	45.8
Private apartment or house	41	13.5	73	9.6
Country of birth				
Singapore	171	56.4	465	60.9
Malaysia	32	10.6	135	17.7
China	94	31.0	149	19.5
Other	6	2.0	15	2.0
Marital status				
Ever married	231	92.7	718	94.0
Never married	22	7.3	46	6.0
Occupational history[b]				
Ever worked outside home	200	66.0	558	73.1
Never worked outside home	103	34.0	205	26.9
Smoking history[b]				
Current smoker	81	26.7	60	7.9
Ex-smoker	46	15.2	40	5.2
Lifetime nonsmoker	176	58.1	663	86.9
Pack-years of smoking (smokers only), median (P25, P75)[c]	47 (36, 56)		36 (18, 51)	
Intake of fruit and vegetable, median (P25, P75)[c] (servings/wk)	21.7 (13.2, 34.4)		28.0 (16.8, 41.2)	

[a] Percentages may not add up to 100 because of rounding.
[b] Data on occupational and smoking history of one subject each are missing.
[c] P25, 25th percentile; P75, 75th percentile.

computation of adjusted OR among smokers. We examined risks associated with higher frequency of stir-frying, stir-frying of meat, having a fume-filled kitchen during cooking, and type of oil used. Reported frequency of cooking-related exposure was grouped as "daily" (including more than once a day) and "less than daily." The types of oil used for frying were grouped into unsaturated (peanut and corn oil) and saturated (palm, blended vegetable which contains mainly palm oil, and lard oil) for the purposes of analysis. Subjects who indicated daily usage of an unsaturated oil and less than daily usage of saturated oils were classified as using "primarily unsaturated oil" and *vice versa*. Where there was no clear distinction in frequency of use, the subject was classified as using "both types equally." The statistical software SAS 6.12 (SAS Institute, Inc., Cary, NC) was used for data analysis. All *P*s quoted are two-sided.

Results

The distribution of demographic factors among cases and controls is given in Table 1. The mean age of diagnosis of lung cancer was 69 years. Despite frequency matching, controls tended to be younger; the ratio of controls to cases was ~2 in the oldest age group and 3 in the 40–59-year age group. Compared with controls, cases were less likely to have received formal education (40% *versus* 53%), be born in Singapore or Malaysia (67% *versus* 79%), and to have ever been used outside the home (66% *versus* 73%). There were altogether 227 smokers (current or ex-smokers), of which 63.9% smoked manufactured cigarettes, 25.6% hand-rolled cigarettes, and 10.6% both types. Cases were markedly more likely to be smokers. As expected, the median weekly number of servings of fruits and vegetables was lower among cases than controls (21.7 and 28.0 standard servings per week, respectively). Among nonsmokers, 391 (47%) reported ever being exposed to passive smoke from household members more often than once a week (data not shown).

The distribution by histological type by smoking status was as follows. Adenocarcinoma was the most frequent histological type in both groups, the number of cases being 40 (31.5%) and 126 (71.6%) among smokers and nonsmokers, respectively. Squamous cell and small cell carcinomas comprised 29.9 and 15.0% of cancers, respectively, among smokers and 10.2 and 1.1% of cancers among nonsmokers. The proportion of large cell undifferentiated carcinomas was similar between the two groups (17.3 and 13.6%, respectively). Eight

Table 2 Risk of lung cancer associated with smoking, by histological type, among Singapore Chinese women

Smoking status[a]	Cases (*n*)/Controls (*n*)	Age-adjusted odds ratio (95% CI)
All confirmed cases		
Lifetime nonsmoker	176/663	1.0
Ex-smoker	46/40	4.3 (2.7–6.8)
Current smoker	81/60	5.0 (3.4–7.3)
Adenocarcinoma		
Lifetime nonsmoker	125/663	1.0
Ex-smoker	15/40	2.0 (1.1–3.8)
Current smoker	25/60	2.2 (1.3–3.7)
Squamous or small cell carcinoma		
Lifetime nonsmoker	20/663	1.0
Ex-smoker	19/40	14.4 (7.0–29.5)
Current smoker	38/60	19.8 (10.8–36.4)

[a] Data on smoking status for one control are missing.

(6.3%) and six (3.4%) cases among smokers and nonsmokers were classified as "carcinoma, type unspecified" after review.

