A Prospective Study of Meat and Fat Intake in Relation to Small Intestinal Cancer

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Abstract

Diets high in red and processed meats are associated with carcinogenesis of the large intestine, but no prospective study has examined meat and fat intake in relation to cancer of the small intestine. We prospectively investigated meat and fat intakes, estimated from a food frequency questionnaire, in relation to small intestinal cancer among half a million men and women enrolled in the NIH-AARP Diet and Health Study. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). During up to 8 years of follow-up, 60 adenocarcinomas and 80 carcinoid tumors of the small intestine were diagnosed. Despite slightly elevated HRs for red meat, there were no clear associations for red or processed meat intake and either adenocarcinoma or carcinoid tumors of the small intestine. In contrast, we noted a markedly elevated risk for carcinoid tumors of the small intestine with saturated fat intake in both the categorical (highest versus lowest tertile: HR, 3.18; 95% CI, 1.62–6.25) and continuous data (HR, 3.72; 95% CI, 1.79–7.74 for each 10-g increase in intake per 1,000 kcal). Our findings suggest that the positive associations for meat intake reported in previous case-control studies may partly be explained by saturated fat intake. [Cancer Res 2008;68(22):9274–9]

Introduction

Despite substantial global variation, very little is known about risk factors for small intestinal cancer. The age-standardized incidence rates for this malignancy range from <0.5/100,000 in some regions of Africa and Asia to 3.7/100,000 in certain areas of the United States (1), where rates have been increasing since the 1970s.[4] In addition, individuals with cancer of the small intestine have a three times higher risk of developing colorectal cancer, as well as a 68% increased risk of subsequently developing any second primary cancer (2).

Of the limited number of epidemiologic investigations of lifestyle factors and small intestinal cancer, smoking and alcohol have been positively associated with this malignancy in some (3, 4), but not all (5, 6), studies. Data for dietary exposures and small intestinal cancer are restricted to a few case-control studies, all of which have found elevated risks associated with red and processed meat intake (4–6), although case-control studies are subject to recall bias (7). Meat is also a source of fat intake, particularly saturated fat, and although there have been many investigations of fat intake and other cancer sites, none of the published studies of small intestinal cancer reported on fat. No prospective study has examined meat or fat intake in relation to cancer of the small intestine. The aim of this study was to prospectively examine whether meat or fat intake elevated the risk for cancer of the small intestine in a cohort of approximately half a million men and women, a study large enough to yield a sufficient number of cases for analysis.

Materials and Methods

Study population. The NIH-AARP (formerly known as the American Association for Retired Persons) Diet and Health Study is a large prospective cohort of men and women, ages 50 to 71 y, from six states in the United States (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). Recruitment began in 1995 when a self-administered questionnaire was mailed to 3.5 million members of AARP. Details of the cohort have been described elsewhere (8, 9). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute (NCI), and written informed consent was obtained from all participants by virtue of completing the baseline questionnaire.

Dietary assessment. A 124-item food frequency questionnaire (FFQ), based on the NCI Diet History Questionnaire, was completed at baseline. The FFQ assessed usual frequency of consumption and portion size information of foods and drinks over the previous 12 mo. Portion sizes and nutrient intakes were calculated from the 1994–1996 U.S. Department of Agriculture Continuing Survey of Food Intake by Individuals (10) based on three categories (<25th, 25th–75th, and >75th percentile) of the portion size distribution for food groups consistent with line items on the FFQ. The FFQ was validated within this study population against two 24-h recall interviews (9); the energy-adjusted correlation coefficients for saturated fat were 0.76 and 0.69 (11) and for red meat were 0.62 and 0.70 for men and women, respectively (9). The meat variables were based on frequency of consumption and portion size information. The red meat variable included all types of beef and pork. Processed meat included both red and white meat sources of bacon, sausage, luncheon meats, cold cuts, ham, and hotdogs. The meat variables also included meats added to complex food mixtures, such as pizza, chili, lasagna, and stew. We investigated total fat, as well as subgroups of saturated, monounsaturated, and polyunsaturated fats. Furthermore, we investigated the fat source; for example, the contribution to total fat from red meat, white meat, dairy, eggs, margarine/oils, butter, and other. Fruit and vegetable intake was based on the U.S. Department of Agriculture Pyramid Servings guidance system, which incorporates frequency of consumption, portion size, and components of mixed dishes (12).

