

Dietary Benzo[a]Pyrene Intake and Risk of Colorectal Adenoma

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Abstract

We carried out a clinic-based case-control study specifically designed to address the hypothesis that dietary intake of polycyclic aromatic hydrocarbons (PAH) is associated with colorectal adenoma risk. We developed a food frequency questionnaire with detailed questions on meat-cooking methods and doneness levels and a benzo[a]pyrene (BaP) database (as a surrogate for total carcinogenic PAHs) based on the collection and analysis of a wide range of food samples. We estimated BaP intake derived from meat and from all foods to test its relationship with risk of colorectal adenomas. The median (10th and 90th percentiles) BaP intake in controls was 5 ng/d (0.2 and 66 ng/d) estimated from meat and 73 ng/d (35 and 140 ng/d) from all foods. In cases, median BaP intake was 17 ng/d (0.5 and 101 ng/d) from meat and 76 ng/d (44 and 163 ng/d) from all foods.

Multivariate analysis was carried out on 146 cases and 228 controls. The odds ratios (95% confidence interval) for dietary BaP from meat with the first quintile as the reference group were 1.19 (0.51-2.80) for the second quintile, 1.71 (0.76-3.83) for the third quintile, 2.16 (0.96-4.86) for the fourth quintile, and 2.82 (1.24-6.43) for the fifth quintile ($P_{\text{trend}} = 0.01$). Increased risk of colorectal adenomas was more strongly associated with BaP intake estimated from all foods: 2.61 (1.08-6.29) for the second quintile, 4.21 (1.79-9.91) for the third quintile, 2.45 (0.98-6.12) for the fourth quintile, and 5.60 (2.20-14.20) for the fifth quintile ($P_{\text{trend}} = 0.002$). This study provides evidence that dietary BaP plays a role in colorectal adenoma etiology. (Cancer Epidemiol Biomarkers Prev 2005; 14(8):2030-4)

Introduction

There is epidemiologic evidence that high intake of meat, especially red meat defined as beef, pork, and lamb probably increases the risk of colon and rectal cancers (1). It is unclear, however, whether cancer risk is related to the amount of red meat consumption *per se* or to certain meat-cooking practices, which produce mutagens and carcinogens such as heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), and possibly other agents (2-6). We have previously shown that certain high-temperature cooking methods, such as grilling and frying, may be associated with increased risk of colon and rectum adenomas (7, 8). We also found that some HCAs from the cooked meats were also associated with increased risk of these tumors (9). Other than HCAs, grilled meats also contain PAHs that form when fat drips onto a heated surface and burns. The smoke formed coats the food with PAHs. PAHs are also present in a wide variety of other foods including certain cereals, fruits, and green leafy vegetables (10). Animal studies have shown that dietary intake of benzo(a)pyrene (BaP), a PAH, causes increased levels of tumors at several sites, particularly in the gastrointestinal tract (11). We have shown that dietary intake of BaP from grilled meat rapidly increases levels of WBC DNA-PAH DNA adducts (12, 13). In support of an association between PAH exposure and carcinogenesis, polymorphisms in genes which govern PAH metabolism have been linked to cancers at several sites, including the colorectum (14-16).

To investigate the role of PAHs in colorectal carcinogenesis, we developed a meat-cooking module embedded within a food frequency questionnaire (FFQ) with detailed questions on meat-cooking practices. Although there are extensive data on PAH in meats, cereals, fruits, vegetables, and other foodstuffs, a database in a form that could be used with a FFQ was not available. Thus, we created a PAH database that collected a wide range of food items that could be linked to various food items in the FFQ (17). We measured BaP concentration as a marker for PAH in each sample by TLC, as well as a wide range of carcinogenic PAHs by high-performance liquid chromatography in a subsample of food items and found that BaP levels strongly correlated with total carcinogenic PAHs (17). Furthermore, BaP is the most known and studied member of the PAHs and is one of the most potent PAH animal carcinogens (18).

