Red Meat, Chicken, and Fish Consumption and Risk of Colorectal Cancer

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Abstract

Background: Red meat and processed meat consumption have been associated with increased risk of colorectal cancer in some, but not all, relevant cohort studies. Evidence on the relationship between risk of colorectal cancer and poultry and fish consumption is inconsistent. Methods: We conducted a prospective cohort study of 37,112 residents of Melbourne, Australia recruited from 1990 to 1994. Diet was measured with a food frequency questionnaire. We categorized the frequency of fresh red meat, processed meat, chicken, and fish consumption into approximate quartiles. Adenocarcinomas of the colon or rectum were ascertained via the Victorian Cancer Registry. Results: We identified 283 colon cancers and 169 rectal cancers in an average of 9 years of follow-up. For rectal cancer, the hazard ratios [95% confidence intervals (95% CI)] in the highest quartile of consumption of fresh red meat and processed meat were 2.3 (1.2–4.2; *P* for trend = 0.07) and 2.0 (1.1–3.4; *P* for trend = 0.09), respectively. The corresponding hazard ratios (95% CIs) for colon cancer were 1.1 (0.7–1.6; *P* for trend = 0.9) and 1.3 (0.9–1.9; *P* for trend = 0.06). However, for neither type of meat was the heterogeneity between subsites significant. Chicken consumption was weakly negatively associated with colorectal cancer (hazard ratio highest quartile, 0.7; 95% CI, 0.6–1.0; *P* for trend = 0.03), whereas hazard ratios for fish consumption were close to unity. Conclusion: Consumption of fresh red meat and processed meat seemed to be associated with an increased risk of rectal cancer. Consumption of chicken and fish did not increase risk. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1509–14)

Introduction

In 1997, the World Cancer Research Fund and the American Institute for Cancer Research stated that consumption of red meat probably increases the risk of colorectal cancer and consumption of processed meat possibly increases its risk (1). Much of the evidence for this assessment came from case-control studies, which are more subject to bias than cohort studies. Sixteen cohort studies with quantitative data on meat intake have been published in 19 reports (2-20), but only two studies showed strong, positive associations with one or more types of meat consumption (4, 6). Because most of the cohort studies included ≤200 cases, few have had sufficient power to exclude modest or weak associations.

Because consumption of red meat is often recommended for its iron content [e.g., as in the current Australian Dietary Guidelines for Adults (21)], recommendations to limit consumption to avoid colorectal cancer need to be based on strong evidence. Because we considered that the evidence was not strong, we analyzed data from the Melbourne Collaborative Cohort Study on consumption of red meat and processed meat in relation to risk of colorectal cancer. We also analyzed data on consumption of chicken and fish because these are often recommended as substitutes for red meat and their associations with risk of colorectal cancer have been inconsistent (1).

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Materials and Methods

Study Population. The Melbourne Collaborative Cohort Study is a prospective cohort study of 41,528 residents (17,049 men) of Melbourne, Australia ages between 27 and 75 years at baseline (99.3% were ages 40–69 years; ref. 22). Italian and Greek migrants were deliberately recruited to extend the range of lifestyle exposures. Recruitment occurred between 1990 and 1994. Subjects were recruited via the electoral rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media (e.g., television, radio, and newspapers). Comprehensive lists of Italian and Greek surnames were also used to target southern European migrants in the phone book and Electoral Rolls.

The Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records.

We excluded 4,416 participants because they had had colorectal cancer, diabetes, a heart attack, or angina before baseline; had no dietary data; or their reported

energy intake was in the lowest or highest 1% of the sex-specific distributions. Subjects with diabetes, heart attacks, or angina were excluded because their reported diets were not representative of the cohort (e.g., they had low intakes of saturated fat) and we were unsure when they changed their diets. These exclusions left 37,112 subjects.

