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Meat Intake Is Not Associated with Risk of Non-Hodgkin Lymphoma in a Large Prospective Cohort of U.S. Men and Women[1–3]

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Abstract

Meat intake has been inconsistently associated with risk of non-Hodgkin lymphoma (NHL), a heterogeneous group of malignancies of the lymphoid tissue etiologically linked to immunomodulatory factors. In a large U.S. cohort, we prospectively investigated several biologically plausible mechanisms related to meat intake, including meat-cooking and meat-processing compounds, in relation to NHL risk by histologic subtype. At baseline (1995–1996), participants of the NIH-AARP Diet and Health Study completed a diet and lifestyle questionnaire (n = 492,186), and a subcohort (n = 302,162) also completed a questionnaire on meat-cooking methods and doneness levels. Over a mean of 9 y of follow-up, we identified 3611 incident cases of NHL. In multivariable Cox proportional hazards regression models, we found no association between intake of red meat, processed meat, fish, poultry, heme iron, nitrite, nitrate, animal fat, or protein and NHL risk. MeIQx (2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline) and DiMeIQx (2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline), heterocyclic amines formed in meats cooked to well done at high temperatures, were inversely associated with chronic lymphocytic leukemia/small lymphocytic lymphoma [n = 979; HR (95% CI) for the highest vs. lowest quintile of intake: 0.73 (0.55, 0.96) and 0.77 (0.61, 0.98), respectively]. In this large U.S. cohort, meat intake was not associated with NHL or any histologic subtypes of NHL. Contrary to findings in animal models and other cancer sites, meat-cooking and -processing compounds did not increase NHL risk. J. Nutr. 142: 1074–1080, 2012.

Introduction

Non-Hodgkin lymphoma (NHL)[7], a heterogeneous group of malignancies of the lymphoid tissue, is the seventh most common cancer in U.S. men and women with more than half of cases occurring in adults aged ≥65 y (1). Immunosuppression, infection, certain medical conditions, and occupational exposures have been implicated in the etiology of NHL with suggestive evidence for other environmental risk factors, such as tobacco use and obesity (2,3). Some prospective studies have linked intake of red meat, poultry, and other animal products to increased NHL risk (4–6), but the evidence is both limited and inconsistent, particularly among histologic subtypes of NHL (7,8). Intriguingly, occupations in the meat industry, such as butchers, have also been linked to an increased risk of NHL (9,10).

A diet high in red meat, which is a significant source of fat and heme iron, may have immunomodulatory and carcinogenic effects (11–13). Cooked and processed meat can also be a source of several known mutagens, including *N*-nitroso compounds (NOC), heterocyclic amines (HCA), and polycyclic aromatic hydrocarbons (PAH) (14,15). Conversely, raw or undercooked meat may contain viral and bacterial contaminants, but it is unclear what role, if any, this may play in human cancer etiology (16). In a large U.S. cohort, we investigated meat intake in relation to NHL risk, with consideration of potential variation by histologic subtype as well as mechanisms related to meat cooking and processing.

Participants and Methods

Ethics statement. The conduct of the NIH-AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute, and all participants gave informed consent by virtue of completing and returning the questionnaire.

Study cohort. The NIH-AARP Diet and Health Study is a large prospective cohort of U.S. men and women, aged 50–71 y, residing in 6

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[3] This trial was registered at clinicaltrials.gov as NCT00340015.
[7] Abbreviations used: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; DLBCL, diffuse large B-cell lymphoma; HCA, heterocyclic amine; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; NHL, non-Hodgkin lymphoma; NOC, *N*-nitroso compound; PAH, polycyclic aromatic hydrocarbon.
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states (CA, FL, LA, NJ, NC, and PA) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI) and is described in detail elsewhere (17). The baseline questionnaire on demographic characteristics, diet, and lifestyle was completed by 567,169 participants during 1995–1996. Of those, 566,401 completed the survey satisfactorily and consented to be a part of the study. We further excluded proxy respondents (n = 15,760) and participants with prevalent cancer (as noted by cancer registry or self-report; n = 51,223) or end-stage renal disease (n = 997) at baseline, a death-only report for any cancer (n = 1804), zero person-years of follow-up (n = 36), or implausibly high (men: >6141 kcal/d; women: >4791 kcal/d) or low (men: <415 kcal/d; women: <318 kcal/d) total energy intake (18) (n = 4395). After exclusions, the baseline analytic cohort included 492,186 participants (n = 293,466 men, 198,720 women). An additional Risk Factor Questionnaire with a meat-cooking module was sent ~6 mo after the baseline questionnaire; 302,162 participants (n = 176,179 men, 125,983 women) responded and met the inclusion criteria above (hereafter referred to as the "subcohort").

