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Meat, Fat, and Their Subtypes as Risk Factors for Colorectal Cancer in a Prospective Cohort of Women

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The authors investigated the association of intakes of meat and fat with colorectal cancer in a prospective cohort of women in the United States. Between 1987 and 1989, 45,496 women completed a 62-item National Cancer Institute/Block food frequency questionnaire, and during 386,716 person-years of follow-up, there were 487 incident cases of colorectal cancer. The authors used Cox proportional hazards regression to estimate relative risks and 95% confidence intervals for total meat, red meat, white meat, processed meat, and well-done meat intakes, as well as for total fat, saturated fat, and unsaturated fat. Relative risks for increasing quintiles of total meat and red meat consumption indicated no association with colorectal cancer (relative risk for high compared with low quintile = 1.10, 95% confidence interval: 0.83, 1.45) for red meat. For total fat, there was also no association with increasing quintiles of consumption (relative risk for high compared with low quintile = 1.14, 95% confidence interval: 0.86, 1.53). Additionally, none of the other subtypes of either meat or fat showed any association with colorectal cancer. This study provided no evidence of an association between either meat or fat (or any of their subtypes) and colorectal cancer incidence, but the authors cannot rule out the possibility of a modest association.

colorectal neoplasms; dietary fats; meat; prospective studies; women

Abbreviations: BCDDP, Breast Cancer Detection Demonstration Project; CI, confidence interval.

Both meat and fat intakes have long been suspected as important risk factors for colorectal cancer in humans. These hypotheses are based on migrant studies, time trends in disease rates within countries, and international correlations between per capita food disappearance data and incidence rates for the disease (1, 2).

A recent report from the American Institute for Cancer Research (3) specified red meat (but not total meat) as a probable risk factor for colorectal cancer. This report also identified processed meat and highly cooked meat as "possible" risk factors (3). Red meat has been thought to promote colorectal cancer through the effects of fat (see below), iron, protein, and, in the case of processed meat, *N*-nitroso compounds (3–5). Additionally, certain cooking practices (e.g., frying or grilling) result in the production of heterocyclic amines in meat, and these compounds have been shown to have high mutagenic activity (6). The role of heterocyclic amines in the diet as causes of specific cancers in humans is not definitively established, but there have been recent reports showing significant positive associations with lung cancer and colonic adenomas (7, 8).

The same American Institute for Cancer Research report also listed both total fat and saturated fat as "possible" risk factors for colorectal cancer (3). As noted in a recent review, the type of fat that has been most strongly associated with colorectal cancer is fat from red meat sources (9). This fat is primarily saturated fat, although fat from dairy foods is also primarily saturated fat, but the association between dairy foods and colorectal cancer is not well established. Numerous investigators have proposed a variety of mechanisms by which dietary fat may increase the risk of colorectal cancer. These include excretion of bile acids into the colon that would have an irritant, proliferative effect on the cells of the lumen. This, however, implies a general fat effect, which

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would not be consistent with the more pronounced association suggested for fat from red meat. Other investigators have also hypothesized as possible mechanisms specific metabolic changes associated with specific saturated fatty acids, insulin resistance, altered immunologic responses, and changes in the fatty acid composition of cell membranes that, in turn, can affect the binding characteristics of colonic epithelial cells (9). Nonetheless, despite these plausible biologic mechanisms, data from previous prospective studies of diet have generally failed to provide support for an overall association of total fat or saturated fat with colorectal cancer or adenomas (10–21).

This study examines the association of prospectively measured dietary meat and fat intake, and various subtypes of each, with colorectal cancer in a large cohort of women.

MATERIALS AND METHODS

Study population

The Breast Cancer Detection Demonstration Project (BCDDP) was a breast cancer-screening program conducted under the joint sponsorship of the National Cancer Institute and the American Cancer Society. The project ran from 1973 through 1980 and enrolled 283,222 women at 29 screening centers in 27 cities across the United States. In 1979, the National Cancer Institute established a follow-up cohort from a subset of the women who had participated in the BCDDP based on their breast cancer-screening status (details have been reported elsewhere (22)). The Institutional Review Board of the National Cancer Institute approved the study, and all subjects provided written informed consent at the time of enrollment. A total of 64,182 women were selected for entry into the follow-up cohort, and of that number, 61,431 women (96 percent) completed the baseline questionnaire and were therefore eligible for further participation in the study.