Dietary Assessment. Subjects completed a dietary questionnaire that was developed from a study of weighed food records in 810 Melburnians of similar age and ethnic origin to the cohort (23). It included a 121-item food frequency questionnaire (FFQ) without portion sizes. The questionnaire had 22 items on intake of fresh red meat, processed meat, chicken, and fish. Fresh red meat was defined as veal or beef schnitzel, roast beef or veal, beef steak, rissoles (meat balls) or meatloaf, mixed dishes with beef, roast lamb or lamb chops, mixed dishes with lamb, roast pork or pork chops, and rabbit or other game (rarely consumed). Processed meat included salami or continental sausages, sausages or frankfurters, bacon, ham including prosciutto, corned beef, and manufactured luncheon meats. Chicken included roast or fried chicken, boiled or steamed chicken, and mixed dishes with chicken. Fish included steamed, grilled, or baked fish; fried fish; smoked fish; and canned fish including tuna, salmon, and sardines.

Nutrient intakes were calculated using mean sex-specific portion sizes from weighed food records (23). Intakes of energy, fat, fiber, and calcium were computed using Australian food composition tables (24). Because these tables do not include folate, we used British data for this nutrient (25). Energy from alcoholic beverages was added to that calculated from the FFQ.

Assessment of Other Risk Factors. A structured interview schedule was used to obtain information on potential risk factors including age, sex, country of birth, alcohol consumption, current physical activity during leisure time, education, and use of hormone replacement therapy. Height, weight, and waist and hip circumferences were measured.

Cohort Follow-up and Case Ascertainment. Cases were identified from notifications to the Victorian Cancer Registry of diagnoses of adenocarcinoma of the colon and rectum (*International Classification of Diseases, Ninth Revision* rubric 153.0–153.4, 153.6–153.9, 154.0, 154.1, 154.8 or *International Classification of Diseases, Tenth Revision* rubric C18.0, C18.2–C18.9, C19, C20, C21.8). We reviewed medical records of reported colorectal tumors and classified them according to anatomic site (rectal, proximal, and distal colons) and stage. Tumors arising in the cecum, ascending colon, hepatic flexure, and transverse colon were defined as proximal; whereas tumors arising in the descending and sigmoid colons were defined as distal. Stage was categorized into four groups based on the American Joint Committee on Cancer staging system: stage I (T_{1-2}, N_0, M_0), stage II (T_{3-4}, N_0, M_0), stage III (T_{any}, N_{1-2}, M_0), and stage IV (T_{any}, N_{any}, M_1).

Addresses and vital status of the subjects were determined by record linkage to Electoral Rolls and Victorian death records, from electronic phone books, and from responses to mailed questionnaires and newsletters. By the end of follow-up on June 30, 2002, 718 (1.9%) subjects were known to have left Victoria and 1,568 (4.2%) were known to have died.

Reproducibility Study. To estimate the reproducibility of the FFQ, between July 1992 and June 1993, we invited 275 subjects to participate in a study that included completing a second FFQ 12 months after baseline. Selection was stratified by sex, country of birth (Australia, Italy, and Greece), 10-year age group (40–49, 50–59, and 60–69 years), and month of attendance. Quota sampling was used to ensure that similar numbers enrolled throughout the recruitment period.

Statistical Analysis. Cox's proportional hazard model, with age as the time metric, was used to estimate rate ratios, 95% confidence intervals (95% CI), and *P*s. Calculation of person-time began at baseline and ended at the earliest of the date of diagnosis of colorectal cancer, date of diagnosis of cancer of unknown primary site, date of death, date last known to be in Victoria, or June 30, 2002 (the date that ascertainment of colorectal cases by the Victorian Cancer Registry was complete). Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves (26) showed no evidence that proportional hazard assumptions were violated for any analyses.

All meat consumption variables were analyzed as categorical, based on approximate quartiles of the distribution of weekly frequency of consumption, and as pseudo-continuous, assuming that, within each quarter, all subjects consumed at its median frequency; *P*s for trend were calculated for these variables. The hazard ratios for these variables correspond to an increase in intake of one time per week. We also calculated the ratio of frequency of consumption of fresh red meat to the combined frequency of consumption of chicken and fish and divided it into groups based on quartiles. The hazard ratio from its analysis as a pseudo-continuous variable corresponds to an increase in the ratio of one unit (which was approximately the interquartile range).