Dietary assessment. Participants were asked to report their usual dietary intake over the past year using a 124-item FFQ developed and validated by the National Cancer Institute (18). Nutrient and total energy intakes were calculated by using the 1994–1996 USDA's Continuing Survey of Food Intakes by Individuals (19). The red meat variable contained all types of fresh (beef, pork, hamburger, steak, and liver) and processed (bacon, cold cuts, ham, hot dogs, and sausage, excluding low-fat versions made from poultry products) red meat. Poultry intake comprised fresh (chicken, turkey, and ground poultry) and processed (poultry cold cuts, low-fat sausages, and low-fat hot dogs) poultry. Fish intake included all types of finfish/shellfish and canned tuna. We further investigated intake of fat (total, saturated, monounsaturated, and polyunsaturated fatty acids), protein, and various animal sources of these nutrients (e.g., the contribution from red meat, white meat, dairy, and eggs). The validated meat-cooking module, in conjunction with the CHARRED (Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease) database (20–22), assessed the usual meat-cooking method and internal and external appearance (browning or doneness level) of hamburgers/cheeseburgers, steak (beef), bacon, and chicken to estimate values of the following: 3 HCA [2-amino-1-methyl-6-phenyl-imidazo(4,5-b)pyridine, 2-amino-3,8-dimethylimidazo(4,5-f) quinoxaline (MeIQx), and 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (DiMeIQx)], one PAH [benzo(a)pyrene], mutagenic activity (a measure of total mutagenic potential incorporating all meat-related mutagens), and heme iron intake by using an exposure index described in detail elsewhere (21,23). Similarly, intake of nitrate and nitrite was estimated by using a database of measured values from 10 types of processed meat, constituting 90% of the processed meat types consumed in the United States (21).

Case ascertainment. Cancer cases were ascertained through linkage with the 8 original state cancer registries plus an additional 2 states (AZ, TX). The cancer registries are certified by the North American Association of Central Cancer Registries as being ≥90% complete within 2 y of cancer incidence (24). Follow-up for each subject began on the date of questionnaire return and continued until the date of cancer diagnosis, date of censoring due to loss to follow-up, death, or December 31, 2006, whichever came first.

Using the *International Classification of Diseases for Oncology,* 3rd edition (ICD-0–3) (25), in accordance with the WHO classification and the International Lymphoma Epidemiology Consortium (InterLymph) guidelines (26), we restricted our definition of primary incident NHL to the following histology codes: 9591, 9670–71, 9673, 9675, 9678–80, 9684, 9687, 9689–91, 9695, 9698–9702, 9705, 9708–09, 9714, 9716–19, 9727–29, 9760–64, 9823, 9826–27, 9831–37, and 9940. In concordance with recent analyses of NHL (8,27), we did not include plasma cell myelomas in our NHL case definition due to distinct etiology and incidence patterns (28). We further investigated the most common subtypes of NHL: diffuse large B-cell lymphoma (DLBCL; histology codes 9678–80, 9684), follicular lymphoma (9690–91, 9695, 9698), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 9670, 9823). Defined subtypes with <100 cases in each sex or NHL of unknown lineage/not otherwise specified were not included in the subtype analysis; the proportion of NHL, not otherwise specified in our study was consistent with overall SEER (Surveillance, Epidemiology, and End Results) data (29).