We observed significantly elevated risks of lung cancer among ex- and current smokers compared with lifetime nonsmokers for all histological types combined, after adjustment for age (Table 2). When examined separately by histology, the risk of squamous or small cell carcinoma among current smokers (OR, 19.8; 95% CI, 11.5–38.4) was an order of magnitude higher than for adenocarcinoma (OR, 2.2; CI, 1.3–3.7). Adjusting for passive smoking did not materially affect these risk estimates (OR, 18.8 and 2.1, respectively) and the others given in Table 2.

The effect of cooking exposure on lung cancer risk was strongly related to smoking status, and the analyses in Tables 3 and 4 are presented separately for smokers and nonsmokers. Among the 127 cases and 100 controls who were smokers, 78.7 and 38.0%, respectively, reported cooking by stir-frying daily or more during the period 20–30 years prior to diagnosis. The OR for daily stir-frying was 2.1 (95% CI, 1.1–4.1) after adjustment for potential confounders. Upon closer examination, this excess in risk was confined to those who stir-fry meat on a daily basis (OR, 2.8; 95% CI, 1.4–5.7; Table 3). In contrast, there was no effect of stir-frying among the 827 nonsmokers in our study population (adjusted OR, 1.0; 95% CI, 0.7–1.5); these estimates were not materially affected by further adjustment for passive smoking. The interaction terms between frequency of stir-frying or stir-frying of meat and smoking were all highly significant ($P < 0.01$). Relative to nonsmokers who reported stir-frying meat less than daily, smokers who stir-fried meat less than daily had an adjusted OR of 2.6 (95% CI, 1.7–4.0), whereas smokers who stir-fried meat daily had an OR of 7.7 (95% CI, 4.8–12.5; data not shown).

We further examined the risks associated with stir-frying of meat, again stratified by smoking status (Table 4). Among smokers who stir-fried meat daily, those who reported a smoke-filled kitchen on a daily basis exhibited a higher risk (OR, 3.5; 95% CI, 1.8–6.9) than those with less smoky kitchens (OR, 1.7; 95% CI, 0.7–3.9). No comparable increases in risk were observed among nonsmokers (Table 4).

Table 4 also suggests that among smokers, those using primarily unsaturated oil for frying experienced a higher risk (OR, 4.3) than those using saturated oil or both types equally (combined OR, 2.2). The risk estimates for those using saturated oil (OR, 2.3) or both types equally (OR, 1.6) were similar, and thus they are grouped together in Table 4 for stability. Among nonsmokers, there was no significant association with either cooking oil category.

Discussion

In summary, we report here for the first time an interaction between cigarette smoking and cooking in relation to lung cancer risk among women. Among smokers, stir-frying of meat on a daily basis was associated with an almost 3-fold elevation in lung cancer risk. There was a dose-response relationship between intensity of the exposure to fumes generated from stir-frying of meat and cancer risk. In contrast, exposure to fumes from meat stir-frying was unrelated to lung cancer risk among nonsmokers. These findings suggest that carcinogens in cooking fumes, possibly heterocyclic amines formed during high temperature cooking of meat, may play a role in the development of lung cancer among cigarette smokers.

The major strengths of our investigation are the inclusion of incident cases that were microscopically confirmed and reviewed by two pathologists. The study population was homogeneous in terms of gender and ethnicity. All interviews were conducted in-person, and verification of information on smoking status against the medical records indicated a high degree of reproducibility. The potential weaknesses include the use of hospital controls, who may have been admitted for conditions linked to the exposures under study. Such an association, if positive, would bias the results toward the null, or if negative may artificially inflate a negative association between the exposure of interest and lung cancer. To our knowledge, there is no evidence suggesting a link between cooking and other common medical conditions, but nevertheless, we attempted to address this potential bias by drawing controls from as wide a range of medical conditions as possible and excluded those with preexisting malignancies and chronic lung disease. The potential for interviewer bias exists in all case-control studies. Although the research nurses were not blinded to case or control status, they were not apprised of the hypothesis under study. The consistent differential risks observed between smokers and nonsmokers also argue against interviewer bias; in addition, it is relevant to note that questions on cooking preceded those on smoking during the interview. Recall and reporting bias by subjects is an inherent concern in retrospective studies. Our questionnaire elicited information on cooking practices during the period 20–30 years before cancer diagnosis, a time frame that was felt to be relevant in the etiology of the disease. Nondifferential misclassification, attributable to memory failure, would have tended again to bias results toward the null. A spurious association could have arisen if cases tended to be more likely to recall, or to overreport, their frequency of meat stir-frying in the past. We feel a situation in which only smokers were subject to this bias, and not nonsmokers, is unlikely. The purported link between cooking method and lung cancer is not common knowledge. Furthermore, in introducing the study, the general term "women's health" was used and not "lung cancer."