Sex, country of birth, and energy intake (kJ/d) were included in all models. Other potential confounding variables were included in all the definitive analyses if they changed the hazard ratios of any of the meat consumption variables for either colon or rectal cancer by at least 5%. First, education, current level of physical activity, folate intake, calcium intake, use of multivitamins, and current alcohol consumption (g/d) were added. Because the hazard ratios from the models with none of these variables were <5% different from the models with all of them, none was retained for further analysis. Second, for women only, hormone replacement therapy use was tested in the same way but not retained. Third, we added consumption of other food groups (fruit, vegetables, all cereal products, wholemeal bread, and breakfast cereal) and macronutrients (fat and fiber) one at a time to the base models. Consumption of all cereal products and fat intake were retained. Finally, body mass index and waist-to-hip ratio were added but not retained.

Polytomous logistic regression models, adjusting for age (as a linear term), sex, country of birth, and consumption of energy, fat, and cereal products, were used to test for homogeneity in odds ratios of the pseudo-continuous meat consumption variables for colon versus rectal cancer, proximal versus distal colon cancer, and early (I and II) versus late (III and IV) stage disease (27).

Before testing, we first determined which of the other covariates in the model could be constrained to have the same effect for each outcome. Odds ratios for the meat consumption variables were not materially different from the hazard ratios obtained from the Cox modeling.

Reproducibility of meat, energy, and other nutrient intakes was assessed by calculating weighed κ statistics from the two questionnaires completed by subjects in the reproducibility study.

Results

Over an average of 9 years of follow-up per person, we identified 451 subjects with incident colorectal cancer (97% were histologically verified) including 283 colon tumors (147 proximal, 111 distal, and 25 that could not be classified) and 169 rectal tumors (one subject had a colon and rectal tumor). Information on stage was available for 376 (83%) cases. Of these, 83 (22%) were stage I, 118 (31%) were stage II, 98 (26%) were stage III, and 77 (20%) were stage IV.

There was a wide range of intakes of fresh red meat and processed meat and, to a lesser extent, chicken, although fish was eaten infrequently (Table 1). The quartiles of the distributions of amount consumed daily were 57, 86, and 126 g of fresh red meat and 9, 18, and 29 g of processed meat.

Meat was eaten more frequently by men than by women: men's weekly median frequencies of consumption were 5.0 times (fresh red meat) and 2.5 times (processed meat) compared with 4.0 and 2.0 times for women. Greek immigrants were the most frequent consumers of fresh red meat (median 5.5 versus 4.5 times/wk for each of the other groups) but were the least frequent consumers of processed meat (median of 2.5 versus 4 times/wk for all other groups). Correlations between other potential confounding variables and meat intake are shown in Table 2. Fresh red meat consumption had moderate positive correlations with intakes of energy, fat, and chicken and with body mass index and waist-to-hip ratio and moderate negative correlations with intakes of fiber, folate, and calcium. It had weak positive correlations with fish, vegetable, and cereal consumption. Processed meat consumption generally had similar correlations, except that the correlation with chicken intake was weak and it had small negative correlations with intakes of vegetables and fruit. Consumption of fresh red meat and processed meat were moderately positively correlated ($r = 0.27$).

Table 3 shows the hazard ratios according to meat consumption. Little evidence of dose-response relationships was seen for fresh red meat consumption—the hazard ratios for colorectal cancer were ~1.4 to 1.5 in each quartile other than the reference category. Most of this association was due to rectal cancer, for which all hazard ratios were ~2.2. When analyzed as a pseudo-continuous variable, there was weak evidence that the trend was stronger for rectal cancer (test of homogeneity of trends, $P = 0.07$). Consumption of processed meat was weakly associated with risk of colorectal cancers. It was more strongly associated with risk of rectal cancer than with colon cancer, but as with consumption of fresh red meat, there was little evidence of increasing risk with increasing consumption. When analyzed as a pseudo-continuous variable, the trends were similar for both sites (test of homogeneity of trends, $P = 0.5$). Processed and fresh red meat consumption were also modeled together. For colorectal cancers, the hazard ratios (95% CIs) for each additional serve per week were 1.02 (0.98–1.08) for fresh red meat and 1.07 (1.01–1.13) for processed meat. The corresponding hazard ratios (95% CIs) were 1.00 (0.94–1.06) and 1.07 (1.00–1.14) for colon cancers and 1.07 (0.99–1.16) and 1.07 (0.98–1.17) for rectal cancers.

