Research Article

Cancer Prevention Research

Meat Consumption, Nonsteroidal Anti-Inflammatory Drug Use, and Mortality among Colorectal Cancer Patients in the California Teachers Study

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Abstract

A low-meat diet and regular use of nonsteroidal anti-inflammatory drugs (NSAID) have been associated with decreased mortality among colorectal cancer (CRC) patients. Here, we investigated the association between prediagnosis 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 cohort. Women joining the California Teachers Study 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 for death and 95% confidence intervals. Prediagnosis 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-sized servings/wk) to those in the higher consumption tertiles. Regular NSAID use (1-3 times/wk, 4-6 times/wk, daily) versus none was associated with decreased CRC-specific mortality among patients in the lowest meat consumption tertile (hazard ratio, 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. *Cancer Prev Res; 3(7); 865–75. ©2010 AACR.*

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 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 emerged, 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 nonsteroidal anti-inflammatory drugs (NSAID) on CRC development, relatively few studies have examined how prediagnosis or postdiagnosis NSAID use affects survival among CRC patients (10, 11). Most recently, prediagnosis 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 postdiagnosis 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

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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 showed that those in the highest quartile of meat consumption had decreased overall survival compared with others—a finding that was statistically significant among patients with a family history of CRC in a first-degree relative (15).

A diet composed of low meat consumption and regular NSAID use may influence survival after CRC diagnosis. Potential biological relationships exist between meat intake and NSAID use on CRC carcinogenesis, including alteration of polyamine metabolism (15–17). Previously, 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 University of California at 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 with 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 prediagnosis NSAIDs on CRC-specific mortality observed among patients from the CTS are specific to those reporting low levels of prediagnosis meat consumption.

Materials 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 compose 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: (*a*) did not develop a CRC diagnosis as the first (or only) invasive cancer diagnosis during the follow-up period (n = 132,721); (*b*) lacked data on family history of CRC (n = 26); (*c*) lacked data on frequency of NSAID use (n = 20); and (*d*) 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 Oncolog 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 more than 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 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 National Cancer Institute-Block food frequency questionnaire administered at baseline (cohort entry), where patients were asked to report their usual eating habits during the 1 year before joining the cohort (23). Micronutrient data, total daily fiber intake, and total daily energy intake were calculated from the self-reported food frequency questionnaire 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 per week by multiplying the frequency of servings per week (never, once a month, 2-3 times/mo, once a week, 2 times/wk, 3-4 times/wk, 5-6 times/wk, everyday) 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/wk; tertile 2, 5.40-9.14 servings/wk; tertile 3, 9.15-29.52 servings/wk.

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 (*a*) aspirin (Anacin, Bufferin, Excedrin) or (*b*) 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 of 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 (nonusers), <5 years, or 5+ years. Combined NSAID variables (combination of aspirin and ibuprofen) in the CTS were used 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 overreporting). If different durations were given for aspirin and ibuprofen, then those durations were summed.

Assessment of CRC 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 socioecomomic status, which is available in the CCR, was used 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 CRC), 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 (*a*) overall mortality (death from any cause) and (*b*) 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 (kilocalories per 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, BMI, 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 because these were not associated with the survival end points and their inclusion influenced risk estimates for NSAID use by <10%. Analyses assessing the interaction between NSAID use and meat consumption tertile on CRC-specific survival were done in the final multivariable models, where we compared a model with all covariates and an 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 done using SAS version 9.2 (SAS Institute, Inc.).

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/wk (range, 0.0-29.52 servings/wk). 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 ($P = 0.77$), socioecomomic status quintile ($P = 0.16$), or annual grams of alcohol intake ($P = 0.13$). BMI 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 1-3 d/wk, 4-6 d/wk, 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).

Table 1. Selected baseline characteristics by meat consumption tertile among 704 CRC patients in the CTS (1995-2007)

	Meat consumption tertile 1 (0.0-5.39 medium-sized servings/wk), *n* = 234	Meat consumption tertile 2 (5.40-9.14 medium-sized servings/wk), *n* = 235	Meat consumption tertile 3 (9.15-29.52 medium-sized servings/wk), *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, *n* (%)				
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, *n* (%)	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/d (median with 95% CI)	1,166 (686-1,859)	1,370 (860-2,178)	1,753 (1,115-2,909)	<0.0001
Total daily calcium intake (median mg with 95% CI)	507 (187-1,380)	628 (210-1,493)	695 (284-1,666)	<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 μg ± 95% CI)	233 (124-515)	281 (149-485)	325 (190-549)	<0.0001
Strenuous and moderate lifetime physical activity (median h/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, *n* (%)				
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, *n* (%)				
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, *n* (%)				
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, *n* (%)				
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, *n* (%)				
Yes	212 (91)	207 (88)	212 (90)	0.92