Using the BaP intake estimated from the FFQ and database, we investigated the association of BaP intake with colorectal adenoma risk in a sigmoidoscopy-based case-control study. We further tried to disentangle the risk associated with BaP ingestion and colorectal adenomas from our previous grilled meat and HCA findings (8, 9). We studied adenomas because the majority of colorectal cancers are thought to arise from these benign precursor lesions and it allows evaluation of risk factors early in the colorectal neoplasia process among essentially healthy subjects. Furthermore, because changes in lifestyle factors after adenoma diagnosis are expected to be minimal, reporting of such information by adenoma patients would be less likely to be subject to recall bias than information from cancer patients.

Materials and Methods

We conducted a case-control study of colorectal adenomas in a medical center serving mainly active and retired military officers and their families. The study was approved by the Institutional Review Boards of the National Cancer Institute

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and the National Naval Medical Center, Bethesda, MD. The study population has been described in detail elsewhere (8). Cases were patients who were diagnosed with colorectal adenomas at sigmoidoscopy (18%) or colonoscopy (82%) between April 1994 and September 1996. All index adenomas were histologically confirmed. Controls were selected among subjects without colorectal adenomas at sigmoidoscopy during the same time period and were frequency matched to cases on age and gender. To be eligible for the study, cases and controls had to be residents of the study area, between ages 18 and 74 years, and never been diagnosed with Crohn's disease, ulcerative colitis, or cancer except non-melanoma skin cancer.

The study was conducted in two phases: at the hospital clinic and in the subject's home. The cases were identified from a colonoscopy clinic register and were consented during a return visit after histologic confirmation of the adenomas. Some cases had flexible sigmoidoscopy before colonoscopy, whereas other cases had only a colonoscopy. Twice a week, a study staff member was present at a flexible sigmoidoscopy clinic where the controls were consented. Before the home visit, a self-given FFQ was delivered to the subject's home. During the home visit, the FFQ was checked for completeness by a trained interviewer. In addition, an in-person interview was conducted to obtain information on meat-cooking practices, demographic background, medication and medical history, physical activity, sun exposure, tobacco and alcohol consumption, and occupational history. The home phase was identical for both cases and controls. Controls were interviewed at a median time of 90 days (10th percentile, 40 days; 90th percentile, 164 days) after sigmoidoscopy and the cases were interviewed at a median time of 66 days (10th percentile, 29 days; 90th percentile, 121 days) after colonoscopy. In addition, subjects provided a blood sample during the clinical visit as well as multiple urine samples during the home visit.

The participation rates were 84% for the cases (244 of the 289 eligible cases identified) and 74% for the controls (231 of 314 eligible controls). The main reason for non-participation was subject refusal (12% of cases and 21% of controls) followed by illness (3% of cases and 4% of controls) and other reasons (1% of cases and 1% of controls). Of the 244 participants, 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.

The validated FFQ, a modified version of the 100-item Health Habits and History Questionnaire (19), was used to obtain information on usual diet (frequency of consumption and portion size) ~1 year before sigmoidoscopy/colonoscopy. In addition, we developed a meat-cooking module that included 23 meat items and how they were prepared. We obtained information on the typical level of doneness and cooking method. We estimated the amount of meat intake (g/d) from frequency of consumption and portion size. To estimate BaP intake, we multiplied grams of meat with the amount of BaP measured in that particular subgroup of meat. Intake of BaP was computed for each doneness level and cooking method subgroup.

Statistical Analysis. Unconditional logistic regression was used to estimate the association of BaP intake with risk of colorectal adenomas. ORs were adjusted for age, gender, total caloric intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of nonsteroidal anti-inflammatory drugs. Additional adjustment for consumption of total fat, saturated fat, fruits, vegetables, fiber, or alcohol, or for education, race, body mass index, bowel frequency, and family history of colorectal cancer did not substantially alter the findings.

