Short Communication

Dietary Intake of Heterocyclic Amines, Meat-derived Mutagenic Activity, and Risk of Colorectal Adenomas[1]

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Abstract

Meats cooked well-done by high temperature techniques produce mutagenic compounds such as heterocyclic amines (HCAs), but the amounts of these compounds vary by cooking techniques, temperature, time, and type of meat. We investigated the role of HCAs in the etiology of colorectal adenomas and the extent to which they may explain the previously observed risk for red meat and meat-cooking methods. In a case-control study of colorectal adenomas, cases ($n = 146$) were diagnosed with colorectal adenomas at sigmoidoscopy or colonoscopy, and controls ($n = 228$) were found not to have colorectal adenomas at sigmoidoscopy. Using a meat-derived HCA and mutagen database and responses from a meat-cooking questionnaire module, we estimated intake of 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and mutagenic activity. We calculated odds ratios and 95% confidence intervals using logistic regression adjusting for several established risk factors for colorectal adenomas or cancer. The odds ratios (95% confidence interval; P for trend test) fifth *versus* first quintiles are: 2.2 (1.2–4.1; $P = 0.02$) for DiMeIQx; 2.1 (1.0–4.3; $P = 0.002$) for MeIQx; 2.5(1.1–5.5; $P = 0.02$) for PhIP; and 3.1 (1.4–6.8; $P = 0.001$) for mutagenic activity. When the three HCAs were adjusted for the other two, only the trend for MeIQx ($P = 0.04$) remained statistically significant. When we tried to disentangle the relative contribution of the three HCAs from the meat variables, we found that MeIQx remained significantly associated with risk even when adjusted for red meat but not *vice versa*. When MeIQx and well-done meat were analyzed in the same model, the risks were attenuated for both. Mutagenic activity from meat remained significantly associated with increased risk even when adjusted for intake of red meat or well-done red meat, whereas the red meat and well-done red meat associations were no longer significant when adjusted for total mutagenic activity. In conclusion, we found an elevated risk of colorectal adenomas associated with high intake of certain HCAs. Further, mutagenic activity from cooked meat consumption, a measure that integrates all of the classes of mutagens, was strongly associated with risk and explained the excess risk with intake of well-done red meat.

Introduction

Epidemiological studies of colorectal adenomas and cancer (1–9) have described increased risk associated with consumption of red meat, cooking techniques used in preparing meat, such as doneness level, surface browning, frying, and intake of gravy. Yet it is unclear what aspect of meat is responsible for this association.

A group of compounds known as HCAs[3] have been proposed as carcinogens. HCAs are formed in meats cooked at high temperature (10–12) and are potent mutagens and animal carcinogens (13–16); however, the carcinogenic potential in humans has not been established (1). Most human studies have used surrogates of HCAs, such as cooking techniques and doneness, rather than estimated values of the actual compounds of interest. HCA intake was estimated in a Swedish population-based case-control study of cancers of the colon, rectum, bladder, and kidney, but no association was observed with HCAs within the usual dietary range in this population (8). However, there was evidence that HCAs may be carcinogenic at the extreme high end of intake because all of the subjects at this level were cases (8).

To assess the risk of meat-cooking mutagens in the etiology of colorectal adenomas, we developed a meat-cooking module and HCA and mutagenic activity database (17–21). We reported previously (22) that subjects were at a higher risk of colorectal adenomas if they consumed well-done red meat as compared with rare and medium-cooked meats. In this study, we evaluate the association between dietary intake of HCAs and mutagenic activity and risk of colorectal adenomas and explore to what extent these may explain our previously reported findings linking red meat and meat-cooking methods to this tumor.

Materials and Methods

This clinic-based case-control study of colorectal adenomas has been described previously (22). In brief, this study was carried out at the National Naval Medical Center in Bethesda, Maryland.

[3] 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; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline; MeIQ, 2-amino-3,4-dimethylimidazo-[4,5-f]quinoline; OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

Table 1   Intake of heterocyclic amines and mutagenic activity from meat in case and control subjects

Intake of HCAs and mutagenic activity	HCAs (ng/day) and mutagenic activity (revertant colonies/day) for cases ($n = 146$)[a]	HCAs (ng/day) and mutagenic activity (revertant colonies/day) for controls ($n = 228$)[a]
DiMeIQx	2.2 (0, 1.1, 5.4)	1.5 (0, 0.7, 4.5)
MeIQx	32.7 (2.9, 21.7, 93.5)	19.6 (1.6, 12.3, 49.3)
PhIP	109.7 (0.6, 69.6, 249.8)	78.2 (0, 38.2, 218.5)
Mutagenicactivity	4,843 (454, 3,666, 10,507)	3,228 (153, 1,842, 8,536)

[a] Mean (10th, 50th, 90th percentiles).