(*Continued on the following page*)

Table 1. Selected baseline characteristics by meat consumption tertile among 704 CRC patients in the CTS (1995-2007) (Cont'd)

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

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; Supplementary Fig. S1). CRC-specific mortality among CRC patients with the lowest meat consumption (tertile 1) was compared with that among patients with higher consumption. After multivariable adjustment for covariates, no significant differences were detected [hazard ratio (HR), 0.73; 95% confidence interval (95% CI), 0.47-1.13].

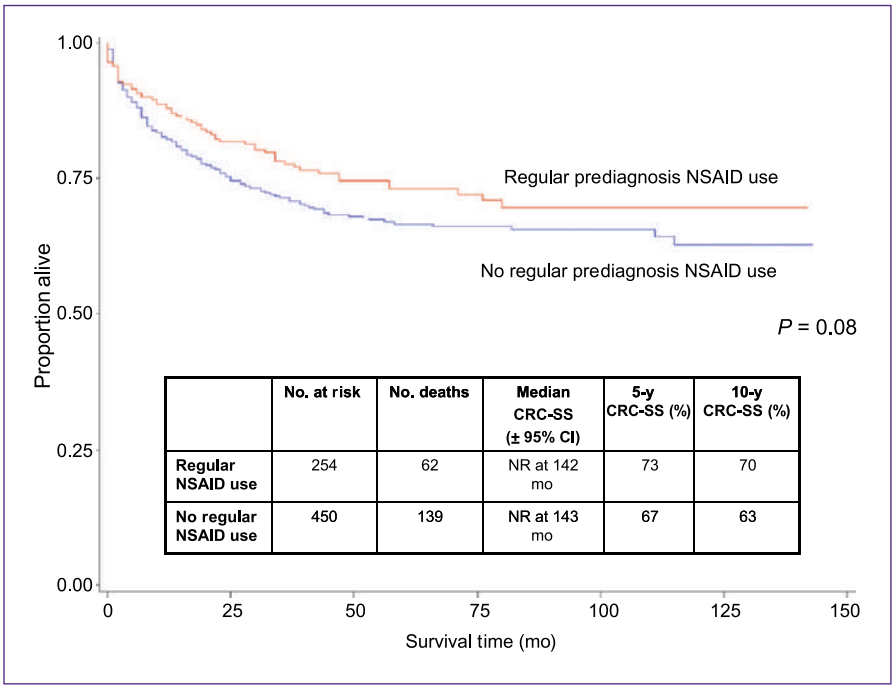
Associations of NSAIDs and survival within each meat consumption tertile

Regular NSAID use before 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

Table 2. Detailed pattern of NSAID frequency and duration of use by meat consumption tertile among 704 CRC patients in the CTS

	Tertile 1 (0.0-5.39 medium-sized servings/wk)	Tertile 2 (5.40-9.14 medium-sized servings/wk)	Tertile 3 (9.15-29.52 medium-sized servings/wk)	All cases combined	*P*
Detailed NSAID frequency, *n* (%)					
No regular NSAID use	143 (62)	155 (65)	152 (65)	450 (64)	0.78
1-3 d/wk	26 (11)	27 (11)	29 (12)	82 (12)	
4-6 d/wk	14 (6)	8 (3)	12 (5)	34 (5)	
Daily	51 (22)	45 (19)	42 (18)	138 (20)	
Duration of NSAID use,* *n* (%)					
No regular NSAID use	143 (61)	155 (66)	152 (65)	450 (64)	0.87
<1 y	14 (6)	11 (5)	8 (3)	33 (5)	
1 y	8 (3)	6 (3)	6 (3)	20 (3)	
2 y	9 (4)	10 (4)	6 (3)	25 (4)	
3-4 y	15 (6)	10 (4)	10 (4)	35 (5)	
5-9 y	12 (5)	10 (4)	8 (3)	30 (4)	
10+ y	30 (13)	30 (13)	41 (18)	101 (14)	

*Data missing for 10 cases.



