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Meat consumption, non-steroidal anti-inflammatory drugs, and mortality among colorectal cancer patients in the California Teachers Study

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Abstract

A low meat diet and regular non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with decreased mortality among colorectal cancer (CRC) patients. Here we investigated the association between pre-diagnosis usual meat consumption and CRC-specific mortality, and whether meat consumption modifies the previously noted association between NSAID use and CRC-specific mortality among women in the California Teachers Study (CTS) cohort. Women joining CTS in 1995–1996 without prior CRC diagnosis, diagnosed with incident CRC during follow-up through December 2007, were eligible for inclusion. Meat intake (frequency and serving size) and NSAID use (aspirin or ibuprofen use) were ascertained via self-administered questionnaires before diagnosis. Vital status and cause of death were determined by linkage with mortality files. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HR) for death and 95% confidence intervals (CI). Pre-diagnosis meat consumption was not associated with CRC-specific mortality among 704 CRC patients (and 201 CRC-specific deaths), comparing patients in the lowest consumption tertile (0–5.4 medium-size servings/week) to those with higher consumption. Regular NSAID use (1–3 times/week, 4–6 times/week, daily) vs. none was associated with decreased CRC-specific mortality among patients in the lowest meat consumption tertile (HR=0.22, 95% CI 0.06–0.82), but not among patients in the higher meat intake tertiles. The previously observed mortality risk reduction among female CRC patients associated with regular NSAID use was restricted to patients who reported low meat intake before diagnosis. These findings have implications for CRC survivorship and tertiary CRC prevention.

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INTRODUCTION

Colorectal cancer (CRC) is a substantial public health burden in the United States, with an estimated 146,970 incident cases and 49,920 deaths expected in 2009 (1). Progress has been made in CRC screening and early detection in parallel with advances in treatment over the past decade. As a result, a sizeable CRC survivorship cohort has developed, drawing attention to the importance of elucidating prognostic factors for survival and developing mortality risk reduction strategies after CRC diagnosis. Accordingly, diet and lifestyle factors have become increasingly active areas of CRC survivorship research.

Despite a long history of experimental research, (2–4) epidemiologic studies, (5–7) and clinical trials (8,9) examining the inhibitory effects of NSAIDs on CRC development, relatively few studies have examined how pre- or post-diagnosis NSAID use affects survival among CRC patients (10,11). Most recently, pre-diagnosis NSAID use (when used regularly, or for a prolonged duration) was associated with decreased CRC-specific mortality in female CRC patients from the California Teachers Study (CTS) cohort (12) and post-diagnosis aspirin use was associated with a similar decreased mortality among stage I-III colon cancer patients (13).

A prospective study of stage III colon cancer patients previously enrolled in an adjuvant chemotherapy trial provided compelling data to support the influence of dietary patterns on CRC outcomes (14). High consumption of a Western dietary pattern (i.e., a diet high in meat, fat, refined grains, and dessert) was associated with decreased time to recurrence and decreased overall survival. In another cohort of CRC patients, members of our group demonstrated that those in the highest quartile of meat consumption had decreased overall survival compared to others—a finding that was statistically significant among patients with a family history of CRC in a first-degree relative (15).

A diet comprised of low meat consumption and regular NSAID use may influence survival after CRC diagnosis. Potential biologic relationships exist between meat intake and NSAID use on CRC carcinogenesis, including alteration of polyamine metabolism (15–17). Previously, in order to test the relevancy of NSAID and diet-based polyamine-inhibitory murine experiments in humans, members of our group investigated these effects using data from the UC Irvine Gene Environment Study of Colorectal Cancer. A significant survival benefit was observed for familial CRC patients reporting regular NSAID use and low meat consumption compared to those reporting infrequent NSAID use and high meat consumption, however the analysis was limited by small sample size (18). Therefore we designed the current study to test whether the beneficial effects of pre-diagnosis NSAIDs on CRC-specific mortality observed among patients from the CTS are specific to those reporting low levels of pre-diagnosis meat consumption.

MATERIAL AND METHODS

Study Population

The CTS is a prospective cohort of current or former female public school teachers and administrators, who were members of the California State Teachers Retirement System at the time of study inception in 1995 (19). A total of 133,479 women comprise the CTS cohort. Conduct of the CTS and data analysis have been approved by the Institutional Review Boards of the State of California, the University of Southern California, the University of California at Irvine, the Northern California Cancer Center, and the City of Hope National Medical Center.

