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ORIGINAL PAPER

Intake of heterocyclic aromatic amines and the risk of prostate cancer in the EPIC-Heidelberg cohort

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Abstract
Background Heterocyclic amines (HCA) are positively associated with prostate cancer risk in animal models. Because of mostly inconsistent results of epidemiological studies, we examined the association between intake of HCA and prostate cancer risk.
Methods In the EPIC-Heidelberg cohort, detailed information on diet, anthropometry, and lifestyle was assessed between 1994 and 1998. Dietary HCA intake was estimated using information on meat consumption, cooking methods, and preferred degree of browning. During 104,195 person-years of follow-up, 337 incident cases of prostate cancer (123 advanced cases) were identified among 9,578 men with valid dietary information. Multivariate Cox proportional hazards regression was used to examine the association between intake of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-dimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and prostate cancer.
Results Men in the highest quartiles of PhIP, MeIQx, and DiMeIQx intake, respectively, had no increased risk of prostate cancer compared with men in the lowest quartiles (HR = 0.89, 95% CI 0.66–1.22 [PhIP]; 1.06, 0.77–1.45 [MeIQx]; 0.98, 0.72–1.34 [DiMeIQx]). There were no associations between HCA intake and advanced prostate cancer or between high consumption of strongly browned meat and prostate cancer.
Discussion Our data do not support the hypothesis that HCA intake as consumed in a regular diet is a risk factor for prostate cancer.

Keywords Heterocyclic aromatic amines · Prostate cancer · Cohort study

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Introduction

In vitro and in vivo experiments indicate that heterocyclic aromatic amines (HCAs) are some of the most potent mutagens [1]. These compounds are formed from amino acids, creatin(in)e, and sugar during cooking of fish and/or meat at high temperatures. The amount depends on cooking temperature, cooking time, type of meat, and cooking method. The most mass-abundant HCAs detected in cooked meat are 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-dimethylimidazo[4,5-f]quinoxaline (DiMeIQx).

In experimental studies, N-hydroxy derivates of PhIP and of MeIQx were shown to be potential carcinogens for the prostate [2]. In a rat model, Nakai et al. [3] have shown that an increased proliferation and cell death in response to PhIP, which indicates that in addition to PhIP acting as an "initiator" of cancer, PhIP might also act like a

lobe-specific tumor "promoter." In humans, a number of epidemiological studies have shown that high intake of well done meat and high exposure to meat carcinogens, like *HCAs*, may increase the risk of a number of common cancers such as breast and colorectal cancer [4–6]. For prostate cancer, some studies have evaluated the association between consumption of different types of meat and prostate cancer risk. Some of them showed a positive association between meat consumption and prostate cancer, especially for well done and red meat [7–10], but others reported no association [11–13]. The few studies with focus on HCA intake revealed inconsistent results; two studies reported no association [8, 10], whereas one study indicated an increasing risk for the intake of PhIP [9] and another one an increased risk for MeIQx and DiMeIQx [7].

Because of mostly inconsistent results, it was the aim of this study to examine the association between intake of meat prepared with different degrees of browning and *HCA* intake with the risk of prostate cancer in the EPIC-Heidelberg cohort study.

Subjects and methods

Population

The EPIC-Heidelberg cohort is part of the European Prospective Investigation into Cancer and Nutrition, a prospective cohort study conducted in ten countries. From 1994 to 1998, a total of 11,928 men aged 40–65 years and 13,612 women aged 35–65 years were recruited from the general population of Heidelberg and surrounding communities. Information on diet, lifestyle, and health was obtained at baseline by means of questionnaires and face-to-face interviews [14]. The cohort is followed up by mailed questionnaires in intervals of about 3 years to assess information on health status, diet, and lifestyle [15]. Diet was assessed by using a validated food-frequency questionnaire (FFQ) [16].