Cases were diagnosed with colorectal adenomas at sigmoidoscopy or colonoscopy, and controls were individuals found not to have colorectal adenomas at sigmoidoscopy. The participation rates were 84% for the cases and 74% for the controls. Of the 244 cases, 93 were excluded from the current report because of a history of previous adenomas. Two cases and three controls were excluded because of implausible dietary information, leaving 146 cases and 228 controls.

HCA content (IQ, MeIQ, MeIQx, DiMeIQx, and PhIP) were determined in meat samples cooked by various methods to different degrees of doneness by the method of Gross and Gruter (23) using solid-phase extraction/high-performance liquid chromatography method. The mutagenic activity of the sample extracts were measured using the standard plate incorporation assay with *Salmonella typhimurium* strain TA98 with 2 mg of aroclor-induced rat liver S9 protein/plate for metabolic activation and tested in doses of 5, 10, 25, 50, and 100 μl. A positive control, 2-aminoanthracene, gave 800–1200 revertants/μg. DMSO was included in the negative controls (spontaneous revertant counts) and gave TA98 values of 30–45 revertant colonies/plate (20, 24).

The subjects completed a standard self-administered food frequency questionnaire (without the meat-cooking module) and an interviewer-administered meat-cooking module. For meats prepared with variable cooking techniques, we obtained information on the typical level of doneness and cooking method detailed in Sinha *et al.* (22). We estimated intake of HCA and mutagenic activity using responses from the FFQ and the database that we developed for the HCA compounds and mutagenic activity in meat. First, by using frequency and portion size, we estimated gram consumption of each meat item (steak, hamburger patty, pork chops, bacon, etc.) by cooking technique and doneness level (verbal response and by photographs). Then, we derived intake of total HCA and mutagenic activity by multiplying grams of meat by concentration measured for each cooking technique/doneness level contribution for that meat type (17–21). We also derived HCA values from red meat only, because PhIP content of grilled chicken can be variable (unpublished observation) and can add to misclassification for this HCA.

ORs and 95% CIs were computed using unconditional logistic regression (25). The strength of association was determined for each HCA and mutagenic activity individually and then further adjusted for the other HCAs. Trend tests were calculated using intake variables as continuous data. All of the ORs were adjusted for age, gender, total caloric intake, fiber intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of NSAIDs. In addition to these adjustment factors, each HCA was controlled for the others and for different types of meat groups.

Results

The mean 10th, 50th, and 90th percentile intakes of DiMeIQx, MeIQx, PhIP, and mutagenic activity are presented in Table 1.
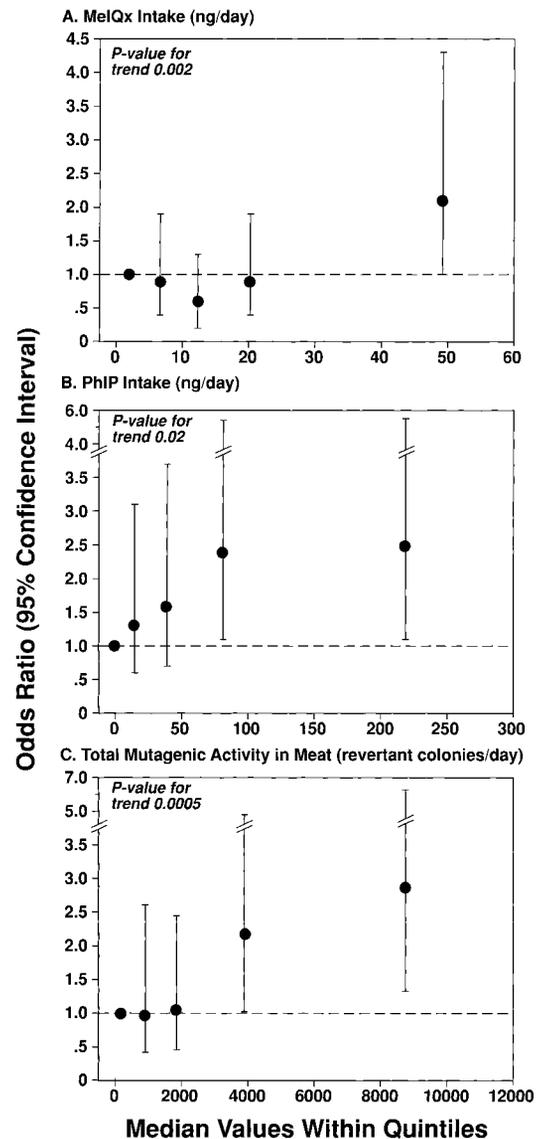

