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Dietary Heterocyclic Amines and the Risk of Lung Cancer among Missouri Women

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ABSTRACT

Heterocyclic amines (HCAs) such as 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx,), and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) are found in meats cooked at high temperatures. In rodents, MeIQx induces lung tumors. The purpose of this study was to investigate lung cancer risk posed by different HCAs in the diet. A population-based case-control study of 593 cases and 623 frequency-matched controls including both nonsmoking and smoking women was conducted in Missouri. An administered food frequency questionnaire with detailed questions on meat consumption, degrees of internal doneness, surface browning/charring, and cooking technique was linked to a database that provided exposure estimates of three HCAs. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. When comparing the 90th and 10th percentiles, significant excess risks were observed for MeIQx (OR, 1.5; CI, 1.1–2.0), but not for DiMeIQx (OR, 1.2; CI, 0.9–1.6) or PhIP (OR, 0.9; CI, 0.8–1.1). MeIQx consumption was associated with increased risk of lung cancer for nonsmokers (OR, 3.6; CI, 1.3–10.3) and light/moderate smokers (OR, 2.1; CI, 1.3–3.3), but not for heavy smokers (OR, 1.0; CI, 0.7–1.5). There was elevated risk with MeIQx intake for subjects with squamous cell carcinomas (OR, 1.9; CI, 1.2–3.1) and "other histological cell types" (OR, 1.6; CI, 1.1–2.5), but not for subjects with small cell carcinomas and adenocarcinomas. Neither DiMeIQx nor PhIP showed an association with smoking categories or lung cancer histology. In conclusion, MeIQx may be associated with lung cancer risk, but DiMeIQx and PhIP are probably not associated with lung cancer risk.

INTRODUCTION

We previously found an association between meat cooking techniques and the risk of lung cancer (1), but it is not clear what chemical compounds are responsible for this association. Meats cooked at high temperatures form various pyrolysis products, with the amount formed depending on the methods used. A family of compounds known as HCAs[2] is produced when meats are cooked at high temperatures, particularly by pan-frying and grilling (2–4). HCAs are formed when creatine and amino acids in meat juices are pyrolyzed and are highly mutagenic in Ames *Salmonella* tests. In rodents, one of these compounds, MeIQx, produces tumors in the lung when fed to rodents at high levels (5, 6). However, the carcinogenic potential of HCAs in humans has not yet been established.

We investigated the role of three HCAs in the etiology of lung cancer. We estimated daily ingestion of three HCA compounds, DiMeIQx, MeIQx, and PhIP, among Missouri women participating in a population-based case-control study of lung cancer. Exposure levels were estimated using a newly created HCA database (2–4) in combination with a FFQ. We also investigated the effect of HCAs by smoking category and histological cell type of lung cancer.

PATIENTS AND METHODS

Study Subjects. The methods used in this population-based case-control study are described in detail elsewhere (1, 7). Among the 742 eligible cases, 13 subjects refused participation, 13 physicians refused participation of their patients, and 19 cases died with no suitable proxy respondent. Of these 697 cases, 32 cases less than 65 years of age were not eligible because they did not have a driver's license, which was an eligibility requirement for controls less than 65 years of age. Of the remaining 665 cases, 610 agreed to an in-person dietary interview, and 593 [84% of the 710 eligible cases (742 minus the 32 without driver's licenses)] had complete and plausible dietary interviews.

Controls between ages 30 and 64 years were randomly selected from driver's license files identified through the Missouri Driver's License Registry. Controls between the ages of 65–84 years were randomly selected from lists provided by the Health Care Finance Administration. A two-stage randomized recruitment was used to avoid the expected imbalance in smoking among cases as compared with controls (8, 9). From the 3386 controls who were found to be eligible, 730 subjects were selected, 700 completed an interview, and 628 (86% of the 730 eligible controls) provided information on diet, meat cooking practices, and relevant potential confounders. Five control subjects were excluded due to implausible dietary information or missing dietary information, resulting in 623 controls (85% of 730 eligible controls).

FFQ, Cooking Methods, and HCA Database. We used a modified version of the 100-item Health Habits and History Questionnaire to obtain information on usual diet (frequency of consumption and portion size) approximately 2–3 years before diagnosis (1, 7). The first of two sections obtained information on consumption frequency and portion size for 22 meat and fish items and other foods including fruits, vegetables, cereals, and grains. The second portion of the questionnaire focused on methods of cooking (*i.e.*, pan-fried, oven-broiled, grilled/barbecued, microwaved, or other) and doneness levels (rare, medium-rare, medium-well, well-done, and very well-done).