To identify incident, invasive CRCs that occurred during follow-up of the CTS, we first delineated a cohort of eligible women, excluding women in the following hierarchical manner:

1) did not develop a CRC diagnosis as the first (or only) invasive cancer diagnosis during the follow-up period (n=132,721), 2) lacked data on family history of CRC (n=26), 3) lacked data on frequency of NSAID use (n=20), and 4) lacked data on frequency of meat consumption (n=8). The resulting cohort consisted of 704 CRC patients (483 with colon cancer, 188 with rectal cancer, and 33 with large bowel cancer of unspecified site).

Case Ascertainment and Follow-up

Incident diagnoses of invasive carcinoma of the colon and rectum (International Classification of Diseases for Oncology, ICD-O, topography codes C18.0–18.9, C19.9, and C20.9) were identified through annual linkages with the California Cancer Registry (CCR). As part of a state mandate for cancer reporting, the CCR receives reports on over 99% of all cancer diagnoses occurring in California (20). Tumors were classified as local, regional, and advanced stage at presentation according to the Surveillance, Epidemiology and End Results (SEER) definition for summary stage, as previously described (21). Treatment during the first course of therapy was ascertained using available CCR data.

Deaths among CTS participants were identified through regular linkages with California state mortality files and with the Social Security Death Master File. Cause of death was provided on the California files and through linkages with the National Death Index. Follow-up of eligible CRC patients was calculated from the date of diagnosis until death, or December 31, 2007. Cause of death was recorded according to the *International Classification of Diseases* criteria in effect at the time of death, as previously described (22). Patients with death from causes other than CRC were censored as were patients who survived to the end of the follow-up period. Overall there were 302 deaths (42.9% of all patients; 207-colon, 69-rectum, and 26-large bowel unspecified), and death due to CRC occurred in 201 (66.5%) CRC patients (134-colon, 49-rectum, and 18-large bowel unspecified). Additional deaths were attributed to heart disease (10.6%), other malignancies (9.6%), chronic obstructive pulmonary disease (2.3%), and other etiologies (11%).

Assessment of Dietary Intake and Meat Consumption

Food consumption was self-reported via a validated 100-item NCI-Block food-frequency questionnaire (FFQ) administered at baseline (cohort entry), where patients were asked to report their usual eating habits during the one year prior to joining the cohort (23). Micronutrient data, total daily fiber intake, and total daily energy intake were calculated from the self-reported FFQ responses (24). The types of meat queried for this analysis were: beef roast or beef steaks or beef sandwiches, beef stew or pot pie, burrito or taco with meat, hamburger or cheeseburger, hot dogs, liver (including chicken livers), lunch meat (including ham, bologna, other lunch meats made with or without turkey), other meat soups, pork (including pork chops and pork roast), sausage, chicken or turkey, chicken stew or mixed chicken dish, fried chicken, fried fish, other types of fish, oysters, shellfish, tuna. Consumption of each meat item was converted to the number of medium-sized servings/week by multiplying the frequency of servings/week (never, once/month, 2–3 times/month, once/week, 2 times/week, 3–4 times/week, 5–6 times/week, every day) by the estimated serving size (0.5 for small, 1.0 for medium, and 1.5 for large). CRC patients were divided into tertiles based on their consumption of medium-sized servings: Tertile 1, 0.0–5.39 servings/week; Tertile 2, 5.40–9.14 servings/week; Tertile 3, 9.15–29.52 servings/week.

Assessment of NSAID Use

The self-administered baseline questionnaire asked “Have you taken any of the following medications regularly (at least once a week)?” Available options included 1) aspirin (Anacin, Bufferin, Excedrin) or 2) ibuprofen (Advil, Motrin, Nuprin). For positive responses, participants indicated the average number of days per week (frequency) (1–3, 4–6, or 7) and

the total numbers of years duration (<1, 1, 2, 3–4, 5–9, or ≥10) of use. For the primary analyses, frequency of medication use was categorized into two categories: no use, or regular use (1–3 days per week, 4–6 days per week, or daily use). Duration of NSAID use was categorized as 0 years (non-users), <5 years, or 5+ years. Combined NSAID variables (combination of aspirin and ibuprofen) in the CTS were utilized for all analyses. Duration and frequency of use variables were created using the midpoint of the usage category. If use of only one NSAID subtype, aspirin or ibuprofen, was reported, the reported category was used. If both types of NSAIDs were used, and the duration of use categories for both types were the same, then that category was used (presuming that the woman alternated use during the same time period and that summing the duration and frequency of use would lead to over-reporting). If different durations were given for aspirin and ibuprofen, then those durations were summed.

