American Journal of Epidemiology

Vol. 148, No. 8
Printed in U.S.A.

Dietary Risk Factors for Colon Cancer in a Low-risk Population

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In a 6-year prospective study, the authors examined the relation between diet and incident colon cancer among 32,051 non-Hispanic white cohort members of the Adventist Health Study (California, 1976–1982) who, at baseline, had no documented or reported history of cancer. The risk of colon cancer was determined from proportional hazards regression with adjustment for age and other covariates. The authors found a positive association with total meat intake (risk ratio (RR) for ≥1 time/week vs. no meat intake = 1.85, 95% confidence interval (CI) 1.19–2.87; p for trend = 0.01) and, among subjects who favored specific types of meat, positive associations with red meat intake (RR for ≥1 time/week vs. no red meat intake = 1.90, 95% CI 1.16–3.11; p for trend = 0.02) and white meat intake (RR for ≥1 time/week vs. no white meat intake = 3.29, 95% CI 1.60–6.75; p for trend = 0.006). An inverse association with legume intake (RR for >2 times/week vs. <1 time/week = 0.53, 95% CI 0.33–0.86; p for trend = 0.03) was observed. Among men, a positive association with body mass index was observed (relative to the RR for tertile III (>25.6 kg/m^2) vs. tertile I (<22.5 kg/m^2) = 2.63, 95% CI 1.12–6.13; p for trend = 0.05). A complex relation was identified whereby subjects exhibiting a high red meat intake, a low legume intake, and a high body mass experienced a more than threefold elevation in risk relative to all other patterns based on these variables. This pattern of putative risk factors would likely contribute to increases in both insulin resistance (high body mass, high red meat intake) and glycemic load (low legume intake), a synergism that, if causal, implicates hyperinsulinemic exposure in colon carcinogenesis. The overall findings from this cohort identify both red meat intake and white meat intake as important dietary risk factors for colon cancer and raise the possibility that the risk due to red meat intake reflects a more complex etiology. *Am J Epidemiol* 1998;148:761–74.

body mass index; colonic neoplasms; diabetes mellitus; diet; insulin; legumes; meat; vegetarianism

Colon cancer is one of the most commonly diagnosed malignancies in the United States and is expected to produce 47,700 cancer deaths in 1998 (1). Although hereditary syndromes are an established risk factor for this disease, current evidence suggests that less than 20 percent of the variation in colon cancer incidence is explained by known hereditary syndromes (2, 3). International correlation studies (4, 5) have shown that the highest incidences of colon cancer occur in North America, Great Britain, and parts of Europe and that the lowest incidences occur in Asia, Latin America, and Africa. Migrant studies (6, 7) show an elevation in risk of colon cancer in populations that have moved from low-incidence (Japan, China) to high-incidence (United States) areas. These findings suggest that the variation in colon cancer incidence is strongly influenced by environmental factors.

Numerous prospective and case-control studies (8) have shown associations between diet and colon cancer. A relation commonly found in epidemiologic studies is an increase in risk associated with a high-fat, low-fiber diet pattern. In some (9–12) but not all studies (13, 14), antioxidant vitamins, calcium, and vitamin D have shown protective effects against colon cancer, colorectal adenomas, or colonic epithelial cell proliferation. Specific foods associated with a decreased risk of colon cancer include cruciferous vegetables, fruits, and legumes (8, 15–17). The association with these foods has been attributed to the putative anticarcinogenic effects of certain compounds (e.g., carotenoids, ascorbic acid, tocopherols, flavonoids, indoles, folate, protease inhibitors, plant sterols, selenium, diallyl sulfide) found in high concentrations in vegetables and fruits (8, 18). Meat intake has shown a positive association with colon cancer risk in a number of populations in the United States (19–21) and other nations (22–28). In a few of these studies, specific components of total meat intake, such as meat fat, meat protein, red meat, and certain methods of cooking and processing meat, have been identified as contributors to the elevation in risk (19, 20,

Received for publication May 28, 1997, and accepted for publication February 19, 1998.

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; RR, risk ratio.

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25, 29). Some recent reports (30–34) indicate that other exogenous factors (physical activity, obesity, aspirin use, cigarette smoking) may contribute to the variation in colon cancer risk and should be considered when investigating the independent effect of diet.

In this study, we investigated the relation between diet and colon cancer among cohort members of the Adventist Health Study (35). Surveillance data reported in an earlier study of a cohort of California Seventh-day Adventists have shown about 60 percent of the mortality rate from colorectal cancer that was found among comparable members of the American Cancer Society cohort and that the lower risk among Adventists persists even after restricting the comparison to members of both cohorts who never smoked (36). By church proscription, the Adventist population is characterized not only by very little tobacco use and alcohol consumption but also by the large proportion of the population that adheres to a church-recommended vegetarian diet pattern (35). Therefore, a reasonable hypothesis would be that the lower risk of colon cancer among Adventists is attributable to a lower intake of animal products. Some support for this hypothesis can be found in clinical data showing lower rates of colonic epithelial cell proliferation among vegetarian cohort members of the Adventist Health Study as compared with either nonvegetarian cohort members or a nonvegetarian general population sample (37). In the current prospective investigation of 32,051 cohort members of the Adventist Health Study, we tested such hypotheses by examining the association between incident colon cancer and intake of selected foods and food groups in the cohort.

MATERIALS AND METHODS

Study population

The Adventist Health Study is a prospective investigation of 34,198 non-Hispanic white California Seventh-day Adventists and others living in Adventist households. Between 1974 and 1976, an attempt was made to identify all California Seventh-day Adventists by using a questionnaire that was mailed to households listed on the membership rosters of all California Seventh-day Adventist churches. The details of this census taken to identify California Seventh-day Adventists have been described elsewhere (35). In 1976, a lifestyle questionnaire was sent to 59,081 persons identified by this census as being age 25 years or older. There was a 75.1 percent response rate to the lifestyle questionnaire among non-Hispanic whites. This respondent group (n = 34,198) became the incidence population for our cohort study.