Cohort follow-up and case ascertainment. Cohort members are followed annually for change of address using the U.S. Postal Service, and

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vital status is ascertained by annual linkage to the U.S. Social Security Administration Death Master File. Follow-up for these analyses was calculated from baseline (1995–1996) until censoring at the end of 2003, or when the participant moved out of one of the study areas, had a cancer diagnosis, or died, whichever came first. Cancer cases were identified by linkage to state cancer registries and the National Death Index. The eight state cancer registry databases are estimated to be 95% complete within 2 y of cancer incidence and are certified by the North American Association of Central Cancer Registries for meeting the highest standard of data quality, capturing ~90% of cancer cases (8). Beyond the eight original states of our cohort, our cancer registry ascertainment area was recently expanded to include three additional states (Texas, Arizona, and Nevada) where participants have most commonly moved to during follow-up.

Small intestine cancers were defined as first primary cancers by the following international classification of diseases (ICD) codes: ICD-O-3 codes C170 to C179, ICD-9 code 152 (which includes codes 152.0, 152.1, 152.2, 152.3, 152.8, and 152.9), or ICD-10 code C17 (which includes codes C17.0, C17.1, C17.2, C17.3, C17.8, and C17.9; ref. 13). Because risk factors may differ according to histologic type, as has been suggested for the relations with tobacco and alcohol (14), we analyzed the data according to the two main histologic subtypes of adenocarcinomas and carcinoid tumors using data provided by the cancer registries.

Statistical analysis. A total of 567,169 persons returned the baseline questionnaire and were available for analysis (9). We excluded those who died before the baseline questionnaire was received and processed (n = 261), had zero person years of follow-up (n = 9), moved out of the study areas before returning the questionnaire (n = 321), requested to be withdrawn (n = 6), had prevalent cancer (n = 51,193) or end-stage renal disease (n = 997) at baseline, had duplicate records (n = 179), had extreme (more than two interquartile ranges above the 75th or below the 25th percentile on the logarithmic scale) daily energy intake (n = 4,381), as well as those whose questionnaire was completed by someone else on their behalf (n = 15,760). After exclusions, our analytic cohort consisted of 294,707 men and 199,293 women.

Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards regression with age as the underlying time metric. We created addition models for meat, with all variables in each model adding up to total meat; for example, the red meat model also contained white meat and the processed meat model also contained nonprocessed meat. The sources of monounsaturated and saturated fats are similar, and due to colinearity, we did not mutually adjust the fat subtypes.

Parsimonious (age, gender, and calories) and multivariable adjusted HRs are reported within tertiles, using the lowest tertile as the reference category, as well as for continuous data (per 10-g increase per 1,000 kcal). Tests for linear trend within the categorical data were calculated using the median value of each tertile. All reported P values are two-sided. Little is known about risk factors for small intestinal cancer; however, we examined variables that have been shown to confound the association between meat or fat and other gastrointestinal cancers. The covariates included in the multivariable models included person years, gender, education, marital status, family history of cancer, race, body mass index (BMI), smoking, frequency of vigorous physical activity (defined as activities at work or home that lasted at least 20 min and caused an increase in breathing or heart rate or worked up a sweat), and intakes of energy, alcohol, fruits, and vegetables. Missing data were minimal for this study. For smoking, BMI, and education, we created "missing" categories; for family history of cancer, marital status, and physical activity, we set individuals missing these data to zero (i.e., no family history, not married, or not physically active). We examined models adjusted for energy by the multivariable nutrient density method, as well as the residual energy adjustment method (7). Both methods gave similar results; here we report the results using the nutrient density method.

To test for heterogeneity between the histologic subtypes, we used a χ^2 test with 1 degree of freedom. We first calculated the weighted average of the two β coefficients from the Cox model, with weights being proportional to the inverse of the variances. Then we calculated the following χ^2 statistic: $T = \sum_{i=1}^{2}(\hat{\beta}_i - \bar{\beta})^2/\sigma_i^2$, where $\hat{\beta_i}$ and σ_i^2 are the coefficient and its variance for each subtype, and $\bar{\beta}$ is the weighted average of the β coefficients.