Assessment of Colorectal Cancer Risk Factors

Family history of CRC was defined as having a first-degree relative (parent, sibling, or child) diagnosed with CRC as reported on the baseline questionnaire. Information on other probable CRC risk factors was collected at baseline including participants' age, race/ethnicity, personal history or family history of colorectal polyps, body mass index (BMI) as calculated from self-reported height and weight at baseline, long-term recreational physical activity, and quintiles of lifetime tobacco exposure. An aggregate variable for socioeconomic status (SES) that is available in CCR was utilized, as previously described (25).

Statistical Analyses

We used multivariable Cox proportional hazards regression analyses to estimate the association between meat consumption and CRC-specific mortality (i.e., death from colorectal cancer), comparing women in the lowest tertile to women in the two higher tertiles combined. Similarly, we used multivariable Cox proportional hazards regression analyses to estimate the association between NSAID use and 1) overall mortality (death from any cause), 2) CRC-specific mortality within each of the three meat consumption tertiles. All regression models included the categorical variable for NSAID frequency or NSAID duration. Stage of disease at presentation and age at baseline questionnaire were included in all models as stratification variables, and multivariable adjusted analyses included other variables known to predict survival in CRC: site (i.e., colon or rectum), CRC family history, and surgical treatment, in addition to adjustment for tertiles of total energy intake (kcal/day). Other potential confounders including strenuous and moderate lifetime physical activity, quintile categories of socioeconomic status, yearly alcohol consumption (in grams), lifetime exposure to tobacco, body mass index, dietary folate intake, dietary Vitamin D intake, and total daily vitamin D intake (including dietary plus supplemental intake) were not included in the final models as they were not associated with the survival endpoints and their inclusion influenced risk estimates for NSAID use by <10%. Analysis assessing the interaction between NSAID use and meat consumption tertile on CRC-specific survival were performed in the final multivariable models, where we compared a model with all covariates and interaction term to a model without the interaction term. Survival curves were constructed using the Kaplan-Meier method and analyzed with log rank tests. *P*-values were not adjusted for multiple comparisons. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, N.C.).

RESULTS

Study population and baseline characteristics prior to CRC diagnosis

The median duration between baseline assessment and CRC diagnosis was 5.5 years, (range 0–11.1 years, mean= 5.6 years); median follow-up duration after CRC diagnosis was 3.4 years (range 0–11.9 years, mean=4.2 years). The median level of meat consumption was 6.97 servings/week (range 0.0–29.52 servings/week). The median duration from time of

questionnaire to development of CRC did not significantly differ across the three meat consumption tertiles ($P=0.44$). The baseline study characteristics are shown in Table 1. Elevated BMI was associated with increasing meat consumption tertile. In addition to certain variables shown in Table 1 such as age and long-term physical activity, no statistically significant differences across the meat consumption tertiles were detected for personal history of polyps ($P=0.16$), history of polyps in a first-degree family member ($P=0.22$), active and passive lifetime tobacco exposure ($P=0.77$), SES quintile ($P=0.16$), or annual grams of alcohol intake ($P=0.13$). Body Mass Index, and dietary micronutrient intake levels were directly associated with meat consumption tertile at baseline (Table 1).

Meat Consumption and NSAID use at baseline

Detailed patterns of NSAID frequency and NSAID duration by meat consumption tertile are shown in Table 2. In total, 36% of the CRC patients were regular NSAID users and 27% were regular aspirin users (where regular use is defined as use 1–3 days/week, 4–6 days/week, or daily use). Across the three meat consumption tertiles, no statistically significant differences in NSAID frequency or NSAID duration were observed. No statistically significant differences were observed for aspirin frequency ($P=0.44$), or aspirin duration ($P=0.78$). Regular NSAID use among all CRC patients was not statistically significantly associated with CRC-specific survival (Fig. 1).