During the follow-up period, incident cancer cases in the study population were ascertained by using two methods. The first involved mailing annual questionnaires to all participants, in which we requested information on any hospitalization during the previous 12 months. Permission to review any relevant medical records was also obtained, and pertinent portions of these hospital records were microfilmed by study field representatives to enable confirmation of the diagnosis by Adventist Health Study physicians. This confirmation required a histology report of primary adenocarcinoma of the colon. Follow-up using this method was completed for 97 percent of the participants. The second method involved linking computerized records (37) with two population-based tumor registries operating in California in 1976 (the Cancer Surveillance Program in Los Angeles County and the Resource for Cancer Epidemiology Program in San Francisco). From chart review (20,702 medical charts) and tumor registry record linkage, 1,406 incident cancer cases were identified during the 6-year period. Of these, we selected the 166 cases who were diagnosed as primary adenocarcinomas of the colon (*International Classification of Diseases,* Ninth Revision (ICD-9) code 153) (38) through the rectosigmoid junction (ICD-9 code 154.0) (38) as the endpoint used in this study.

For this analysis, we excluded subjects who reported on their questionnaires that they had a previous history of cancer and subjects whose medical charts indicated a previous history of cancer (n = 2,147). Hence, the analytic population at baseline consisted of 32,051 subjects, with 157 cases (colon, 135 cases; rectosigmoid junction, 22 cases) diagnosed during the follow-up.

Lifestyle questionnaire

Subjects completed a mailed lifestyle questionnaire that included questions on demographics, diet, physical activity, psychosocial factors, socioeconomic factors, and medical history. The dietary section consisted of 55 semiquantitative food frequency questions. Most dietary questions had eight frequency categories ranging from "never" to "more than once each day." The meat index was determined from responses to six questions on the current frequency of consumption of specific meats (beef (hamburger, steak, other), pork, poultry (chicken, turkey), and fish) and one question on the current frequency of consumption of any meat.

A physical activity index was calculated from subjects' responses to questions about their participation in vigorous leisure-time or occupational activities and was considered "high" for frequent (≥15 minutes per session, ≥three times per week) participation, "moderate" for less frequent (<15 minutes per session, <three times per week) participation, or "none/low" for "rarely or never" participation in vigorous activity.

Body mass index (kg/m^2) was determined from weight and height information reported on the questionnaire. In a random sample of 168 cohort members (39), the correlation was 0.95 (Pearson's r) between the weight reported on the 1976 questionnaire and the weight measured during an in-person interview up to 1 year after the questionnaire was returned. Other variables considered in the analysis were obtained from responses to questions on smoking (current, past, never), alcohol consumption (beer, wine, liquor combined), age at first pregnancy (age ≤24 years, age >24 years), hormone replacement therapy (recent or prior use, never used), aspirin use (≥1 time/week, <1 time/week), diabetes (any type, no history), and parental history of colon cancer (one or two parents, neither parent).

Validity study

The validity of the dietary data was tested in a random sample of 147 cohort members who participated in a detailed dietary substudy that has been described in other reports (40–41). The substudy participants completed a food frequency questionnaire similar to the one used in the present study, and they also provided five 24-hour recalls on random days during a 3-month period. Using the averaged 24-hour recall data as a standard, we calculated corrected correlation coefficients (42–43) between the frequency of consumption and use of foods and food groups reported on the questionnaire and the estimated gram weight of the corresponding items reported on the 24-hour recalls. For pertinent foods examined in this study, these correlations were similar in magnitude to those documented in other populations (44–45) and were as follows: meat index, 0.83; beef index, 0.49; poultry, 0.57; and legumes, 0.31. All were statistically significant at $\alpha = 0.02$. Among those subjects in the higher intake categories of meat (≥1 time/week) and legumes (>2 times/week) as measured by 24-hour recalls, corresponding questionnaire categories correctly classified 93 percent of the meat intake and 57 percent of the legume intake. In a random sample of cohort members for whom stool samples were collected up to 1 year after baseline (46), a significant positive correlation was found between the intake of legumes as reported on the baseline questionnaire and the total fiber content of the stool ($r = 0.30$); similar positive correlations were found with the stool content of water-insoluble fibers (cellulose, lignin, hemicelluloses) but not of water-soluble fiber (pectin).

Statistical analysis

For the analysis, food and food group data were each divided into three frequency levels. Specifically, for total meat intake, the index described above contained the following three levels to enable investigation of the major meat intake patterns in this cohort: 1) strict vegetarian (no meat intake), 2) occasional meat intake (>0–<1 time/week), and 3) nonvegetarian (meat intake ≥1 time/week). Criteria for categorization of the food variables were established before the analysis began. Subjects with missing values for dietary and nondietary variables were retained in all analyses by using methods described by Woodward et al. (47).

The association between dietary variables and the risk of colon cancer was investigated by using Cox proportional hazards models that included covariates for age, sex, body mass index, parental history of colon cancer, physical activity level, current smoking, past smoking, alcohol consumption, and aspirin use. The time variable for each subject was the duration of follow-up as measured from the date on which the questionnaire was returned (1976–1977). Cases were assigned follow-up time from the date that they returned the questionnaire to the date of their colon cancer diagnosis; noncases were censored at the end of the follow-up period (January 1, 1983), the date of death (if mortality was ascertained during follow-up), or the date of last contact (loss to follow-up affected less than 3 percent of the subjects).

Two statistical tests were performed for each dietary variable. To assess the overall significance of the individual food variables, we performed a log-likelihood ratio test of the indicator food variables. A multivariate test for linear trend across food intake levels was performed by replacing the indicator food variables in each multivariate model with a single variable representing the median frequency of consumption for a given intake level and by using the Wald χ^2 value computed for the regression coefficient of this variable to test the null hypothesis of no linear trend component in colon cancer risk across levels of intake. Variables for the trend test included eight intake levels taken directly from the questionnaire for the nondairy food variables (never, >0–<1 time/month, 1–2 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, 1 time/day, >1 time/day); seven levels from the questionnaire for the dairy variables (never, >0–<1 time/week, 1–6 times/week, 1 time/day, 2–3 times/day, 4–5 times/day, >5 times/day); and three levels for the meat indices (never, >0–<1 time/week, ≥1 time/week) computed from questionnaire variables.

RESULTS

During 178,544 person-years of follow-up (1977–1982), 157 colon cancer cases were identified in the analytic population. Baseline characteristics of the

population are presented in table 1. Results are shown by level of meat intake, as this was an exposure of particular interest. Subjects in each of the meat intake groups were compared, and the significance of between-group differences was assessed by using χ^2, analysis of variance, or Kruskal-Wallis tests, as appropriate. We found no significant differences between the meat intake groups based on age, sex, parental history of colon cancer, or physical activity level. Nonvegetarians had a significantly higher body mass index than the other two groups. This group also used more aspirin, drank more alcohol, and were more likely to be current or past smokers. Among nonvegetarians, the mean intake level of all meats was five times per week, and beef was consumed most frequently.