Inclusion of a quadratic term for age or dietary variables did not improve the fit of the model. The assumption of constant risk for proportional hazards was verified using an age interaction model. Interactions were evaluated by including cross product terms in multivariable models. We conducted a lag analysis excluding the first 1 or 2 y of follow-up to evaluate the possibility of reverse causation. All statistical analyses were carried out using Statistical Analytic Systems (SAS) software (SAS Institute, Inc.).

Results

During a median follow-up time of 7.5 years, a total of 165 small intestinal cancers were diagnosed (111 male cases and 54 female cases). The cases were composed of 60 adenocarcinomas (45 male and 15 female) and 80 carcinoid tumors (50 male and 30 female); the remaining 25 cases were excluded from this analysis because they were a mixture of histologically not otherwise specified (n = 13), sarcomas (n = 10), one mesothelioma, and one nerve sheath tumor. Regarding subsites within the small intestine, adenocarcinomas occurred most frequently in the duodenum and jejunum, and carcinoid tumors were mainly located in the ileum.

In general, individuals in the highest tertile of red meat or saturated fat intake were more likely to be White, to be current smokers, and to have a higher BMI and energy intake than those in the lowest tertile. In contrast, those in the highest tertile of red meat or saturated fat tended to be less educated and less likely to consume fruits, vegetables, and alcohol than those in the lowest tertile (Table 1).

Although the HRs were elevated for red meat and the risk of both adenocarcinomas and carcinoids, the confidence intervals were very wide and not statistically significant (Table 2). With regard to processed meat, there was no association for either adenocarcinoma or carcinoids of the small intestine. Furthermore, splitting processed meats into those derived from red or white meats did not reveal any associations for small intestinal cancer (data not shown).

The energy-adjusted correlation between red meat and total fat (r = 0.50) was essentially the same as the correlation between red meat and saturated fat (r = 0.49). Individuals in the highest, compared with those in the lowest, tertile of total fat intake had an elevated risk of carcinoid tumors of the small intestine (HR, 2.16; 95% CI, 1.10–4.25; P_{trend} = 0.03), and there was a suggestion of an elevated risk in the continuous data (HR, 1.32; 95% CI, 0.96–1.82, per 10-g increase; Table 2).

An investigation by subgroups of fat revealed that individuals in the highest, compared with those in the lowest, tertile of saturated fat intake had an increased risk of carcinoid tumors of the small intestine (HR, 3.18; 95% CI, 1.62–6.25; P_{trend} = 0.0008); this risk was also evident in the continuous data (HR, 3.72; 95% CI, 1.79–7.74; Table 2). Although the HR for adenocarcinoma of the small intestine was elevated for the top tertile of saturated fat intake, the risk was not statistically significant. However, the risk difference for saturated fat intake between the two histologic subtypes was not statistically significant ($P_{heterogeneity}$ = 0.29). Neither monounsaturated nor polyunsaturated fat intakes were statistically significantly associated with small intestinal cancer, although the HRs for adenocarcinoma were elevated for polyunsaturated fat intake in both the second and third tertiles.

Although we had limited statistical power, we were able to examine the association between the major food groups

Table 1. Means and proportions for baseline characteristics of the NIH-AARP Diet and Health Study cohort (n = 494,000) by tertiles of red meat and saturated fat