To further examine the association of BaP and grilled meat with adenoma risk, we adjusted for grilled meat for the

categorical analyses of BaP from all foods. For BaP from meat only, we first modeled using a linear relationship the reported intake and the log odds of disease. The linear relationship was checked by adding a quadratic term to the regression model. The quadratic term for BaP from meat was statistically significant and therefore included in the reported analyses. The quadratic term for the other meats and HCAs were not statistically significant and hence excluded from further analyses. We present odds ratio (OR) and 95% confidence intervals (95% CI) intervals that reflect the relative risk associated with a 10 ng/d increase in BaP and a 10 g/d increase in reported daily consumption of different types of meat or 10 ng/d of HCAs. Because a linear relationship is used for meats and HCAs, the OR for a 10 or 10 ng/d increase is the same irrespective of the starting value. That is, the OR is the same for a change from 20 to 30 g/d as it is from 120 to 130 g/d. Because of the quadratic term, this equality does not hold for BaP and we report the effect of a 10 ng/d increase for a person with the median BaP intake. That is, we report the OR for a change from m^{-5} ng/d to m^{+5} ng/d, where m is the median BaP intake.

Results

The population characteristics of this clinic-based case-control study have been described previously (8, 9). In summary, the study population was mainly of Caucasian origin with median age of 58 years for the cases and 59 for the controls. Approximately 80% of the participants were male. The mean quantities of intake for the various meats and meat-derived carcinogens, along with their SDs are presented in Table 1. Controls, in general, had lower intakes of most of these variables compared with the cases. The main exposure of interest, BaP intake, was lower in controls for BaP from meats but not total BaP from all foods. There was large variability in the intake of many of these food items and compounds as shown by the SD values.

The main contributors of BaP intake in the control population from meat sources only and from total diet are shown Table 2. For this population, over 50% of the BaP from meat sources came from steak that was grilled to a medium level of doneness. BaP from the whole diet seems more evenly distributed, although grilled steak was still the top contributor. BaP consumption was moderately correlated with intake of 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine ($r = 0.44$), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline ($r = 0.39$), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline ($r = 0.33$), total meat ($r = 0.33$), red meat ($r = 0.32$), barbecued red meat

Table 1. Distribution of intake of meat, meat-derived mutagens, and mutagenic activity of cooked meat in cases and controls

Variable*	Cases, $n = 146$	Controls, $n = 228$
Total meat (g/d)	103.0 ± 53.90	92.6 ± 50.28
Red meat (g/d)	58.6 ± 41.86	45.0 ± 35.14
Well-done meat (g/d)	11.0 ± 14.16	7.5 ± 10.73
Grilled meat (g/d)	13.3 ± 16.32	9.3 ± 11.82
BaP from meat (ng/d)	22.4 ± 37.26	16.5 ± 31.29
BaP from total diet (ng/d)	77.3 ± 31.29	76.5 ± 30.91
DiMeIQx (ng/d)	2.2 ± 3.06	1.5 ± 2.34
MeIQx (ng/d)	32.7 ± 37.26	19.6 ± 23.45
PhIP (ng/d)	109.7 ± 130.12	78.2 ± 107.86
Mutagenic activity (1,000 revertant colonies/d)	5,246 ± 4723	3,494 ± 3,873

Abbreviations: PhIP, 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline.

*Values are means ± SD.

