SHORT COMMUNICATION

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A prospective investigation of fish, meat and cooking-related carcinogens with endometrial cancer incidence

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Background: There are limited prospective studies of fish and meat intakes with risk of endometrial cancer and findings are inconsistent.

Methods: We studied associations between fish and meat intakes and endometrial cancer incidence in the large, prospective National Institutes of Health-AARP Diet and Health Study. Intakes of meat mutagens 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and benzo(a)pyrene (BaP) were also calculated. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: We observed no associations with endometrial cancer risk comparing the highest to lowest intake quintiles of red (HR = 0.91, 95% CI 0.77–1.08), white (0.98, 0.83–1.17), processed meats (1.02, 0.86–1.21) and fish (1.10, 95% CI 0.93–1.29). We also found no associations between meat mutagen intakes and endometrial cancer.

Conclusion: Our findings do not support an association between meat or fish intakes or meat mutagens and endometrial cancer.

Endometrial cancer is the fourth most common incident cancer among US women, with an estimated 47 130 new cases in 2012 (National Cancer Institute, 2012). Previous studies on meat intake and endometrial cancer provide mixed results, with some suggesting a positive association (Shu *et al*, 1993; Goodman *et al*, 1997; Terry *et al*, 2002a; Salazar Martinez *et al*, 2005; Cross *et al*, 2007; Bravi *et al*, 2009) and others showing no association (Potischman *et al*, 1993; Zheng *et al*, 1995; McCann *et al*, 2000; Littman *et al*, 2001; Genkinger *et al*, 2012). However, the majority of these studies are retrospective, case–control studies (and thus subject to recall bias). Most studies of fish intake and endometrial cancer are also retrospective and report no relationship (Levi *et al*, 1993; Hirose *et al*, 1996; Goodman *et al*, 1997; Fernandez *et al*, 1999; Jain *et al*, 2000; McCann *et al*, 2000; Bravi *et al*, 2009). Limited studies suggest positive (Shu *et al*, 1993; Xu *et al*, 2006) or inverse associations (Terry *et al*, 2002b; Arem *et al*, 2012) between fish intake and endometrial cancer. Several mutagens can form during high-temperature meat cooking, including heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), which are also found in tobacco smoke (Voutsinas *et al*, 2012). Although smoking has been inversely associated with endometrial cancer (Amant *et al*, 2005), meat mutagens and endometrial cancer risk has not been studied.

Given these gaps in the literature, we investigated fish, meat and meat mutagen intakes with incident endometrial cancer in the large, prospective National Institutes of Health (NIH)-AARP Diet and Health Study.

MATERIALS AND METHODS

Study population. The NIH-AARP Diet and Health Study has been previously described (Schatzkin *et al*, 2001). In brief, 566 398 individuals aged 50–71 years satisfactorily completed mailed questionnaires in 1995–1996. Following exclusions (males,

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$n = 339\,666$; proxy respondents, $n = 1265$; baseline cancers other than non-melanoma skin cancer, $n = 24\,715$; end-stage renal disease, $n = 371$; hysterectomy, $n = 81\,646$; menstrual periods stopped because of surgery/radiation/chemotherapy, $n = 2342$; calorie intake >2 interquartile ranges >75th or <25th percentile on the log scale, $n = 1070$; body mass index (BMI) <12 or $>80\,kg\,m^{-2}$, $n = 3951$; zero person-time; $n = 16$) an analytic cohort of 111 356 women remained, from which we identified 1486 incident endometrial cancer cases. Within 6 months of baseline questionnaire, a risk factor questionnaire (RFQ) was administered inquiring about meat preparation methods (response rate = 67%). Of women who met baseline exclusion criteria, 72 796 also completed the RFQ and 966 developed endometrial cancer. The Special Studies Institutional Review Board of the National Cancer Institute (NCI) approved the study.