We have developed a HCA database (2–4, 10) for three HCA compounds: (*a*) MeIQx; (*b*) DiMeIQx; and (*c*) PhIP. Using the responses from the FFQ, we estimated gram consumption of the meat groups using frequency and portion size by cooking technique and doneness level. HCA consumption was then derived by multiplying grams of the meat type (doneness level and cooking method) by the HCA concentration measured in that meat. The HCA concentration was summed across all meat items in the diet to estimate total intake for individual study subjects. For subjects with missing data on cooking practices of an individual meat item, the doneness level was imputed using the median value among controls, whereas the cooking method was imputed using the most common choice among controls. No imputations were made for 86% of the subjects, 11% had one imputation, 2% had two imputations, and less than 1% had more than two imputations.

The tumor slides were examined simultaneously using multiheaded microscopes by three pathologists who were blinded regarding the referring pathologists' diagnoses. Consensus diagnoses were obtained for surgical specimens with the criteria outlined in the WHO classification scheme (11). When only cytological material was available, a consensus was obtained with cytological criteria (12).

Analyses. ORs were computed separately for dietary DiMeIQx, MeIQx, and PhIP using both categorical and continuous data. For the latter, the ORs were calculated using the fitted logistic regression (13) taking the ratio of the

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[2] The abbreviations used are: HCA, heterocyclic amine; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; FFQ, food frequency questionnaire; OR, odds ratio; CI, confidence interval.

estimated odds at two different consumption levels, the medians of the fifth and first quintiles (*i.e.*, the 90th and 10th percentiles) based on the controls. We checked for nonlinearity by adding a quadratic term to the continuous model. In no case was the quadratic term statistically significant; thus, it was left out of the final logistic regression model. This does not necessarily mean that the true relation is linear, but any existing nonlinearity is not strong enough to be determined with the current sample size. The 95% CIs are given for the ORs. To test for trend, we determined whether the fitted logistic regression parameter was significantly different from 0. The trend is significant at the 0.05 level, if the 95% CI did not contain 1. The magnitude of the ORs based on quintiles or percentiles cannot be directly compared to one another because the levels of ingestion in the upper and lower quintiles are different for various subsets of HCAs (1). Therefore, we present a second set of ORs reflecting the relative risk associated with an increased consumption of 10 ng HCA/day.

These models included age, pack-years of smoking, smoking status (never/ever/current), years-quit-smoking, BMI, calories, fat, fruit/fruit juices, and vegetables using continuous variables and education using a categorical variable (<12 years, 12 years, and >12 years). In addition to these variables, subsequent analysis for lung cancer risk was further controlled for the effect of cooking practice and doneness level. This analysis was performed to assess whether the excess risk associated with a specific HCA could be explained by meat cooking method and doneness level. We also examined the role of HCAs on the risk stratified by smoking status and for specific histological types (squamous cell carcinomas, small cell carcinomas, adenocarcinomas, and others types) of lung cancer.

RESULTS

The potential risk factor characteristics of case and control subjects were outlined in Sinha *et al.* (1). Briefly, the mean age of both cases and controls was 66 years. The controls had a higher level of education and greater BMI, smoked less, and consumed slightly fewer calories and fat but more fruits and vegetables. Compared with cases, control subjects had a lower dietary intake of DiMeIQx and MeIQx, but a higher dietary intake of PhIP (Table 1). Considerable variability in dietary HCA concentrations was observed for all compounds, as seen in the HCA concentrations at the 10th *versus* 90th percentile.

In Table 2, age-adjusted ORs, multivariate-adjusted ORs, and multivariate analysis accounting for all three HCAs simultaneously are shown both for 10 ng/day increments of HCAs in the diet and for comparisons of lung cancer risk at the 90th and 10th percentiles of HCA intake. After multivariate adjustments were made for the ORs comparing the 90th and 10th percentiles of ingested HCAs, risk was significantly elevated for MeIQx (OR, 1.5; CI, 1.1–2.0), but not for DiMeIQx (OR, 1.2; CI, 0.9–1.6) or PhIP (OR, 0.9; CI, 0.8–1.0). Across quintiles of MeIQx consumption, the ORs were 0.9 (CI, 0.6–1.3), 1.1 (CI, 0.7–1.7), 1.2 (CI, 0.8–1.8), and 1.4 (CI, 0.9–2.1) for the second, third, fourth, and fifth quintiles, respectively. The test for trend was $P = 0.006$ (Table 2).

For every 10 ng/day increment of MeIQx, there was a 4% excess in lung cancer risk (Table 2). A 23% excess risk was associated with a 50 ng/day increase in MeIQx. A 50% excess lung cancer risk was observed for a 100 ng/day increase in MeIQx. Moreover, the OR for MeIQx remained elevated when further adjusted with DiMeIQx and PhIP. Neither dietary DiMeIQx nor PhIP was associated with significant excess lung cancer risk in the adjusted models.