Chicken consumption showed a weak inverse association with risk of colorectal cancers (Table 3). The

Table 1. Demographic characteristics and consumption of meat, chicken, and fish in the Melbourne Collaborative Cohort Study

	Colorectal cancer [*n* (%)]	Total
Baseline age, y		
<50	49 (0.4)	12,633
50–59	121 (1.0)	12,252
60+	281 (2.3)	12,227
Sex		
Male	225 (1.5)	14,643
Female	226 (1.0)	22,469
Country of birth		
Australia and other*	343 (1.2)	28,649
Greece	49 (1.3)	3,841
Italy	59 (1.3)	4,622
Education		
Primary school	100 (1.5)	6,713
Some high school	182 (1.3)	14,184
Completed high school	97 (1.3)	7,718
Degree/diploma	72 (0.8)	8,497
Fresh red meat intake, times/wk		
<3	66 (0.8)	7,896
3.0–4.4	123 (1.3)	9,836
4.5–6.4	142 (1.4)	10,191
6.5+	120 (1.3)	9,189
Processed meat intake, times/wk		
<1.5	80 (1.1)	7,509
1.5–1.9	105 (1.4)	7,688
2.0–3.9	129 (1.0)	12,460
4.0+	137 (1.4)	9,455
Chicken intake, times/wk		
<1.5	153 (1.4)	11,271
1.5–2.4	87 (1.2)	7,033
2.0–3.4	131 (1.3)	10,239
3.5+	80 (0.9)	8,569
Fish intake, times/wk		
<1	91 (1.3)	7,104
1.0–1.4	106 (1.2)	8,659
1.5–2.4	141 (1.1)	12,576
2.5+	113 (1.3)	8,773
Ratio of intake of fresh red meat to chicken and fish†		
<0.8	94 (1.0)	9,270
0.8–1.2	106 (1.2)	9,056
1.3–1.9	104 (1.1)	9,184
2+	147 (1.5)	9,602

*Australia (n = 25,659), United Kingdom (n = 2,387), New Zealand (n = 265), and other (n = 338).
†Ratio of frequencies of consumption.

Table 2. Spearman correlation coefficients between potential confounding variables and frequency of consumption of fresh red meat and processed meat

	Fresh red meat	Processed meat
Baseline age, y	0.03	−0.08
Education	−0.10	0.06
Energy, kJ/d	0.37	0.30
Fat, g/MJ*	0.29	0.22
Fiber, g/MJ*	−0.25	−0.28
Folate, μg/MJ*	−0.23	−0.23
Calcium, mg/MJ*	−0.28	−0.17
Chicken, times/wk	0.22	0.08
Fish, times/wk	0.08	0.04
Vegetables, times/d	0.06	−0.02
Fruit, times/d	0.01	−0.04
Cereal products, times/wk	0.08	0.14
Body mass index, kg/m^2	0.11	0.05
Waist-to-hip ratio	0.14	0.12
Physical activity score	−0.08	−0.03

*Nutrient density (i.e., intake of nutrient/energy intake).

association was more consistent for colon cancer than rectal cancer, but the hazard ratios for each additional serve per week were similar (test of homogeneity of trends, $P = 0.8$). Fish consumption had little or no association with risk of colorectal cancers overall or with either subsite.

We also examined the ratio of fresh red meat consumption to chicken and fish consumption (Table 3). Overall, there was a weak positive association. The association was slightly stronger for rectal cancer (test of homogeneity of trends, $P = 0.2$).

There was no persuasive evidence that any of these results differed by stage or that the associations with colon cancer differed by subsite or that they were modified by sex or country of birth. Exclusion of the first 2 years of follow-up made no material difference to any of the results.

Of the 275 people asked to participate in the reproducibility study, 242 (88%) completed the second questionnaire. The weighed κ statistics for the reproducibility of the quartiles of meat intake were 0.42 (95% CI, 0.30–0.55) for fresh red meat, 0.60 (95% CI, 0.48–0.73) for processed meat, 0.44 (95% CI, 0.32–0.56) for chicken, and 0.48 (95% CI, 0.35–0.61) for fish.

