Population and Prevention Science

Cancer Research

Influence of Smoking, Body Mass Index, and Other Factors on the Preventive Effect of Nonsteroidal Anti-Inflammatory Drugs on Colorectal Cancer Risk

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Abstract

Nonsteroidal anti-inflammatory drugs' (NSAID) use has consistently been associated with lower risk of colorectal cancer; however, studies showed inconsistent results on which cohort of individuals may benefit most. We performed multivariable logistic regression analysis to systematically test for the interaction between regular use of NSAIDs and other lifestyle and dietary factors on colorectal cancer risk among 11,894 cases and 15,999 controls. Fixed-effects meta-analyses were used for stratified analyses across studies for each risk factor and to summarize the estimates from interactions. Regular use of any NSAID, aspirin, or nonaspirin NSAIDs was significantly associated with a lower risk of colorectal cancer within almost all subgroups. However, smoking status and BMI were found to modify the NSAID–colorectal cancer association. Aspirin use was associated with a 29% lower colorectal cancer risk among never-smokers [odds ratios (OR) = 0.71; 95% confidence intervals (CI): 0.64–0.79], compared with 19% and 17% lower colorectal cancer risk among smokers of pack-years below median (OR, 0.81; 95% CI, 0.71–0.92) and above median (OR, 0.83; 95% CI, 0.74–0.94), respectively (P interaction = 0.048). The association between any NSAID use and colorectal cancer risk was also attenuated with increasing BMI (P interaction = 0.075). Collectively, these results suggest that obese individuals and heavy smokers are unlikely to benefit as much as other groups from the prophylactic effect of aspirin against colorectal cancer.

Significance: Obesity and heavy smoking attenuate the benefit of aspirin use for colorectal cancer prevention.
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Introduction

Colorectal cancer is one of the most common and fatal cancers in the world. Nonsteroidal anti-inflammatory drugs (NSAID), including aspirin and nonaspirin NSAIDs, are consistently observed to be protective against colorectal cancer (1, 2). Long-term use of aspirin was found to significantly reduce the incidence of colorectal cancer by 24%, and the benefit increased with longer duration of treatment based on 20-year follow-up of five randomized trials (1). A similar association was also reported in a meta-analysis of observational studies (2). Despite its promising chemopreventive effects, aspirin is recommended only to prevent cardiovascular disease and colorectal cancer in those who are at high risk of cardiovascular disease; no broad recommendation from national organization is in place due to concerns about gastrointestinal bleeding (3).

The main chemopreventive mechanism of NSAIDs is the inhibition of cyclooxygenase-2 (COX-2) activity and subsequent formation of prostaglandin E2 (PGE_2; ref. 4). Aspirin also inhibits the oncogenic Wnt/β-catenin pathway (5, 6) and the

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ERK signaling pathway (7). In addition, NSAIDs may function partially through the NFκB signaling pathway (8) and the PI3K signaling pathway (9) in colorectal carcinogenesis. Other pathways related to transcription factors, cell proliferation, and apoptosis have also been suggested (10).

It is suspected that the association of NSAID use and colorectal cancer risk may be modified by other risk factors that are also related to inflammation, but the results have been inconsistent. Regular use of aspirin was associated with a larger decrease in colorectal cancer risk in men than in women in cohort studies (11, 12), but meta-analyses did not find this difference to be statistically significant (2, 13). Nonaspirin NSAID use was associated with a lower risk of colorectal cancer among individuals with body mass index (BMI) >25, but not with BMI ≤25, in a cohort study (14), but it was not reported in other studies (15–18). A case–control study found current use of NSAIDs was associated with larger reduction of colorectal cancer risk among individuals who had smoked for >40 years, compared with nonsmokers (19). However, cohort studies found no interaction between NSAID use and smoking on colorectal cancer risk (16, 17). In contrast, recent clinical trials found that aspirin was statistically significantly associated with lower risk of colorectal adenomas among nonsmokers, but not among current smokers (20–22). A case–control study found that NSAID use was associated with lower colon cancer risk among postmenopausal hormone therapy (PMH) nonusers, but not among PMH users (23). In addition, a randomized clinical trial reported synergistic effects of calcium and any NSAID use in lowering the risk of advanced colorectal neoplastic polyps (24), but the interaction between NSAID use and calcium on colorectal cancer risk was not found in a cohort study (17).

To our knowledge, no subgroups of the population stratified by lifestyle or dietary risk factors have been consistently identified who have a clearly larger benefit from use of aspirin or nonaspirin NSAIDs. Most previous studies did not have sufficient power to detect statistically significant differences between population subgroups. Thus, we aimed to evaluate the potential effect modification of other colorectal cancer risk factors on the associations of regular use of any NSAID, aspirin, and nonaspirin NSAIDs with colorectal cancer risk using studies from a large, international consortium.

Materials and Methods

Study participants

Study participants were from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR), an international collaboration that involves 12 case–control and cohort studies from North America and Europe (25). The studies included are listed in Table 1, and details have been described previously (9). In brief, we used data from 7 nested case–control studies in prospective cohorts [Health Professionals Follow-up Study (HPFS); Multiethnic Cohort Study (MEC); Nurses' Health Study (NHS); Physician's Health Study (PHS); Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO); VITamins And Lifestyle Study (VITAL); Women's Health Initiative (WHI)] and 5 case–control studies [Assessment of Risk for Colorectal Tumors in Canada (ARCTIC); Hawai'i Colorectal Cancer Studies 2 and 3 (Colo2&3); Darmkrebs: Chancen der Verhutüng durch Screening (DACHS); Diet, Activity and Lifestyle Survey (DALS); and Postmenopausal Hormone Study (PMH)]. Written informed consent was given by all participants, and studies were approved by their respective Institutional Review Boards. Studies were conducted in accordance with the Declaration of Helsinki.