Table 1 *HAC intake among lung cancer cases and controls*

	Cases (n = 593)	Controls (n = 623)
HAC intake (ng/day)	Mean (10th, 50th, 90th percentiles)	Mean (10th, 50th, 90th percentiles)
DiMeIQx	4.1 (0.3, 2.8, 10.0)	3.5 (0.2, 2.4, 8.0)
MeIQx	64.0 (11.2, 48.1, 134.0)	52.1 (7.9, 39.3, 111.1)
PhIP	137.5 (9.2, 73.7, 311.1)	158.3 (8.3, 70.1, 317.7)

Table 2 *The risk associated with HCA consumption and lung cancer*

HCAs	OR (95% CIs; 10 ng per increment difference)[a,d]	OR (CIs) 10th *vs.* 90th percentiles (HCA consumption among controls)[a,d]	*P*
Age-adjusted models			
DiMeIQx	1.52 (1.13–2.03)	1.4 (1.1–1.7)	0.005
MeIQx	1.05 (1.02–1.07)	1.6 (1.3–2.1)	0.0001
PhIP	1.00 (0.99–1.00)	0.9 (0.8–1.0)	0.21
Multivariate models[b]			
DiMeIQx	1.27 (0.90–1.80)	1.2 (0.9–1.6)	0.17
MeIQx	1.04 (1.01–1.07)	1.5 (1.1–2.0)	0.006
PhIP	1.00 (0.99–1.00)	0.9 (0.8–1.1)	0.45
Adjusted for the other HCAs[c]			
DiMeIQx	0.85 (0.51–1.41)	0.9 (0.6–1.3)	0.53
MeIQx	1.06 (1.01–1.10)	1.8 (1.2–2.7)	0.009
PhIP	1.00 (0.99–1.00)	0.9 (0.7–1.1)	0.20

[a] The relative risk estimate is presented to one significant figure for both 10th *versus* 90th percentiles (one decimal place) and for the relative risk/10 g (two decimal places).
[b] The multivariate models included age, pack-years of smoking, BMI, calories, fat, fruit/fruit juices, and vegetables using continuous variables and education using a categorical variable (<12 years, 12 years, and >12 years).
[c] In addition to the multivariate adjustment variables, these analyses controlled for the other HCAs.
[d] A total of 593 cases and 623 controls.

We examined the association of lung cancer risk with MeIQx ingestion, controlling for the effects of the baseline covariates as well as meat groups (*i.e.*, total meats, red meat, red meat doneness, fried and nonfried red meat, grilled meat, and smoked meat) to investigate whether MeIQx is associated with lung cancer above and beyond what can be explained by the different meat variables. Comparing the 90th to 10th percentile of MeIQx ingestion, statistically significant elevations in risk continue to be observed when controlling for total meat (OR, 1.4; CI, 1.0–1.9; $P = 0.03$), red meat (OR, 1.4; CI, 1.0–1.9; $P = 0.05$), barbecued red meat (OR, 1.5; CI, 1.1–2.0; $P = 0.007$), and smoked meat (OR, 1.5; 1.1–2.0; $P = 0.009$). The association of lung cancer and MeIQx was still elevated but was not statistically significant when controlled for intake of well-done red meat (OR, 1.3; CI, 0.9–1.9; $P = 0.13$) or fried red meat (OR, 1.3; CI, 0.9–1.8; $P = 0.19$). In contrast, the risk associated with well-done meat and fried meat disappeared when adjusted for MeIQx but not when adjusted for DiMeIQx and PhIP.

The correlation of cigarette smoking and MeIQx and PhIP intake were very small. The nonparametric Spearman correlation coefficients are 0.10 for packyears and MeIQx; 0.02 for packyears and the PhIP; −0.13 for years-quit-smoking and MeIQx; and 0.01 for years-quit-smoking and PhIP. Furthermore, there was no association of cigarette smoking and various meat cooking techniques (7).

When stratifying the subjects based on pack-years of smoking (0, 0.1–39.9, or 40+ pack-years), higher MeIQx consumption was associated with increased risk of lung cancer for nonsmokers (OR, 3.6; CI, 1.3–10.3; $P = 0.015$) and light/moderate smokers (OR, 2.1; CI, 1.3–3.3; $P = 0.003$), but not for heavy smokers [OR, 1.0; CI, 0.7–1.5; $P = 0.97$ (Table 3)]. Looking at the interaction, the difference in MeIQx ORs for the different strata was statistically significant for the nonsmokers *versus* heavy smokers ($P = 0.04$), but not for the light smokers *versus* the heavy smokers ($P = 0.09$).

We investigated the effect of the three HCAs on the risk of specific histological types of lung cancer (Table 2). There was elevated risk with MeIQx intake in subjects with squamous cell carcinomas (OR, 1.9; CI, 1.2–3.1) and "other" histological cell type (OR, 1.6; CI, 1.1–2.5). There was no statistically significant risk associated with small cell carcinomas and adenocarcinomas. Neither DiMeIQx nor PhIP showed associations with any histological type of lung cancer.