Participants subsequently completed a mailed questionnaire during three separate follow-up periods: 1987–1989, 1992–1995, and 1995–1998. Nonresponders to the questionnaires received vigorous follow-up, including repeated mailings and phone calls.

For the purposes of the current analysis, entry into the analytic cohort took place at the completion of the 1987–1989 questionnaire, the time of the dietary assessment. We excluded from the study women who did not complete a questionnaire at that stage (n = 9,740), women with a diagnosis of colorectal cancer at the time of the 1987–1989 questionnaire or earlier (n = 479), women whose reported entry date occurred after their exit date (n = 6; see definition of exit dates below), and women who skipped more than 30 items on their food frequency questionnaires or who had a reported total energy intake above 3,800 or below 400 kcal per day (n = 5,647). For this study, we also excluded 65 women with unusually high intakes of meat (reported frequency of consumption exceeding nine times per day), leaving 45,496 women in the final analytic cohort. Including women reporting consumption of meat more often than nine times per day in the analyses did not materially alter the results (data not shown). General descriptive statistics for the analytic cohort appear in table 1.

TABLE 1. Descriptive characteristics of the analytic cohort, Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998

	% distribution
Age (years) at entry into analytic cohort	
<50	4.6
50–59	40.2
60–69	38.8
70–79	14.1
≥80	2.3
Ethnicity	
Caucasian	88.8
African American	3.6
Asian	4.8
Hispanic	1.9
Other/unknown	0.9
Place of residence in the United States by region	
Northeast	15.2
Southeast	22.9
Midwest	28.4
Mountain states	4.1
Southwest (Texas, New Mexico, Arizona)	7.5
Pacific	21.8
Maximum educational attainment	
Less than high school	10.8
High school graduate	42.1
Some college	23.9
College graduate	12.4
Postcollegiate study	9.9
Unknown	0.8

Cohort follow-up

As described above, follow-up began with completion of the 1987–1989 questionnaire. We defined "end of study date" as the date the subject completed the 1995–1998 questionnaire or, if the subject did not complete a 1995–1998 questionnaire, as the date of last contact in the 1995–1998 follow-up period. For participants with whom we had no contact in the 1995–1998 follow-up period, we imputed an "end of study date" by estimating the date on which subjects would have completed the 1995–1998 questionnaire (using mean time intervals from the rest of the cohort) had they actually completed one. We defined "exit date from the study" as the earliest among end of study date, date of colorectal cancer diagnosis, or date of death from a cause other than colorectal cancer.

In the final analytic cohort, 90 percent (n = 41,073 women) had complete follow-up through 1995–1998, meaning their exit date corresponded to the date of their first colorectal cancer diagnosis, the date they filled out the 1995–1998

questionnaire, or their date of death from a cause other than colorectal cancer.

Case ascertainment

We identified colorectal cancer cases from self-reports on the 1992–1995 and 1995–1998 questionnaires, from statewide cancer registries, and from the National Death Index (through 1997). We obtained pathology reports for 245 (79 percent) of the 311 women who provided self-reports of a diagnosis of colorectal cancer. The pathology reports confirmed 231 (94 percent) of the cases as adenocarcinoma of the colon or rectum (*International Classification of Diseases for Oncology* site codes 153.0–153.4 and 153.6–153.9 for colon cancer and 154.0–154.1 for rectal cancer). Because of this high correspondence between the self-reports and medical records, we included the remaining 66 self-reports of colorectal cancer without pathology reports as cases. Exclusion of these 66 cases did not materially affect the results (data not shown). Women with pathology reports contradicting self-reported colorectal cancers were not included as cases, unless they also appeared in a state cancer registry as described below. Pathology reports obtained for self-reported conditions unrelated to colorectal cancer identified 17 more cases of colorectal cancer. A search of the National Death Index identified an additional 107 individuals with death certificates indicating a diagnosis of colorectal cancer. Finally, we used the last-known place of residence for each subject to match against state cancer registries for those states whose registries consented to participate in the study (accounting for 73.5 percent of the analytic cohort). Subjects residing in states with participating registries did not differ in any material way with respect to distribution of risk factors from subjects residing in states whose registries did not consent to participate. This procedure resulted in the identification of a further 66 colorectal cancer cases. Thus, the total number of cases in the analytic cohort over the follow-up period was 487.