Statistical analyses. All dietary variables were adjusted for total energy intake by using the nutrient density method and presented for ease of interpretability as units per 1000 kcal/d of total energy intake. Residual energy adjustment (30) produced similar results. The association between meat intake and risk of NHL was evaluated with Cox proportional hazards regression models with time since entry (person-years) as the underlying time metric. The HR, 95% CI, and P values for linear trend (using the median value within quintiles) are reported across sex-specific quintiles of intake with the lowest intake quintile representing the referent group. Given the limited range of intake, rare meat was modeled as a dichotomous variable (any vs. none), whereas well-done meat was modeled in tertiles. We confirmed that the Cox proportional hazards assumption was met through assessment of interaction terms for the exposures with follow-up time. Multivariable models included age (continuous), sex, education (less than high school, high school graduate, some college, college graduate), family history of any cancer (first-degree relative), race (non-Hispanic white, non-Hispanic black, other), BMI [<25 (reference), 25 to <30, ≥30 kg/m^2], smoking status (never, quit ≥10 y ago, quit 1 to 9 y ago, quit <1 y ago or currently smoking), alcohol intake (none, >0 to <5, 5 to <15, 15 to <30, ≥30 g/d), frequency of vigorous physical activity (never/rarely, 1–3 times/mo, 1–4 times/wk, ≥5 times/wk), and intake of fruit, vegetables [MyPyramid Equivalents Database (31) servings per 1000 kcal/d], and total energy (continuous). Risk estimates were mutually adjusted for quintiles of other meat intake, such that the sum of all the meat variables in the model would represent total meat intake [i.e., red meat intake was adjusted for poultry and fish intake, and vice versa (32)].

Results are presented for both sexes combined, because we did not observe any statistically significant interactions with sex. We also assessed whether associations varied by smoking status, BMI, or alcohol intake and conducted a lag analysis that excluded the first 2 y of follow-up. Statistical tests for interaction evaluated the significance of categorical cross-product terms in the multivariate-adjusted models. All statistical tests were 2-sided and considered significant at $P < 0.05$. All statistical analyses were conducted by using SAS 9.2 (SAS Institute, Inc.).

Results

Over a mean follow-up of 9 y, we ascertained 3611 NHL cases (n = 888 DLBCL, n = 612 follicular, n = 979 CLL/SLL) in the baseline analysis and 2155 NHL cases (n = 509 DLBCL, n = 368 follicular, n = 586 CLL/SLL) in the subcohort analysis. Individuals in the highest compared with the lowest category of red meat intake were more likely to be non-Hispanic white, current smokers, and to have a higher BMI (**Table 1**).

We observed no significant associations between meat intake and NHL (**Table 2**). We found a nonsignificant inverse trend between total processed meat intake and follicular lymphoma (P-trend = 0.07) and between processed red meat intake and CLL/SLL (P-trend = 0.08). Fish intake above the first quintile (Q) appeared to be associated with an increased risk of follicular lymphoma [HR(95% CI), Q2 vs. Q1 (reference): 1.41 (1.10, 1.82)] but was attenuated across the upper categories of intake [Q5 vs. Q1: 1.27 (0.97, 1.65); P-trend = 0.19]. We also observed no associations in analyses of individual meat items (chicken, pork, sausage, etc.) or other animal products and related nutrients, such as intake of eggs, dairy, animal fat or protein, total fat, saturated fat, (n-3) or (n-6) PUFA, and fat or protein from dairy or meat sources (data not shown).

Endogenous (heme iron and N-nitroso compounds) and exogenous (HCA and PAH) compounds related to meat intake were not associated with total NHL risk (**Table 3**). We also

TABLE 1 Selected characteristics of the NIH-AARP Diet and Health Study cohort by red meat intake (n = 492,186)[1]