Characteristics	Tertile of red meat			Tertile of saturated fat		
	1	2	3	1	2	3
Men (n = 294,707)						
Median red meat (g/1,000 kcal)	16.9	35.1	58.0	—	—	—
Median saturated fat (g/1,000 kcal)	—	—	—	7.4	10.4	13.7
Age (y)	62.6	62.3	61.6	62.4	62.1	61.9
Race						
Non-Hispanic White (%)	90.2	93.3	94.1	91.0	92.6	93.9
Non-Hispanic Black (%)	3.7	2.5	1.9	3.0	2.8	2.3
Hispanic, Asian, Pacific Islander, American Indian, Alaskan native, or unknown (%)	6.2	4.2	4.0	6.0	4.6	3.8
Positive family history of cancer (%)	46.3	47.4	47.1	46.4	47.2	47.2
Currently married (%)	82.7	86.3	85.9	84.3	86.5	84.0
BMI (kg/m^2)	26.4	27.3	28.2	26.5	27.4	27.9
Smoking history						
Never smoker (%)	32.4	28.7	26.2	30.2	30.0	27.1
Former smoker (%)	55.7	55.2	53.5	58.3	55.4	50.8
Current smoker or having quit <1 y ago (%)	7.8	12.2	16.4	7.6	10.7	18.1
Education, college graduate or post graduate (%)	49.8	44.0	39.7	50.2	44.5	38.7
Vigorous physical activity, ≥5 times per week (%)	18.6	22.9	24.0	18.8	23.2	23.6
Dietary intakes						
Energy (kcal/d)	1,930	2,010	2,102	1,894	1,974	2,174
Fruit (Pyramid servings/1,000 kcal)	2.0	1.5	1.2	2.1	1.5	1.0
Vegetables (Pyramid servings/1,000 kcal)	2.2	2.0	1.9	2.3	2.0	1.8
Alcohol (g/d)	20.3	16.8	13.1	27.8	13.5	8.9
Women (n = 199,293)						
Median red meat (g/1,000 kcal)	11.4	26.3	46.6	—	—	—
Median saturated fat (g/1,000 kcal)	—	—	—	7.2	10.0	13.4
Age (y)	62.0	62.0	61.5	62.0	61.8	61.7
Race						
Non-Hispanic White (%)	86.5	90.3	91.4	87.7	89.1	91.3
Non-Hispanic Black (%)	7.4	5.3	4.1	6.4	6.0	4.5
Hispanic, Asian, Pacific Islander, American Indian, Alaskan native, or unknown (%)	6.1	4.5	4.5	6.0	4.9	4.2
Positive family history of cancer (%)	50.6	51.8	51.0	50.9	51.0	51.5
Currently married (%)	38.1	44.9	49.8	44.3	45.5	43.0
BMI (kg/m^2)	25.8	26.9	27.9	25.8	27.1	27.7
Smoking history						
Never smoker (%)	45.7	44.3	41.8	45.3	45.3	41.4
Former smoker (%)	39.3	36.2	33.6	40.2	36.4	32.4
Current smoker or having quit <1 y ago (%)	11.0	16.0	21.3	10.8	14.8	22.7
Education, college graduate or postgraduate (%)	35.8	29.1	24.4	35.1	29.5	24.8
Vigorous physical activity, ≥5 times per week (%)	19.2	21.7	21.9	19.5	21.9	21.4
Dietary intakes						
Energy (kcal/d)	1,527	1,561	1,625	1,452	1,553	1,707
Fruit (Pyramid servings/1,000 kcal)	2.5	1.9	1.5	2.6	1.8	1.3
Vegetables (Pyramid servings/1,000 kcal)	2.8	2.4	2.3	2.9	2.4	2.1
Alcohol (g/d)	5.8	6.2	5.4	8.1	5.2	4.2

contributing to total fat intake and small intestinal cancer on the continuous scale (per 10-g increase). The risk for carcinoid tumors was the highest for fat from dairy products (HR, 3.64; 95% CI, 1.94–6.83; P_{trend} < 0.0001) and was also elevated, but not statistically significant, for fat from red meat (HR, 1.65; 95% CI, 0.83–3.28; P_{trend} = 0.16).

In a lag analysis of the continuous data, the positive association for saturated fat intake and carcinoid tumors of the small intestinal cancer remained if we excluded the first year of follow-up (n = 72 cases; HR, 3.69; 95% CI, 1.70–7.99) or the first 2 years (n = 65 cases; HR, 3.36; 95% CI, 1.47–7.68). The variables confounding the fat association the most were smoking and fruit intake. The interaction analyses of saturated fat with smoking ($P_{interaction}$ = 0.80) and fruit ($P_{interaction}$ = 0.45) were not statistically significant.

In a sensitivity analysis, we additionally adjusted the multivariable saturated fat model for red meat intake. The risks for carcinoid tumors for those in the highest, compared with those in the lowest, tertile of saturated fat remained (HR, 3.27; 95% CI, 1.60–6.67; P_{trend} < 0.001). Furthermore, using residual energy adjustment did not change the risk estimates for carcinoid tumors

and intake of red meat (HR for the third versus first tertile, 1.46; 95% CI, 0.78–2.71; P_{trend} = 0.36) or saturated fat (HR, 3.04; 95% CI, 1.59–5.83; P_{trend} = 0.0006).