Of these 487 colorectal cancer cases, 15.0 percent were located in the rectum, 23.0 percent in the distal colon, and 36.1 percent in the proximal colon; for 25.9 percent, information on the subsite location was unavailable. In terms of grade, 13.2 percent were grade I, 45.5 percent were grade II, 11.9 percent were grade III, 0.3 percent were grade IV, and 29.0 percent were undetermined or were lacking information on grade. More than 96 percent of the cancers on which histology information was available were adenocarcinomas.

Dietary assessment

With the 1987–1989 questionnaire, respondents completed a 62-item National Cancer Institute/Block food frequency questionnaire to assess usual dietary intake over the previous year. Detailed descriptions of this food frequency questionnaire and its validity have appeared elsewhere (23–25). Software designed for this food frequency questionnaire yielded estimates of daily intakes for total energy, macronutrients, and micronutrients (25).

The food frequency questionnaire had 17 line items containing meat. Twelve of these (bacon, beef, fried chicken, fried fish, hamburger, ham or other lunch meat, hot dogs, liver, other chicken, other fish, pork, and sausage) contained primarily meat. The remaining five line items (beef stew, chili, salad, spaghetti, and vegetable soup) were mixed dishes containing meat, and these we apportioned so that only the meat component counted toward the total for meat consumption. Apportionment was based on US Department of Agriculture recipe information indicating grams of meat per 100 g of the mixed food. For meat subtypes, we defined red meat to include bacon, beef, hamburger, ham or other lunch meat, hot dogs, liver, pork, sausage, and the meat components of beef stew, chili, salad, spaghetti, and vegetable soup. White meat included fried chicken, fried fish, other chicken, and other fish, and we defined processed meat as bacon, ham or other lunch meat, hot dogs, and sausage.

Statistical analysis

We used Cox proportional hazards regression (PROC PHREG in SAS version 6.12 software; SAS Institute, Inc., Cary, North Carolina) with age as the underlying time metric to generate rate ratios and 95 percent confidence intervals for dietary fat and meat consumption both separately and in combination. All p values were two sided. To test for trend, we entered grams of meat or percentage of energy from fat into the model as continuous terms and reported the p value associated with the estimated beta coefficient.

We adjusted both meat and fat consumption for energy using the multivariate nutrient density method (grams of meat per 1,000 kcal per day or percentage of total energy from fat, both with total energy also in the model) as described by Willett (26). Other energy adjustment methods yielded similar results as the nutrient density models (data not shown).

We also considered additional variables for inclusion into our models as potential confounders. In evaluating these risk factors, we entered each separately by quintiles into the energy-adjusted models for total meat and total fat. We judged a change of greater than 10 percent in the parameter estimate from the energy-adjusted-only model as evidence for confounding. We tested the following variables in this manner: smoking (ever/never), education (through high school/more than high school), body mass index (weight (kg)/height $(m)^2$), height, weekday physical activity index expressed in units of metabolic equivalent time (as defined by Ainsworth et al. (27)), alcohol, folate, vitamin D, calcium, fiber, fruits, vegetables, grains, and nonsteroidal antiinflammatory drug use (yes/no) that included aspirin, ibuprofen (Advil (Wyeth, Madison, New Jersey); Motrin (McNeill-PPC, Inc., Ft. Washington, Pennsylvania); Nuprin (Bristol-Myers Squibb Company, New York, New York)), Naprosyn (Hoffmann-La Roche, Inc., Nutley, New Jersey), and other pain-relieving drugs but excluded Tylenol (McNeill-PPC, Inc.). We defined women to be users of nonsteroidal antiinflammatory drugs if they had used these drugs at least once a week for at least 1 year. After performing all of these tests, we found that none of the factors listed above generated any material changes in either the meat or the fat model (data not shown) and thus did not include them in any of the final meat or fat models.