TABLE 1. Selected demographic and lifestyle characteristics of the study population at baseline, by level of meat intake: Adventist Health Study, California, 1976–1982

Variable	Vegetarian*	Occasional meat intake†	Non-vegetarian‡
Mean age (years) at time of questionnaire return	54	54	52
Sex (%)			
Male	39	37	55
Female	61	63	45
Body mass index§ (mean, kg/m²)	23	24	25
Parental history of colon cancer (%)	5	5	5
Physical activity level¶ (%)			
None/low	38	41	43
Moderate	19	19	19
High	43	40	38
Aspirin use§ (%)	13	20	29
Alcohol consumption§ (%)	<1	<1	9
Smoking history§,# (%)			
Current	<1	<1	7
Past	12	18	28
Never	88	81	65
Mean frequency (times per month) of meat consumption§ (type)			
Beef	0	1	14
Pork	0	0	1
Poultry	0	<1	3
Fish	0	<1	2

* No current meat intake.
† Current meat intake < once per week.
‡ Current meat intake ≥ once per week.
§ $p < 0.05$ by χ^2, analysis of variance, or Kruskal-Wallis test for the distribution of the variable across levels of meat intake.
¶ None/low indicates a "rarely or never" response to items describing vigorous activity; moderate indicates less frequent (<15 minutes per session, <3 times per week) participation in vigorous activity; high indicates frequent (≥15 minutes per session, ≥3 times per week) participation in vigorous activity.
# Numbers do not total 100% because of rounding.

The risk estimates for certain nondietary factors are presented in table 2, with adjustment for age, sex, and parental history of colon cancer. Positive associations were found for a parental history of colon cancer, alcohol consumption, body mass index, and diabetes. When analyses were stratified by sex (men, 65 cases; women, 92 cases), strong positive associations for body mass index and diabetes were evident among men but not among women.

The risk estimates for 12 food variables are presented in table 3, with adjustment for age, sex, parental history of colon cancer, and other covariates. The following food variables were also tested but showed little evidence of important associations: eggs, tomatoes, white rice, brown rice, a fruit index, total milk products, vegetarian protein products, vitamin supplements (A, C, E), and coffee.

The strongest risk factor association among the food variables listed in table 3 was found for total meat intake. An elevated risk was also apparent for red meat and white meat (poultry + fish), but the overall strength of these associations in the total population was of a lower magnitude when compared with total meat intake. A high intake of legumes (beans, lentils, and split peas) showed the strongest protective association among the foods shown in table 3, and, in further analyses, we found that legume intake was not strongly correlated with body mass index ($r = -0.08$) or total meat ($r = -0.27$). A significant inverse relation was also evident for cottage cheese, and similar although nonsignificant ($p \leq 0.10$) trends were shown for salad and green vegetables.

We found that in the total study population, red meat intake and white meat intake were highly correlated ($r = 0.77$). This finding raises the possibility that risk ratios for specific meats listed in table 3 reflect confounding by other meat types. Therefore, to more closely examine the independent contribution of red meat and white meat to the risk identified for total meat intake, we used stratified analyses (table 4) to estimate the risk among subjects who consumed a particular type of meat more frequently than other types. Strong positive trends were shown for red meat intake among subjects who consumed low levels (0–<1 time/week) of white meat and for white meat intake among subjects who consumed low levels (0–<1 time/week) of red meat. These associations remained evident after further categorization of the red meat (relative to no red meat intake: risk ratio (RR) for >0–<1 time/week = 1.38, 95 percent confidence interval (CI) 0.86–2.20; RR for 1–4 times/week = 1.77, 95 percent CI 1.05–2.99; and RR for >4 times/

TABLE 2. Association between selected nondietary factors and the risk of colon cancer in the total study population: Adventist Health Study, California, 1976–1982

Variable	RR*	95% CI*	Cases (no.)	Person-years
Parental history of colon cancer				
None	1.00		144	170,077
One or two parents	1.69	0.95–2.98	13	8,477
Smoking history				
Never	1.00		119	135,950
Past	1.13	0.75–1.70	34	36,626
Current	1.39	0.50–3.82	4	5,977
Aspirin use†				
<1/week	1.00		116	132,317
≥1/week	0.83	0.56–1.25	30	38,246
Alcohol consumption†				
<1/week	1.00		138	163,021
≥1/week	2.05	1.00–4.23	8	7,542
Physical activity level‡				
None/low	1.00		54	70,262
Moderate	1.13	0.74–1.73	36	33,970
High	1.04	0.72–1.51	62	70,507
Body mass index (tertiles of kg/m^2)				
Total				
<22.5	1.00		39	52,525
22.5–25.6	1.27	0.84–1.94	52	54,265
>25.6	1.33	0.88–2.06	51	54,686
Men§				
<22.5	1.00		7	15,144
22.5–25.6	2.67	1.16–6.13	28	26,045
>25.6	2.63	1.12–6.13	24	25,947
Women				
<22.5	1.00		32	37,381
22.5–25.6	0.91	0.54–1.55	24	28,220
>25.6	1.05	0.63–1.75	27	28,739
Diabetes¶				
Total				
Absent	1.00		130	159,608
Present	1.24	0.70–2.20	13	8,316
Men				
Absent	1.00		52	66,543
Present	2.48	1.22–5.03	9	2,997
Women				
Absent	1.00		78	93,065
Present	0.59	0.21–1.60	4	5,318
Reproductive variables (women)				
Age at first pregnancy (years)#				
≤24	1.00		44	54,097
>24	0.83	0.50–1.38	22	28,842
Hormone replacement therapy**				
Never	1.00		38	37,663
Current/past	1.01	0.63–1.62	39	24,498
Parity (no. of livebirths)				
0	1.00		22	18,384
1	0.71	0.36–1.40	13	15,522
2	0.77	0.42–1.41	20	28,902
3	0.65	0.32–1.30	12	20,127
>4	0.79	0.43–1.46	20	18,771

* The risk ratio (RR) and 95% confidence interval (CI) for each variable were adjusted for age, sex, and parental history of colon cancer in a Cox proportional hazards model; estimates for parental history were adjusted for age and sex only.

† Frequency subcategories are given as the number of times per unit of time.