We conducted an exploratory analysis by gender, but only in the continuous data due to small case numbers. The risk of carcinoid tumors was elevated in both women (HR, 3.83; 95% CI, 1.23–12.0; P_{trend} = 0.02) and men (HR, 3.56; 95% CI, 1.35–9.38; P_{trend} = 0.01) per 10-g increase in saturated fat. There were too few small intestinal adenocarcinomas in women (n = 15) to report on this histologic subtype by gender.

There were additional 13 cases of carcinoid tumors and 4 cases of adenocarcinoma of the small intestine that occurred after a separate diagnosis of cancer at a different site during follow-up. These cases were excluded from our primary analysis because the presence of the first cancer may have prompted a dietary change, which may mask any associations between diet and small intestinal

Table 2. Multivariable HRs and 95% CIs (both genders combined) for small intestinal cancer in the NIH-AARP Diet and Health Study

		Tertiles				Continuous
		1	2	3	P_{trend} across tertiles	Per 10-g increase per 1,000 kcal
Red meat (g/1,000 kcal)*		14.2	31.4	53.9		
Cases (adenocarcinomas/carcinoids)		12/22	27/31	21/27		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	2.12 (1.07–4.20)	1.65 (0.80–3.38)	0.31	1.10 (0.99–1.22)
	HR (95% CI) MV ‡	Reference	1.92 (0.95–3.85)	1.41 (0.66–3.01)	0.61	1.08 (0.96–1.21)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.37 (0.79–2.37)	1.22 (0.69–2.18)	0.49	1.04 (0.94–1.14)
	HR (95% CI) MV ‡	Reference	1.51 (0.85–2.68)	1.44 (0.78–2.69)	0.27	1.07 (0.96–1.19)
Processed meat (g/1,000 kcal)*		2.6	7.6	17.8		
Cases (adenocarcinomas/carcinoids)		16/26	19/27	25/27		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	1.15 (0.58–2.27)	1.36 (0.71–2.62)	0.42	0.98 (0.76–1.26)
	HR (95% CI) MV ‡	Reference	1.04 (0.53–2.07)	1.20 (0.61–2.35)	0.64	0.94 (0.72–1.22)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.02 (0.59–1.76)	0.92 (0.53–1.63)	0.68	0.87 (0.67–1.12)
	HR (95% CI) MV ‡	Reference	1.09 (0.62–1.91)	1.05 (0.58–1.89)	0.98	0.91 (0.70–1.18)
Total fat (g/1,000 kcal)*		25.1	33.7	41.9		
Cases (adenocarcinomas/carcinoids)		14/20	23/30	23/30		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	1.63 (0.84–3.17)	1.59 (0.82–3.11)	0.19	1.28 (0.96–1.72)
	HR (95% CI) MV ‡	Reference	1.47 (0.73–2.93)	1.31 (0.61–2.82)	0.53	1.19 (0.84–1.69)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.50 (0.85–2.64)	1.44 (0.82–2.55)	0.22	1.10 (0.85–1.41)
	HR (95% CI) MV ‡	Reference	1.86 (1.01–3.42)	2.16 (1.10–4.25)	0.03	1.32 (0.96–1.82)
Saturated fat (g/1,000 kcal)*		7.3	10.3	13.6		
Cases (adenocarcinomas/carcinoids)		12/18	23/27	25/35		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	1.92 (0.95–3.86)	2.01 (1.00–4.02)	0.06	1.55 (0.74–3.24)
	HR (95% CI) MV ‡	Reference	1.77 (0.86–3.65)	1.82 (0.83–3.96)	0.17	1.25 (0.52–3.00)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.51 (0.83–2.74)	1.88 (1.06–3.33)	0.03	1.89 (1.01–3.52)
	HR (95% CI) MV ‡	Reference	2.03 (1.07–3.84)	3.18 (1.62–6.25)	0.0008	3.72 (1.79–7.74)
Monounsaturated fat (g/1,000 kcal)*		9.2	12.7	16.0		
Cases (adenocarcinomas/carcinoids)		17/22	20/31	23/27		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	1.16 (0.61–2.22)	1.29 (0.69–2.42)	0.43	1.75 (0.86–3.57)
	HR (95% CI) MV ‡	Reference	0.99 (0.50–1.94)	0.97 (0.47–2.01)	0.93	1.36 (0.58–3.21)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.41 (0.81–2.43)	1.18 (0.67–2.08)	0.58	1.10 (0.59–2.04)
	HR (95% CI) MV ‡	Reference	1.70 (0.94–3.07)	1.68 (0.85–3.30)	0.14	1.68 (0.77–3.66)
Polyunsaturated fat (g/1,000 kcal)*		5.5	7.5	9.9		
Cases (adenocarcinomas/carcinoids)		13/24	23/35	24/21		
Adenocarcinomas (n = 60)	HR (95% CI) †	Reference	1.79 (0.91–3.54)	1.89 (0.96–3.72)	0.08	2.21 (0.90–5.43)
	HR (95% CI) MV ‡	Reference	1.75 (0.87–3.52)	1.74 (0.85–3.58)	0.18	1.83 (0.70–4.76)
Carcinoids (n = 80)	HR (95% CI) †	Reference	1.47 (0.87–2.46)	0.86 (0.48–1.54)	0.55	0.65 (0.26–1.63)
	HR (95% CI) MV ‡	Reference	1.47 (0.86–2.52)	0.89 (0.48–1.66)	0.62	0.64 (0.23–1.78)