TABLE 2. Baseline characteristics of 45,496 women according to quintile of total meat intake, Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998*

	Quintile of meat (g/1,000 kcal)				
	1 (<26.5)	2 (26.5–39.3)	3 (39.4–53.7)	4 (53.8–77.7)	5 (≥77.8)
Total meat (g/1,000 kcal)	17.6	33.1	46.3	64.3	114
Age (years)	63.5	62.1	61.6	61.4	60.7
Energy (kcal)	1,333	1,296	1,290	1,266	1,210
% of energy from fat	32.3	34.2	35.1	36.3	36.7
Grains (g/1,000 kcal)	132	130	130	129	130
Vegetables (g/1,000 kcal)	254	261	262	266	281
Fruit (g/1,000 kcal)	182	166	160	153	151
Fiber (g/1,000 kcal)	10.0	9.5	9.2	9.0	8.9
Dietary folate (μg/1,000 kcal)	238	221	215	207	203
Calcium (mg/1,000 kcal)	593	563	534	508	471
Vitamin D (mg/1,000 kcal)	136	131	125	120	112
Alcohol (g)	4.6	4.3	4.1	3.6	3.1
Body mass index (kg/m^2)	23.8	24.3	24.7	25.0	25.5
Height (inches†)	63.9	64.0	64.0	64.0	63.9
Physical activity index (METs‡)	56.6	56.9	57.1	57.1	57.0
NSAIDs‡ (% ever regular users)	37.4	38.2	39.5	39.3	39.4
Smokers (% current or former)	42.5	43.7	42.8	43.7	43.0
Greater than high school education (%)	48.2	48.0	46.3	44.0	44.7

* All values are means in the units listed or percentages.
† One inch = 2.5 cm.
‡ METs, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs.

RESULTS

Women in the BCDDP follow-up cohort completed the dietary questionnaire at an average of 61.9 years of age and contributed an average of 8.5 years of follow-up. Tables 2 and 3 present baseline characteristics of the analytic cohort at the time of entry into the study according to quintile of meat and fat, respectively. The range of meat intake in the cohort was broad. Quintile means spanned from 17.6 to 114 g per 1,000 kcal per day. Across meat quintiles, there were only modest variations in most other dietary and lifestyle characteristics.

In the lowest quintile of fat, the mean intake was 22.9 percent of calories from fat compared with 46.5 percent in quintile 5. The cutpoint for the low quintile was 28.0 percent of calories, however, indicating that few of the women in the cohort ate a truly low-fat diet. Unlike meat, where other baseline characteristics varied only slightly across quintiles, for fat, these variables showed more pronounced differences. Consumption of grains, vegetables, fruit, fiber, folate, calcium, and vitamin D all decreased markedly with increasing fat intake, much as we would expect since these low-fat foods and these nutrients generally derived from low-fat foods could not contribute substantially to a high-fat diet. Total energy also increased with quintile of fat, as did total meat intake. Variation in meat across the fat quintiles, however, was quite modest (45.3 g per 1,000 kcal per day in quintile 1 of fat intake vs. 60.8 in quintile 5) when compared with the total variation in meat intake for the whole cohort (17.6 g per 1,000 kcal per day in quintile 1 of meat intake vs. 114 g in quintile 5). In fact, the Spearman correlation between grams of meat intake per 1,000 kcal and percentage of calories from fat for this cohort was only 0.15.

Results from the proportional hazards regression analyses for meat and meat subtypes appear in table 4. For total meat, we saw no association between increased consumption and colorectal cancer, with the relative risk in the top quintile being 1.05 (95 percent confidence interval (CI): 0.80, 1.38) and the test for trend having a p value of 0.27.

We analyzed meat subtypes using two different substitution models. In the first, we held total energy constant and thus analyzed the substitution of one meat subtype for any other food (including possibly other meat subtypes). In the second substitution model, we held total energy as well as total meat constant, enabling us to observe the effect of substituting one subtype of meat for other subtypes of meat. Regardless of the model we used or which subtype we

TABLE 3. Baseline characteristics of 45,496 women according to quintile of total fat, Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998*