Associations of Meat Consumption with Survival Time

Univariate CRC-specific survival analysis of all CRC cases by meat consumption tertile revealed no statistically significant differences (Fig. 2). Similarly, univariate overall survival analysis revealed no statistically significant differences in survival based on meat consumption tertile ($P=0.42$; Supplemental Fig. 1). CRC-specific mortality among CRC patients with the lowest meat consumption (Tertile 1) was compared to that among patients with higher consumption. After multivariable adjustment for covariates, no significant differences were detected (hazard ratio, $HR=0.73$, 95% confidence interval, $CI\ 0.47-1.13$).

Associations of NSAIDs and Survival within each Meat Consumption Tertile

Regular NSAID use prior to diagnosis was associated with significantly decreased risk of CRC-specific mortality ($HR=0.63$, 95% $CI\ 0.42-0.95$) after multivariable adjustment for covariates. Regular NSAID use was associated with a statistically significant decreased risk of CRC-specific death compared to no regular NSAID use in Tertile 1 of meat intake ($HR=0.22$, 95% $CI\ 0.06-0.82$), but not in Tertile 2 ($HR=0.81$, 95% $CI\ 0.3224-3.00$) or Tertile 3 ($HR=1.08$, 95% $CI\ 0.36-3.24$) (Table 3). Sensitivity analysis of survival among the 646 patients having >1 year from time of baseline questionnaire to CRC diagnosis were consistent with the data for all CRC patients (data not shown). Univariate stage-specific survival analyses revealed that among patients in meat consumption Tertile 1, pre-diagnosis regular NSAID (vs. none) was associated with significantly increased CRC-specific survival (CRC-SS) among CRC patients with regional and advanced stage but not local stage (Fig. 3A–C). A formal test for statistical interaction was done to test the differential effect of NSAIDs and meat consumption (across tertiles) on CRC-specific mortality. This interaction term was not significant ($P=0.19$). HR estimates for all cause mortality were similar to those for CRC-specific mortality (Table 3).

Duration of NSAID use categorized as either no use (referent value, $HR=1.00$), use <5 years, or use ≥ 5 years was associated with statistically significant decreased CRC-specific mortality in multivariable analysis for meat consumption Tertile 1 (<5 years $HR=0.26$; ≥ 5 years $HR=0.19$; $P-trend=0.032$), but not Tertile 2 (<5 years $HR=0.57$; ≥ 5 years $HR=0.98$; $P-trend=0.54$) or Tertile 3 (<5 years $HR=1.54$; ≥ 5 years $HR=2.66$; $P-trend=0.33$).

Exploratory analyses by type of meat consumption were conducted. Red meat was not associated with CRC-specific mortality after adjustment for the aforementioned covariates (HR=0.99, 95% CI 0.77–1.28). The CRC-specific HRs for mortality for regular NSAID use by red meat consumption tertiles were as follows: Tertile 1 (HR=0.48, 95% CI 0.17–1.42), Tertile 2 (HR=0.60, 95% CI 0.19–1.95), Tertile 3 (HR=2.03, 95% CI 0.67–6.12); *P*-interaction = 0.14. Fish consumption was not associated with CRC-specific mortality after adjustment for the aforementioned covariates (HR=1.07, 95% CI 0.85–1.36). The CRC-specific HRs associated with regular NSAID use among patients by fish consumption tertile were as follows: Tertile 1 (HR=0.46, 95% CI 0.15–1.40), Tertile 2 (HR=1.23, 95% CI 0.36–4.18), Tertile 3 (HR=0.33, 95% CI 0.09–1.16); *P*-interaction = 0.61.

DISCUSSION

Among female CRC patients, the previously observed reduction in CRC-specific mortality associated with pre-diagnosis regular NSAID use (12) was observed only for patients reporting the lowest level of pre-diagnosis meat consumption (i.e., <5.4 medium-sized servings/week). This effect was most pronounced in patients with regional or advanced disease. The formal test of the interactive effects of NSAID use and meat consumption (across the three tertiles) on CRC-specific mortality was not statistically significant. Pre-diagnostic meat consumption itself was not associated with tumor-related outcomes (including survival) among CRC patients. Consumption of meat from all sources was utilized for this analysis in accordance with prior data demonstrating survival effects related to dietary patterns in colorectal cancer patients (14,15).