Each study identified incident, invasive colorectal cancer cases (International Classification of Disease for Oncology Code 18.0–18.9, 19.9, and 20.9), confirmed by medical record, pathology report, or death certificate. Age at diagnosis, cancer subsites, and stages were obtained from medical records and registries. Controls were individuals without history of colorectal cancer at the time of selection and were selected based on study-specific eligibility and matching criteria (mostly sex and age; as well as smoking status for PHS).

Participants reported as members of racial/ethnic groups other than White were excluded, and European ancestry was confirmed using principal components analysis (26). Participants with missing information on both aspirin and nonaspirin NSAID

Table 1. Definition of regular use of NSAIDs among participating studies

Study design	Study	Country	Case *N*	Control *N*	Male *N* (%)	Age mean (SD), year	Definition of regular use of aspirin and/or nonaspirin NSAIDs[a]
Cohort (nested case–control)	PLCO	United States	1,096	2,719	2,597 (68.1)	69.0 (6.1)	≥2 times/week in the last 12 months
	WHI	United States	1,740	2,962	0	73.1 (7.3)	≥1 time/week for at least the last 2 weeks
	HPFS	United States	646	1,164	1,810 (100)	69.6 (9.1)	Currently taking ≥2 times/week
	MEC	United States	356	366	381 (52.8)	70.0 (8.3)	≥2 times/week for ≥1 month
	NHS	United States	1,001	1,817	0	66.5 (8.2)	Currently using ≥15 days/month
	PHS	United States	309	455	764 (100)	69.2 (9.6)	Currently using ≥1 time/week
	VITAL	United States	333	337	365 (54.3)	70.5 (6.6)	≥4 days/week for 1 year
Case–control	ARCTIC	Canada	1,066	1,204	1,098 (48.4)	62.1 (8.7)	≥2 times/week for >1 month about 2 years ago
	DALS	United States	1,451	1,474	1,644 (56.2)	65.0 (9.9)	≥3 times/week for ≥1 month within the last 2 years
	DACHS	Germany	2,859	2,355	3,136 (60.2)	68.6 (10.5)	Currently using for ≥2 time/week for ≥1 years
	Colo2&3	United States	94	131	128 (56.8)	64.7 (11.4)	Currently using
	PMH	United States	943	1,015	0	64.5 (7.2)	≥2 times/week for >1 month
Overall			11,894	15,999	11,922 (42.7)	68.2 (9.1)	

Abbreviations: ARCTIC, Assessment of Risk for Colorectal Tumors in Canada; Colon 2&3, a case–control study from the University of Hawai'i; DACHS, Darmkrebs: Chancen der Verhutüng durch Screening Study; DALS, Diet, Activity and Lifestyle Study; HPFS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort; NHS, Nurses' Health Study; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PMH, Postmenopausal Hormone Study–Colon Cancer Family Registry; VITAL, Vitamins and Lifestyle Study; WHI, Women's Health Initiative.

[a]Definition of regular use of aspirin and/or NSAIDs was assessed at corresponding referent period: in cohort studies, baseline; case–control studies, at the time of diagnosis for cases, and at analog time for controls.

use were excluded. A total of 11,894 colorectal cases and 15,999 controls were included in the analysis.

Assessment of NSAID use and covariates

Demographics and environmental exposures were self-reported at either in-person interview or via structured self-administered questionnaires, based on each participating study. A multistep, iterative data harmonization procedure was applied, reconciling each study's unique protocols and data collection instruments (27). Numerous quality-control checks were performed, and outlying values of variables were truncated to the minimum or maximum value of an established range for each variable. Variables were combined into a single dataset with common definition, standardized coding, and standardized permissible values.

For the main exposure variables (regular use of any NSAID, aspirin, and nonaspirin NSAIDs), we attempt to capture both frequency and duration of use in defining regular use. Study-specific definitions of regular use of aspirin and/or nonaspirin NSAIDs were used instead of an identical definition due to variability in questions across studies (Table 1). Use of aspirin included both low-dose aspirin (81 mg) and regular or extra-strength aspirin ($\geq$325 mg). Use of nonaspirin NSAIDs included ibuprofen, naproxen, or other pain relievers, based on each study. Regular use of any NSAID was defined as regular use of either aspirin or nonaspirin NSAIDs.

An *a priori* list of potential confounders were also ascertained and harmonized, including study, age, sex, education, BMI, smoking, physical activity, first-degree family history of colorectal cancer, history of endoscopy, diabetes, and PMH use in women. Age was defined as age at diagnosis for cases and age at selection for controls. Dietary covariates were ascertained using food frequency questionnaires, including intakes of alcohol (nondrinker, 1–28 g/day and >28 g/day), fruit, vegetables, dietary fiber, red meat, processed meat and total energy, and total (diet plus supplemental) intakes of calcium and folate. Sex- and study-specific quartiles were created for smoking, physical activity, and all dietary variables except alcohol. For studies with dietary information in categories that did not allow conversion into quartiles, binary variables defined by sex-study–specific medians were used. The binary variable was coded as quartiles 2 and 3 for these studies.

Statistical analyses

Statistical analyses were conducted using individual-level data. For each study, logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for each NSAID variable (any NSAID use, aspirin use, and nonaspirin NSAID use) by comparing regular users and non-regular users after adjusting for covariates (as specified in footnotes to tables). Indicators were used for missing covariates. Regular use of nonaspirin NSAIDs was also adjusted for in the analyses for aspirin and vice versa. Study-specific estimates were combined, using a fixed-effects model, into summary ORs and corresponding 95% CIs. Heterogeneity across studies was assessed using percentage of variance (I^2) and tested using Cochran Q test (28).