During the second follow-up of the cohort (2002–2004), 11,605 men have been contacted; of these, 9,864 participants completed a 158-item FFQ. This FFQ included detailed questions on meat preparation methods and preferred degree of browning, i.e., the outside appearance of the meat, using four pictures (lightly/moderately/strongly/extremely browned) as reference and assistance. Mean daily dietary intake of HCAs from meat was calculated by using published data of the HCA content of different types of meat in combination with information on degree of browning, cooking methods, and the amount of meat intake [17].

Identification of incident prostate cancer cases was based on self-reported primary prostate cancer during follow-up or on death certificates that were coded for prostate cancer as the underlying cause of death. All cases were verified by medical records, death certificates, or both. Information on stage and grade of prostate cancer was extracted by the study physician from pathology reports, including tumor nodal metastasis (TNM) stage and Gleason histologic grade. Advanced prostate cancer was defined as prostate cancer with a Gleason sum score equal or higher than seven, a TNM staging score of T3/T4, N1-N3, or M1, or prostate cancer as the underlying cause of death. Although prone to detection bias, stage T1a cases were included in the analysis because their low number (seven T1a cases [2.8% of all cases]) was unlikely to affect the results.

After excluding men with prevalent cancer or with missing information on food preparation methods and preferred degree of browning, our study population comprises a total of 9,578 men. Among these, 337 incident cases of prostate cancer (including 123 advanced cases, which included 22 fatal cases) have been diagnosed until 31 July 2009.

All participants gave written informed consent. EPIC-Heidelberg has been approved by the ethical committee of Heidelberg University Medical School.

Statistical analyses

The association of total and advanced prostate cancer with intake of the three most abundant HCAs (PhIP, MeIQx, and DiMeIQx) and meat consumption by degree of browning was analyzed using Cox proportional hazards regression, modeling the intake variables as a categorical variable based on quartiles of intake in the cohort, with the first quartile being the reference category. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, and time of exit was the age at which participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by age at recruitment in 1-year categories. In multivariate regression models, we adjusted for smoking status at baseline (never, former, or current), family history of prostate cancer (yes/no), participation in prostate-specific antigen (PSA)-screening tests (yes/no), and intake of dairy products (entered as quartiles). Additional adjustment for other possible confounders (tomato products, body mass index, total energy intake, alcohol intake, and vigorous physical activity) had no statistically significant effects on the risk of prostate cancer ($p < 0.20$).

The results are given as hazard ratios (HR) and 95% confidence intervals (CI). We also examined whether the observed associations of HCA intake and prostate cancer changed if we examined the three HCAs in a combined

model additionally controlled for red and processed meat (entered as quartiles).

To test for linear trend across categories, we used the continuous variables. All tests were two-sided; p values < 0.05 were considered to be statistically significant. All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC).

Results

Baseline characteristics of the study participants are shown in Table 1. Compared with men in the lowest quartile of total HCA intake, men in the highest quartile tended to have a higher BMI and a higher total energy intake, to consume more alcohol, tomato products, a lower consumption of dairy products, and were more likely to be current smokers (Table 1). There was no significant association between HCA intake and risk of prostate cancer; men in the highest quartiles of PhIP, MeIQx, and DiMeIQx intake, respectively, did not have an increased risk of prostate cancer compared with men in the lowest quartiles (HR = 0.89, 95% CI 0.66–1.22 [PhIP]; 1.06, 0.77–1.45 [MeIQx]; 0.98, 0.72–1.34 [DiMeIQx]; Table 2). No statistically significant associations were observed when we considered advanced cases (Table 2). In addition, we did not see clear relationships with prostate cancer stratified by stage or grade (data not shown).

There were also no consistent associations between consumption of meat by degree of browning and total or advanced prostate cancer incidence; men in the second and third quartile of strongly and extremely browned meat had an increased risk of prostate cancer, but there was no statistically significant association when comparing men with the highest consumption of strongly browned meat to those with the lowest intake (Table 2).

As already seen in the entire EPIC cohort [18], we observed no statistically significant association between red or processed meat intake and prostate cancer risk in the EPIC-Heidelberg cohort (data not shown).