Characteristic	Quintile of red meat intake 1	2	3	4	5
n	98,365	98,366	98,366	98,366	98,366
Red meat, *g/1000 kcal*	9.7 ± 0.02	21.8 ± 0.01	31.6 ± 0.02	42.9 ± 0.02	66.8 ± 0.06
Age, *y*	62.4 ± 0.02	62.4 ± 0.02	62.1 ± 0.02	61.9 ± 0.02	61.3 ± 0.02
Male, *%*	59.6	59.6	59.6	59.6	59.6
Race, *%*					
White, non-Hispanic	87.5	90.7	92.0	93.1	92.8
Black, non-Hispanic	5.7	4.3	3.7	3.7	2.8
College and post-college, *%*	46.4	40.6	37.9	35.6	32.4
Currently married, *%*	63.3	67.3	69.7	71.1	71.3
Positive family history of cancer, *%*	47.6	48.8	49.2	49.2	48.3
Smoking status, %					
Never smoker	40.8	40.1	37.0	37.5	33.8
Current smoker or quit <1 y ago	7.4	11.3	13.0	16.0	18.6
Alcohol intake, *g/d*	14.5 ± 0.14	14.1 ± 0.11	12.5 ± 0.09	11.2 ± 0.08	9.4 ± 0.06
BMI, *kg/m²*	25.8 ± 0.01	26.7 ± 0.02	27.1 ± 0.02	27.6 ± 0.02	28.3 ± 0.02
Physical activity (vigorous ≥20 min), *%*					
<1 times/mo	13.6	15.8	17.3	19.4	23.4
≥5 times/wk	27.2	20.7	18.0	16.1	14.2
Daily dietary intake					
White meat, *g/1000 kcal*	36.6 ± 0.10	33.4 ± 0.08	32.4 ± 0.07	32.3 ± 0.07	32.8 ± 0.07
Processed meat, *g/1000 kcal*	5.3 ± 0.02	8.2 ± 0.02	10.6 ± 0.02	13.6 ± 0.03	19.1 ± 0.04
Fruit, *MPED*[2] *servings/1000 kcal*	1.7 ± 0.003	1.3 ± 0.003	1.1 ± 0.002	1.0 ± 0.002	0.8 ± 0.002
Vegetables, *MPED servings/1000 kcal*	1.3 ± 0.003	1.1 ± 0.002	1.1 ± 0.002	1.1 ± 0.002	1.0 ± 0.002
Total energy intake, *kcal/d*	1760 ± 2.5	1790 ± 2.5	1830 ± 2.5	1870 ± 2.6	1930 ± 2.7

[1] Values are means ± SE or percentages.
[2] MPED, MyPyramid Equivalents Database.

observed no association with rare red meat intake, but few participants reported consuming hamburger (<6%) or steak (<17%) that was red or deep pink on the inside. Ever consuming "just done (still juicy)" chicken was associated with an increased risk of follicular lymphoma [HR (95% CI): 1.42 (1.09–1.85)]. Conversely, intake of red meat cooked well to very well done [HR (95% CI): 1.00 (reference), 0.77 (0.63, 0.95), 0.78 (0.62, 0.98); *P*-trend = 0.12] and 2 HCA, MeIQx and DiMeIQx, was inversely associated with risk of CLL/SLL [HR (95% CI) for Q5 vs. Q1: 0.78 (0.62, 0.98), *P*-trend = 0.12; 0.73 (0.55, 0.96), *P*-trend = 0.01; 0.77 (0.61, 0.98), *P*-trend = 0.07, respectively]. The associations we observed between total mutagenic activity and risk of total NHL and the 3 main subtypes were consistent with the overall results presented for individual cooking mutagens [HR (95% CI) for Q5 vs. Q1: 0.95 (0.82, 1.08); 0.96 (0.73, 1.28); 1.21 (0.86, 1.69); 0.84 (0.64, 1.10) for total NHL, DLBCL, follicular lymphoma, and CLL/SLL, respectively; data in text only]. No associations were observed with "medium-done" meat intake (data not shown). We found no significant interactions with gender, smoking status, BMI, or alcohol intake across any of the exposures or NHL subtypes.

Discussion

In this large U.S. cohort, we found no association between intake of meat or other animal products and risk of NHL. However, the highest versus lowest quintiles of MeIQx and DiMeIQx intakes were associated with a 20–30% lower risk of the CLL/SLL subtype. We had a limited range of intakes to assess rare or potentially undercooked meat but ever consuming "just done" chicken appeared to be associated with an increased risk of follicular lymphoma. We cannot rule out the possibility of chance as an explanation for the few significant findings by subtype. Overall, our results do not support the hypothesis that meat intake increases NHL risk.