	No. at risk	No. deaths	Median CRC-SS (± 95% CI)	5-y CRC-SS (%)	10-y CRC-SS (%)
Regular NSAID use	254	62	NR at 142 mo	73	70
No regular NSAID use	450	139	NR at 143 mo	67	63

Fig. 1. CRC-specific survival (CRC-SS) among all CRC patients based on prediagnosis NSAID use. NR, not reached. No. at risk indicates the number at risk at the time of CRC diagnosis. The *P* value presented is from the log-rank test.

statistically significant decreased risk of CRC-specific death compared with 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 analyses 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, prediagnosis regular NSAID use (versus none) was associated with significantly increased CRC-specific survival 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 effects 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 no use (reference 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), and 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), and tertile 3 (HR, 0.33; 95% CI, 0.09-1.16); *P*-interaction = 0.61.

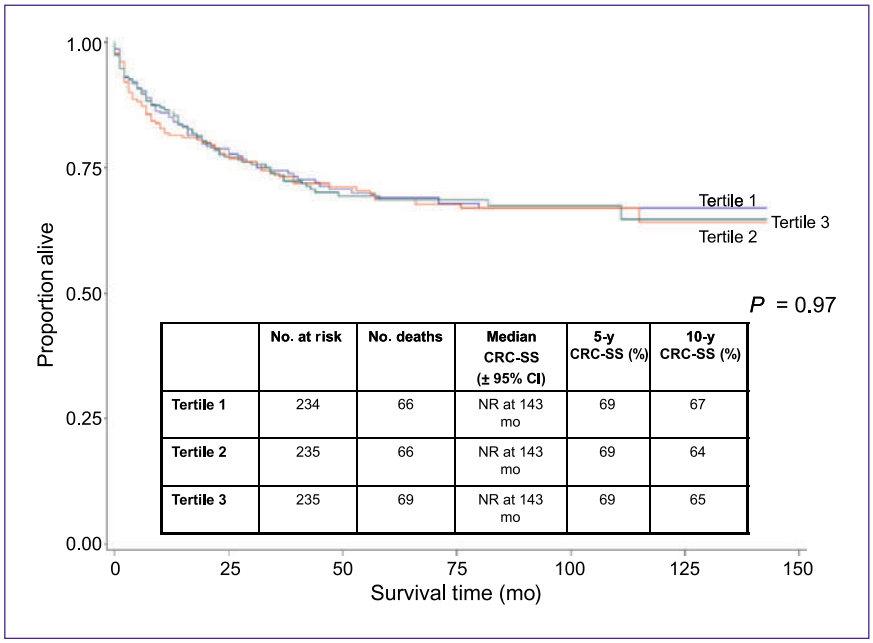
Discussion

Among female CRC patients, the previously observed reduction in CRC-specific mortality associated with prediagnosis regular NSAID use (12) was observed only for patients reporting the lowest level of prediagnosis meat consumption (i.e., <5.4 medium-sized servings/wk). 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. Prediagnostic meat consumption itself was not associated with tumor-related outcomes (including survival) among CRC patients. Consumption of meat from all sources was used for this analysis in accordance with prior data showing survival effects related to dietary patterns in CRC patients (14, 15).

NSAIDs exert their antiproliferative effects on colonic cells by inhibiting prostaglandin synthesis through reversible binding to cyclooxygenase (COX), 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 COX-2–selective inhibitors have shown 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; ref. 6), with selectivity against COX-2–overexpressing tumors (27).

COX-independent actions of NSAIDs include polyamine inhibition (28, 29). 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 (30, 31) and are found in high quantities in meat, among other foods (32). Polyamines are derived from arginine, which is itself derived primarily from dietary meat (e.g., beef, pork, chicken, fish, shellfish, and other meats; refs. 15, 33). 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 (34). Dietary arginine increases total (17) 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 N^1-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) and inhibited by eflornithine (difluoromethylornithine; an *ODC* inhibitor), and cellular polyamine export is enhanced by NSAIDs through induction of spermidine spermine acetyltransferase (15, 28, 29). Furthermore, a single-nucleotide polymorphism has been identified in the *ODC1* gene at intron-1 +316, which is prognostic for CRC-specific survival among CRC patients (35) and which modifies the efficacy of aspirin in reducing the risk of metachronous colorectal adenomas among patients with sporadic colorectal adenomas (36–38). The clinical relevance of polyamine inhibition in colorectal carcinogenesis was recently shown in humans. Colorectal adenoma patients treated for 3 years with a polyamine-inhibitory regimen of eflornithine and the nonselective NSAID sulindac versus placebo had marked reduction of recurrent colorectal adenomas and advanced adenomas, with minor differences in adverse events (39–41). In the present study, mortality risk reduction was observed among regular NSAID users in the lowest meat consumption tertile exclusively, which is consistent with the previously noted study showing 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 colorectal adenoma patients showing 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 (42). However, without tissue analysis, the relevance of polyamine regulation to our epidemiologic findings remains speculative.