Dietary assessment. At baseline, participants completed a 124-item food frequency questionnaire (FFQ, developed at the US NCI) on usual frequency of food and beverage consumption (10 categories) and usual portion size (3 categories) over the past year. Line items were linked to the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals to calculate nutrient and energy intakes (Subar *et al*, 2000). Separate line items questioned about fresh and processed red meats, poultry, finfish/shellfish, canned tuna and fried fish. The RFQ further queried on usual cooking method (grilled/barbequed, pan-fried, microwaved and broiled), outside and inside appearance, and doneness (well-done/very well-done and medium/rare) of meat. These line items were used in conjunction with the NCI CHARRED database to estimate values for HCAs 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), and benzo(a)pyrene (BaP), a marker for PAHs (National Cancer Institute, 2006; Cantwell *et al*, 2004; Sinha *et al*, 2005).

Case ascertainment. Endometrial cancer cases were ascertained by record linkage to 11 state cancer registries. Case ascertainment has been reported as >90% complete (Havener, 2004; Michaud *et al*, 2005). Our analysis included eligible cases of incident endometrial cancer diagnosed through 12/31/2006 (International Classification of Diseases for Oncology, third edition, codes 54–55).

Statistical analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between meat, fish and meat mutagens with endometrial cancer were estimated using Cox proportional hazards regression. Follow-up time was calculated from baseline questionnaire for meat/fish models and from date of RFQ for meat mutagen models. Individuals were censored at endometrial cancer diagnosis, death, emigration from study area or end of follow-up, whichever occurred first. Proportionality of data were verified by graphical inspection. Multivariable models were adjusted for endometrial cancer risk factors age, BMI, smoking status, physical activity, ages at menarche, first live birth, and menopause, parity, diabetes, hormone therapy (HT) use, and oral contraceptive use. Ethnicity, family history of cancer, alcohol and coffee consumption and use of non-steroidal anti-inflammatory drugs were evaluated as potential covariates but were not included in final models because inclusion did not alter risk estimates. We also performed analyses stratified by smoking status (never/ever), use of HT (never/ever) and

Table 1. Distribution of selected endometrial cancer risk factors by quintile of red meat intake among women in the NIH-AARP Diet and Health Study ($N = 111\,356$ in baseline cohort, $N = 72\,796$ in risk factor cohort)