Discussion

We found that consumption of fresh red meat was associated with moderately increased risks of rectal cancer but had little association with risk of colon cancer. When analyzed categorically, processed meat consumption also had a moderate association with risk of rectal cancer and little association with colon cancer. However, when analyzed pseudo-continuously, it had similar trends with risk of colon and rectal cancer. Some caution is necessary when interpreting any differences in the subsite-specific associations because the statistical evidence for heterogeneity was weak. A much larger study would be

Table 3. Hazard ratios of colorectal cancer, colon cancer, and rectal cancer by consumption of fresh red meat, processed meat, chicken, and fish

	Quarter of frequency of consumption [Hazard ratio (95% CI)*]			Hazard ratio (95% CI) for increase of one time per week†	P for trend‡
	2	3	4 (Highest)		
Fresh red meat					
Colorectal	1.4 (1.1–1.9)	1.5 (1.1–2.1)	1.4 (1.0–1.9)	1.03 (0.98–1.08)	0.2
Colon	1.2 (0.8–1.7)	1.3 (0.9–1.9)	1.1 (0.7–1.6)	1.00 (0.94–1.07)	0.9
Rectal	2.2 (1.3–4.0)	2.2 (1.2–3.9)	2.3 (1.2–4.2)	1.08 (0.99–1.16)	0.07
Processed meat					
Colorectal	1.3 (1.0–1.7)	1.0 (0.8–1.4)	1.5 (1.1–2.0)	1.07 (1.02–1.13)	0.01
Colon	1.1 (0.8–1.6)	0.8 (0.6–1.1)	1.3 (0.9–1.9)	1.07 (1.00–1.14)	0.06
Rectal	1.9 (1.1–3.2)	1.7 (1.0–2.9)	2.0 (1.1–3.4)	1.08 (0.99–1.18)	0.09
Chicken					
Colorectal	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.7 (0.6–1.0)	0.92 (0.85–0.99)	0.03
Colon	1.0 (0.8–1.4)	0.8 (0.6–1.1)	0.7 (0.5–1.1)	0.92 (0.83–1.01)	0.08
Rectal	0.9 (0.6–1.5)	1.4 (1.0–2.0)	0.7 (0.5–1.2)	0.91 (0.80–1.04)	0.2
Fish					
Colorectal	0.9 (0.7–1.2)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	0.99 (0.91–1.08)	0.8
Colon	0.9 (0.6–1.3)	0.9 (0.6–1.3)	1.0 (0.7–1.4)	1.01 (0.90–1.12)	0.9
Rectal	0.9 (0.6–1.5)	0.8 (0.5–1.2)	0.9 (0.6–1.4)	0.97 (0.84–1.12)	0.8
Ratio of fresh red meat to chicken and fish					
Colorectal	1.1 (0.9–1.5)	1.1 (0.8–1.4)	1.3 (1.0–1.7)	1.13 (1.00–1.28)	0.05
Colon	1.2 (0.8–1.7)	1.0 (0.7–1.4)	1.2 (0.9–1.7)	1.09 (0.93–1.27)	0.3
Rectal	1.1 (0.7–1.8)	1.2 (0.7–1.9)	1.4 (0.9–2.2)	1.19 (0.98–1.46)	0.08

*Adjusted for sex, country of birth, and intake of energy, fat, and cereal products using Cox's proportional hazard model with age as the time metric. See Table 1 for ranges of each quarter.
†For ratio of consumption of fresh red meat to chicken and fish, hazard ratio is for a one-unit increase in the ratio.
‡See text for details on calculation of P.

necessary to provide more definitive evidence about subsite specificity. Chicken consumption was weakly associated with decreased risk of colorectal cancer, whereas fish consumption had little association with either colon or rectal cancer.

Confounding by other dietary factors is unlikely to bias these results because the estimates were adjusted for intake of energy and cereal products, and adding other dietary factors previously shown to be associated with colorectal cancer did not alter them. The inclusion of measures of obesity, central adiposity, and physical activity also did not alter the estimates although the measurement of physical activity was imprecise, and there may therefore be some residual confounding.