To assess factors that may modify the association between NSAID use and colorectal cancer risk, we computed stratum-specific estimates in each study, using logistic regression within each stratum of each factor adjusting for all other covariates, which were then combined into summary stratum-specific ORs and corresponding 95% CIs. Interaction was tested as the significance of the cross product of the NSAID variable and the effect modifier in the multivariable model that also included the main associations of the NSAID variable and the potential effect modifier. Demographic characteristics and lifestyle factors were evaluated including age (<70 and $\geq$70 years old), sex, BMI (kg/m^2; normal [18.5–24.9], overweight [25–29.9] and obese [$\geq$30]), smoking (pack-years; nonsmoker, $\leq$median and >median), moderate/vigorous physical activity (quartiles; hours/week), first-degree family history of colorectal cancer, history of endoscopy (colonoscopy or sigmoidoscopy), diabetes, and PMH use in women. Dietary factors were also tested for potential effect modification, including alcohol intake (nondrinker, 1–28 g/day and >28 g/day), fruit intake (quartiles), vegetable intake (quartiles), red meat intake (quartiles), processed meat intake (quartiles), dietary fiber intake (quartiles), total calcium intake (quartiles), and total folate intake (quartiles). The potential effect modifiers with more than two categories were modeled as group linear (trend) in multiplicative interaction terms. The study-specific estimates for cross products were combined into summary estimates for a single two-sided *P* value for interaction, using a fixed-effect meta-analysis. Most interaction analyses did not show significant heterogeneity across studies. Therefore, we did not use a random-effects meta-analysis. For each potential effect modifier, studies with constant values were excluded from corresponding interaction analyses: specifically, WHI, NHS, HPFS, and PHS were excluded in the interaction analysis of NSAID use and sex; PHS was excluded in the interaction analysis of NSAID use and smoking; and HPFS and PHS were excluded in the interaction analysis of NSAID and PMH use. For statistically significant effect modifiers, we further tested whether the observed interactions differed by sex or study type (case–control and cohort). In addition, we also performed sensitivity analyses for statistically significant effect modifiers using multiple imputation methods to impute missing values in the adjusted covariates in the interaction analysis.

Stratified analyses by cancer subsites (proximal colon, distal colon, and rectal) and stages (local, regional, and distant) were also performed for the association between regular NSAID use and colorectal cancer risk. Site-specific or stage-specific cases were compared with the same control group in stratified analyses; logistic regression limited to cases was used to test for heterogeneity. A *P* value of <0.05 was considered statistically significant in all analyses. All analyses were performed in Stata v.14 (StataCorp).

Results

Descriptions of the study populations and the definitions of regular NSAID use in each participating study are shown in Table 1. The main associations of NSAID use on colorectal cancer risk were examined for all studies (Fig. 1). For each type of NSAID use (any NSAID, aspirin use, and nonaspirin NSAID use), regular NSAID use was statistically significantly associated with lower risk of colorectal cancer after adjusting for all the covariates, compared with nonregular users ($P <$ 0.001). Any NSAID use was associated with 25% lower risk of colorectal cancer, compared with nonregular NSAID use (OR, 0.75; 95% CI, 0.71–0.79; $P < 0.001$; P heterogeneity < 0.001). The association was stronger among case–control studies.

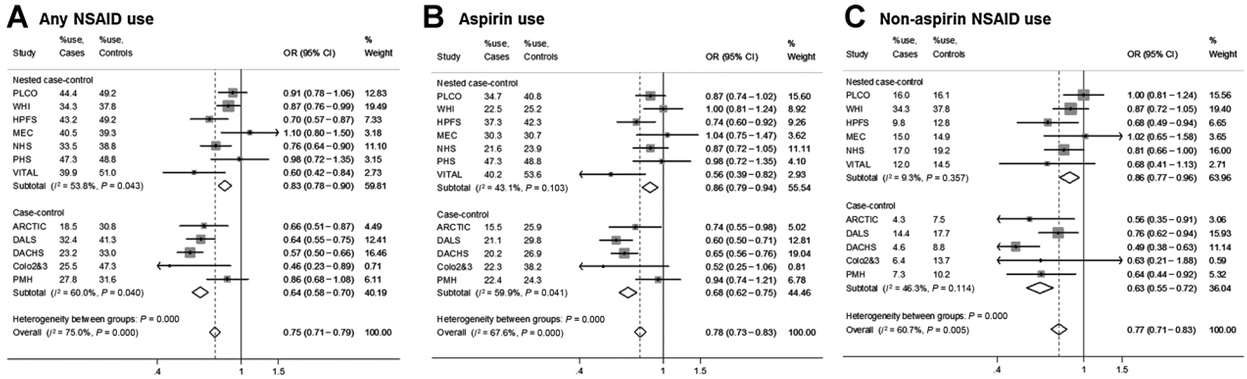

Figure 1.

Estimated associations between regular use of aspirin and/or NSAIDs and colorectal cancer risk. The size of the data markers is proportional to the precision of the estimate, which is the inverse of the variance. Study-specific ORs and 95% CIs are estimated using logistic regression models, adjusting for age, sex, education (less than high school, high school graduate or GED, some college, college graduate, graduate degree), first-degree family history of colorectal cancer (yes/no), history of endoscopy (yes/no), postmenopausal hormone use among women (yes/no), history of diabetes(yes/no), BMI (kg/m^2), moderate/vigorous activity (hours/week), smoking (nonsmokers and quartiles of pack-years), alcohol intake (none, 1–28 g/day, >28 g/day), dietary intakes (quartiles) of fruit, vegetables, red meat, processed meat, and fiber, total energy intake (quartiles), total (dietary and supplemental) intakes of calcium and folate (quartiles). Covariates in quartiles are adjusted as group linear variables in the model. For aspirin or nonaspirin NSAID use only, the other type was also adjusted. Subtotal and overall ORs and 95% CIs are estimated using fixed-effect meta-analysis. The estimates using random-effect are any aspirin or NSAID use (**A**): OR = 0.75 (0.67–0.85); aspirin use (**B**): OR = 0.79 (0.70–0.89); nonaspirin NSAID use (**C**): OR = 0.74 (0.64–0.86).