	Quintile of total fat (% of total energy)				
	1 (<28.0)	2 (28.0–32.9)	3 (33.0–37.1)	4 (37.2–41.7)	5 (≥41.8)
% of energy from fat	22.9	30.7	35.1	39.4	46.5
Age (years)	62.9	62.3	62.0	61.3	60.7
Energy (kcal)	1,172	1,194	1,260	1,330	1,437
Total meat (g/1,000 kcal)	45.3	53.0	56.4	59.4	60.8
Grains (g/1,000 kcal)	163	141	129	117	101
Vegetables (g/1,000 kcal)	315	286	260	242	219
Fruit (g/1,000 kcal)	250	187	155	127	92
Fiber (g/1,000 kcal)	12.4	10.3	9.2	8.1	6.7
Dietary folate (μg/1,000 kcal)	291	238	212	187	155
Calcium (mg/1,000 kcal)	623	575	534	497	439
Vitamin D (mg/1,000 kcal)	157	138	124	111	94
Alcohol (g)	5.9	4.4	3.8	3.2	2.5
Body mass index (kg/m^2)	23.8	24.3	24.7	25.0	25.5
Height (inches†)	63.8	63.9	64.0	64.1	64.1
Physical activity index (METs‡)	57.3	57.1	56.9	56.8	56.6
NSAIDs‡ (% ever regular users)	36.9	38.6	39.3	39.2	39.7
Smokers (% current or former)	42.0	42.6	41.6	43.8	45.7
Greater than high school education (%)	50.8	48.8	46.7	44.5	40.3

* All values are means in the units listed or percentages.
† One inch = 2.5 cm.
‡ METs, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs.

analyzed, in no case did we observe an association with colorectal cancer.

The analysis of total fat (table 5) indicated no increase in risk of colorectal cancer with increasing quintile of intake (rate ratio in quintile 5 compared with quintile 1 = 1.14, 95 percent CI: 0.86, 1.53; p for trend = 0.99). In the analysis of subtypes, neither saturated fat nor unsaturated fat had any association with colorectal cancer in either the model controlling only for total energy or the model controlling for total energy and total fat.

Results for multivariate analyses in which we controlled for either meat in the fat analyses or fat in the meat analyses appear in table 6. For both meat and fat, there was no meaningful difference in the pattern of risk estimates when controlling for the other risk factor in the multivariate compared with the univariate models. Table 7 presents results from cross-classification analyses of combinations of meat and fat. These analyses provided little evidence to suggest that risk of colorectal cancer increased with simultaneous increases in total meat and total fat.

None of these results changed in any qualitative sense after excluding women with a prior history of any cancer (previously we had excluded only those with a prior history of colorectal cancer) or after excluding cases diagnosed within 2, 3, or 4 years of completing their 1987–1989 questionnaire. Results were also similar within strata for ethnicity, body mass index, smoking status, 10-year age group, or breast cancer-screening status from the original BCDDP screening study. When stratifying on nonsteroidal antiinflammatory drug use, we observed trend tests that were suggestive of an elevated risk with increasing meat intake among those who reported never having been a regular user of nonsteroidal antiinflammatory drugs, but none of the point estimates was significantly different from 1.0 (data not shown). Among those who did report ever having been a regular user, we observed no significant associations between colorectal cancer and meat intake (data not shown). The results from the fat analyses did not change after stratifying on nonsteroidal antiinflammatory drugs.

DISCUSSION

These results provide little support for the hypothesis that total meat has an association with colorectal cancer, and they do not offer evidence of an association between total fat and colorectal cancer. In addition to total meat and total fat, the

TABLE 4. Relative risk of colorectal cancer by quintile of total meat and meat subtypes (total cases = 487), Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998