Random error in measuring meat intake and dietary change during follow-up is likely to have attenuated the associations. Our measurement of diet was based on a single FFQ administered at baseline that may not have been representative of consumption during the average of 9 years of follow-up. In a subset of 242 participants, the FFQ showed only moderate agreement when administered on two occasions, 12 months apart. Because the FFQ did not measure portion sizes, the associations would be further attenuated if between-person differences in portion size contribute to between-person variability in amount consumed.

Sandhu et al. did a meta-analysis of 12 cohort studies in which the relationship between meat consumption and risk of colorectal cancer was examined. The pooled relative risks (95% CIs) were 1.14 (1.04–1.25) per 100 g/d for ''all meat,'' 1.17 (1.05–1.31) for ''red meat,'' and 1.49 (1.22–1.81) per 25 g/d for ''processed meat'' (28). Similar estimates were obtained in another meta-analysis, which included case-control studies (29). Three additional cohort studies were published after the Sandhu et al. meta-analysis was undertaken (18-20), one study (11) has been extended with additional cases (12), and another was not included in the meta-analysis (15). The largest of these found no associations with meat intake, although the estimates were not inconsistent with the meta-analysis (20). In the other recent studies, one or more components of red meat were associated with increased risk, although the trends were not generally significant. Thus, on balance, the cohort studies are consistent with a small increased risk associated with consumption of red meat and processed meat.

Although we found only weak evidence that processed meat and fresh red consumption were more strongly associated with risk of rectal cancer than with colon cancer, such a difference is consistent with the meta-analysis of Norat et al. (29). Their analysis was largely based on case-control studies because in only two other cohort studies was each subsite analyzed separately (3, 12). Furthermore, it is not clear whether the site-specific meta-analyses were restricted to those studies that reported separate results for both subsites. If not, then separating heterogeneity between subsites from heterogeneity among studies is difficult.

Mechanisms by which red meat and processed meat consumption might increase the risk of colorectal cancer have been discussed at length (1, 29-31). Constituent nutrients of red meat and methods of processing and cooking have all been considered. The fat content of red meat is unlikely to explain the effect because colorectal cancer seems to have a weaker association with saturated fat than with red meat consumption (30). Another potential mechanism is via an increased production of potentially carcinogenic *N*-nitroso compounds in the bowel (32), which seems to be mediated by the heme content of red meat (33). The association with consumption of processed meats may be partly due to the presence of *N*-nitroso compounds already present in the meat. Production of heterocyclic amines when meat is cooked at high temperatures has also been suggested as a potential mechanism, but the epidemiologic evidence is sparse (29).

Most cohort studies that have reported data on red meat and processed meat consumption have also reported on consumption of poultry (usually chicken) and/or fish (3-8, 11-14, 16-20). A protective effect of poultry consumption was reported for one study only (4), whereas, in another study, in which consumption was measured simply as any versus none, there was an increased risk (12). Other studies of poultry consumption reported little evidence of a relationship, with about as many showing weak positive as negative associations. A positive association was found with consumption of smoked or cured fish, but no association with consumption of other fish in one study (11), another study reported a negative association with fish consumption (14), and the others reported no associations. In four studies (4, 6, 14, 18), the authors constructed a ratio of red meat to poultry and fish intake as we did to examine the effect of substituting poultry and fish for red meat. In two studies, the relative risks increased consistently with increasing consumption of red meat relative to that of chicken and fish (4, 6), and in a third study, the relative risks in all quartiles (apart from the reference quartile) were close to two (14). All relative risks for this ratio were close to unity in a Finnish study that also showed no association between consumption of red meat and risk of colorectal cancer (18). The World Cancer Research Fund concluded that ''diets high in fish consumption possibly have no relationship with risk of colorectal cancer'' and that, although poultry consumption may have no relation with risk of colorectal cancer, ''no judgment is possible'' because of the inconsistency of the evidence (1). We found no reason to disagree with these conclusions.

In conclusion, our prospective study has found evidence that people who consume red meat and processed meat frequently have higher risk of rectal cancer than people who consume these products infrequently, and this raises the possibility that they could reduce their risk by substituting other types of meat such as chicken or fish.

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