Although the range of red meat intake in this large cohort is comparable to that of similarly sized pooled prospective analyses (33,34), our null results are in contrast to other prospective studies reporting positive associations between intake of red meat (4,5), poultry (6), processed meat (6), animal fat (4), and a "fat and meat" dietary pattern (35) and NHL risk. However, results were largely inconsistent across studies, particularly by subtype. Our null findings for meat intake across NHL subtypes were consistent with the null associations we observed for meat components, including heme iron, nitrate and nitrite, fat, and protein intake by NHL subtype. In general, many of the previously reported associations between various types of meat intake and NHL subtypes have been for follicular lymphoma (6,35–37), whereas in the largest pooled prospective investigation to date of diet and CLL/SLL risk, no associations with food groups were observed (33). Although the inverse associations in this cohort between intake of well-done red meat, DiMeIQx, and MeIQx and CLL/SLL appear to contradict direct associations observed for other cancer sites (14), the literature suggests that the association between meat-cooking and NHL risk may be less straightforward. Well-done meat intake was previously associated with lower risk of NHL in 2 prospective cohorts of U. S. women (4,5), whereas across retrospective case-control studies both significant positive and inverse associations with intake of pan-fried red meat, well-done meat, and HCA have been reported (8,37–39). Similar to our findings, one case-control study reported an inverse association between DiMeIQx

TABLE 2 Intake of meat and risk of NHL: NIH-AARP Diet and Health Study baseline questionnaire (n = 492,186)[1]

Median intake within quintile, *g/1000 kcal*	NHL (n = 3,611)			DLBCL (n = 888)			Follicular (n = 612)			CLL/SLL (n = 979)		
	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI
	n			*n*			*n*			*n*		
Red meat, total												
9.8	696	1.00		169	1.00		118	1.00		199	1.00	
21.4	763	1.08	0.97, 1.20	185	1.13	0.92, 1.40	131	1.07	0.83, 1.37	214	1.03	0.84, 1.25
31.6	790	1.12	1.01, 1.25	190	1.19	0.96, 1.48	137	1.10	0.85, 1.42	215	1.03	0.84, 1.26
42.9	678	0.97	0.87, 1.09	174	1.11	0.89, 1.39	109	0.87	0.66, 1.15	166	0.80	0.64, 0.99
62.7	684	1.01	0.90, 1.14	170	1.11	0.88, 1.40	117	0.94	0.71, 1.25	185	0.93	0.75, 1.16
P-trend		0.41			0.64			0.27			0.16	
Red meat, nonprocessed												
6.8	716	1.00		182	1.00		118	1.00		195	1.00	
15.3	757	1.01	0.91, 1.12	178	0.99	0.80, 1.23	130	1.01	0.78, 1.31	221	1.08	0.88, 1.32
22.7	747	0.99	0.89, 1.11	175	0.98	0.78, 1.23	122	0.92	0.70, 1.21	200	0.98	0.79, 1.21
31.6	720	0.97	0.86, 1.09	179	1.02	0.81, 1.29	131	0.98	0.74, 1.30	187	0.94	0.75, 1.18
48.1	671	0.93	0.83, 1.05	174	1.02	0.80, 1.29	111	0.84	0.63, 1.13	176	0.94	0.75, 1.19
P-trend		0.27			0.77			0.33			0.48	
Processed meat, total												
2.2	705	1.00		174	1.00		119	1.00		196	1.00	
5.3	729	1.03	0.93, 1.15	177	1.06	0.86, 1.31	120	0.98	0.76, 1.27	209	1.04	0.86, 1.27
8.6	767	1.09	0.98, 1.22	176	1.07	0.86, 1.33	146	1.19	0.92, 1.52	207	1.04	0.85, 1.27
13.3	719	1.03	0.92, 1.15	185	1.14	0.92, 1.42	124	1.00	0.77, 1.30	184	0.92	0.75, 1.14
23.6	691	0.99	0.89, 1.11	176	1.07	0.86, 1.34	103	0.83	0.63, 1.10	183	0.93	0.75, 1.15
P-trend		0.45			0.68			0.07			0.20	
Processed meat, red												
1.4	681	1.00		181	1.00		108	1.00		190	1.00	
3.7	748	1.10	0.99, 1.23	171	0.99	0.80, 1.24	122	1.13	0.86, 1.48	213	1.09	0.89, 1.34
6.4	747	1.12	1.00, 1.25	176	1.04	0.83, 1.31	135	1.26	0.96, 1.66	215	1.11	0.90, 1.37
10.1	730	1.10	0.98, 1.24	182	1.09	0.87, 1.38	127	1.19	0.89, 1.59	193	1.00	0.80, 1.26
19.9	705	1.07	0.95, 1.20	178	1.07	0.84, 1.35	120	1.13	0.84, 1.52	168	0.88	0.70, 1.11
P-trend		0.91			0.66			0.90			0.08	
Poultry												
4.4	700	1.00		181	1.00		113	1.00		189	1.00	
10.3	746	1.04	0.94, 1.16	175	0.98	0.80, 1.21	135	1.14	0.88, 1.47	197	1.01	0.82, 1.23
16.7	747	1.04	0.94, 1.16	192	1.08	0.88, 1.33	120	1.00	0.77, 1.31	185	0.95	0.77, 1.17
26.0	713	1.00	0.90, 1.12	163	0.92	0.74, 1.15	122	1.02	0.78, 1.33	207	1.08	0.88, 1.33
47.1	705	1.00	0.90, 1.12	177	0.99	0.80, 1.24	122	1.02	0.78, 1.34	201	1.08	0.88, 1.34
P-trend		0.77			0.79			0.80			0.25	
Fish												
2.1	688	1.00		193	1.00		106	1.00		184	1.00	
4.9	698	1.01	0.91, 1.12	171	0.90	0.73, 1.11	114	1.07	0.82, 1.40	188	1.01	0.82, 1.24
7.9	765	1.10	0.99, 1.23	158	0.83	0.67, 1.03	149	1.41	1.10, 1.82	214	1.14	0.93, 1.39
12.5	728	1.06	0.95, 1.18	184	0.98	0.79, 1.20	113	1.08	0.82, 1.45	204	1.09	0.88, 1.33
23.1	732	1.07	0.96, 1.16	182	0.96	0.78, 1.19	130	1.27	0.97, 1.65	189	1.01	0.82, 1.25
P-trend		0.24			0.75			0.19			0.98	