Discussion

In this prospective cohort study, the estimated dietary intake of *HCAs* was not associated with the risk of prostate cancer. The consumption of strongly/extremely browned meat was also not consistently related to prostate cancer incidence.

Our result of no association between HCA intake and prostate cancer incidence is comparable with some [8, 10] but not other [7, 9] previous studies. A case–control study with 317 cases in New Zealand [8] did not find an association between HCA intake and prostate cancer risk. Cross et al. [9] observed in their cohort study with 29,361 men and 868 incident cases of prostate cancer no association between intake of different types of meat or the intake of MeIQx and DiMeIQx, respectively, and risk of prostate cancer. However, an increased risk of prostate cancer was observed in subjects with high intake of PhIP [all cases: relative risk (RR) 1.22, 95% CI (1.01–1.48); incident cases: 1.28, 95% CI (1.01–1.61), top vs bottom quintile] and very well done meat [all cases: RR 1.42, 95% CI (1.05–1.92); incident cases: 1.69, 95% CI (1.19–2.40)]. Within the Agricultural Health Study, Koutros et al. [6] observed a positive association of well and very well done meat consumption with risk of prostate cancer. For MeIQx and DiMeIQx intake, they observed a non-significantly increased risk of prostate cancer. In a large prospective cohort study in the United States, a high intake of red, processed as well as grilled/barbecued meat was associated with elevated risks of total and advanced prostate cancer, but they did not observe statistically significant associations between HCA intake and prostate cancer [10].

The estimation of daily HCA intake is mostly based on data derived from *FFQs* that are commonly used in epidemiological studies. However, HCA intake estimations suffer from imprecision. Assessing a person's dietary intake by means of a FFQ is prone to recall bias, such that study participants may over- or underestimate their dietary intake leading to misclassification with respect to dietary intake. Second, the use of limited data on the HCA content in differently prepared meats for the computation of HCA intake [17] is another major shortcoming of this approach to quantify intake. HCA intake was lower in our cohort than in previous studies, in particular US studies, and food sources contributing most to HCA intake also differs between studies [17]. This may partly explain differences in results between studies. However, we have previously shown in our cohort a positive association between HCA intake, in particular PhIP, and the risk of colorectal adenomas [5], which is in line with findings from other studies. HCA formation is a function of duration and temperature of the cooking process as well as of the cooking method itself [19], such that the content of HCAs depends on the degree of browning as well as on the degree of doneness of the meat. For example, cooking short time by high temperature and long time by lower temperature can result in the same degree of browning but not in the same degree of doneness and, thus, in different amounts of HCAs. It has been shown that this effect may lead to an underestimation of exposure [19]. Nevertheless, recent investigations have shown that validated *FFQs* can result in reasonable estimations of levels of HCA intake [20]. Kobayashi et al. [21] compared the intake of some HCAs and total HCA intake estimated from a FFQ with the PhIP level in hair samples.

Table 1 Baseline characteristics of men of the EPIC-Heidelberg cohort over quartiles of total HCA intake