Table 2. Contribution of different foods to total and meat-derived BaP

Food items	Contribution of all foods to total BaP (>1%)	Contribution of different meats to meat-derived BaP(>1%)
Meats		
Steak/grilled/medium	12.3	53.0
Steak/grilled/well done	2.8	12.2
Chicken/grilled/well done	2.4	10.2
Chicken with skin/grilled/well done	1.6	6.6
Hamburger/grilled/well done	—	3.7
Chicken skinless/grilled/well done	—	2.9
Chicken/grilled/just until done	—	1.5
Hamburger/grilled/medium	—	1.4
Chicken/deep fried	—	1.2
Chicken skinless/broil/very well done	—	1.0
Other meats	—	7.3
Total meats	19.1	100
All other foods		
Potatoes other than fried	6.4	—
Rice	5.8	—
Tomato and tomato juice	5.5	—
Cooked cereals	4.9	—
Apples and applesauce	4.2	—
Spaghetti	4.2	—
Oranges/tangerines	4.0	—
White bread, rolls	3.7	—
Flavored yogurt, frozen yogurt	3.0	—
Pizza	2.8	—
Salty snacks (chips and popcorns)	2.7	—
French fries, fried potatoes	2.6	—
Broccoli	2.6	—
Carrots, mixed vegetables with carrots	2.4	—
Tuna and other fish	2.3	—
Peach, apricot, nectarine	2.0	—
Corn	1.6	—
Chocolate candy	1.5	—
Green beans	1.4	—
Bran and granola cereal	1.3	—
Doughnuts, cookies, cakes	1.0	—
Other foods	15.0	—

($r = 0.40$), total meat-derived mutagenicity (ref. 9; $r = 0.44$), and total calories ($r = 0.50$).

Intake of higher levels of BaP from meats was associated with increased risk of colorectal adenomas (Fig. 1A). There was a 2.8-fold increased risk when we compared the fifth to the first quintile. The ORs (95% CI) for dietary BaP from meat with the first quintile as the reference group were 1.19 (0.51-2.80) for the second quintile, 1.71 (0.76-3.83) for the third quintile, 2.16 (0.96-4.86) for the fourth quintile, and 2.82 (1.24-6.43) for the fifth quintile ($P_{\text{trend}} = 0.01$). Increased risk of colorectal adenomas was also associated with BaP intake estimated from all foods (Fig. 1B): 2.61 (1.08-6.29) for the second quintile, 4.21 (1.79-9.91) for the third quintile, 2.45 (0.98-6.12) for the fourth quintile, and 5.60 (2.20-14.20) for the fifth quintile ($P_{\text{trend}} = 0.002$). To make the selection of cases comparable with controls who only had sigmoidoscopy, we restricted the analyses to 116 cases with left-sided colon adenomas. We essentially observed similar results as those for all subjects. The OR for dietary BaP from meat with the first quintile as the reference group were 1.58 (0.62-4.02) for the

second quintile, 1.49 (0.59-3.79) for the third quintile, 2.88 (1.17-7.09) for the fourth quintile, and 2.83 (1.12-7.14) for the fifth quintile ($P_{\text{trend}} = 0.03$). Increased risk for left-sided colorectal adenomas was also associated with BaP intake estimated from all foods: 3.47 (1.28-9.38) for the second quintile, 5.56 (2.10-14.75) for the third quintile, 3.57 (1.29-9.89) for the fourth quintile, and 6.60 (2.31-18.92) for the fifth quintile ($P_{\text{trend}} = 0.005$).

We attempted to untangle the effect of BaP from grilled meat and vice versa. Following adjustment for grilled meat, the relation between total BaP from all foods and adenoma was attenuated somewhat but remained statistically significant. OR (95% CI) for the association between total BaP and colorectal adenoma, with the first quintile as reference were 2.53 (1.04-6.15) for the second quintile, 4.06 (1.70-9.70) for the third quintile, 2.11 (0.81-5.50) for the fourth quintile, and 4.17 (1.39-12.50) for the fifth quintile. In contrast, the association between grilled meat and colorectal adenoma was diminished following adjustment for total BaP. Risk estimates (OR, 95% CI) for the association between grilled meat and adenoma, with the lowest quintile as reference and following adjustment for age, sex, smoking, energy intake, fiber, and nonsteroidal anti-inflammatory drug use were 0.34 (0.07-1.70) for the second quintile, 0.78 (0.39-1.54) for the third quintile, 1.25 (0.67-2.35)