‡ None/low indicates a "rarely or never" response to items describing vigorous activity; moderate indicates less frequent (<15 minutes per session, <3 times per week) participation in vigorous activity; high indicates frequent (≥15 minutes per session, ≥3 times per week) participation in vigorous activity.

§ Significant linear trend across tertiles of body mass index.

¶ Determined from an indication on the baseline questionnaire of physician-diagnosed diabetes (any type).

Excluding nulliparous women.

** Among postmenopausal women.

TABLE 3. Association between the current frequency* of consumption of selected foods and food groups and the risk of colon cancer in the total study population: Adventist Health Study, California, 1976–1982

Food variable	RR†	95% CI†	Cases (no.)	Person-years	*p* for trend‡	*p* for log-likelihood ratio§
Total meat¶						
Never	1.00		32	49,870	0.01	0.02
>0 to <1/week	1.50	0.92–2.45	33	36,547		
≥1/week	1.85	1.16–2.87	75	82,476		
Red meat#						
Never	1.00		42	58,438	0.46	0.11
>0 to <1/week	1.58	1.01–2.45	40	42,211		
≥1/week	1.41	0.90–2.21	45	63,209		
White meat**						
Never	1.00		36	54,780	0.70	0.04
>0 to <1/week	1.67	1.11–2.51	76	82,084		
≥1/week	1.46	0.86–2.48	26	31,087		
Nonfat milk						
Never	1.00		85	98,793	0.30	0.48
>0 to <1/week	0.80	0.48–1.33	18	28,864		
≥1/week	0.78	0.48–1.28	20	29,689		
Lowfat milk						
Never	1.00		65	69,952	0.97	0.63
>0 to <1/week	0.80	0.49–1.30	22	38,210		
≥1/week	0.97	0.66–1.42	45	54,564		
Whole milk						
Never	1.00		46	65,669	0.28	0.35
>0 to <1/week	1.33	0.88–1.99	47	55,048		
≥1/week	1.04	0.69–1.59	42	46,099		
Cheese (excluding cottage cheese)						
Never to <2/month	1.00		56	54,000	0.91	0.36
2/month to <2/week	1.27	0.86–1.87	51	63,582		
≥2/week	1.31	0.84–2.03	35	53,947		
Cottage cheese						
Never to <2/month	1.00		48	56,557	0.03	0.11
2/month to <2/week	1.11	0.75–1.65	52	55,107		
≥2/week	0.74	0.49–1.11	46	57,075		
Green vegetables						
Never to 2/week	1.00		27	28,660	0.10	0.25
3–6/week	0.99	0.63–1.54	70	79,383		
≥1/day	0.74	0.46–1.19	47	60,753		
Salad						
Never to 2/week	1.00		37	37,078	0.08	0.04
3–6/week	1.27	0.85–1.90	73	78,132		
≥1/day	0.75	0.47–1.21	33	55,178		
Nuts						
Never to <1/week	1.00		61	61,196	0.22	0.07
1–4/week	0.67	0.45–0.98	47	69,262		
>4/week	0.68	0.45–1.04	37	38,180		
Legumes††						
Never to <1/week	1.00		74	67,407	0.03	0.02
1–2/week	0.71	0.49–1.02	48	64,350		
>2/week	0.53	0.33–0.86	22	37,812		

* Frequency subcategories are given as the number of times per unit of time.

† The risk ratio (RR) and 95% confidence interval (CI) for each intake category of a specific food or food group were computed (relative to the low intake category) from a proportional hazards regression with the following covariates: age at baseline, sex, body mass index (kg/m^2), physical activity (none/low, moderate, high levels of leisure plus occupational activities), parental history of colon cancer (one parent, both parents, neither parent), current smoking, past smoking, alcohol consumption, and aspirin use.

‡ Determined from a model in which the indicator variables for food frequency categories were replaced with a single variable representing the median frequency at a given intake level.

§ A log-likelihood ratio test of the indicator variables for food frequency categories.

¶ Current intake of beef, pork, poultry, and fish and/or current intake of any meat.

Current intake of beef or pork.

** Current intake of poultry or fish.

†† Current intake of beans, lentils, or split peas.

week = 1.98, 95 percent CI 1.00–3.89) and white meat (relative to no white meat intake: RR for >0–<1 time/week = 1.55, 95 percent CI 0.97–2.50; RR for 1–4 times/week = 3.37, 95 percent CI 1.60–7.11; and RR for >4 times/week = 2.74, 95 percent CI 0.37–20.19) variables to higher intake levels. Taken to-

TABLE 4. Associations between current intake* of specific meats and colon cancer risk in subsets of the population with meat intake patterns that favor specific types of meat: Adventist Health Study, California, 1976–1982

	Never	>0 to <1/week		≥1/week		Cases (no.)	p for trend‡	p for log-likelihood ratio§
	RR†	RR	95% CI†	RR	95% CI			
Red meat intake among subjects with white meat intake of <1/week	1.00	1.40	0.87–2.25	1.90	1.16–3.11	112	0.02	0.04
White meat intake among subjects with red meat intake of <1/week	1.00	1.55	0.97–2.50	3.29	1.60–6.75	82	0.006	0.008

* Frequency subcategories are given as the number of times per unit of time.

† The risk ratio (RR) and 95% confidence interval (CI) for each intake category of a specific meat were computed (relative to never consumers of the specific meat) from a proportional hazards regression with the following covariates: age at baseline, sex, body mass index (kg/m²), physical activity (none/low, moderate, high levels of leisure plus occupational activities), parental history of colon cancer (one parent, both parents, neither parent), current smoking, past smoking, alcohol consumption, and aspirin use.

‡ Determined from a model in which the indicator variables for food frequency categories were replaced with a single variable representing the median frequency at a given intake level.

§ A log-likelihood ratio test of the indicator variables for food frequency categories.

gether, these data suggest that both red meat and white meat are important contributors to the overall risk observed for total meat intake.

The associations with total meat intake and with legume intake that were identified in single food models were examined further in a model containing both food groups along with the usual potential confounders. In this model, high intakes of total meat (≥1 time/week) and legumes (>2 times/week) continued to have significant associations with colon cancer risk, the overall significance of each food variable was borderline, and strong estimated trends remained. Adding other foods (cottage cheese, salad) to this model diminished the magnitude of their estimated associations without, however, indicating major confounding of the risk estimates for total meat and legumes.