NSAIDs exert their antiproliferative effects on colonic cells by inhibiting prostaglandin synthesis through reversible binding to cyclooxygenase, as well as through other mechanisms. Aspirin has been noted to reduce the recurrence of adenomatous polyps in patients at moderate risk and with acceptable toxicity (8,9), whereas cyclooxygenase-2 (COX-2) selective inhibitors have demonstrated efficacy but with significantly increased cardiovascular events, and thus are not warranted for CRC prevention among average-risk individuals (26). Efficacy of aspirin in CRC prevention has been noted particularly after prolonged use (i.e., >6–10 years) (27), with selectivity against COX-2 overexpressing tumors (28).

Cyclooxygenase-independent actions of NSAIDs include polyamine inhibition (29,30). Indeed, polyamine metabolism represents a common mechanism that could explain the observed interactive effects of NSAID use and meat consumption on CRC-specific mortality. Polyamines have been implicated in colorectal carcinogenesis (31,32), and are found in high quantities in meat, among other foods (33). Polyamines are derived from arginine – which is itself derived primarily from dietary meat (e.g., beef, pork, chicken, fish, shellfish, and other meats) (15,34). Arginine is converted into ornithine by the hepatic arginases; ornithine decarboxylase (ODC, the rate-limiting enzyme in polyamine synthesis) converts ornithine into the various polyamines (35). Dietary arginine increases total (36) and high grade (15) colon adenoma incidence in *Apc^{Min/+} Nos2^{+/+}* mice. NSAIDs suppress intestinal steady state ODC RNA levels, induce steady state spermidine/spermine N¹-acetyltransferase RNA levels, decrease polyamine levels, and decrease tumor number in the small intestines of *Apc^{Min/+} Nos2^{+/+}* mice (15). Polyamine synthesis is dependent on arginine (derived primarily from meat), inhibited by eflornithine (difluoromethylornithine, or DFMO, an ODC inhibitor), and cellular polyamine export is enhanced by NSAIDs through induction of spermidine spermine acetyltransferase (SSAT) (15,29,30). Furthermore, a single nucleotide polymorphism has been identified in the *ODC1* gene at intron-1 +316 that is prognostic for CRC-specific survival among CRC patients (37), and which modifies the efficacy of aspirin in reducing risk of metachronous colorectal adenomas (CRAs) among patients with sporadic CRAs (38–40). The clinical relevance of polyamine inhibition on colorectal carcinogenesis was recently

demonstrated in humans. Colorectal adenoma patients treated for 3 years with a polyamine-inhibitory regimen of eflornithine and the non-selective NSAID sulindac versus placebo had marked reduction of recurrent CRAs, and advanced adenomas, with minor differences in adverse events (41–43). In the present study, mortality risk reduction among regular NSAID users in the lowest meat consumption tertile exclusively, which is consistent with the previously noted study demonstrating survival improvements for CRC patients reporting regular NSAID use and low meat consumption (18). If polyamine regulation is indeed the operative pathway underlying our observations, these findings suggest that polyamine-inhibitory effects of NSAIDs may not be sufficient to overcome higher dietary polyamine consumption. Supporting this theory is a recent study of dietary polyamine intake among CRA patients demonstrating significant metachronous adenoma risk reduction after polyamine inhibitory treatment with eflornithine and sulindac in the lower dietary polyamine group, but no benefit in the higher dietary polyamine group (44). However, without tissue analysis, the relevance of polyamine regulation to our epidemiologic findings remains speculative.

Other potential biologic mechanisms may explain our observations. Meat consumption, particularly processed meat and red meat, has been associated with risk of CRC development (45). Various carcinogenic compounds in meat have been investigated, including those associated with smoked or processed meat, including heterocyclic amines, and nitrosamines. Heterocyclic amines are mutagenic (46). When added to the diet of rats, certain heterocyclic amines cause high rates of colorectal tumorigenesis (47). In a case-control study, heterocyclic amines were associated with risk of colorectal adenomas (48). Interestingly, the COX-2 selective NSAID celecoxib has been shown to decrease heterocyclic amine-induced colonic mutagenicity in experimental rats (49). Late effects on CRC progression or survival attributed to these carcinogenic agents are unknown. Furthermore, an understanding of how NSAIDs influence heterocyclic amine effects on survival after CRC diagnosis is unknown. In our study, data on the types of cooking methods used were not available, although contemporary dietary questionnaires have been designed to capture this information (50).