	Relative risk for quintiles of meat or meat subtype (g/1,000 kcal)					*p* value, trend*
	1	2	3	4	5	
Total meat						
Quintile median	18.9	33.1	46.2	63.5	101.6	
Energy-adjusted RR†,‡	1.00	0.91	0.85	0.95	1.05	0.28
95% CI†	Referent	0.69, 1.20	0.64, 1.13	0.72, 1.25	0.80, 1.38	
Red meat						
Quintile median	6.1	14.6	22.6	32.7	52.2	
Energy-adjusted RR‡	1.00	1.04	0.97	0.98	1.10	0.39
95% CI	Referent	0.79, 1.37	0.73, 1.28	0.74, 1.30	0.83, 1.45	
RR adjusted for total meat§	1.00	1.04	0.95	0.95	1.04	0.73
95% CI	Referent	0.79, 1.36	0.72, 1.26	0.71, 1.27	0.77, 1.41	
White meat						
Quintile median	2.1	9.3	17.8	32.0	66.5	
Energy-adjusted RR‡	1.00	1.03	0.83	1.07	1.01	
95% CI	Referent	0.78, 1.36	0.62, 1.11	0.81, 1.40	0.76, 1.34	0.47
RR adjusted for total meat§	1.00	1.02	0.81	1.01	0.88	0.73
95% CI	Referent	0.77, 1.34	0.60, 1.09	0.76, 1.35	0.60, 1.27	
Processed meat¶						
Quintile median	0.02	2.4	5.9	11.0	22.2	
Energy-adjusted RR‡	1.00	0.90	0.84	1.11	1.00	0.22
95% CI	Referent	0.68, 1.18	0.63, 1.12	0.85, 1.45	0.76, 1.31	
RR adjusted for total meat§	1.00	0.90	0.83	1.09	0.97	0.35
95% CI	Referent	0.68, 1.18	0.63, 1.11	0.84, 1.43	0.73, 1.28	

* Trend test using the Wald test statistic.
† RR, relative risk; CI, confidence interval.
‡ Adjusting for energy using the multivariate nutrient density method.
§ Adjusting for energy using the multivariate nutrient density method and also controlling for total meat.
¶ Processed meat as defined in the text.

possibility that specific subgroupings of these might show unusually strong associations with colorectal cancer was explored. Neither red meat nor white meat nor saturated fat nor unsaturated fat showed any association with colorectal cancer in this cohort.

We also investigated processed meat. Processed meat is high in fat, particularly saturated fat, and is rich in potentially carcinogenic agents. In this cohort, however, we saw no evidence that eating increasing amounts of processed meat conferred any additional risk. Although not high in absolute terms, the consumption of processed meat in the BCDDP cohort (mean = 12.1 g/day in a diet with mean energy = 1,279 kcal) was on a par with that observed among adult women in the United States generally (mean = 15 g/day in a 1,646-kcal diet) (28). Thus, although we cannot rule out the possibility that exceptionally high intakes of processed meat could increase risk, the results from this study suggest that, within the range of consumption typically observed in the United States, processed meat is not associated with colorectal cancer.

Consistent with almost all prior prospective studies of fat and colorectal cancer, this study showed no association between fat or any fat subtype and colorectal cancer. One of these studies did observe an increased risk of colorectal cancer with increasing total fat, fat from animal products, and monounsaturated fat (21), and a similarly designed cohort study found increased risk among men with higher fat intake for adenomas (13), but, interestingly, not for colorectal cancer (14). Outside of these two studies, however, the results have been largely null (10–12, 14–20).

One explanation for these null results could lie in the method of dietary assessment we used for this cohort. Others have highlighted the complications arising from measurement error in food frequency questionnaire-based dietary assessment in cohort studies, specifically that it could result in serious attenuation of risk estimates (29). The misclassification from this type of measurement error could account for the failure of this study to observe an association if the true effect of meat or fat (or one of the subtypes) is modest.

All food frequency questionnaire-based epidemiologic studies suffer from this important limitation, and the apparent brevity of the BCDDP food frequency questionnaire (62 items) may have exacerbated the problem. In reviewing the published literature on meat intake and

TABLE 5. Relative risk of colorectal cancer by quintile of total fat and fat subtypes (total cases = 487), Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998