To investigate a possible complex relation between these food variables and the risk of colon cancer, we formally tested for a multiplicative interaction using a model in which the product term for meat × legumes attained significance ($p = 0.03$). Next, we further evaluated the interaction from a model (figure 1) that provided risk ratios (relative to vegetarians with a legume intake of <1 time/week) for nine categories of total meat (nonvegetarian, occasional meat intake, vegetarian) by legume intake (>2 times/week, 1–2 times/week, <1 time/week) and adjusted for age, sex, and parental history of colon cancer (refer to the Appendix for specific values). This model identified an especially potent increase in risk for nonvegetarians who had a low legume intake (RR = 2.54, 95 percent CI 1.20–5.37).

To examine whether the apparent complex relation between meat intake and legume intake was restricted to specific meats, we tested separate models for red meat by legume intake and white meat by legume intake (figure 2; refer to the Appendix for specific values). As noted above, to investigate the contribution of specific meats, we restricted the analysis of red meat to those subjects who consumed low levels (<1 time/week) of white meat (112 cases) and the analysis of white meat to those who consumed low levels (<1 time/week) of red meat (82 cases). The models in figure 2 show that the apparent modification in risk for meat intake by legume intake (figure 1) was evident only for red meat intake (RR for a red meat intake of ≥1 time/week + a legume intake of <1 time/week = 2.28 , 95 percent CI 1.28–4.05).

To examine whether the complex relation for the intake of red meat and legumes was further modified by body mass index, we calculated risk estimates from a model (figure 3; refer to the Appendix for specific values) that evaluated the risk for red meat intake (≥1 time/week, <1 time/week) by legume intake (≥1 time/week, <1 time/week) by body mass index (at or

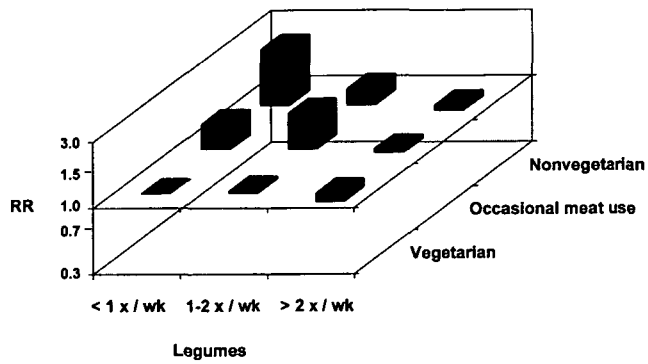

FIGURE 1. Risk ratios (RR) from a model relating nine categories of total meat (vegetarian, no meat intake; occasional meat use, >0–<1 time (×)/week (wk); nonvegetarian, ≥1 time/week) by legume intake to the risk of colon cancer; risk ratios (refer to the Appendix for risk ratios and 95% confidence intervals) are expressed relative to vegetarians with a legume intake of <1 time/week and are adjusted for age, sex, and parental history of colon cancer: Adventist Health Study, California, 1976–1982.

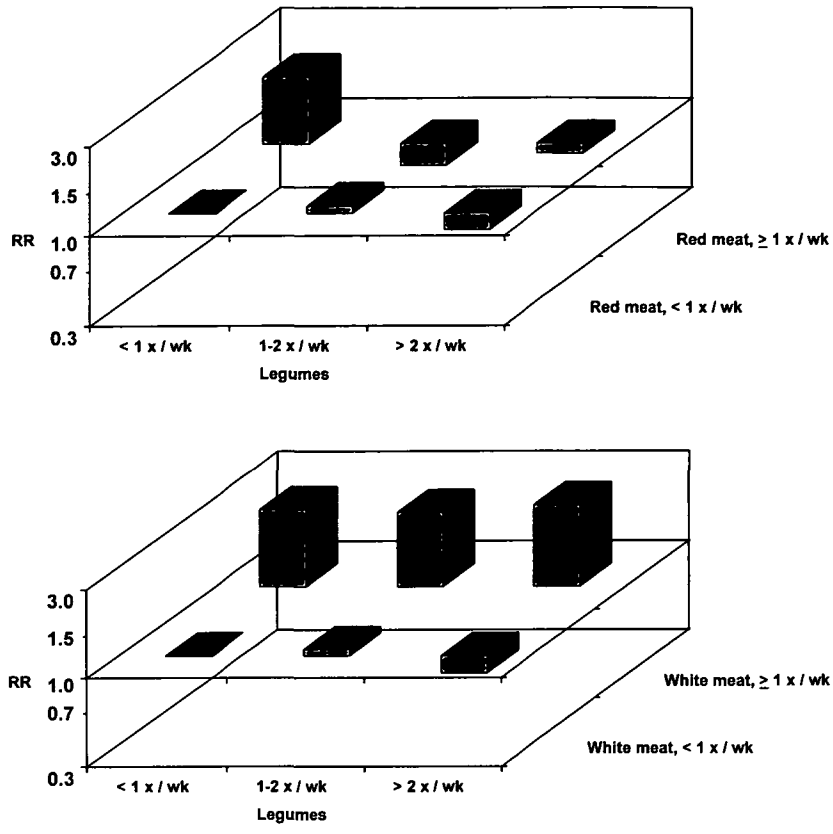

FIGURE 2. Risk ratios (RR) from two models relating six intake categories of red meat (never to <1 time (×)/week (wk), ≥1 time/week) by legume intake (never to <1 time/week, 1-2 times/week, >2 times/week) and six categories of white meat (never to <1 time/week, ≥1 time/week) by legume intake (never to <1 time/week, 1-2 times/week, >2 times/week) to the risk of colon cancer in two subsets of the population in which meat intake patterns favor red meat and white meat, respectively; risk ratios (refer to the Appendix for risk ratios and 95% confidence intervals) are expressed relative to the category in which intake of the specific meat and legumes occurred <1 time/week and are adjusted for age, sex, and parental history of colon cancer: Adventist Health Study, California, 1976–1982.

above the mean of 25 kg/m^2, below the mean of 25 kg/m^2). This model (figure 3) showed that the especially potent increase in risk for a red meat intake of ≥1 time/week + a legume intake of <1 time/week (figure 2) was entirely restricted to those with a body mass index of ≥25 kg/m^2 (RR for a red meat intake of ≥1 time/week + a legume intake of <1 time/week + a body mass index of ≥25 kg/m^2 vs. a red meat intake of <1 time/week + a legume intake of <1 time/week + a body mass index of <25 kg/m^2 = 3.19, 95 percent CI 1.62–6.26). Sex-specific models (figure 3) indicated that the markedly increased risk for this category was stronger in men (RR = 5.10, 95 percent CI 1.48–17.5) than in women (RR = 2.00, 95 percent CI 0.78–5.11). However, physical-activity-specific models (not shown in figure 3) showed that the markedly increased risk for this category was not materially different for a "high-moderate" physical activity level (RR = 2.82, 95 percent CI 1.23–6.46) as compared with a "none/low" physical activity level (RR = 3.42, 95 percent CI 0.99–11.9).