Abbreviation: MV, multivariable model.

*Nutrient density energy-adjusted median.

† Age-, gender-, and calorie-adjusted.

‡ Multivariable model includes person years (continuous), gender, education (<high school/complete high school, post–high school, some college, college/postgraduate), marital status, family history of cancer, race (non-Hispanic White, non-Hispanic Black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown), BMI (18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), smoking (never, quit ≥5 y ago, quit 1–4 y ago, quit <1 y or currently smoking), frequency of vigorous physical activity (never/rarely, 1 to 3 times/mo to 1 to 2 times a week, 3 to 4 times a week or more), and intakes of total energy (continuous), alcohol (none, 0 to <5, 5 to <15, 15 to <30, ≥30 g/d), fruits (Pyramid servings/1,000 kcal), and vegetables (Pyramid servings/1,000 kcal).

cancer. When we included these cases in a sensitivity analysis, the positive association for saturated fat intake and carcinoid tumors remained (n = 93; HR, 2.59; 95% CI, 1.39–4.84; P_{trend} = 0.003 for the third versus first tertile; HR, 2.64; 95% CI, 1.31–5.29 for the continuous data).

Discussion

This study reports a positive association between saturated fat intake and carcinoid tumors of the small intestine. Small intestinal cancer arises from various cell types; ~35% tend to be carcinoids, 30% to 40% adenocarcinomas, 15% to 20% lymphomas, and 10% to 15% sarcomas (15). In agreement with previous findings from case-control studies (16), the cases in this prospective study were mainly adenocarcinomas of the duodenum and jejunum and carcinoids of the ileum. Previous studies have suggested that risk factors for this malignancy may differ according to histologic subtype (14), yet no previous dietary study has had the power to investigate risks within the subtype of incident carcinoid tumors.

The association between meat intake and cancer has been investigated for various anatomic sites, with the majority of studies focusing on subsites within the gastrointestinal tract. The evidence supporting red meat and processed meat as risk factors for colorectal cancer is increasingly consistent (17). Furthermore, meat intake has been positively associated with cancers of the esophagus (18, 19) and stomach (18). With regard to cancer of the small intestine, very little epidemiologic research and no prospective study has addressed this association; the few case-control studies that have investigated this malignancy have found elevated risks for red and processed meat intake (4–6).

Several supportive mechanisms indicate that meat may have deleterious effects on the gastrointestinal tract. Meat is a source of several known multisite mutagens, including heterocyclic amines (20), polycyclic aromatic hydrocarbons (21), and *N*-nitroso compounds (22, 23). All of these meat-related mutagens have been associated with gastrointestinal cancers, including colorectal (17, 24) and esophageal (25, 26) cancers. However, we did not find a clear positive association for red or processed meat intake and small intestinal cancer risk in our study.