Regular use of any NSAID, aspirin, or nonaspirin NSAIDs was statistically significantly associated with a lower risk of colorectal cancer across almost all subgroups, stratified by demographic and lifestyle factors (Table 2) and by dietary factors (Table 3). There was minimal heterogeneity by study in the test for interaction for all analyses, except for age and processed meat. The association between aspirin and colorectal cancer risk statistically significantly differed by smoking status after adjusting for other risk factors in the meta-analysis (P interaction = 0.048). Regular use of aspirin was associated with a 29% lower risk of colorectal cancer among nonsmokers (OR, 0.71; 95% CI, 0.64–0.79), whereas it was associated with 19% and 17% lower risk of colorectal cancer among individuals with below the median of pack-years of smoking (OR, 0.81; 95% CI, 0.71–0.92) and above the median of pack-years (OR, 0.83; 95% CI, 0.74–0.94), respectively. There was a suggestive interaction between regular use of any NSAID and BMI (P interaction = 0.075), where the association between any NSAID use and colorectal cancer risk was attenuated with increasing BMI (normal: OR, 0.69; 95% CI, 0.63–0.77; overweight: OR, 0.76; 95% CI, 0.70–0.83; obese: OR, 0.85; 95% CI, 0.75–0.96). This possible interaction was primarily driven by aspirin (P interaction = 0.074). The association of regular use of aspirin on colorectal cancer risk was stronger among individuals with normal BMI (OR, 0.75; 95% CI, 0.67–0.84) and overweight (OR, 0.75; 95% CI, 0.68–0.83), and statistically nonsignificant among the obese (OR, 0.93; 95% CI, 0.80–1.08). No other interactions between NSAIDs and other risk factors of colorectal cancer were observed in meta-analyses. Similar results were observed using multiple imputations for missing values in covariates for both BMI and smoking (Supplementary Table S1). The interaction between regular use of aspirin and smoking remained statistically significant after multiple imputation (P interaction = 0.021). There was still suggestive interaction between regular use of any NSAIDs and BMI on colorectal cancer risk (P interaction = 0.078). We examined the effect modification of smoking and BMI on the association between NSAID use and colorectal cancer, stratified by sex (Table 4). Results for interactions were stronger among men for interaction between aspirin use and BMI (P interaction = 0.024), and between use of aspirin and smoking (P interaction = 0.097). While the direction of effect modifications was similar in women as men, the tests for interaction were nonsignificant.

Because there were significant differences in the main associations of NSAID use on colorectal cancer risk between case–control and cohort studies (Fig. 1), we evaluated whether the effect modification of smoking and BMI differed by study type. The interaction terms for smoking and aspirin were almost identical for case–control (interaction OR, 1.08; 95% CI, 0.97–1.21) and cohort studies (interaction OR, 1.07; 95% CI, 0.98–1.18; between-group P heterogeneity = 0.95). Similarly, the interaction terms for BMI and any NSAIDs were similar for case–control (interaction OR, 1.12; 95% CI, 0.94–1.34) and cohort studies (interaction OR, 1.09; 95% CI, 0.95–1.26; between-study P heterogeneity = 0.82). However, the interaction terms for BMI and aspirin use appeared to differ between case–control (interaction OR, 1.17; 95% CI, 1.03–1.33) and cohort studies (interaction OR, 1.02; 95% CI, 0.92–1.12; between-group P heterogeneity = 0.085).No statistically significant differences in the associations between regular use of NSAIDs and colorectal cancer risk were observed between cancer subsites or stages (Supplementary Table S2).

Discussion

Consistent with evidence from randomized clinical trials and observational studies, regular use of aspirin and/or nonaspirin NSAIDs was statistically significantly associated with lower risk of colorectal cancer in this large consortium study. The association remained statistically significant among almost all the population subgroups stratified by other colorectal cancer risk factors.

Table 2. Interactions between regular use of NSAIDs and demographic and lifestyle factors in relation to colorectal cancer risk