The present study was based on a prospective study design such that NSAID and dietary reporting pre-dated CRC diagnosis, however, survival effects may be more closely related to post-diagnosis NSAID use and dietary consumption, which was not available. Our study lacks of information on CRC screening practices such as fecal occult blood testing or endoscopy, which impacts the interpretation of our findings. It is acknowledged that recent red meat consumption and NSAIDs use have been associated with positive hemoccult testing, which could prompt early follow-up colonoscopy procedures, and lead to screen-detected cancers that have a more favorable prognosis. Dietary intake was limited to analysis of data items in the food frequency questionnaire, which itself is not as detailed as 24-hour food surveys. Detailed NSAID history (other than differentiating aspirin compounds from ibuprofen or other NSAIDs) was not available, including information on specific NSAID type and dosage, or current versus former use, and the study was not powered to investigate differences for aspirin vs. non-aspirin NSAIDs. The median follow-up duration, which is directly influenced by survival time, was relatively short (3.4 years, with a range of 0–11.9 years). Detailed treatment information (such as dose of radiation therapy or specific chemotherapy regimens) was not available in CCR. Additionally, our study had insufficient statistical power to investigate previously demonstrated risk differences based on tumor subsite location within the colorectum (51), or to assess whether our observed associations vary according to family history (52) of CRC or disease stage at diagnosis as the follow-up time was limited. Therefore we were unable to conduct analyses to confirm published results on dietary patterns in stage III colon (15) or familial CRC patients.

Presently, two large phase III NSAID-based colon cancer tertiary prevention trials are in development within the oncology cooperative group setting. One, through the Southwest

Oncology Group (SWOG 0820), involves polyamine inhibition with eflornithine, sulindac, or placebo for prevention of high risk adenomas and second primary tumors among non-metastatic colon cancer patients (53). The other is being developed through Cancer and Leukemia Group B (CALGB 80702), which involves randomization to celecoxib vs. placebo in colon cancer patients after completion of variable-length adjuvant chemotherapy (54). If implemented, dietary analyses from these and other relevant clinical trials could yield important information about the effects of diet on clinical outcomes after CRC diagnosis, and further clarify the role of NSAIDs in this process. More directly related to the findings of the present report is the ongoing, NCI-supported phase IIa clinical biomarker trial in CRC patients being conducted at the University of California, Irvine (UCI 07-47, ClinicalTrials.gov Identifier NCT00578721). This trial involves a 12-week intervention of arginine restriction (primarily through a 50% reduction in meat intake) plus daily oral aspirin 325mg, with assessment of pre- and post- intervention colorectal tissue polyamine-related biomarkers. It is hoped that findings from tertiary prevention trials such as these will help to uncover underlying mechanisms for how NSAID use and meat consumption affect CRC progression.

In conclusion, we have observed that the previously reported CRC-specific mortality risk reduction associated with pre-diagnosis NSAID use is greatest among CRC patients reporting low meat intake (<1 serving/day) prior to diagnosis. Further investigations are warranted to determine underlying mechanisms for this potentially important finding. Such information has obvious implications for improving outcomes among CRC survivors, but replication of these results in other cohorts, and results from ongoing and future clinical trials are needed before formal recommendations can be issued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Colorectal cancer-specific survival (CRC-SS) among all CRC patients based on pre-diagnosis NSAID use. NR, not reached; CI, confidence interval; No. at risk indicates the number at risk at the time of CRC diagnosis. P-value presented is from the log-rank test.

Fig. 2.

Colorectal cancer-specific survival (CRC-SS) among all CRC patients based on pre-diagnosis meat consumption tertile. NR, not reached; CI, confidence interval; Vertical tick marks indicate data censoring. P-value presented is from the log-rank test.

Fig. 3. Colorectal cancer-specific survival (CRC-SS) for CRC patients in meat consumption Tertile 1, based on pre-diagnosis NSAID use. A) Local stage, B) Regional stage, C) Advanced stage. NR, not reached; CI, confidence interval; No. at risk indicates the number at risk at the time of CRC diagnosis; Vertical tick marks indicate data censoring. . P-value presented is from the log-rank test.