	Quartiles of total HCA intake [ng/day]				
	<26.09	26.09 to <61.45	61.45 to <148.14	≥148.14	*p* value[a]
Total (*n*)	2,394	2,395	2,394	2,395	0.02
Cases (*n*, %)	99 (4.1)	97 (4.1)	70 (2.9)	71 (3.0)	0.01
Advanced (*n*, %)	36 (1.5)	37 (1.5)	31 (1.3)	19 (0.8)	0.02
Age (years)[b]	52.9 ± 7.1	52.5 ± 7.1	51.4 ± 6.9	50.8 ± 7.0	<0.01
Body mass index (kg/m^2)[b]	26.3 ± 3.4	26.7 ± 3.4	27.1 ± 3.7	27.4 ± 3.7	<0.01
HCA intake (ng/d)					
PhIP[c]	6.7 (0.0–24.1)	22.6 (0.5–59.5)	59.9 (1.0–143.9)	197.2 (32.1–5,967)	<0.01
MeIQx[c]	4.8 (0.0–23.0)	14.6 (0.0–44.9)	28.5 (0.4–101.5)	69.5 (1.7–3,097)	<0.01
DiMeIQx[c]	0.7 (0.0–9.1)	1.9 (0.0–14.6)	3.3 (0.0–26.3)	5.1 (0.0–271.0)	<0.01
Energy intake (kcal/d)[b]	1,999 ± 632	2,130 ± 623	2,291 ± 830	2,407 ± 853	<0.01
Dairy products (g/d)[b]	253.0 ± 270.0	228.0 ± 224.0	233.7 ± 231.7	232.9 ± 245.8	<0.01
Tomatoes, tomato products (g/d)[b] (g/d)*	22.4 ± 15.2	22.8 ± 13.8	24.4 ± 15.5	25.9 ± 21.5	<0.01
Red meat (g/d)[b]	22.6 ± 20.1	36.1 ± 23.2	47.4 ± 31.2	58.7 ± 48.0	<0.01
Processed meat (g/d)[b]	45.1 ± 35	61.2 ± 39.5	72.6 ± 49.5	78.4 ± 57.6	<0.01
White meat (g/d)[b]	8.5 ± 9.7	13.5 ± 13.7	14.9 ± 14.3	18.8 ± 20.3	<0.01
Alcohol (g/d)[b]	22.0 ± 26.3	25.9 ± 26.0	26.4 ± 26.6	28.0 ± 28.0	<0.01
Vigorous physical activity (%)[d]					
None	34.3	34.3	34	31.5	0.08
≤2 h/wk	38.9	37.5	37.2	37.8	0.61
>2 h/wk	26.9	28.1	28.8	30.7	<0.01
Smoking status (%)					
Never	36.1	32	28.7	29	<0.01
Former	48	47.5	46.8	45.6	0.09
Current	15.9	20.5	24.6	25.3	<0.01
Family history of prostate cancer (%)	4.7	4.1	4.1	3.9	0.2
Participation in PSA screening (%)[e]	63.2	62.3	57.4	58.5	0.02

[a] Jonckheere–Terpstra Test

[b] Mean ± SD

[c] Median and interquartile range by quintile of total HCA intake

[d] Unknown/missing information on physical activity for 101/91 participants

[e] 758 participants with no information about PSA screening

Under adjustment for melanin content, they observed statistically significant correlations for PhIP and total HCA intake by FFQ with the respective levels in hair ($r = 0.47$ and $r = 0.51$, respectively) [22].

The results of our and also some other studies showing no association between intake of HCA and prostate cancer risk could possibly be explained by the fact that food, e.g., processed meat, also contains other compounds than HCAs that can act as mutagens/carcinogens. Nitrite and nitrate, polycyclic aromatic hydrocarbons, and heme iron are such compounds [10, 23]. In this case, however, one might expect a positive association between meat, meat subgroups (e.g., red or processed meat), or strongly browned meat as reported by Sinha et al. [10]. However, we did not observe a consistently increased risk of prostate cancer with high consumption of strongly/extremely browned meat. A second factor that needs to be taken into account is the role of genetic polymorphisms that affect the metabolism of HCAs and, thus, their potential carcinogenic effect [24]. Thirdly, it is difficult to consider all factors that can affect and modulate the risk of prostate cancer; bias arising from unrecognized confounding remains a potential weak point in any observational study design especially because there are only few well-recognized prostate cancer risk factors. Lastly, the number of cases in our study is smaller than in other studies [9, 10, 24] and the power was, thus, lower to observe a small to moderate but statistically significant association.