	Any NSAID				Aspirin				Nonaspirin NSAIDs			
	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value
Age, years												
<70	6,518	8,213	0.74 (0.68–0.80)	<0.001	6,467	8,181	0.79 (0.72–0.87)	<0.001	6,337	7,910	0.75 (0.67–0.84)	<0.001
≥70	5,376	7,786	0.76 (0.70–0.82)	<0.001	5,321	7,733	0.76 (0.69–0.83)	<0.001	5,195	7,593	0.79 (0.70–0.90)	<0.001
P value for interaction[b]				0.672				0.320				0.954
Sex[c]												
Male	3,993	5,355	0.68 (0.61–0.75)	<0.001	3,943	5,314	0.72 (0.65–0.80)	<0.001	3,970	5,337	0.70 (0.59–0.83)	<0.001
Female	3,262	3,231	0.71 (0.63–0.80)	<0.001	3,222	3,194	0.69 (0.60–0.79)	<0.001	3,238	3,213	0.80 (0.68–0.95)	0.009
P value for interaction[b]				0.963				0.436				0.309
BMI, kg/m^2												
Normal (18.5–24.9)	4,113	6,311	0.69 (0.63–0.77)	<0.001	4,080	6,286	0.75 (0.67–0.84)	<0.001	3,944	6,028	0.72 (0.61–0.84)	<0.001
Overweight (25–29.9)	4,827	6,322	0.76 (0.70–0.83)	<0.001	4,783	6,284	0.75 (0.68–0.83)	<0.001	4,663	6,139	0.80 (0.70–0.91)	0.001
Obese (≥30)	2,647	2,957	0.85 (0.75–0.96)	0.006	2,623	2,939	0.93 (0.80–1.08)	0.361	2,621	2,928	0.79 (0.67–0.93)	0.005
P value for interaction[b]				0.075				0.074				0.967
Smoking, pack-years[d]												
Nonsmoker	4,902	6,930	0.71 (0.65–0.77)	<0.001	4,854	6,889	0.71 (0.64–0.79)	<0.001	4,882	6,911	0.74 (0.65–0.84)	<0.001
≤Median	2,934	4,211	0.79 (0.70–0.88)	<0.001	2,913	4,192	0.81 (0.71–0.92)	0.002	2,915	4,204	0.79 (0.67–0.93)	0.005
>Median	3,444	4,053	0.77 (0.69–0.86)	<0.001	3,412	4,030	0.83 (0.74–0.94)	0.004	3,434	4,040	0.78 (0.66–0.91)	0.002
P value for interaction[b]				0.167				0.048				0.459
Physical activity												
Quartile 1	2,092	2,574	0.63 (0.54–0.72)	<0.001	2,047	2,538	0.65 (0.55–0.76)	<0.001	1,999	2,455	0.70 (0.57–0.86)	0.001
Quartile 2	1,724	2,289	0.74 (0.63–0.86)	<0.001	1,721	2,286	0.73 (0.61–0.86)	<0.001	1,556	2,016	0.84 (0.66–1.07)	0.154
Quartile 3	1,484	2,258	0.77 (0.65–0.90)	0.001	1,474	2,246	0.75 (0.63–0.91)	0.003	1,471	2,256	0.80 (0.62–1.03)	0.084
Quartile 4	1,399	1,681	0.73 (0.61–0.88)	0.001	1,382	1,668	0.78 (0.64–0.96)	0.018	1,340	1,610	0.66 (0.50–0.87)	0.003
P value for interaction[b]				0.218				0.263				0.894
CRC family history												
Yes	1,955	1,941	0.77 (0.66–0.90)	0.001	1,941	1,926	0.81 (0.67–0.97)	0.023	1,948	1,935	0.90 (0.71–1.13)	0.363
No	9,325	13,117	0.74 (0.69–0.79)	<0.001	9,236	13,049	0.76 (0.70–0.81)	<0.001	9,285	13,090	0.75 (0.69–0.83)	<0.001
P value for interaction[b]				0.659				0.764				0.143
History of endoscopy												
Yes	4,595	6,100	0.75 (0.69–0.82)	<0.001	4,544	6,049	0.78 (0.70–0.86)	<0.001	4,560	6,084	0.75 (0.65–0.86)	<0.001
No	6,166	8,321	0.73 (0.67–0.79)	<0.001	6,117	8,290	0.76 (0.69–0.83)	<0.001	6,160	8,305	0.79 (0.70–0.88)	<0.001
P value for interaction[b]				0.900				0.886				0.679
Diabetes												
Yes	954	877	0.73 (0.59–0.92)	0.007	953	877	0.77 (0.60–0.98)	0.031	954	877	0.60 (0.42–0.87)	0.007
No	7,366	11,153	0.76 (0.71–0.82)	<0.001	7,351	11,146	0.81 (0.75–0.88)	<0.001	7,360	11,148	0.78 (0.71–0.87)	<0.001
P value for interaction[b]				0.442				0.442				0.674
PMH use in women[e]												
Yes	2,002	3,362	0.87 (0.77–0.99)	0.035	1,985	3,342	0.92 (0.78–1.09)	0.304	2,000	3,354	0.89 (0.76–1.05)	0.178
No	4,259	4,909	0.75 (0.68–0.83)	<0.001	4,224	4,889	0.75 (0.66–0.85)	<0.001	4,241	4,896	0.75 (0.65–0.87)	0.001
P value for interaction[b]				0.147				0.178				0.242

Abbreviations: CRC, colorectal cancer; BMI, body mass index; PMH, postmenopausal hormone.

[a]Study-specific ORs and 95% CIs are estimated using logistic regression models, adjusting for age, sex, education (less than high school, high school graduate or GED, some college, college graduate, graduate degree), first-degree family history of colorectal cancer (yes/no), history of endoscopy (yes/no), postmenopausal hormone use among women (yes/no), history of diabetes(yes/no), BMI (kg/m^2), moderate/vigorous activity (hours/week), smoking (nonsmokers and quartiles of pack-years), alcohol intake (none, 1–28 g/day, >28 g/day), dietary intakes (quartiles) of fruit, vegetables, red meat, processed meat and fiber, total energy intake (quartiles), total (dietary and supplemental) intakes of calcium and folate (quartiles). Covariates in quartiles are adjusted as group linear variables in the model. For aspirin or nonaspirin NSAID use only, the other type was also adjusted for.

[b]*P* for interaction based on interaction of dichotomous NSAID variable and linear (trend) effect-modifier variable using fixed-effect meta-analysis. The *P* values for heterogeneity were all >0.05, except for age. More details are described in Materials and Methods.

[c]WHI, NHS, HPFS, PHS, and PMH were excluded in subgroup and interaction analyses for sex because all participants have the same sex in each study.

[d]PHS was excluded in subgroup and interaction analyses for smoking because cases and controls were matched on smoking status in PHS.

[e]HPFS and PHS were excluded in subgroup and interaction analyses for PMH use in women because all participants were men.