Fig. 1. Colorectal adenoma risk, MeIQx, PhIP, and dietary intake of total mutagenic activity from meat. HCA data categorized into quintiles, according to the HCA intake distribution in the control population. The ranges for each quintile (first, second, third, fourth, and fifth) were: 0–4.59, 4.60–9.43, 9.50–15.57, 16.60–26.63, and 27.00–179.65 ng/day for MeIQx; 0–0.94, 1.00–24.89, 25.00–62.82, 63.00–139.24, and 140.24–728.50 ng/day for PhIP; and 0–470, 471–1,300, 1,310–2,590, 2,591–5,600, and 5,661–22,500 revertant colonies/day for mutagenic activity. ORs and 95% CIs were computed using unconditional logistic regression. All of the ORs were adjusted for age, gender, total caloric intake, fiber intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of NSAIDs. *P* for trend is for continuous variable.

Table 2 ORs and 95% CIs for total mutagenic activity from meat, red meat, doneness of red meat, and HCAs in relation to risk of colorectal adenomas

Total mutagenic activity, meat, and HCAs	OR[a] (95% CI)	P	OR[a] (95% CI) models include both meat or HCA and total mutagenic activity	P
Total mutagenic activity (/1000 revertants colonies)	1.11 (1.04–1.17)	0.0005		
Meat type				
(Total mutagenic activity)			1.10 (1.04–1.17)	0.001
Red meat (/10 gm of meat)	1.09 (1.02–1.18)	0.02	1.06 (0.98–1.15)	0.12
Red meat doneness[b]				
(Total mutagenic activity)			1.08 (1.01–1.16)	0.02
Well/very well done (/10 gm of meat)	1.29 (1.08–1.54)	0.005	1.10 (0.98–1.37)	0.35
HCAs				
(Total mutagenic activity)			1.08 (0.99–1.17)	0.08
MeIQx (/10 ng)	1.15 (1.05–1.25)	0.002	1.06 (0.94–1.20)	0.35
(Total mutagenic activity)			1.10 (1.03–1.19)	0.008
PhIP (/10 ng)	1.02 (1.00–1.04)	0.02	1.00 (0.98–1.03)	0.98

[a] All of the ORs and 95% CIs were estimated using continuous variables and were adjusted for age, gender, total caloric intake, fiber intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, use of NSAIDs, and white meat.
[b] The model used for "red meat doneness" also included the rare/medium red meat variable.

The cases consumed 47, 67, 40, and 50% higher amounts of DiMeIQx, MeIQx, PhIP, and mutagenic activity, respectively, as compared with the control subjects. Considerable variability in dietary intakes was observed for all of the HCA compounds and meat types as evidenced by intake at the 10th *versus* 90th percentiles. The Spearman correlation between the HCA estimated using verbal doneness response and photographs was 0.92 for MeIQx and 0.93 for PhIP.

High intake of the three HCA compounds individually more than doubled the risk (fifth *versus* first quintile) of colorectal adenomas, but the excess risk was confined to the fifth quintile for DiMeIQx (data not shown) and MeIQx and to both the fourth and fifth quintiles for PhIP (Fig. 1, *A* and *B*). Given that the overall distribution of HCA intake in our population was log-normal, with most people consuming relatively low quantities of HCAs, only subjects in the top quintile had substantially different intakes levels than those in the lowest quintiles, so that only marginal differences in true risk can be expected in the lower categories.

The OR for 10-ng/day increments for MeIQx was 1.15 (CI, 1.05–1.25) and for PhIP, it was 1.02 (CI, 1.00–1.04). The OR for 10-ng/day increment of MeIQx from red meat only was 1.13 (CI, 1.03–1.23) and from white meat only was 1.95 (CI, 0.98–3.85). The OR for 10-ng/day increment of PhIP from red meat only was 1.05 (CI, 1.01–1.10) and from white meat only was 1.01 (CI, 0.99–1.34). The OR for 1000 revertant colonies/day increments was 1.11 (CI, 1.04–1.17) for total mutagenic activity from meat (Table 2). Reporting the OR as a continuous variable allows investigation of the relative potency of the different HCAs and makes it easier to compare results between studies with different populations, where the amounts consumed might differ.

We evaluated the relative importance of the different HCAs by adjusting each one for the other two. We found risks attenuated for all three because they were modestly to highly correlated with each other (Spearman correlation: PhIP and MeIQx, $r = 0.44$; PhIP and DiMeIQx, $r = 0.48$; and DiMeIQx and MeIQx, $r = 0.74$). However, the trend for MeIQx intake remained significant ($P = 0.04$), but it was not for either DiMeIQx ($P = 0.76$) or PhIP ($P = 0.14$).