[1] CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL; diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma.
[2] Cox proportional hazards regression multivariable model adjusted for age, sex, education, family history of any cancer, race, BMI, smoking status, physical activity, and intake of alcohol, fruit, vegetables, and total energy; mutually adjusted for other meat intake.

and NHL (38). However, in direct contrast to our findings, a larger case-control study of NHL subtypes reported a positive association between MeIQx and DiMeIQx intake and CLL/SLL (8).

A dual hypothesis for meat-cooking and NHL risk may be plausible. The primary hypothesis that carcinogenic compounds formed in well-done grilled and pan-fried meat may increase NHL risk is largely supported by animal-feeding studies in which HCA derived from cooked meat induced lymphomas in rodent models (40). The potential role of chronic immune stress, viruses, and other infectious agents in NHL etiology (2) suggests a secondary hypothesis that rare or undercooked meat may be a source of viral or bacterial contaminants destroyed by cooking to a high level of doneness and temperature (41). In support of the latter, occupational exposure to meat (e.g., butchers, slaughterhouse workers, farmers) has also been linked to increased NHL risk (9,10). The role of oncogenic viruses and other contaminants were also cited as a potential explanation for the positive association observed between poultry intake and follicular lymphoma in the EPIC (European Prospective Investigation into Cancer and Nutrition) study (6). Although we found no associations with total poultry intake, we found that ever consuming "just done" chicken was associated with higher risk of follicular lymphoma. In our analysis, intake of MeIQx

TABLE 3 Intake of meat cooked to different doneness levels, meat-cooking mutagens, and meat-related compounds in relation to risk of NHL: NIH-AARP Diet and Health Study subcohort (n = 302,162)[1]