We found a statistically significant interaction between regular use of aspirin and smoking, where regular use of aspirin was associated with a larger decrease in colorectal cancer risk among nonsmokers, than among smokers. Similar to our findings, recent clinical trials among patients with colorectal adenomas suggested that aspirin was associated with lower risk of colorectal adenomas among nonsmokers, but not among current smokers (20–22). In a large randomized trial of low-dose aspirin in combination with the calcium supplements among patients with colorectal adenomas, the treatment was suggested to be protective against adenoma recurrence among nonsmokers, but was associated with higher risk of recurrence among current smokers (20). Similar interactions were observed in two small trials of colorectal adenomas in Asian populations such that the protective effect of low-dose aspirin was abrogated among current smokers (21, 22). A cross-sectional study of colonoscopy patients also found that daily NSAID use was associated with lower risk of colorectal polyps among nonsmokers, but not among current smokers (29). However, a cohort study reported no statistically significant interaction between NSAID use and smoking on colorectal cancer risk (16). In contrast, a case–control study found that current NSAID use

Table 3. Interactions between regular use of NSAIDs and dietary factors in relation to colorectal cancer risk

	Any NSAID				Aspirin				Nonaspirin NSAIDs			
	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value
Alcohol												
Nondrinker	3,785	5,364	0.77 (0.70–0.85)	<0.001	3,759	5,328	0.77 (0.69–0.87)	<0.001	3,720	3,720	0.78 (0.68–0.90)	<0.001
1–28 g/day	4,131	6,219	0.72 (0.66–0.79)	<0.001	4,097	6,195	0.80 (0.72–0.88)	<0.001	3,890	3,890	0.74 (0.64–0.85)	<0.001
>28 g/day	1,204	1,377	0.65 (0.53–0.80)	<0.001	1,188	1,373	0.66 (0.53–0.82)	<0.001	1,367	1,186	0.84 (0.61–1.15)	0.265
P value for interaction[b]				0.572				0.790				0.540
Fruit intake												
Quartile 1	2,125	3,079	0.81 (0.71–0.92)	0.002	2,108	3,060	0.84 (0.71–0.98)	0.030	2,013	2,945	0.83 (0.69–1.01)	0.067
Quartile 2	4,848	5,452	0.69 (0.63–0.77)	<0.001	4,805	5,431	0.76 (0.68–0.84)	<0.001	4,763	5,335	0.65 (0.56–0.76)	<0.001
Quartile 3	2,516	3,888	0.73 (0.64–0.82)	<0.001	2,493	3,867	0.72 (0.63–0.83)	<0.001	2,425	3,766	0.83 (0.70–1.00)	0.045
Quartile 4	1,594	2,793	0.74 (0.64–0.86)	<0.001	1,581	2,775	0.80 (0.67–0.95)	0.010	1,527	2,677	0.70 (0.56–0.87)	0.001
P value for interaction[b]				0.428				0.337				0.120
Vegetable intake												
Quartile 1	1,889	2,785	0.73 (0.63–0.84)	<0.001	1,868	2,770	0.81 (0.69–0.96)	0.014	1,787	2,668	0.74 (0.60–0.90)	0.003
Quartile 2	5,122	5,817	0.73 (0.66–0.80)	<0.001	5,086	5,786	0.78 (0.70–0.87)	<0.001	5,017	5,686	0.69 (0.59–0.80)	<0.001
Quartile 3	2,501	3,869	0.72 (0.63–0.81)	<0.001	2,476	3,853	0.73 (0.63–0.84)	<0.001	2,408	3,741	0.74 (0.62–0.89)	0.001
Quartile 4	1,623	2,771	0.83 (0.71–0.95)	0.009	1,607	2,754	0.78 (0.66–0.93)	0.006	1,567	2,658	0.91 (0.74–1.11)	0.354
P value for interaction[b]				0.234				0.881				0.119
Fiber intake												
Quartile 1	1,516	2,356	0.69 (0.60–0.81)	<0.001	1,500	2,342	0.71 (0.59–0.86)	<0.001	1,509	2,353	0.81 (0.66–1.00)	0.048
Quartile 2	1,532	2,411	0.82 (0.71–0.95)	0.009	1,516	2,395	0.82 (0.68–0.98)	0.027	1,529	2,407	0.87 (0.71–1.07)	0.173
Quartile 3	1,337	2,407	0.79 (0.68–0.92)	0.002	1,323	2,390	0.84 (0.70–1.01)	0.063	1,334	2,404	0.78 (0.63–0.97)	0.027
Quartile 4	1,405	2,415	0.83 (0.71–0.96)	0.015	1,390	2,403	0.76 (0.63–0.91)	0.003	1,403	2,413	0.90 (0.73–1.11)	0.328
P value for interaction[b]				0.142				0.495				0.559
Red meat intake												
Quartile 1	2,739	4,239	0.76 (0.67–0.85)	<0.001	2,712	4,219	0.84 (0.73–0.96)	0.012	2,653	4,109	0.71 (0.58–0.86)	<0.001
Quartile 2	3,041	4,110	0.73 (0.65–0.82)	<0.001	3,011	4,087	0.78 (0.68–0.89)	<0.001	2,953	3,989	0.72 (0.61–0.86)	<0.001
Quartile 3	2,922	3,714	0.72 (0.64–0.81)	<0.001	2,905	3,696	0.69 (0.60–0.79)	<0.001	2,817	3,579	0.79 (0.67–0.94)	0.009
Quartile 4	2,439	3,251	0.75 (0.66–0.85)	<0.001	2,417	3,235	0.78 (0.67–0.91)	0.001	2,367	3,159	0.79 (0.66–0.95)	0.012
P value for interaction[b]				0.484				0.146				0.876
Processed meat intake												
Quartile 1	1,795	2,693	0.74 (0.64–0.86)	<0.001	1,779	2,675	0.81 (0.68–0.96)	0.014	1,719	2,576	0.74 (0.58–0.93)	0.011
Quartile 2	3,325	5,045	0.74 (0.67–0.82)	<0.001	3,301	5,032	0.79 (0.70–0.89)	<0.001	3,210	4,884	0.74 (0.64–0.86)	<0.001
Quartile 3	2,019	2,877	0.76 (0.67–0.87)	<0.001	2,006	2,865	0.77 (0.65–0.90)	0.001	1,956	2,799	0.81 (0.66–0.98)	0.028
Quartile 4	1,993	2,392	0.71 (0.61–0.82)	<0.001	1,974	2,375	0.68 (0.57–0.81)	<0.001	1,929	2,293	0.81 (0.66–1.00)	0.051
P value for interaction[b]				0.508				0.181				0.627
Total calcium intake												
Quartile 1	2,602	3,172	0.71 (0.63–0.81)	<0.001	2,581	3,159	0.73 (0.63–0.85)	<0.001	2,514	3,054	0.79 (0.65–0.96)	0.015
Quartile 2	3,737	4,583	0.72 (0.65–0.81)	<0.001	3,697	4,548	0.75 (0.66–0.86)	<0.001	3,637	4,452	0.69 (0.58–0.82)	<0.001
Quartile 3	2,806	4,193	0.81 (0.72–0.91)	<0.001	2,782	4,171	0.85 (0.74–0.97)	0.016	2,706	4,063	0.80 (0.67–0.96)	0.014
Quartile 4	1,983	3,266	0.72 (0.63–0.82)	<0.001	1,965	3,252	0.77 (0.66–0.90)	0.001	1,916	3,154	0.72 (0.60–0.88)	0.001
P value for interaction[b]				0.726				0.896				0.644
Total folate intake												
Quartile 1	1,608	2,540	0.72 (0.62–0.84)	<0.001	1,584	2,530	0.74 (0.62–0.89)	0.001	1,603	2,535	0.82 (0.67–1.01)	0.061
Quartile 2	3,375	4,679	0.82 (0.73–0.91)	<0.001	3,342	4,640	0.88 (0.77–1.00)	0.044	3,096	4,295	0.73 (0.61–0.87)	<0.001
Quartile 3	1,851	3,086	0.79 (0.69–0.91)	0.001	1,833	3,067	0.80 (0.68–0.94)	0.007	1,786	2,989	0.82 (0.67–1.00)	0.051
Quartile 4	1,467	2,589	0.79 (0.68–0.91)	0.001	1,452	2,574	0.79 (0.67–0.95)	0.009	1,463	2,586	0.83 (0.68–1.01)	0.058
P value for interaction[b]				0.679				0.848				0.703