We tested whether the major findings of this study were affected by the presence of clinical or subclinical gastrointestinal disease at the beginning of follow-up by excluding those cases who were diagnosed during the first 2 years of follow-up. We found that this exclusion did not substantially alter the associations reported above for the intake of all meats, red meat, white meat, or legumes; for body mass index; or for a complex relation between red meat intake, legume intake, and body mass index (RR for a red meat intake of ≥1 time/week + a legume intake of <1 time/week + a body mass index of ≥25 kg/m^2 vs. a red meat intake of <1 time/week + a legume intake of <1 time/week + a body mass index of <25 kg/m^2 = 3.43, 95 percent CI 1.66–7.07).

We also tested whether associations with high meat intake, low legume intake, and high body mass index in this Adventist Health Study cohort may reflect a lack of adherence to other church recommendations (tobacco use, alcohol consumption). This hypothesis was also shown to be unlikely, since exclusion of current smokers, past smokers, and alcohol consumers did not substantially alter the associations reported

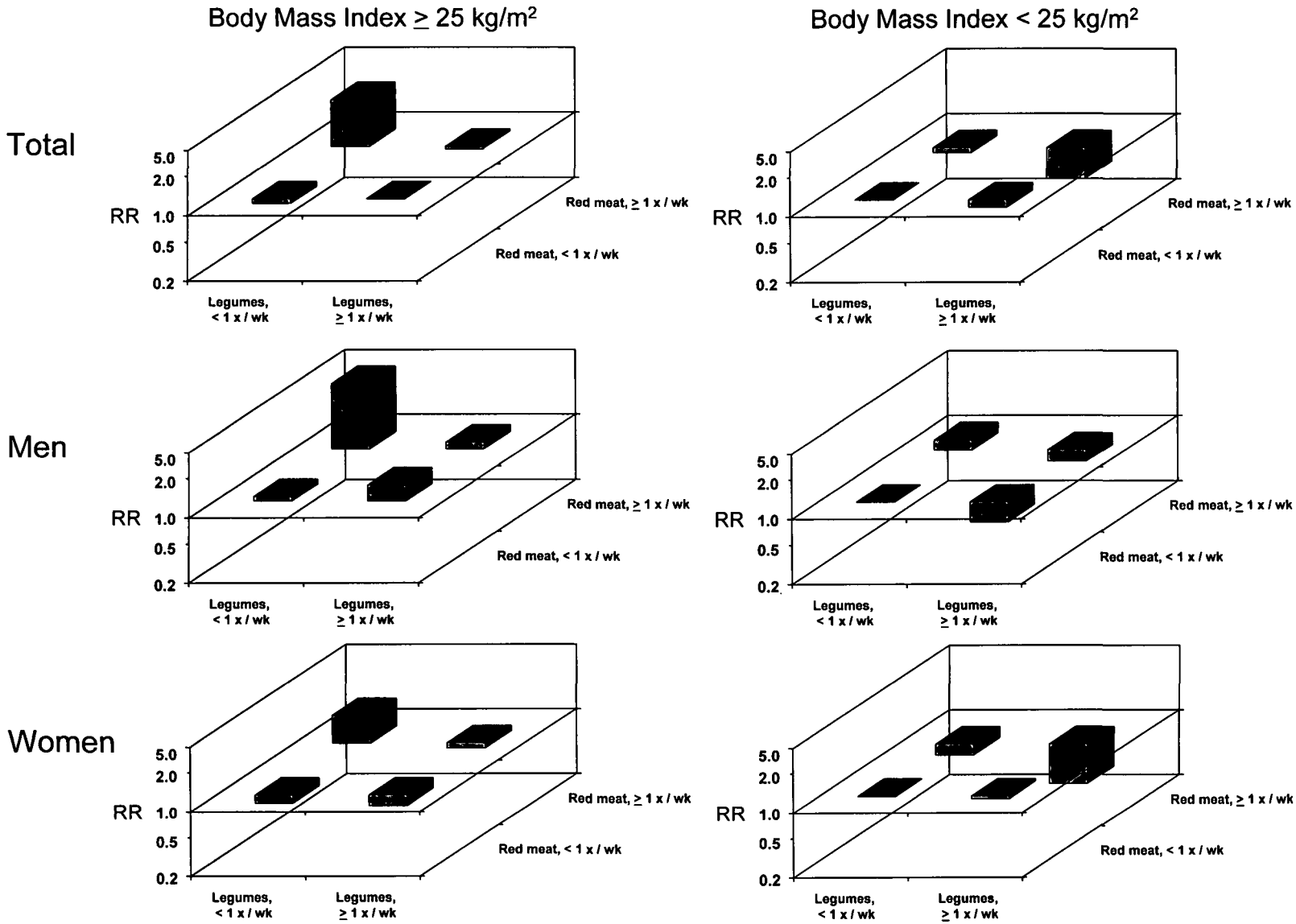

FIGURE 3. Risk ratios (RR) from three models (total, men, women) relating eight categories of red meat intake (never to <1 time (×)/week (wk), ≥1 time/week) by legume intake (never to <1 time/week, ≥1 time/week) by body mass index (<25 kg/m^2, ≥25 kg/m^2) to the risk of colon cancer in the subset of the population in which the meat intake pattern favors red meat; risk ratios (refer to the Appendix for risk ratios and 95% confidence intervals) for each category are adjusted for age, sex, and parental history of colon cancer and are expressed relative to the category in which intake of red meat and legumes occurred <1 time/week and body mass index was <25 kg/m^2: Adventist Health Study, California, 1976–1982.

above for all meats, red meat, white meat, legumes, or body mass index or for the complex relation between red meat, legumes, and body mass index (RR for a red meat intake of ≥1 time/week + a legume intake of <1 time/week + a body mass index of ≥25 kg/m^2 vs. a red meat intake of <1 time/week + a legume intake of <1 time/week + a body mass index of <25 kg/m^2 = 3.03, 95 percent CI 1.38–6.65).