	Quintiles of red meat intake, g per 1000 kcal				
	1st	**2nd**	**3rd**	**4th**	**5th**
Baseline questionnaire, *N* (cases)	290	278	315	286	317
Daily red meat (g per 1000 kcal), mean (s.d.)	7.1 (3.6)	17.2 (2.5)	25.9 (2.6)	36.2 (3.6)	58.5 (15.7)
Daily white meat (g per 1000 kcal), mean (s.d.)	37.4 (34.3)	36.1 (27.9)	35.3 (24.6)	35.2 (23.5)	35.5 (23.1)
Daily processed meat (g per 1000 kcal), mean (s.d.)	3.4 (6.0)	5.5 (5.7)	7.4 (6.2)	9.8 (7.6)	14.5 (12.0)
Age in years, mean (s.d.)	61.8 (5.5)	61.9 (5.5)	61.8 (5.5)	61.5 (5.5)	61.1 (5.4)
Non- Hispanic White (*N*, %)	19 492 (87.5%)	20 090 (90.2%)	20 334 (91.3%)	20 621 (92.6%)	20 532 (92.2%)
Obese, BMI $\geqslant 30\,kg\,m^{-2}$ (*N*, %)	3148 (14.1%)	4124 (18.5%)	4819 (21.6%)	5580 (25.1%)	6721 (30.1%)
Ever use of hormone therapy (*N*, %)	9329 (41.9%)	9307 (41.8%)	9106 (40.9%)	8763 (39.4%)	7959 (35.7%)
Ever use of oral contraceptives (*N*, %)	8641 (38.8%)	8815 (39.6%)	8915 (40.0%)	9131 (41.0%)	9290 (41.7%)
Age at menarche $\leqslant 10$ years (*N*, %)	1408 (6.3%)	1297 (5.8%)	1360 (6.1%)	1275 (5.7%)	1492 (6.7%)
Age at first birth $\geqslant 30$ years (*N*, %)	1727 (7.8%)	1574 (7.1%)	1672 (7.5%)	1561 (7.0%)	1522 (6.8%)
Nulliparous (*N*, %)	4276 (19.2%)	3907 (17.5%)	3648 (16.4)	3700 (16.6%)	3751 (16.8%)
Age at menopause $\geqslant 55$ years (*N*, %)	2452 (11.0%)	2332 (10.5%)	2199 (9.9%)	2169 (9.7%)	2137 (9.6%)
Current smoker (*N*, %)	1790 (8.0%)	2627 (11.8%)	3128 (14.0%)	3772 (16.9%)	4548 (20.4%)
Physical exercise $\geqslant 1$ time per week (*N*, %)	16 101 (72.3%)	15 000 (67.4%)	14 019 (62.9%)	13 147 (59.0%)	11 770 (52.9%)
Energy (kcal day^{-1})	1530 (630)	1531 (623)	1553 (631)	1592 (645)	1634 (681)
Risk factor questionnaire, *N* (cases)	194	191	214	187	209
DiMeIQx (ng per 1000 kcal day^{-1}), mean (s.d.)	0.24 (0.8)	0.37 (0.8)	0.49 (0.9)	0.67 (1.2)	1.1 (2.6)
MeIQx (ng per 1000 kcal day^{-1}), mean (s.d.)	2.2 (3.3)	4.9 (6.1)	7.3 (8.6)	10.5 (12.7)	18.4 (25.6)
PhIP (ng per 1000 kcal day^{-1}), mean (s.d.)	24.0 (63.8)	31.3 (59.9)	37.3 (60.1)	47.2 (69.6)	72.3 (106.2)
BaP (ng per 1000 kcal day^{-1}), mean (s.d.)	4.5 (11.7)	7.5 (12.6)	10.3 (14.9)	14.4 (19.0)	23.7 (34.4)

Abbreviations: BaP = benzo(a)pyrene; BMI = body mass index; DiMeIQx = 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; MeIQx = 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

BMI (<25 or ⩾25 kg m^{-2}) and created interaction terms between meat or fish and potential effect modifiers using the Wald test for statistical significance. Analyses were performed using SAS version 9.2 (Cary, NC, USA). All tests were two-sided.

RESULTS

During a mean 9.3 years of follow-up, 1486 women were diagnosed with endometrial cancer.

Table 1 presents distributions of endometrial cancer risk factors across quintiles of red meat intake. Women who consumed more red meat had higher rates of obesity, lower HT usage, were more likely to be current smokers and less likely to be physically active.

HR estimates and 95% CIs for red (0.91, 0.77–1.08), white (0.98, 0.83–1.17) and processed meat (1.02, 0.86–1.21) intakes showed no associations with endometrial cancer (Table 2). Neither total fish (HR = 1.10, 95% CI 0.93–1.29) nor fried fish intakes (HR = 0.99, 95% CI 0.85–1.15) were associated with risk. PhIP, MeIQx, DiMeIQx and BaP were also not associated with risk comparing extreme quintiles, although a suggested positive trend was observed for DiMeIQx intake ($P = 0.049$).

For red meat, interactions with HT and smoking were significant ($P = 0.001$ and $P = 0.049$, respectively; Supplementary Table 1). Analyses stratified by HT showed no association between red meat intake and endometrial cancer among never HT users (HR = 1.00, 95% CI 0.80–1.24), whereas among ever HT users the association was inverse but not significant (0.83, 0.63–1.09). In analyses stratified by smoking, higher red meat intake among ever smokers was associated with a lower risk of endometrial cancer (0.77, 0.60–0.98), whereas no association was observed for never smokers (1.07, 0.84–1.36). Interaction terms between intakes

Table 2. Associations between intake of fish, meat and meat mutagens with risk of endometrial cancer in the NIH-AARP Diet and Health Study[a]