	Relative risk for quintiles of total fat or fat subtype (% of energy)					*p* value, trend*
	1	2	3	4	5	
Total fat						
Quintile median	23.9	30.7	35.1	39.4	45.3	
Energy-adjusted RR†,‡	1.00	1.24	1.07	0.99	1.14	0.99
95% CI†	Referent	0.95, 1.63	0.81, 1.42	0.74, 1.33	0.86, 1.53	
Saturated fat						
Quintile median	7.1	9.7	11.5	13.3	15.7	
Energy-adjusted RR‡	1.00	1.02	0.90	0.76	1.02	0.74
95% CI	Referent	0.78, 1.33	0.68, 1.18	0.57, 1.02	0.77, 1.34	
RR adjusted for total fat§	1.00	0.97	0.83	0.69	0.87	0.33
95% CI	Referent	0.73, 1.28	0.61, 1.13	0.49, 0.97	0.60, 1.27	
Unsaturated fat						
Quintile median	16.1	20.4	23.3	26.3	30.5	
Energy-adjusted RR‡	1.00	0.93	0.82	0.95	1.07	0.87
95% CI	Referent	0.71, 1.23	0.61, 1.09	0.72, 1.25	0.82, 1.41	
RR adjusted for total fat§	1.00	0.93	0.81	0.94	1.06	
95% CI	Referent	0.70, 1.25	0.59, 1.12	0.67, 1.34	0.70, 1.62	0.70

* Trend test using the Wald test statistic.
† RR, relative risk; CI, confidence interval.
‡ Adjusting for energy using the multivariate nutrient density method.
§ Adjusting for energy using the multivariate nutrient density method and also controlling for total fat.

colorectal cancer, however, we found that only seven of the 16 prospective studies used substantially larger food frequency questionnaires than we did in the BCDDP: three Harvard studies using a 127-item Willett questionnaire (13, 14, 21), two Iowa Women's Health Study analyses using the same Willett questionnaire (10, 30), one from the Netherlands cohort using its own 150-item food frequency questionnaire (15), and one from the Finnish Alpha-Tocopherol, Beta-Carotene Study cohort that used its own 276-item food frequency questionnaire (18). Interestingly, of these studies with longer food frequency questionnaires, only the three Harvard analyses found an increased risk with higher red meat intake, and only the Netherlands cohort observed a significantly increased risk with processed meat intake. There were no reports of an increased risk with total meat in any of the seven studies that used a longer food frequency questionnaire. Furthermore, despite its shorter length, the BCDDP food frequency questionnaire captured almost iden-

TABLE 6. Relative risk of colorectal cancer by quintile of total meat or total fat after adjusting for the other (total cases = 487), Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998

	Relative risk for quintiles of total meat or total fat					*p* value, trend*
	1	2	3	4	5	
Total meat						
Quintile median (g/1,000 kcal)	18.9	33.1	46.2	63.5	101.6	
RR† adjusted for total fat‡	1.00	0.91	0.85	0.95	1.05	0.28
95% CI†	Referent	0.69, 1.20	0.64, 1.13	0.72, 1.25	0.79, 1.38	
Total fat						
Quintile median (% of energy)	23.9	30.7	35.1	39.4	45.3	
RR adjusted for total meat§	1.00	1.23	1.06	0.98	1.13	0.88
95% CI	Referent	0.94, 1.62	0.80, 1.41	0.73, 1.31	0.84, 1.50	

* Trend test using the Wald test statistic.
† RR, relative risk; CI, confidence interval.
‡ Adjusting for energy using the multivariate nutrient density method and also controlling for total fat.
§ Adjusting for energy using the multivariate nutrient density method and also controlling for total meat.

TABLE 7. Relative risk of colorectal cancer cross-classifying by level of total meat and total fat intakes, Breast Cancer Detection Demonstration Project Follow-up Cohort, 1987–1998

Total fat category	Total meat category		
	Quintile 1	Quintiles 2–4	Quintile 5
Quintile 1			
No.	2,903 (31)*	5,016 (56)	1,177 (8)
RR†	1.00	1.12	0.74
95% CI†	Referent	0.72, 1.74	0.34, 1.61
Quintiles 2–4			
No.	4,926 (61)	16,718 (164)	5,660 (72)
RR	1.20	1.04	1.43
95% CI	0.78, 1.85	0.71, 1.52	0.93, 2.17
Quintile 5			
No.	1,270 (20)	5,564 (55)	2,262 (20)
RR	1.60	1.14	1.05
95% CI	0.91, 2.80	0.73, 1.77	0.60, 1.84

* Numbers in parentheses, number of cases.
† RR, relative risk; CI, confidence interval.

tical information as the Willett questionnaire with respect to meat intake. This similarity does not eliminate from the BCDDP study the general problem of possible relative risk attenuation due to misclassification in food frequency questionnaire-based epidemiologic research, but it does suggest that any differences in results between the earlier studies and this one are not likely due to differences in the dietary assessment instruments.