There are multiple factors that could explain the discrepancy between the findings for red and processed meat intake in previous epidemiologic studies and this study. The previous studies were vulnerable to reporting bias due to their case-control design, where diet was assessed after diagnosis, and one of the studies relied on data obtained from the next of kin (5). Furthermore, compared with our study, diet was more crudely assessed in the previous studies, with one study only asking about 5 food groups (5), another about 10 food groups (4), and the third using either a 34-item or 78-item questionnaire (6). Although two of the previous studies were also in American populations, one of these was a study of small intestinal cancer mortality (with no data on histologic subtype; ref. 5) and the other study was only of adenocarcinomas of the small intestine (4). The third study was in an Italian population and also only addressed adenocarcinomas of the small intestine (6). Furthermore, the previous studies did not extensively investigate potential confounding variables and presented models simply adjusted for age (5); age, sex, and race (4); or age, sex, study, center, and BMI (6), whereas we adjusted our models for a range of variables known to confound the association between diet and colorectal cancer.

A possible explanation of the previous findings from case-control studies of meat and small intestinal cancer may be the contribution of red and processed meats to fat intake. Of the few epidemiologic studies to investigate diet and cancer of the small intestine, none reported on fat intake. Fat intake has been linked to multiple gastrointestinal cancers, including cancers of the colon (27, 28) and the esophagus (29). In our study, there was a clear positive association between saturated fat intake and carcinoid tumors of the small intestine, in addition to a suggestive elevation in risk for adenocarcinoma with polyunsaturated fat intake, but no association for monounsaturated fat. A summary of the epidemiologic literature on saturated fat and colorectal cancer, however, reported that there is limited evidence to support an association, although a meta-analysis of cohort data revealed a nonsignificant increased risk for intake of animal fat (30).

Laboratory investigations have reported an increased number of tumors and larger tumors in the small intestine of rodents fed a high-fat diet (31). A potential mechanism relating fat intake to carcinogenesis is the production of bile acids from cholesterol, which are secreted into the small intestine to digest fat. Bile acids are thought to induce DNA damage via the production of reactive oxygen species (32) and have been positively associated with tumors of the small intestine in animal models (33). With regard to polyunsaturated fats, for which we observed an elevated HR for adenocarcinomas, there is some evidence that ω-6 fatty acids may be linked with proinflammatory pathways in colorectal carcinogenesis via prostaglandin synthesis from arachidonic acid metabolism (34).

Identifying modifiable risk factors for small intestinal cancer is important not only because the incidence of this cancer is on the rise but also because it may enable us to further understand other gastrointestinal malignancies. Furthermore, individuals diagnosed with small intestinal cancer are subsequently at higher risk for developing other malignancies. A pooled analysis using data from 13 cancer registries reported a 68% higher risk of a second primary cancer in individuals diagnosed with small intestinal cancer and more than three times the risk of having colon or rectal cancer (2). There is some evidence to suggest that adenocarcinomas of the small and large bowel both arise from adenomatous polyp precursor lesions, suggesting that the adenoma-carcinoma sequence is relevant to both sites (35); however, for unknown reasons, the large intestine is more susceptible to malignant transformation. Identifying risk factors that are unique as well as those that are similar for the two sites may aid our understanding of the comparative resistance of the small intestine to carcinogenesis.

The principal strengths of our study include the size of the cohort, which enabled us to conduct the first prospective study of dietary factors and small intestinal cancer and resulted in a wide range of reported meat and fat intake. Recall bias and reverse causation were minimized in this study by the assessment of diet before the diagnosis of cancer. Potential limitations include a lack of data on nonsteroidal anti-inflammatory drug use from baseline; however, although regular use confers a reduced risk for colorectal cancer (36, 37), there is no established association with small intestinal cancer in individuals without inflammatory conditions. Furthermore, the observed risk estimates could potentially be unstable as a result of a relatively small sample size, as well as some degree of measurement error associated with the assessment of dietary and lifestyle variables. Although we attempted to minimize this measurement error, which usually results in attenuated risks (38), by energy adjustment of the models (39), we cannot exclude the possibility that some error remains. The associations identified

in this study should be considered exploratory and need to be further investigated in a study with a larger number of cases by pooling existing studies with relevant data.

In conclusion, we report the first prospectively collected data on diet and cancer of the small intestine. We observed a positive association between saturated fat intake and carcinoid tumors of the small intestine.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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