[a]Study-specific ORs and 95% CIs are estimated using logistic regression models, adjusting for age, sex, education (less than high school, high school graduate or GED, some college, college graduate, graduate degree), first-degree family history of colorectal cancer (yes/no), history of endoscopy (yes/no), postmenopausal hormone use among women (yes/no), history of diabetes (yes/no), BMI (kg/m^2), moderate/vigorous activity (hours/week), smoking (nonsmokers and quartiles of pack-years), alcohol intake (none, 1–28 g/day, >28 g/day), dietary intakes (quartiles) of fruit, vegetables, red meat, processed meat and fiber, total energy intake (quartiles), total (dietary and supplemental) intakes of calcium and folate (quartiles). Covariates in quartiles are adjusted as group linear variables in the model. For aspirin or nonaspirin NSAID use only, the other type was also adjusted for.

[b]*P* for interaction based on interaction of dichotomous NSAID variable and linear (trend) effect-modifier variable, using fixed-effect meta-analysis. The *P* values for heterogeneity were all >0.05, except for processed meat. More details are described in Materials and Methods.

was associated with larger decrease in colorectal cancer risk among individuals who smoked for >40 years than among nonsmokers (19).

The mechanisms by which smoking modifies the preventive effect of NSAIDs on colorectal cancer risk remain unclear. Cigarette smoking was found to be more strongly associated with colorectal tumors that arise from nonconventional pathways, such as the serrated polyp pathway (30, 31). Smoking status was found to be significantly associated with risk of advanced serrated polyps in a screening population (32). Smoking is also associated with colorectal cancer that are more likely to be microsatellite instability (MSI) positive (19), a hallmark of the serrated polyp pathway (33). Pooled analysis of three randomized trials to prevent serrated polyps found that aspirin use was only significantly associated with a lower risk of polyps in the right colon, whereas smoking was associated with an increased risk of polyps in the left colon (34), suggesting that aspirin and smoking may be associated with

Table 4. Interaction between regular use of NSAIDs and BMI/smoking in relation to colorectal cancer by sex