	Q1		Q2		Q3		Q4		Q5		
	N **(cases)**	**HR**	***N*** **(cases)**	**HR (95% CI)**	***N*** **(cases)**	**HR (95% CI)**	***N*** **(cases)**	**HR (95% CI)**	***N*** **(cases)**	**HR (95% CI)**	***P*-trend**
Red meat											
Model 1	281	1.00	270	0.88 (0.74–1.04)	310	0.97 (0.82–1.14)	279	0.84 (0.71–1.00)	307	0.89 (0.75–1.05)	0.293
Model 2	271	1.00	265	0.90 (0.76–1.07)	295	0.97 (0.82–1.14)	271	0.85 (0.72–1.01)	302	0.91 (0.77–1.08)	0.450
White meat											
Model 1	260	1.00	284	1.05 (0.89–1.24)	307	1.12 (0.95–1.32)	313	1.14 (0.96–1.34)	283	1.00 (0.85–1.19)	0.955
Model 2	249	1.00	281	1.07 (0.90–1.28)	299	1.13 (0.96–1.34)	305	1.14 (0.97–1.36)	270	0.98 (0.83–1.17)	0.660
Processed meat											
Model 1	269	1.00	272	0.94 (0.79–1.11)	296	0.97 (0.82–1.15)	281	0.89 (0.75–1.06)	329	1.01 (0.85–1.19)	0.660
Model 2	255	1.00	268	0.97 (0.82–1.16)	289	1.00 (0.84–1.19)	273	0.91 (0.76–1.09)	319	1.02 (0.86–1.21)	0.695
Total fish											
Model 1	280	1.00	280	0.99 (0.84–1.17)	263	0.91 (0.77–1.08)	310	1.09 (0.92–1.28)	315	1.11 (0.94–1.30)	0.059
Model 2	269	1.00	274	1.01 (0.85–1.19)	255	0.92 (0.77–1.09)	304	1.11 (0.94–1.30)	303	1.10 (0.93–1.29)	0.095
Fried fish											
Model 1	455	1.00	99	0.93 (0.74–1.16)	303	1.02 (0.88–1.17)	273	0.89 (0.77–1.04)	318	0.98 (0.85–1.13)	0.797
Model 2	444	1.00	96	0.94 (0.75–1.18)	297	1.02 (0.88–1.18)	263	0.90 (0.77–1.05)	305	0.99 (0.85–1.15)	0.914
PhIP											
Model 1	174	1.00	212	1.17 (0.96–1.43)	214	1.19 (0.97–1.45)	176	0.96 (0.78–1.19)	190	1.01 (0.82–1.25)	0.286
Model 2	170	1.00	207	1.17 (0.95–1.43)	209	1.20 (0.98–1.47)	167	0.95 (0.77–1.18)	185	1.02 (0.82–1.26)	0.303
MeIQx											
Model 1	179	1.00	183	1.00 (0.81–1.23)	202	1.07 (0.87–1.30)	212	1.08 (0.88–1.32)	190	0.92 (0.75–1.14)	0.321
Model 2	169	1.00	182	1.06 (0.86–1.31)	197	1.12 (0.91–1.38)	207	1.13 (0.92–1.39)	183	0.96 (0.77–1.18)	0.346
DiMeIQx											
Model 1	353	1.00	10	0.89 (0.48–1.67)	173	0.94 (0.79–1.13)	202	1.05 (0.88–1.25)	228	1.14 (0.96–1.35)	0.066
Model 2	342	1.00	9	0.84 (0.43–1.64)	167	0.95 (0.79–1.14)	198	1.07 (0.90–1.28)	222	1.15 (0.97–1.37)	0.049
BaP											
Model 1	165	1.00	221	1.28 (1.04–1.56)	209	1.19 (0.97–1.46)	204	1.18 (0.96–1.45)	167	0.97 (0.78–1.20)	0.060
Model 2	160	1.00	212	1.27 (1.04–1.56)	206	1.22 (0.99–1.50)	200	1.22 (0.99–1.50)	160	0.98 (0.79–1.22)	0.084