The magnitude of the risk associated with smoking by histological type is consistent with the range reported by studies among women in various populations worldwide (29–31, 47–49). The proportion of adenocarcinomas among our cases is higher than the 30–40% overall for female lung cancer patients in the West (8, 30, 35, 50), where the proportion of smokers ranges from 30–80% and is consistent with that reported for predominantly nonsmoking female populations as being between 50 and 80% (33, 51).

The most significant finding in this study is the interaction

Table 3 Adjusted ORs and 95% CIs for lung cancer by frequency of stir-frying and smoking status

Exposure group	Current or ex-smokers		Lifetime nonsmokers	
	No. of cases/controls	OR[a] (95% CI)	No. of cases/controls	OR[a] (95% CI)
Stir-frying less frequent than daily	25/37	1.0 (ref)	52/182	1.0 (ref)
Daily stir-frying	97/60	2.0 (1.0–3.8)	122/471	1.0 (0.7–1.5)
Less than daily with meat	21/25	1.0 (0.5–2.4)	41/161	0.9 (0.6–1.5)
Daily with meat[b]	75/34	2.7 (1.3–5.5)	76/301	0.9 (0.6–1.4)

[a] Adjusted for age (years), education (some *versus* no formal education), place of birth (local or China-born), and intake of fruits and vegetables (number of standard servings/week) by logistic regression analysis. For smokers, ORs were additionally adjusted for duration of smoking (in years) and number of cigarettes smoked per day (1–5, 6+/day).
[b] The number of subjects with missing information on meat cooking was 16 (6 cases and 10 controls).

Table 4 Adjusted ORs and 95% CIs for lung cancer by intensity of exposure to kitchen fumes from frying meat and type of oil used, by smoking status

Exposure group	Current or ex-smokers		Lifetime nonsmokers	
	No. of cases/controls	OR[a] (95% CI)	No. of cases/controls	OR[a] (95% CI)
Stir-frying meat less frequent than daily	46/63	1.0 (ref)	93/338	1.0 (ref)
Daily stir-frying of meat[b]	75/34	2.7 (1.5–4.8)	76/301	1.0 (0.7–1.4)
Less than daily fume-filled kitchen	23/15	1.7 (0.7–3.9)	34/129	1.1 (0.7–1.7)
Daily fume-filled kitchen	52/18	3.7 (1.8–7.5)	42/171	1.0 (0.6–1.4)
Primarily unsaturated oil	21/6	4.6 (1.6–13.0)	23/73	1.4 (0.8–2.4)
Primarily saturated oil/both types equally	54/28	2.2 (1.2–4.2)	53/228	0.9 (0.6–1.3)

[a] Adjusted for age (years), education (some *versus* no formal education), place of birth (local or China-born), and intake of fruits and vegetables (number of standard servings/week) by logistic regression analysis. For smokers, ORs were additionally adjusted for duration of smoking (in years) and number of cigarettes smoked/day (1–5, 6+/day).
[b] The number of subjects with missing information on kitchen fumes was two (one case and one control).

between cigarette smoking and cooking practices, specifically stir-frying of meat. Another model in which the effect of one carcinogen is observed primarily in the presence of another potent carcinogen is that of aflatoxin exposure, which interacts with hepatitis B virus carrier status in its effect on liver cancer risk (52). The presence of cocarcinogens in cooking fumes is another possible mechanism for the interaction with smoking observed in this study. The possibility that our findings reflect a relationship between meat intake, and hence meat cooking, and smoking should also be considered. There is some evidence from the literature that smokers consume meat more frequently (53, 54), and consumption increases with number of cigarettes smoked (53). In the present study, duration and intensity of smoking were both controlled for in the multivariate model, but the presence of residual confounding by smoking cannot be totally discounted.