Table 3 *Effect of MeIQx on the risk of lung cancer stratified by pack-years of smoking and by specific histological types*[a]

Stratified analyses	No. of cases	No. of controls	OR (CIs) 10^{th} *vs.* 90^{th} percentiles (HCA consumption among controls)	*P*
All controls and all lung cancers	593	623	1.5 (1.1–2.0)	0.006
Subjects stratified by pack-years				
Nonsmokers	47	83	3.6 (1.3–10.3)	0.015
Light/moderate smokers (<40 pack-years)	203	340	2.1 (1.3–3.3)	0.003
Heavy smokers (≥40 pack-years)	343	200	1.0 (0.7–1.5)	0.97
Cancer stratified by cell type				
Squamous cell carcinoma	116	623	1.9 (1.2–3.1)	0.008
Small cell carcinoma	136	623	1.3 (0.8–2.2)	0.30
Adenocarcinoma	190	623	1.1 (0.7–1.7)	0.66
Other	151	623	1.6 (1.1–2.5)	0.03

[a] The multivariate models included age, pack-years of smoking, BMI, calories, fat, fruit/fruit juices, and vegetables using continuous variables and education using a categorical variable (<12 years, 12 years, and >12 years).

DISCUSSION

MeIQx intake was associated with increased risk of lung cancer, but high intakes of DiMeIQx and PhIP were not associated with increased risk of lung cancer. The increase in risk of lung cancer with MeIQx intake appeared to be mainly associated with nonsmokers and light/moderate smokers as well as with squamous cell carcinomas and "other" histological cell types.

In an earlier analysis of dietary data from this study (1), consumption of well-done red meat and consumption of fried red meat were observed to be risk factors for lung cancer. In the analysis presented here, we investigated whether specific HCAs found in well-done red meats could explain this association. Our data support the hypothesis that MeIQx, but not DiMeIQx or PhIP, may be part of the reason for the elevated risk of lung cancer observed from meat consumption. There is also evidence from animal carcinogenesis studies (5, 6) that MeIQx may be a lung carcinogen.

The correlation between HCA intake and the amount of meat consumed makes it difficult to separate an effect due to a specific HCA *versus* that of meat or meat cooking practices in general without a very large sample size. However, they do not measure the same thing. For example, well-done pan-fried steak contains 4.1 ng of MeIQx per gram, whereas well-done oven-broiled hamburger patty does not contain any measurable amount of MeIQx. When we controlled for various correlates, such as total meat, red meat, barbecued meat, or smoked meats, the statistically significant lung cancer risk associated with MeIQx remained. The MeIQx effect was still present but was no longer statistically significantly associated with lung cancer risk when the model included well-done red meat or fried red meat. The opposite was also true; the previously significant effects of well-done and fried red meat were no longer significant after adjusting for MeIQx.

It is interesting that we observe increased risk due to MeIQx intake only in nonsmokers and light/moderate smokers and not in heavy smokers. Cigarette smoking is a major risk factor for lung cancer that it is likely to overwhelm the risk associated with MeIQx.

This is the first effort to assess the role that specific HCAs play in the etiology of human lung cancer. However, the limitations of our study should be recognized. Because the current HCA database is limited to a fraction of the compounds associated with high-temperature cooking of meats, the excess risk observed here may be explained by an unidentified meat pyrolysis byproduct that is strongly associated with MeIQx. We also recognize that the evidence from the literature for the relationship between meat consumption and lung cancer is equivocal. Both cohort and case-control studies have examined the role of meat intake in lung cancer (1, 14–25). A few studies have examined the relationship between meat cooking methods and the risk of lung cancer (26, 27). In a Swedish study (26), lung cancer risk was not associated with consumption of meat or fish cooked and preserved by various methods. In contrast, a study from Uruguay (27) found results compatible with ours, showing an increase in lung cancer risk with higher consumption of fried meat.

The biological relevance of our observation that MeIQx is associated with a significant excess risk of squamous cell carcinoma and "other" cell types but not of small cell or adenocarcinoma is unclear because the link between exposure and histological type of lung cancer remains uncertain. Some studies have observed an increase in risk of squamous cancer with red meat, fried meat, and smoked meat and poultry consumption (22, 27). Evidence suggests for other exposures, such as smoking, there is a stronger risk factor for squamous and small cell carcinomas (28) and a weaker risk factor for adenocarcinomas, whereas adenocarcinoma of the lung has been associated with asbestos and pesticide exposure (15, 29).

In conclusion, even after adjusting for smoking, we found evidence of increased lung cancer risk among the high consumers of MeIQx, but not among consumers of DiMeIQx and PhIP. The increased risk of lung cancer with MeIQx consumption may be associated with smoking status and certain histological types of lung cancer. However, these preliminary findings need to be replicated.

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