Table 1

Selected baseline characteristics by meat consumption tertile among 704 colorectal cancer patients in the California Teachers Study (1995–2007).

	Meat Consumption Tertile 1 (0.0–5.39 medium- sized servings/week) (n=234)	Meat Consumption Tertile 2 (5.40–9.14 medium- sized servings/week) (n=235)	Meat Consumption Tertile 3 (9.15–29.52 medium- sized servings/week) (n=235)	P
Age at Diagnosis (median years with range)	68.2 (35.9–92.3)	65.8 (26.3–92.8)	64.6 (35.9–93.7)	0.23
Race				
Caucasian	203 (87%)	213 (91%)	207 (88%)	0.51
African-American	11 (5%)	9 (4%)	8 (3%)	
Other Race/Ethnicity	20 (8%)	13 (5%)	20 (9%)	
Family history of CRC in 1st degree relative	28 (12%)	23 (10%)	32 (14%)	0.43
BMI** (kg/m ² , median with 95% CI*)	23.8 (18.7–33.9)	24.5 (19.5–36.9)	25.9 (20.4–40.0)	<0.0001
Total KCAL/day (median with 95% CI)	1166 (686–1859)	1370 (860–2178)	1753 (1115–2909)	<0.0001
Total Daily Calcium Intake (median mg with 95% CI)	507 (187–1380)	628 (210–1493)	695 (284–1666)	<0.0001
Total Daily Iron Intake (median mg +/- 95% CI)	7.8 (4.6–15.9)	10.0 (5.9–16.1)	12.5 (7.8–19.7)	<0.0001
Total Daily Fiber Intake (median g +/- 95% CI)	12.4 (5.4–26.7)	13.4 (6.6–24.5)	15.7 (8.2–26.5)	<0.0001
Total Daily Folate Intake (median mcg +/- 95% CI)	233 (124–515)	281 (149–485)	325 (190–549)	<0.0001
Strenuous & Moderate Lifetime Physical Activity (median hrs/wk +/- 95% CI)	2.4 (0.0–11.2)	2.6 (0.0–13.8)	2.9 (0.1–13.6)	0.09
Tumor Site				
Colon	166 (71%)	166 (71%)	151 (64%)	0.23
Rectum	54 (23%)	60 (26%)	74 (31%)	
Colorectum-Not Otherwise Specified	14 (6%)	9 (4%)	10 (4%)	
Histology				
Adenocarcinoma	183 (78%)	193 (84%)	184 (79%)	0.48
Carcinoma-Not Otherwise Specified	15 (6%)	7 (3%)	16 (7%)	
Mucinous Adenocarcinoma	29 (12%)	25 (11%)	30 (13%)	
Not Otherwise Specified	7 (3%)	6 (3%)	4 (2%)	
Stage at Presentation				
Local	96 (41%)	97 (41%)	96 (41%)	0.81
Regional	86 (37%)	86 (37%)	75 (32%)	
Advanced	41 (18%)	43 (18%)	51 (22%)	
Not available	11 (5%)	9 (4%)	13 (6%)	
Tumor Grade				
Grade 1	24 (10%)	14 (6%)	15 (6%)	0.79
Grade 2	130 (56%)	130 (55%)	136 (58%)	
Grade 3	46 (20%)	52 (22%)	46 (20%)	
Grade 4	2 (1%)	3 (1%)	2 (1%)	
Not available	32 (14%)	36 (15%)	36 (15%)	
Primary treatment involved surgery				0.92

	Meat Consumption Tertile 1 (0.0–5.39 medium- sized servings/week) (n=234)	Meat Consumption Tertile 2 (5.40–9.14 medium- sized servings/week) (n=235)	Meat Consumption Tertile 3 (9.15–29.52 medium- sized servings/week) (n=235)	P
Yes	212 (91%)	207 (88%)	212 (90%)	0.64
No	21 (9%)	27 (11%)	22 (9%)	
Not available	1 (0.4%)	1 (0.4%)	1 (0.4%)	
Primary treatment involved radiation therapy				0.21
Yes	20 (9%)	28 (12%)	20 (9%)	
No	212 (91%)	206 (88%)	214 (91%)	
Not available	2 (0.9%)	1 (0.4%)	1 (0.4%)	0.21
Primary treatment involved chemotherapy				
Yes	72 (31%)	78 (33%)	83 (35%)	
No	137 (58%)	145 (62%)	132 (56%)	0.21
Not available	25 (11%)	12 (5%)	20 (9%)	

CI, confidence interval; BMI, Body Mass Index.