In the light of increasing evidence as to the carcinogenicity of heterocyclic aromatic amines, the possibility that the presence of these compounds in cooking fumes increases the risk of lung cancer deserves consideration. We demonstrate specifically that stir-frying of meat enhances risk. It is known that heterocyclic amines are present on pan residues and on the charred surface of broiled or fried meat (12). Rappaport *et al.* (27) reported that heating of ground beef to high temperatures resulted in the volatilization of a significant proportion of the basic mutagens formed. Analyses of airborne particulates from domestic environments for mutagenicity levels reported high values for fumes generated during cooking of meat (55). Other studies, which analyzed the cooking aerosols from fried beef patties (23) and Chinese stir-fried fish (25), identified these volatile compounds as heterocyclic amines and showed that the mutagenic activity increased with temperature (26). Our findings suggest that frequent exposure to heterocyclic amines through cooking of meat may pose an additional hazard to health among women who smoke.

If true, the interaction between cooking and smoking lends itself to another interesting hypothesis. As mentioned previously, women smokers exhibit a higher risk of lung cancer than men smokers, after adjusting for dose. Ryberg *et al.* (56) showed that, among smokers after adjusting for smoking dose, the levels of aromatic DNA adducts in female lung cancer patients was higher than in males. It is possible, and not inconceivable, that exposure to carcinogens in cooking fumes accounts in part for the difference in risks between women smokers, who are more likely to cook, and men, who generally do not cook. The effect of other cooking methods, such as those commonly used in the West, deserves further investigation.

Among subjects who stir-fried meat daily, we also found a higher risk among women who more frequently used unsaturated oil for cooking. Although the numbers supporting this observation are small, we note that this is consistent with previous reports of a higher mutagenicity observed with heated polyunsaturated oils, especially with linolenic acid, relative to saturated oils (39, 57, 58). At high temperatures in the presence of oxygen, fatty acids undergo peroxidation, during which free radicals are produced; the rate of their formation is dependent, among other things, on the initial degree of unsaturation of the fat (59). Thus far, there is no consistent evidence of any effect of degree of unsaturation of cooking oil on heterocyclic amine formation in particular (60, 61), and further research, including experimental approaches, may be helpful in this regard.

In contrast to the strong positive associations in smokers, we did not find any association between frequency of cooking and lung cancer risk among nonsmokers. This is in contrast to a recent study in Taiwan among nonsmoking women (38), in which the OR for women cooking three meals/day (*versus* 1 meal) was 3.4 (95% CI, 1.6–7.0). In Shanghai, Gao *et al.* (36) reported a relative risk of 2.6 with stir-frying of 30 or more dishes a week among smokers and nonsmokers combined. We note that there are some differences between cooking practices in Singapore and those in China; for example, Chinese rapeseed oil, which has been implicated in a few studies (36, 39), is not available here. In addition, the method of rapid stir-frying over very high temperatures ("bao"), which in the case of meat would generate greater amounts of heterocyclic amines, is likely to be less often practiced here. The Singapore Chinese population, however, offers some advantages in terms of heterogeneity of exposure, which may not have been present in more traditional Chinese societies, where >95% of women cooked daily or more (38) or used the same cooking oil (36, 62). Our observed lack of association with daily meat frying among nonsmokers should not be viewed as suggesting that such exposure has no effect on lung cancer risk in this subgroup of individuals. Even a moderate interaction effect (such as an interaction relative risk of 2) implies that the relative risk associated with meat frying would be around 1.3–1.4 in nonsmokers. The statistical power of this study to detect a relative risk of this magnitude is only 33% given a two-sided significance level of 5%. The current study was also not designed to examine the effect of other sources of heterocyclic amines, chiefly dietary (63), on lung cancer risk.

In conclusion, among Chinese women, we found evidence that exposure to heterocyclic amines in fumes emitted during meat cooking may increase the risk of lung cancer among smokers. Although this is intriguing and deserves further study because of its potential public health implications, we also recognize that because meat cooking and eating are closely related to smoking, traditional epidemiological methods would find it difficult to separate their effects. Further studies, particularly those that incorporate molecular markers relevant to metabolic pathways or genetic changes specific to heterocyclic amines, are needed to confirm or refute these findings.

Acknowledgments

We are grateful to the Medical Boards of the National University Hospital, Singapore General Hospital, and Tan Tock Seng Hospital; to the doctors and nurses who facilitated the inclusion of their patients; and to the women who participated for their contribution to this study. Thanks are also due to Dr. Chia Kee Seng for helpful advice on the manuscript. We thank Treena Tan, Esther Lim, Shirley Tan, Ang Jen Li, Josephine Chin, and Esther Quek for help in the data collection and Alice Chew and Angela Chan for clerical assistance.

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