Median intake within	NHL (n = 2155)			DLBCL (n = 509)			Follicular (n = 368)			CLL/SLL (n = 586)		
quantile, *U/1000 kcal*	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI
	n			*n*			*n*			*n*		
Steak and hamburgers, rare, *g*												
0	1946	1.00		463	1.00		330	1.00		529	1.00	
5.4	209	1.03	0.89, 1.20	46	0.93	0.68, 1.27	38	1.17	0.82, 1.66	57	1.01	0.79, 1.35
Chicken, just done, *g*												
0	1478	1.00		339	1.00		245	1.00		405	1.00	
4.9	677	1.03	0.91, 1.15	170	1.06	0.84, 1.35	123	1.42	1.09, 1.85	181	0.93	0.74, 1.16
Steak and hamburgers, well to very well done, *g*												
0.06	769	1.00		186	1.00		119	1.00		224	1.00	
1.6	671	0.87	0.78, 0.96	153	0.86	0.69, 1.07	115	0.95	0.73, 1.23	177	0.77	0.63, 0.95
8.1	715	0.90	0.80, 1.01	170	0.94	0.74, 1.20	134	1.08	0.81, 1.44	185	0.78	0.62, 0.98
P-trend		0.31			0.97			0.39			0.12	
Chicken, well to very well done, *g*												
0	797	1.00		199	1.00		139	1.00		220	1.00	
1.6	632	1.11	0.91, 1.35	134	1.00	0.67, 1.50	112	1.46	0.86, 2.48	166	0.87	0.61, 1.23
8.9	726	1.16	0.95, 1.41	176	1.16	0.77, 1.73	117	1.44	0.85, 2.46	200	0.97	0.68, 1.37
P-trend		0.22			0.20			0.65			0.47	
PhIP, *ng*												
2.1	471	1.00		100	1.00		78	1.00		136	1.00	
10.9	424	0.90	0.79, 1.03	95	0.97	0.73, 1.29	80	1.01	0.74, 1.38	114	0.83	0.64, 1.06
24.7	432	0.93	0.81, 1.06	106	1.11	0.84, 1.46	71	0.90	0.65, 1.25	122	0.90	0.70, 1.15
49.4	389	0.85	0.74, 0.98	101	1.07	0.81, 1.42	62	0.80	0.57, 1.12	100	0.75	0.58, 0.98
123.6	439	0.98	0.86, 1.12	107	1.14	0.87, 1.51	77	0.99	0.72, 1.36	114	0.90	0.69, 1.14
P-trend		0.71			0.29			0.85			0.72	
MeIQx, *ng*												
0.5	453	1.00		119	1.00		75	1.00		128	1.00	
2.4	450	1.00	0.87, 1.13	95	0.81	0.62, 1.07	71	0.94	0.68, 1.30	134	1.03	0.81, 1.32
5.3	415	0.92	0.80, 1.05	97	0.84	0.64, 1.10	73	0.96	0.69, 1.32	117	0.90	0.70, 1.16
10.3	435	0.97	0.85, 1.11	90	0.79	0.59, 1.04	70	0.91	0.65, 1.27	116	0.90	0.70, 1.17
24.4	402	0.90	0.78, 1.04	108	0.95	0.72, 1.24	79	1.01	0.73, 1.40	91	0.73	0.55, 0.96
P-trend		0.12			0.82			0.91			0.01	
DiMeIQx, *ng*												
0	789	1.00		190	1.00		132	1.00		230	1.00	
0.04	93	1.05	0.85, 1.31	24	1.16	0.76, 1.78	12	0.84	0.47, 1.53	23	0.85	0.55, 1.30
0.19	428	0.96	0.85, 1.08	94	0.88	0.69, 1.13	72	0.97	0.73, 1.30	113	0.86	0.69, 1.08
0.58	408	0.93	0.82, 1.04	87	0.83	0.64, 1.07	71	0.95	0.71, 1.27	124	0.96	0.77, 1.20
1.7	437	1.01	0.90, 1.14	114	1.10	0.87, 1.39	81	1.08	0.82, 1.43	96	0.77	0.61, 0.98
P-trend		0.98			0.38			0.59			0.07	
BaP, *ng*												
0.2	435	1.00		90	1.00		77	1.00		121	1.00	
1.5	435	1.00	0.88, 1.15	121	1.36	1.03, 1.78	70	0.90	0.65, 1.24	114	0.95	0.73, 1.22
6.2	429	0.98	0.86, 1.13	102	1.14	0.85, 1.51	71	0.90	0.65, 1.25	111	0.91	0.71, 1.18
16.8	424	0.99	0.86, 1.13	91	1.04	0.77, 1.39	80	1.02	0.75, 1.41	115	0.96	0.74, 1.24
44.0	432	1.04	0.91, 1.19	105	1.25	0.94, 1.66	70	0.91	0.66, 1.27	125	1.09	0.85, 1.41
P-trend		0.42			0.74			0.86			0.20	
Heme iron, *μg*												
48.1	446	1.00		107	1.00		70	1.00		124	1.00	
100.9	442	0.97	0.85, 1.11	102	0.96	0.73, 1.26	69	0.96	0.68, 1.34	129	1.01	0.79, 1.30
151.3	438	0.96	0.84, 1.10	108	1.02	0.77, 1.34	82	1.13	0.81, 1.56	106	0.84	0.64, 1.09
212.7	414	0.92	0.80, 1.06	94	0.90	0.68, 1.20	68	0.93	0.66, 1.32	117	0.94	0.72, 1.22
336.0	415	0.96	0.83, 1.10	98	0.98	0.68, 1.20	79	1.10	0.78, 1.55	110	0.93	0.71, 1.23
P-trend		0.37			0.77			0.82			0.54	
Nitrate + nitrite from processed meat sources, *mg*												
0.04	398	1.00		110	1.00		67	1.00		94	1.00	
0.10	442	1.07	0.94, 1.23	95	0.86	0.65, 1.13	87	1.26	0.91, 1.74	124	1.25	0.95, 1.63
0.18	445	1.06	0.92, 1.22	97	0.87	0.66, 1.16	65	0.93	0.66, 1.32	140	1.36	1.04, 1.78