DISCUSSION

The relation between diet and incident colon cancer was examined in a prospective study of 32,051 non-Hispanic white cohort members of the Adventist Health Study. These subjects had a low prevalence of current smoking and alcohol consumption, and 30 percent of them reported no meat intake. Our major findings from this population were as follows: 1) a positive association between meat intake and colon cancer risk and evidence that both red meat and white meat (fish + poultry) contribute independently to the elevation in risk due to meat intake; 2) an inverse association between legume intake and colon cancer risk; 3) a positive association for body mass index among men; and 4) evidence for a complex association whereby high red meat intake, low legume intake, and high body mass interact to produce an excess colon cancer risk.

The findings from this population add to the data from numerous studies that implicate meat intake in colon carcinogenesis (8). These findings also complement data from earlier studies of a sample of Adventist Health Study cohort members (39, 46, 48–51) indicating that the prevalence of several biomarkers for colon cancer (colonic epithelial cell proliferation, bile acid residues, serum hexosaminidase) was significantly lower among vegetarian cohort members than among either nonvegetarian cohort members or nonvegetarians from a general population sample.

Currently, there is good evidence to support a "meat/vegetable" hypothesis (52) that intake of these foods explains much of the variation in the regional incidence of colon cancer. Most of the large, well-designed case-control and cohort studies have shown a positive association for meat intake and/or a protective association for at least one vegetable item (8). Of these studies, two also reported a substantial increase in colon cancer risk for a high meat-to-vegetable ratio (22, 26), an association that parallels our findings of a relation between colon cancer and the relative intake of meat and legumes.

In this cohort, there is evidence of an excess risk of colon cancer for higher intakes of both red meat and white meat (poultry + fish). These findings suggest the presence of factors in *all meats* that contribute to colon carcinogenesis. Meat fat has long been cited as a contributor to the excess colon cancer risk associated with meat intake, although a number of recent prospective investigations of large populations have reported either no association (20, 29, 53) or an elevated risk that may reflect confounding by red meat (19). The mutagenic and carcinogenic properties of heterocyclic amines derived from cooked meat protein are particularly noteworthy (54–60) since, in concordance with the findings presented in this paper, the mechanism predicts risk for both red meat and white meat. Other factors related to the nitrosable compounds in processed (salting, curing, nitrite additives) and unprocessed meats (29, 61, 62), the pyrolysis of meats (benzo[a]pyrene and other polycyclic hydrocarbons) (4, 25, 56, 63, 64), and the oxidative properties of the iron content of blood meats (65) have also been identified as possible contributors to colon carcinogenesis.

In addition to the simple associations with total meat and specific meats, we also identified a complex association between the intake of red meat and legumes, whereby the hazard due to red meat intake is evident among only those with a low intake of legumes (figure 2). These findings raise the possibility that a specific factor in legumes inhibits one or more of the hypothesized carcinogenic mechanisms that occur in the colon because of a higher red meat intake.

One such factor is the high fiber content of legumes, which could modify the deleterious effects of ingested red meat by diluting putative carcinogens in the higher fecal bulk, by decreasing the overall transit time of this bulk, by binding bile acids (8, 18, 66–68), or by a volatile fatty-acid-mediated lowering of the colonic pH that could slow conversion of primary to secondary bile acids (67). Another possible "modifying" factor in legumes is protease inhibitors. An indirect mechanism has been proposed whereby the Bowman-Birk inhibitor binds digestive proteases of the duodenum, thus preventing protein digestion and increasing excretion of the ingested proteins (69). Other potential factors in legumes include saponins, which have been shown to bind bile acids and cholesterol (70), and perhaps the estrogen-receptor binding and other properties of isoflavones (71). Despite the numerous putative anticarcinogens found in biologically important quantities in legumes, these hypotheses do not entirely explain the complex relation between red meat and legumes in the cohort we studied, since the "substrates" (fatty acids, cooked meat protein) for these "anticarcinogen reactions" can be found in both red meat and white meat.

McKeown-Eyssen (33) and Giovannucci (34) have proposed that if insulin induces hyperproliferation of the normal and neoplastic colonic mucosa, as shown in animal models (72–76), then many of the dietary risk factor associations with colon cancer observed at the

population level may reflect the effect of hyperinsulinemia. According to Giovannucci's hypothesis (34), given adequate pancreatic β-cell function, a synergism between factors that increase insulin resistance and factors that increase glycemic load should be causal. In contrast to the anticarcinogen hypotheses, this hypothesis is specifically consistent with the complex relation for red meat and legumes presented in figure 2, assuming that the characteristically low polyunsaturated/saturated fat ratio from a higher red meat intake contributed to insulin resistance (77–79), while the low intake of legumes, a food of characteristically low glycemic response (80), contributed to a heavier glycemic load.

We found further support for this hypothesis when simultaneously considering obesity (figure 3), a major contributor to insulin resistance. The possibility that, in the Adventist Health Study cohort, obesity is linked to colon cancer through insulin-induced hyperproliferation of colonic epithelial cells is particularly noteworthy, since it is consistent with recent data from healthy, nondiabetic, stable-weight Adventist Health Study cohort members indicating a positive association between body mass index and colonic epithelial cell proliferation (81). Also, the marked increase in risk due to obesity among men (table 2, figure 3) further supports an insulin-related hypothesis, since the greater tendency for abdominal deposition of body fat among men would likely result in higher insulin levels in obese men relative to women of equivalent fat mass (82). The marked increase in risk due to diabetes in men (table 2) could potentially represent a biologic intermediate of the obesity relation. However, this finding should be regarded as preliminary, since the baseline data do not allow for study of the relevant type of diabetes (i.e., diabetes mellitus).

Therefore, in the Adventist Health Study cohort we found evidence that several possible components of hyperinsulinemic exposure (high red meat intake, low legume intake, obesity) seem to interact to produce an excess risk of colon cancer. A similar association between several possible components of hyperinsulinemic exposure (high sucrose-to-fiber ratio, low physical activity, obesity) and an excess colon cancer risk was recently reported in a large case-control study (83), and preliminary evidence from another recent case-control study linked plasma insulin levels to the risk of both colorectal cancer and adenomatous polyps (84). Nevertheless, the insulin hypothesis does not so easily explain the increased risk for white meat intake among Adventist Health Study cohort members (table 4, figure 2), raising the possibility that different causal pathways for red meat and white meat underlie the overall risk due to meat intake that was observed in the cohort.