	No. at risk	No. deaths	Median CRC-SS (± 95% CI)	5-y CRC-SS (%)	10-y CRC-SS (%)
Tertile 1	234	66	NR at 143 mo	69	67
Tertile 2	235	66	NR at 143 mo	69	64
Tertile 3	235	69	NR at 143 mo	69	65

Fig. 2. CRC-specific survival among all CRC patients based on prediagnosis meat consumption tertile. NR, not reached. No. at risk indicates the number at risk at the time of CRC diagnosis. The *P* value presented is from the log-rank test.

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/wk)		Meat consumption tertile 2 (5.40-9.14 medium-sized servings/wk)		Meat consumption tertile 3 (9.15-29.52 medium-sized servings/wk)	
	No regular NSAID use	Regular NSAID use	No regular NSAID use	Regular NSAID use	No regular NSAID use	Regular NSAID use
Overall mortality						
No. of events	63	32	70	38	67	32
No. 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						
No. of events	45	21	45	21	49	20
No. 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)

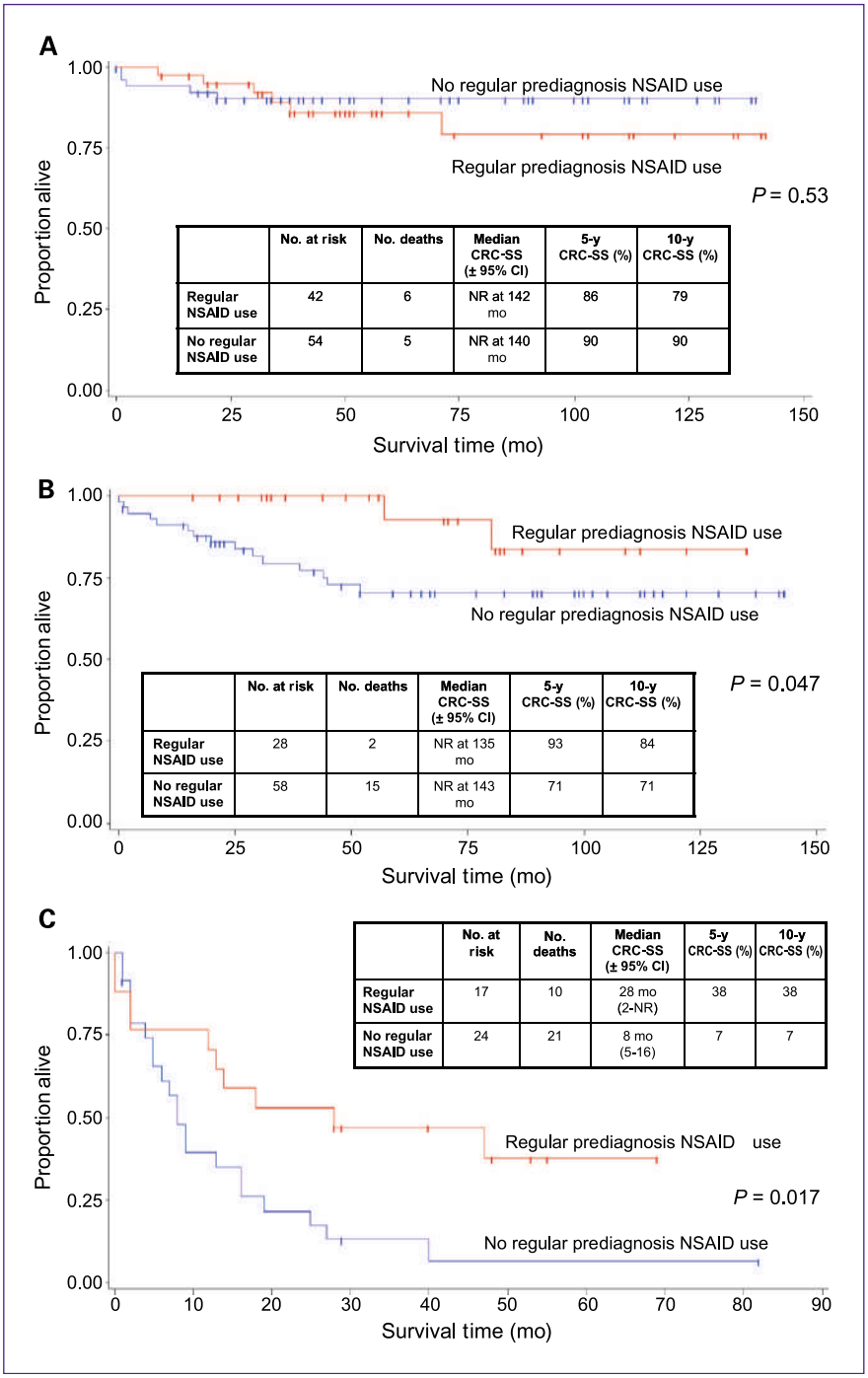
NOTE: Regular NSAID use was defined as prediagnosis use reported as 1-3 d/wk, 4-6 d/wk, or daily use.
*Includes stratification for age at baseline questionnaire (years) and stage.
†Includes stratification for age at baseline questionnaire (years) and stage, with adjustment for family history of CRC in a first-degree relative, site (colon or rectum), treatment with surgery, and total daily energy intake (kcal/d).