(Continued)

TABLE 3 *Continued*

Median intake within quantile, *U/1000 kcal*	NHL (*n* = 2155)			DLBCL (*n* = 509)			Follicular (*n* = 368)			CLL/SLL (*n* = 586)		
	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI	Cases	HR[2]	95% CI
0.27	425	0.99	0.85, 1.14	102	0.91	0.68, 1.21	81	1.15	0.82, 1.61	110	1.02	0.77, 1.36
0.47	445	1.02	0.88, 1.18	105	0.93	0.70, 1.24	68	0.96	0.67, 1.37	118	1.08	0.81, 1.44
P-trend		0.68			0.95			0.50			0.50	

[1] BaP, benzo(a)pyrene; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DiMeIQx, 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline; DLBCL; diffuse large B-cell lymphoma; MeIQx, 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline; NHL, non-Hodgkin lymphoma; PhIP, 2-amino-1-methyl-6-phenyl-imidazo(4,5-b)pyridine.
[2] Cox proportional hazards regression multivariable model adjusted for age, sex, education, family history of any cancer, race, BMI, smoking status, physical activity, and intake of alcohol, fruit, vegetables, and total energy; meat types cooked to different levels of doneness were mutually adjusted for other cooked and uncooked meat intake.

and DiMeIQx may simply be a proxy for well-done red meat intake (42), which was also significantly associated with lower risk of CLL/SLL.

In the largest prospective investigation of meat intake and NHL risk to date, we were able to consider various mechanisms related to meat cooking and processing, as well as risk by histologic subtypes. Although the prospective design avoids recall and selection bias, diet and lifestyle information obtained by self-report among older adults is subject to measurement error and may not entirely reflect lifelong cumulative exposures or the most pertinent time period for NHL etiology. In this analysis, intake was only estimated at one point in time (baseline); however, red meat intake or cooking preference earlier in life may be more relevant for NHL risk than diet in later life, which may reflect greater health awareness. Due to a large number of comparisons, we cannot exclude the possibility that the few significant results may be attributable to chance, but it is also unlikely, given the size of the study, that any strong associations would have been missed. Previously reported associations between meat and NHL in case-control and early prospective studies may have been subject to recall bias and/or residual confounding, because many lacked adjustment for risk factors such as BMI. However, given the inconsistency of our findings across intake categories and subtypes, we also cannot rule out the possibility of residual confounding by unknown or unmeasured factors in this analysis. The statistically significant inverse associations we observed for intake of MeIQx and DiMeIQx were confined to the top quintile, which followed a skewed distribution with most of the population consuming relatively low amounts of these compounds (43).

Intakes of red meat, processed meat, poultry, fish, heme iron, nitrite, nitrate, or other animal products were not associated with NHL or with any of the histologic subtypes in this large U.S. cohort. Contrary to findings in animal models and in other cancer sites, meat-cooking and -processing compounds did not appear to increase NHL risk. MeIQx and DiMeIQx, which are HCA found in well-done meat cooked at high temperatures, were inversely associated with CLL/SLL, the most common subtype among older adults in the Western world. To our knowledge, this is the first prospective investigation of potentially mutagenic compounds related to meat intake, meat cooking, and NHL risk by subtype. Although these findings may be due to chance, the potential relationship between undercooked meat and NHL risk deserves further attention, because the limited range of "rare" meat intake within this population may not have been adequate to evaluate this hypothesis.

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Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDC) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services.

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