Abbreviations: BaP = benzo(a)pyrene; CI = confidence interval; DiMeIQx = 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; HR = hazard ratio; HT = hormone therapy; MeIQx = 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

[a]Model 1 was adjusted for age (<55, 55–59, 60–64, 65–69 or ⩾70 years); Body mass index (<18.5, 18.5-<25, 25-<30, ⩾30 kg m^{-2}); smoking status (never, former, current); continuous total energy intake and was mutually adjusted for other meat intake. Model 2 was additionally adjusted age at menarche (⩽10, 11-12, ⩾13 years), age at first child's birth(<20, 20–29, ⩾30 years), parity (nulliparous, 1-2 children, ⩾3 children), age at menopause (still menstruating, <44, 44–49, 50–54, ⩾55 years), HT use (never, ever), oral contraceptive use (never, ever), diabetes (yes, no) and physical activity (never/rarely, 1–3 times per month, ⩾1 time per week).

of white or processed meat and fish with HT, smoking status and BMI were not significant (P-interactions > 0.1).

DISCUSSION

In this large, prospective investigation of US women, we observed no association between meat, fish or meat mutagens intakes and endometrial cancer incidence; furthermore, risk was not modified by BMI, HT or smoking status. Stratified analyses showed that the suggested protective association observed with higher red meat intake could be due to confounding, as the HRs were close to 1.00 among never smokers and never HT users.

Our findings contrast with a previous all-cancer investigation in this cohort that reported a 25% lower endometrial cancer risk comparing extreme red meat intake quintiles (P-trend $= 0.02$; Cross *et al*, 2007). Discrepant findings are likely due to endometrial cancer-specific risk factors not adjusted for in the all-cancer analysis, or could be due to more cases and follow-up time in this study. A 2007 meta-analysis (Bandera *et al*, 2007) on meat intake and endometrial cancer risk reported a 44% increased odds of endometrial cancer comparing highest *vs* lowest intake categories in five 'robust' case–control studies (>200 cases, calorie and BMI adjustment; Potischman *et al*, 1993; Shu *et al*, 1993; Goodman *et al*, 1997; Littman *et al*, 2001; Xu *et al*, 2006). This association was strongest for red meat and fish intakes (59% and 88% increased risks, respectively). Another case–control study (454 cases) also found a positive association between red meat intake and endometrial cancer (Bravi *et al*, 2009), whereas a recent cohort study (718 cases) reported no association with red or processed meat (Genkinger *et al*, 2012).

Of the studies on fish in the meta-analysis, most found no association (Levi *et al*, 1993; Hirose *et al*, 1996; Goodman *et al*, 1997; Fernandez *et al*, 1999; Jain *et al*, 2000; McCann *et al*, 2000; Bravi *et al*, 2009), while two Chinese studies reported higher risk with more fresh-water fish consumption (Shu *et al*, 1993; Xu *et al*, 2006). Two other studies suggested inverse associations between fatty fish consumption and endometrial cancer (Terry *et al*, 2002b; Arem *et al*, 2012). However, all but one of the reviewed studies (Jain *et al*, 2000) were case–control design where recall bias is a concern.

Our large sample size, prospective data and wide range of dietary intakes are strengths that provide a more definite conclusion about the lack of association between meat/fish intakes and endometrial cancer. To our knowledge, this study is the first to assess meat mutagens and endometrial cancer. An additional strength in the study size is the ability to assess effect modification and to restrict analyses to never smokers and never HT users. Limitations include the single dietary assessment and differences in FFQs between studies, making comparison of intake quantity difficult. Also, we lacked data on specific types of meat (lean *vs* non-lean) or fish (fatty *vs* non-fatty), which may have different associations with risk.

Overall, we found no association between meat intake and endometrial cancer. Future research could investigate specific types of meat or fish not detailed in this study.

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