Other potential biological mechanisms may explain our observations. Meat consumption, particularly processed meat and red meat, has been associated with risk of CRC development (43). Various carcinogenic compounds in meat have been investigated, such as those associated with smoked or processed meat, including heterocyclic amines and nitrosamines. Heterocyclic amines are mutagenic (44). When added to the diet of rats, certain heterocyclic amines cause high rates of colorectal tumorigenesis (45). In a case-control study, heterocyclic amines were associated with risk of colorectal adenomas (46). Interestingly, the COX-2–selective NSAID celecoxib has been shown to decrease heterocyclic amine–induced colonic mutagenicity in experimental rats (47). 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 (48).

The present study was based on a prospective study design such that NSAID and dietary reporting predated CRC diagnosis; however, survival effects may be more closely related to postdiagnosis NSAID use and dietary consumption, which was not available. Our study lacks information on CRC screening practices such as fecal occult blood testing or endoscopy, which affects 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 versus 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 the CCR. Additionally, our study had insufficient statistical power to investigate previously shown risk differences based on tumor subsite location within the colorectum (49) or to assess whether our observed associations vary according to family history (50) of CRC or disease stage at diagnosis because the follow-up time was limited. Therefore, we were

unable to conduct analyses to confirm published results on dietary patterns in stage III colon (14) 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 (S0820), involves polyamine inhibition with eflornithine, sulindac, or placebo for prevention of high-risk adenomas and second primary tumors among nonmetastatic colon cancer patients (51). The other is being developed through Cancer and Leukemia Group B (CALGB 80702), which involves randomization to celecoxib versus placebo in colon cancer patients after completion of variable-length adjuvant chemotherapy (52). If implemented, dietary analyses from these and other relevant clinical trials could yield important information



	No. at risk	No. deaths	Median CRC-SS (± 95% CI)	5-y CRC-SS (%)	10-y CRC-SS (%)
Regular NSAID use	42	6	NR at 142 mo	86	79
No regular NSAID use	54	5	NR at 140 mo	90	90

	No. at risk	No. deaths	Median CRC-SS (± 95% CI)	5-y CRC-SS (%)	10-y CRC-SS (%)
Regular NSAID use	28	2	NR at 135 mo	93	84
No regular NSAID use	58	15	NR at 143 mo	71	71

	No. at risk	No. deaths	Median CRC-SS (± 95% CI)	5-y CRC-SS (%)	10-y CRC-SS (%)
Regular NSAID use	17	10	28 mo (2-NR)	38	38
No regular NSAID use	24	21	8 mo (5-16)	7	7

Fig. 3. CRC-specific survival for CRC patients in meat consumption tertile 1, based on prediagnosis NSAID use. A, local stage. B, regional stage. C, advanced stage. NR, not reached. No. at risk indicates the number at risk at the time of CRC diagnosis. Vertical tick marks indicate data censoring. The *P* value presented is from the log-rank test.

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 National Cancer Institute–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 at 325 mg, with assessment of preintervention and postintervention 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 prediagnosis NSAID use is greatest among CRC patients reporting low meat intake (<1 serving/d) before 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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