We examined colorectal adenoma risk with an estimate of total meat-derived mutagenic activity because it provides a biologically relevant and integrated measure of mutagenicity. We observed a strong increase in risk (P for trend, 0.0005; Fig. 1*C* and Table 2) associated with mutagenic activity from meat. Mutagenic activity remained significantly associated with increased risk even when adjusted for intake of red meat or well-done red meat

(Table 2), previously shown to be associated with increased risk of colorectal adenomas. In contrast, the red meat and well-done red meat associations were no longer statistically significant when adjusted for total mutagenic activity. The association between mutagenic activity and risk of colorectal adenomas was minimally affected when adjusted for PhIP (which became nonsignificant) and was weakened when adjusted for MeIQx (which was attenuated to a much greater extent; Table 2). Mutagenic activity is highly correlated with HCAs (Spearman correlation: mutagenic activity and PhIP, $r = 0.65$; mutagenic activity and MeIQx, $r = 0.71$).

Discussion

We observed over a 2-fold increase in risk of colorectal adenomas associated with mutagenic activity, MeIQx, and possibly PhIP. Total mutagenic activity from cooked meat was a somewhat better predictor of risk than MeIQx and PhIP and appeared to explain the association we have reported previously (22) for intake of well-done red meat.

Total mutagenic activity is a biological measure that integrates all of the classes of mutagens according to their mutagenic potential. We believe that using total mutagenic activity is a superior measure compared with the sum of different HCAs. Adding individual HCAs does not take into account different mutagenic potentials of each compound and is weighted by the HCA that is the most abundant in meat, *i.e.,* PhIP (which is the least mutagenic of the three HCAs most commonly found in cooked meats). In fact, because of the abundance of PhIP, the results of total HCAs and PhIP tend to be almost identical.

One of the main advantages of this case-control study was that it was specifically designed to investigate the role of HCAs and colorectal adenomas. We developed a HCA database (17–21) integrated with a detailed questionnaire on meat-cooking techniques. This questionnaire had details on key individual meat items, meat cooking, and doneness levels. We are in the process of validating the HCA intake estimated from this food frequency questionnaire using biomarkers (*e.g.*, urinary HCA parent compounds and metabolites, and DNA- and protein-adducts) as well as multiple food diaries. Ultimately, the results presented in this report will need to be interpreted in the context of the validation study.

In the course of developing the database, we learned that it is crucial to obtain details on individual meat items such as beefsteak and beef roasts and not to combine these in the questionnaire

because different cuts of meats are generally cooked by dissimilar methods, and levels of HCAs vary dramatically. We also found that the high temperature cooking methods needed to be separated because different amounts of HCAs are produced by frying, grilling, and broiling attributable to the way meat cooks. In frying, the heat source is in contact with the bottom of the meat surface, so that the juices with the precursors of HCAs are in contact with it. In broiling, the heat source is above the meat surface, and the juices with the precursors drip away from the meat and heat source. In grilling, the heat source is below the meat, with fat dripping onto the heated surface causing flashing of flames and intermittent contact of meat surface with very high temperatures.

The cases had adenomas rather than cancer and, thus, were less likely to have changed their current dietary habits after diagnosis. Furthermore, their responses to questions about usual dietary habits were less likely to be influenced by their treatment. Even with intensive biological components, with both a clinic and a home component, the participation rates were relatively high for this study. Finally, cases and controls were recruited from a well-defined base of individuals.

One of the limitations for this study was that we interviewed subjects after their diagnostic and treatment procedures so there is potential for recall bias, but this is likely to be less of a problem when studying precancerous tumors as compared with cancer. Furthermore, cases had a colonoscopy, whereas the controls had only a sigmoidoscopy; therefore, some controls might have had undetected adenomas in the right side of the colon. But, when analysis was restricted to cases with left-sided colon adenomas detectable by sigmoidoscopy, the results were essentially unchanged.

Our results are consistent with animal carcinogenicity studies of HCAs, which have consistently found increased gastrointestinal tumor production with high intake of specific HCAs (26–28). In humans, only one study, conducted in Sweden, has investigated directly the role of HCAs in the etiology of colon and rectal cancers. This study did not find risk associated within the usual dietary range of HCA intake in the study population, but they did observe increased risk associated at the extreme end of the daily intake (8). In our study, we find risk associated with MeIQx and possibly PhIP, mainly in the top quintiles.

We and other investigators in Japan, New Zealand, and various countries in Europe, North America, and South America are actively pursuing the meat cooking, HCA-cancer hypothesis in ongoing prospective and case-control studies of cancers that are known targets for HCA carcinogenicity in animal studies (*e.g.,* breast, prostate, and gastrointestinal tract). Over the next few years, these studies should shed more light on the carcinogenicity of HCAs in humans.

Acknowledgments

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