Table 2 Hazard ratios (HR) and 95% CI of prostate cancer across quartiles of PhIP, MeIQx, and DiMeIQx intake and consumption of meat with different degree of browning

	Quartile							*p* for trend[a]
	1	2		3		4		
	HR	HR	95% CI	HR	95% CI	HR	95% CI	
PhIP [ng/day]	<13.06	13.06–<36.11		36.11–<98.45		≥98.45		
All cases (*n*)	100	98		69		70		
HR[b]	1.00 (ref.)	1.04	(0.78, 1.37)	0.80	(0.59, .08)	0.90	(0.66, 1.22)	0.86
HR[c]	1.00 (ref.)	1.02	(0.77, 1.35)	0.83	(0.61, 1.13)	0.89	(0.66, 1.22)	0.86
HR[d]	1.00 (ref.)	0.93	(0.69, 1.27)	0.74	(0.51, 1.06)	0.76	(0.49, 1.17)	0.58
Advanced cases (*n*)	30	45		27		21		
HR[c]	1.00 (ref.)	1.56	(0.98, 2.48)	1.07	(0.63, 1.81)	0.89	(0.51, 1.56)	0.49
MeIQx [ng/day]	<8.03	8.03–<18.94		18.94–<41.65		≥41.65		
All cases (*n*)	88	99		78		72		
HR[b]	1.00 (ref.)	1.18	(0.88, 1.57)	1.03	(0.76, 1.39)	1.03	(0.76, 1.42)	0.72
HR[c]	1.00 (ref.)	1.14	(0.85, 1.52)	1.07	(0.78, 1.45)	1.06	(0.77, 1.45)	0.67
HR[d]	1.00 (ref.)	1.24	(0.89, 1.72)	1.29	(0.87, 1.92)	1.45	(0.88, 2.41)	0.37
Advanced cases (*n*)	32	38		30		23		
HR[c]	1.00 (ref.)	1.20	(0.74, 1.92)	1.12	(0.68, 1.86)	0.91	(0.53, 1.57)	0.91
DiMeIQx [ng/day]	<0.74	0.74–<2.06		2.06–<4.71		≥4.71		
All cases (*n*)	89	85		89		74		
HR[b]	1.00 (ref.)	0.99	(0.73, 1.33)	1.04	(0.78, 1.40)	1.00	(0.73, 1.36)	0.91
HR[c]	1.00 (ref.)	0.94	(0.69, 1.26)	1.01	(0.75, 1.35)	0.98	(0.72, 1.34)	0.84
HR[d]	1.00 (ref.)	0.90	(0.66, 1.22)	0.95	(0.68, 1.33)	0.99	(0.67, 1.45)	0.88
Advanced cases (*n*)	27	34		37		25		
HR[c]	1.00 (ref.)	1.24	(0.75, 2.06)	1.37	(0.83, 2.26)	1.05	(0.61, 1.82)	0.71
Degree of browning								
Strong/extreme [g/day]	<2.38	2.38–<14.44		14.44–<35.13		≥35.13		
All cases (*n*)	55	73		65		39		
HR[c]	1.00 (ref.)	1.48	(1.04, 2.11)	1.45	(1.01, 2.09)	1.05	(0.69, 1.60)	0.87
Advanced (*n*)	24	39		34		17		
HR[c]	1.00 (ref.)	1.70	(1.02, 2.83)	1.66	(0.98, 2.80)	0.94	(0.50, 1.77)	0.16
Light/moderate [g/day]	<8.67	8.67–<21.67		21.67–<40.91		≥40.91		
All cases (*n*)	53	58		70		51		
HR[c]	1.00 (ref.)	0.93	(0.64, 1.35)	1.06	(0.74, 1.52)	0.75	(0.51, 1.11)	0.26
Advanced cases (*n*)	26	33		32		23		
HR[c]	1.00 (ref.)	1.10	(0.65, 1.84)	1.00	(0.59, 1.68)	0.73	(0.41, 1.28)	0.21

[a] Trend tests were performed using the continuous intake of each variable

[b] Cox proportional hazards models, stratified by age

[c] Cox proportional hazards models, stratified by age and adjusted for smoking (never, former, current), family history of prostate cancer, participation in PSA screening, and intake of dairy products (entered as quartile-dummies)

[d] Combined Cox proportional hazards models for the three HCAs, stratified and adjusted as in footnote 2, with additional adjustment for intake of processed and red meat (quartiles)

In conclusion, our data do not support the hypothesis that HCA intake as consumed in a regular diet is a risk factor for prostate cancer.

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