An alternative explanation for the null results may lie in the inability of our dietary instrument to classify people according to exposure to heterocyclic amines. Unfortunately, we did not have direct measures of cooking practices in this cohort, and therefore we could not isolate exposure to these compounds in our analyses. We did attempt to address this question by devising a proxy variable for exposure to heterocyclic amines, but we did not observe any association between increased exposure and colorectal cancer (data not shown). The possibility of misclassification using this proxy variable was substantial, however, and thus a null result does not exclude a true association between heterocyclic amines and colorectal cancer in this cohort. A study with more-precise estimates of exposure to heterocyclic amines might identify an association with meat that we were unable to find in the BCDDP.

The lack of association we observed between meat and colorectal cancer stands in contrast to several (12–16, 21, 31), but not all (10, 18, 20, 30, 32–36), published results from prospective studies of this dietary risk factor. However, it is important to recognize that, for the vast majority of the prior investigations that did observe an association, the notable associations have not been between total meat and colorectal cancer, but between either red meat or processed meat and either colorectal cancer or adenoma. Among the 16 published studies, there were only two exceptions. The Seventh-day Adventist cohort did observe an elevated risk for total meat, but the "high" exposure group was defined as eating only one or more servings of total meat per week (31). The Finnish Mobile Clinic Health Examination Survey cohort study showed increased risk for poultry, but the comparison was merely between those who did and those who did not report eating this type of meat (16).

The evidence from individual prospective studies to support an association with total meat, and even for red or processed meat, is somewhat less than consistent or persuasive. Definitions or classifications for the subcategories of "red" or "processed" meat, however, are not necessarily straightforward or clearly delineated. The variation in results between those studies that observe subtype associations and those that do not could be due to differences in the cohort populations, measurement error, chance, and so on, but they could also depend critically on how the authors defined their subcategories. The inconsistencies in these results suggest that thoughtful consideration of exactly how we define "red" or "processed" meat could be an important next step in bringing into higher resolution a picture of exactly what type of meat, if any, has an impact on risk of colorectal neoplasia.

Finally, a recent meta-analysis of the data from all published cohort studies of meat and colorectal cancer provided an interesting quantitative assessment of these results. In this paper, Sandhu et al. (37) reported a pooled summary odds ratio of 1.21 (95 percent CI: 1.10, 1.33) for a 100-g/day increase in total meat consumption and of 1.30 (95 percent CI: 1.13, 1.49) for a 100-g/day increase in red meat. Norat et al. (38) also performed a meta-analysis of cohort studies and reported similar findings. Thus, although individual studies typically did not produce notable associations between total meat and colorectal cancer, and only occasionally did so for red meat and colorectal cancer, taken as a whole, the modest positive associations from these studies became statistically significant. If the true association between total meat or red meat and colorectal cancer is of this magnitude (i.e., 1.1–1.3), the BCDDP cohort did not have adequate power to observe it (lower limit for detectable relative risks was 1.3 given 80 percent power and alpha = 0.05). On the other hand, the confidence intervals for the rate ratios we calculated in the BCDDP cohort include both of these point estimates, suggesting that the findings from our study were not inconsistent with the results from these meta-analyses.

Case-control studies do differ somewhat in their results from the cohort studies described above. In the meta-analysis by Norat et al. (38), the authors reported a summary relative risk of 1.18 (95 percent CI: 0.99, 1.40) for all case-control studies that considered total meat intake, but for red meat and processed meat, the summary relative risks were 1.35 (95 percent CI: 1.21, 1.51) and 1.31 (95 percent CI: 1.13, 1.51), respectively, suggesting a modest but statistically significant relation between the intakes of these types of meat and the risk of colorectal cancer. Case-control studies, however, are subject to specific types of recall bias and selection bias that do not affect prospective studies, and thus they suffer important interpretive limitations relative to cohort studies.

In summary, our results provide no evidence to support an association between total meat, total fat, or any of their

subtypes and colorectal cancer, but we cannot rule out the possibility of a real yet modest association of the magnitude described by Sandhu et al. (37) in their meta-analysis of prospective studies of meat and colorectal cancer.

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