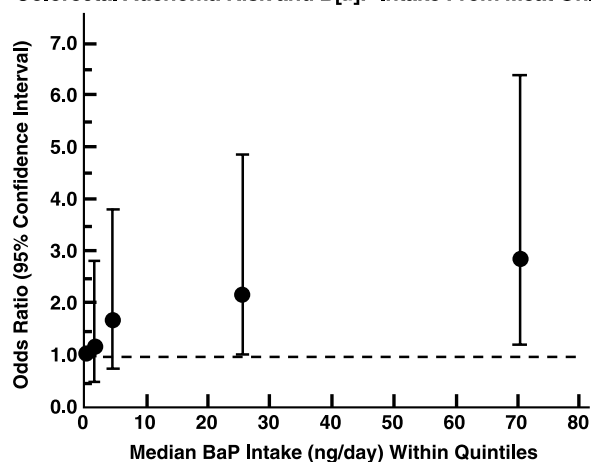
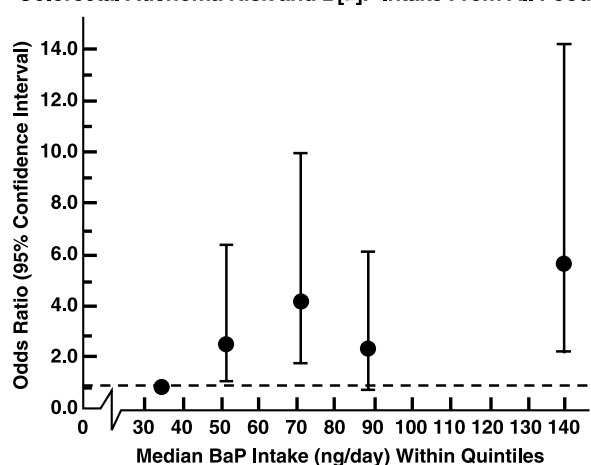
A Colorectal Adenoma Risk and B[a]P Intake From Meat Only**B** Colorectal Adenoma Risk and B[a]P Intake From All Foods

Figure 1. A and B. Relation between quintile of BaP intake from meat only and all foods and risk of colorectal adenoma. Increasing consumption of BaP was positively associated with adenoma risk.

for the fourth quintile, and 1.71 (0.92-3.20) for the fifth quintile. After adjustment for total BaP, these estimates were 0.40 (0.08-2.12) for the second quintile, 0.62 (0.29-1.30) for the third quintile, 0.86 (0.41-1.79) for the fourth quintile, and 1.07 (0.48-2.42) for the fifth quintile.

We also tried to disentangle the effect of meat-derived BaP from that of other meat types (e.g., total meat, red meat, and well-done red meat) and additional mutagens in meat (e.g., DiMeIQx, MeIQx, PhIP, and meat-derived mutagenicity). The effect of meat-derived BaP was not influenced by including other meat mutagens such as DiMeIQx, MeIQx, PhIP, or meat-derived mutagenicity in the regression model. Moreover, other meat variables did not have a significant effect either on the grilled meat or meat-derived BaP associations (Table 3). Furthermore, we could not disentangle the effect of meat derived BaP from that of grilled meat and vice versa as they are relatively well correlated ($r = 0.57$).

Discussion

We carried out a clinic-based case-control study specifically designed to address the hypothesis that dietary intake of PAHs is associated with increased risk of colorectal adenomas. BaP intake was positively associated with colorectal adenoma risk in this sigmoidoscopy-based case-control study from all foods and also in analyses restricted to BaP intake from meat. Previously in this study, we have also found that grilled meat was associated with increased colorectal adenoma risk (8). Therefore, to separate the role of grilled meat and BaP, we adjusted grilled meat with meat-derived BaP as well as BaP from all foods. Grilled meat was no longer associated with adenoma risk, but BaP from all foods remained significantly associated with increased risk. In contrast, we could not disentangle the role of grilled meat and BaP from meat.

PAH exposure in the United States comes primarily from smoking, environmental pollution, and diet. The agency for Toxic Substances and Disease Registry finds one of the major exposures of PAH to be from food. In this study, we estimated BaP, a marker of PAHs, from total diet and from meat using a BaP database that we developed for use in this study (17). We observed increased risk with higher intake of BaP from both total diet and from meat only. Although our study is relatively small and confidence intervals are wide, the point estimates for the fifth quintile are substantial and the P_{trend} values are highly significant.