Detailed pattern of NSAID* frequency and duration of use by meat consumption tertile among 704 CRC patients in the California Teachers Study.

Table 2

	Tertile 1 (0.0–5.39 medium-sized servings/week)	Tertile 2 (5.40–9.14 medium-sized servings/week)	Tertile 3 (9.15–29.52 medium-sized servings/week)	All Cases Combined	P
Detailed NSAID Frequency					
No Regular NSAID use	143 (62%)	155 (65%)	152 (65%)	450 (64%)	0.78
1–3 days/week	26 (11%)	27 (11%)	29 (12%)	82 (12%)	
4–6 days/week	14 (6%)	8 (3%)	12 (5%)	34 (5%)	
Daily	51 (22%)	45 (19%)	42 (18%)	138 (20%)	
Duration of NSAID Use*					
No Regular NSAID use	143 (61%)	155 (66%)	152 (65%)	450 (64%)	0.87
< 1 year	14 (6%)	11 (5%)	8 (3%)	33 (5%)	
1 year	8 (3%)	6 (3%)	6 (3%)	20 (3%)	
2 years	9 (4%)	10 (4%)	6 (3%)	25 (4%)	
3–4 years	15 (6%)	10 (4%)	10 (4%)	35 (5%)	
5–9 years	12 (5%)	10 (4%)	8 (3%)	30 (4%)	
10+ years	30 (13%)	30 (13%)	41 (18%)	101 (14%)	

NSAID, non-steroidal anti-inflammatory drug; CRC, colorectal cancer.

* Data missing for 10 cases

Table 3

Univariate and multivariate adjusted* overall mortality and CRC-specific mortality for CRC patients according to self-reported NSAID frequency by meat consumption category; total number of patients at risk = 704, total number of deaths from any cause = 302, number of CRC-specific deaths = 201.

	Meat Consumption Tertile 1 (0.0–5.39 medium-sized servings/week)		Meat Consumption Tertile 2 (5.40–9.14 medium-sized servings/week)		Meat Consumption Tertile 3 (9.15–29.52 medium-sized servings/week)	
	No Regular NSAID use	Regular NSAID use	No Regular NSAID use	Regular NSAID use	No Regular NSAID use	Regular NSAID use
Overall Mortality						
Number of events	63	32	70	38	67	32
Number at risk	143	91	155	80	152	83
Unadjusted HR (95% CI)*	1 (Reference)	0.49 (0.24–1.02)	1 (Reference)	1.42 (0.70–2.88)	1 (Reference)	0.76 (0.36–1.64)
Adjusted HR (95% CI)**	1 (Reference)	0.28 (0.10–0.75)	1 (Reference)	1.46 (0.62–3.42)	1 (Reference)	1.03 (0.43–2.45)
CRC-Specific Mortality						
Number of events	45	21	45	21	49	20
Number at risk	143	91	155	80	152	83
Unadjusted HR (95% CI)*	1 (Reference)	0.38 (0.16–0.92)	1 (Reference)	1.02 (0.39–2.63)	1 (Reference)	0.91 (0.36–2.32)
Adjusted HR (95% CI)**	1 (Reference)	0.22 (0.06–0.82)	1 (Reference)	0.81 (0.22–3.00)	1 (Reference)	1.08 (0.36–3.24)

CRC, colorectal cancer; NSAID, non-steroidal anti-inflammatory drug; CI, confidence interval; HR, hazards ratio. Regular NSAID use was defined as pre-diagnosis use reported as 1–3 days per week, 4–6 days per week, or daily use.

* Includes stratification for age at baseline questionnaire (years) and stage.

** Includes stratification for age at baseline questionnaire (years) and stage, with adjustment for family history of CRC in a 1st degree relative, site (colon or rectum), treatment with surgery, and total daily energy intake (kcal/day).