It is important to note that if hyperinsulinemic exposure was causal in the Adventist Health Study cohort, then physical activity levels should have been an important predictor of colon cancer, given the increase in insulin sensitivity that results from exercise. Despite the equivocal colon cancer risk by physical activity level that was observed in this cohort (table 2), the physical activity index reported in this paper is a significant predictor of coronary events (85), breast cancer (86), and all-cause mortality (87) in the cohort. In addition, survey measures of vigorous activity are correlated with physical fitness among Adventists (88). Thus, it seems unlikely that the absence of an association between this index and colon cancer risk is entirely attributable to measurement error. It is noteworthy that among non-Hispanic whites, we found a significantly higher physical fitness level (treadmill time) (88) and frequency of participation in vigorous activities (88–89) among Adventists than among non-Adventists. This finding raises the possibility that the absence of an inverse physical activity–colon cancer relation in this analysis may reflect the low prevalence of inactivity levels in this cohort that could contribute to colon carcinogenesis.

Certain limitations of our study should be considered. The food frequency items listed on the questionnaire tended to reflect a combination of certain foods of similar composition (e.g., vegetarian protein products). Although an exhaustive list of items on a food frequency questionnaire increases the likelihood of overestimation bias (90), a wider range of questionnaire items would have enhanced our ability to distinguish the effects of individual foods, particularly those specific to a vegetarian diet pattern. For those subjects in this cohort who consumed meat, no data are available on the methods of cooking and processing the meats.

In summary, our findings from the Adventist Health Study cohort identify red meat intake and white meat intake as important dietary risk factors for colon cancer and further suggest that the increased risk due to red meat intake occurred only at lower legume intakes and higher body mass. These associations raise the possibility that the risk due to meat intake is mediated by multiple mechanisms, one of which may involve red meat intake in a constellation of causal factors that produces higher plasma insulin levels.

ACKNOWLEDGMENTS

This study was supported by grant 2R01-CA14703–15A1 from the National Cancer Institute.

The authors acknowledge the important contribution of Roland Phillips (deceased), the original principal investigator, to the study of diet and colon cancer in the Adventist Health Study cohort.

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Appendix follows

APPENDIX

Risk Ratios and 95 Percent Confidence Intervals for the Findings Depicted in Figures 1–3

Figure 1: Values are given for frequency categories of <1 time (×)/week (wk), 1–2 times/week, and >2 times/week of legume intake. Among the nonvegetarians, RR = 2.54, 95 percent CI 1.20–5.37; RR = 1.33, 95 percent CI 0.57–3.06; and RR = 0.93, 95 percent CI 0.30–2.86, respectively. Among the occasional meat users, RR = 1.55, 95 percent CI 0.63–3.78; RR = 1.84, 95 percent CI 0.78–4.35; and RR = 0.93, 95 percent CI 0.30–2.84, respectively. Among the vegetarians, RR = 1.00 (referent); RR = 1.05, 95 percent CI 0.43–2.53; and RR = 0.86, 95 percent CI 0.33–2.24, respectively.

Figure 2: Values are given for the frequency categories of <1 time (×)/week (wk), 1–2 times/week, and >2 times/week of legume intake. For a red meat intake of ≥1 time/week, RR = 2.28, 95 percent CI 1.28–4.05; RR = 0.77, 95 percent CI 0.29–2.02; and RR = 0.89, 95 percent CI 0.21–3.80, respectively. For a red meat intake of <1 time/week, RR = 1.00 (referent); RR = 1.09, 95 percent CI 0.63–1.86; and RR = 0.82, 95 percent CI 0.44–1.53, respectively. For a white meat intake of ≥1 time/week, RR = 2.59, 95 percent CI 0.99–6.83; RR = 2.49, 95 percent CI 0.75–8.30; and RR = 2.73, 95 percent CI 0.64–11.63, respectively. For a white meat intake of <1 time/week, RR = 1.00 (referent); RR = 1.08, 95 percent CI 0.63–1.86; and RR = 0.81, 95 percent CI 0.43–1.52, respectively.

Figure 3 (Total): Values are given for the frequency categories of <1 time (×)/week (wk) and ≥1 time/week) of legume intake. For a body mass index of ≥25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 3.19, 95 percent CI 1.62–6.26 and RR = 0.96, 95 percent CI 0.35–2.66, respectively. For a body mass index of ≥25 kg/m^2 and a red meat intake of <1 time/week, RR = 1.00, 95 percent CI 0.52–1.95 and RR = 0.89, 95 percent CI 0.39–2.01, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 0.47, 95 percent CI 0.11–2.01 and RR = 0.89, 95 percent CI 0.33–2.38, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of <1 time/week, RR = 1.00 (referent) and RR = 0.83, 95 percent CI 0.46–1.48, respectively.

Figure 3 (Men): Values are given for frequency categories of <1 time (×)/week (wk) and ≥1 time/week) of legume intake. For a body mass index of ≥25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 5.10, 95 percent CI 1.48–17.5 and RR = 1.18, 95 percent CI 0.24–5.75, respectively. For a body mass index of ≥25 kg/m^2 and a red meat intake of <1 time/week, RR = 1.47, 95 percent CI 0.42–5.11 and RR = 1.11, 95 percent CI 0.23–5.36, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 1.28, 95 percent CI 0.22–7.18 and RR = 0.75, 95 percent CI 0.08–6.92, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of <1 time/week, RR = 1.00 (referent) and RR = 0.60, 95 percent CI 0.16–2.26, respectively.

Figure 3 (Women): Values are given for frequency categories of <1 time (×)/week (wk) and ≥1 time/week of legume intake. For a body mass index of ≥25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 2.00, 95 percent CI 0.78–5.11 and RR = 0.89, 95 percent CI 0.20–3.98, respectively. For a body mass index of ≥25 kg/m^2 and a red meat intake of <1 time/week, RR = 0.82, 95 percent CI 0.31–2.18 and RR = 0.77, 95 percent CI 0.32–1.82, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of ≥1 time/week, RR = 0.77, 95 percent CI 0.22–2.63 and RR = 0.38, 95 percent CI 0.05–2.84, respectively. For a body mass index of <25 kg/m^2 and a red meat intake of <1 time/week, RR = 1.00 (referent) and RR = 0.94, 95 percent CI 0.49–1.80, respectively.