BaP, a marker of PAH, is ubiquitous in food (20-26), forms DNA adducts in WBC of exposed humans (12, 13), and is a potent carcinogen in animals (27). Rodents fed BaP developed

leukemia and tumors of the fore stomach, small intestine, esophagus, tongue, and pulmonary adenoma (28-31).

Although there are voluminous data on BaP levels in meat that have evaluated cooking methods, data have not been reported on BaP levels in meat cooked by different techniques and to varying levels of doneness. In addition, samples in studies with BaP and/or total PAH concentrations in food were not collected in a way that could be linked to FFQs used in epidemiologic studies. Therefore, we created a database of food items with BaP concentrations based on a wide range of foods commonly available in supermarkets and in restaurants located in the same geographic region as subjects in this study. Foods were sampled and analyzed in a way such that the BaP concentrations could be linked to a FFQ that included detailed questions on meat-cooking practices developed for use in this study. We note, however, that the "regional" PAH database used in our study would have some limitations when applied to other areas of the country and that a more extensive national dietary PAH database would be needed to comprehensively address the role of dietary PAH and cancer. Other strengths of this study were that the cases had adenomas rather than cancer and thus were less likely to have changed their current dietary habits following diagnosis. Furthermore, their responses to questions about usual dietary habits were less likely to be influenced by treatment. Finally, cases and controls were recruited from a well-defined base of individuals and the study had high participation rates.

One of the limitations for this study was that we interviewed subjects after their diagnostic and treatment procedures; thus, 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. However, when analysis was restricted to cases with left-sided colon adenomas detectable by sigmoidoscopy, the results were essentially unchanged. We could not carry out stratified analyses by smokers (15 cases) and gender (35 female cases) due to small numbers.

Several studies have suggested an association between smoked or barbecued/grilled meats, which contain PAHs, and several types of cancer such as stomach and esophagus (32), colorectal (33-37), pancreatic (38), and bladder cancer (39). Because there are multiple carcinogens in addition to PAHs in smoked and barbecued/grilled meats, such as heterocyclic amines, it has been unclear what component(s) in meat are contributing to the excess observed in these studies. Results from our study to date suggest a role for both

Table 3. Modification of the association of meat-derived BaP and grilled meat and colorectal adenoma risk with the addition of other meat and mutagen variables

Adjustment for baseline variables plus	Effect of 10 ng increase at the median 50th percentile consumption of BaP	Effect of 10 g increase of grilled red meat
No adjustment	1.20 (1.06-1.36)	1.27 (1.05-1.52)
Total meat	1.19 (1.05-1.35)	1.32 (1.07-1.63)
Red meat	1.17 (1.03-1.33)	1.17 (0.96-1.44)
Well-done red meat	1.17 (1.02-1.33)	1.21 (0.98-1.49)
Grilled red meat	1.15 (0.99-1.34)	—
BaP	—	1.14 (0.98-1.49)
DiMeIQx	1.18 (1.04-1.34)	1.26 (1.04-1.51)
MeIQx	1.18 (1.04-1.34)	1.24 (1.03-1.49)
PhIP	1.18 (1.04-1.34)	1.24 (1.03-1.49)
Mutagenicity	1.16 (1.02-1.32)	1.22 (1.01-1.47)

NOTE: ORs were adjusted for age, gender, total caloric intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of nonsteroidal anti-inflammatory drugs.

Abbreviations: PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline.

HCA (9) and BaP, especially when considering BaP exposure from all food sources, in the etiology of colon adenomas.

In conclusion, we found increased risk of colorectal adenomas with high intake of BaP both from meat only and from all food sources. Although our study was designed to address this specific hypothesis, it is relatively small and the findings require replication in large, epidemiologic studies. These findings are, however, provocative given that animal experiments have found BaP to be multi-site carcinogen and PAHs are present throughout the diet.

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