	Any NSAID				Aspirin				Nonaspirin NSAIDs			
	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value	Cases	Controls	OR (95% CI)[a]	*P* value
Men												
BMI, kg/m^2												
Normal (18.5–24.9)	1,403	2,413	0.65 (0.55–0.77)	<0.001	1,390	2,412	0.68 (0.57–0.81)	<0.001	1,245	2,150	0.73 (0.53–1.01)	0.061
Overweight (25–29.9)	2,473	3,302	0.68 (0.60–0.77)	<0.001	2,446	3,284	0.71 (0.62–0.81)	<0.001	2,323	3,125	0.68 (0.55–0.85)	0.001
Obese (≥30)	982	1,104	0.93 (0.74–1.18)	0.560	972	1,093	1.07 (0.84–1.36)	0.587	960	1,082	0.67 (0.48–0.92)	0.014
P value for interaction[b]				0.058				0.024				0.546
Smoking, pack-years[c]												
Nonsmoker	1,587	2,512	0.62 (0.53–0.73)	<0.001	1,572	2,495	0.67 (0.56–0.79)	<0.001	1,452	2,312	0.50 (0.38–0.67)	<0.001
≤Median	1,443	2,064	0.79 (0.66–0.93)	0.005	1,429	2,052	0.79 (0.66–0.94)	0.007	1,420	2,044	0.87 (0.67–1.15)	0.372
>Median	1,658	2,012	0.69 (0.58–0.81)	<0.001	1,638	2,002	0.77 (0.66–0.92)	0.003	1,636	1,988	0.71 (0.54–0.93)	0.012
P value for interaction[b]				0.143				0.097				0.075
Women												
BMI, kg/m^2												
Normal (18.5–24.9)	2,710	3,888	0.73 (0.64–0.82)	<0.001	2,690	3,874	0.82 (0.70–0.95)	0.010	2,699	3,878	0.72 (0.60–0.87)	0.001
Overweight (25–29.9)	2,354	3,020	0.84 (0.74–0.95)	0.007	2,337	3,000	0.81 (0.69–0.95)	0.010	2,340	3,014	0.86 (0.72–1.03)	0.093
Obese (≥30)	1,665	1,853	0.83 (0.71–0.98)	0.024	1,651	1,846	0.88 (0.72–1.08)	0.217	1,661	1,846	0.86 (0.71–1.06)	0.161
P value for interaction[b]				0.458				0.852				0.631
Smoking, pack-years[c]												
Nonsmoker	3,443	4,612	0.76 (0.69–0.85)	<0.001	3,410	4,588	0.76 (0.66–0.87)	<0.001	3,430	4,599	0.82 (0.71–0.95)	0.010
≤Median	1,504	2,165	0.79 (0.67–0.93)	0.004	1,497	2,158	0.85 (0.69–1.04)	0.119	1,495	2,160	0.75 (0.61–0.93)	0.008
>Median	1,803	2,056	0.85 (0.73–1.00)	0.045	1,791	2,043	0.93 (0.77–1.13)	0.453	1,798	2,052	0.82 (0.66–1.01)	0.067
P value for interaction[b]				0.628				0.333				0.898

[a]Study-specific ORs and 95% CIs are estimated using logistic regression models, adjusting for age, sex, education (less than high school, high school graduate or GED, some college, college graduate, graduate degree), first-degree family history of colorectal cancer (yes/no), history of endoscopy (yes/no), postmenopausal hormone use among women (yes/no), history of diabetes (yes/no), BMI (kg/m^2), moderate/vigorous activity (hours/week), smoking (nonsmokers and quartiles of pack-years), alcohol intake (none, 1–28 g/day, >28 g/day), dietary intakes (quartiles) of fruit, vegetables, red meat, processed meat and fiber, total energy intake (quartiles), and total (dietary and supplemental) intakes of calcium and folate (quartiles). Covariates in quartiles are adjusted as group linear variables in the model. For aspirin or nonaspirin NSAID use only, the other type was also adjusted for.

[b]*P* for interaction based on interaction of dichotomous NSAID variable and linear (trend) effect-modifier variable using fixed-effect meta-analysis. All *P* values for heterogeneity were >0.05. More details are described in Materials and Methods.

[c]PHS was excluded in subgroup and interaction analyses for smoking because cases and controls were matched on smoking status in PHS.

different tumor subsites. In addition, it was previously reported that smoking was strongly associated with increased risk of aspirin resistance (35), probably due to smoking-induced platelet hyperreactivity (36). It is likely that the effect of aspirin is dependent on different carcinogenesis pathways of colorectal tumors among smokers and nonsmokers.

Although the NSAID–colorectal cancer association was similar in men and women, we found that the interaction between aspirin and smoking status was statistically significant among men only. No previous study has reported this sex difference. Men had higher cumulative levels of smoking than women (means, 29.7 pack-years among men; 24.1 pack-years among women), which allowed a larger window for interactions between aspirin and smoking. In addition, there were approximately 20% women that were PMH users in our study, and NSAIDs were previously shown to be associated with lower colon cancer risk among PMH nonusers only, but not among PMH users (23), which was also suggested in our study (Table 2). Thus, the sex difference of the interaction between aspirin and smoking may also be partially due to PMH use among women.

We also found a suggestion of interaction between NSAID use and BMI, by which regular use of any NSAID was associated with the lowest relative risk of colorectal cancer among individuals with normal BMI, followed by overweight, and the protective effect of NSAIDs was least among obese individuals. Consistently, a slightly more pronounced protection of regular NSAID use on the prevalence of left-sided colorectal adenomas was observed among individuals with normal BMI than among those who were overweight or obese (P interaction = 0.09), in a multicenter cancer screening trial (37). However, cohort studies observed no interaction between BMI and aspirin on colon cancer risk (14–16, 18). This could be due to the fact that previous studies combined the overweight and obese subgroups or had imprecise estimates for three BMI categories due to small sample sizes. Individuals with higher BMI have higher chronic inflammation levels, and it has been proposed that NSAIDs inhibit PGE_2 synthesis and chronic inflammation to inhibit tumor development (38). High doses of salicylates were also shown to reverse insulin resistance in obese rodents (39), which could otherwise contribute to tumor development (40). In addition, NSAIDs and obesity may both act through the gut microbiome on colorectal tumorigenesis. NSAIDs inhibits inflammatory cytokines and mucin secretion (41), which may shape the composition of gut microbiota (42), whereas obesity was observed to disrupt microbial composition in the gut and promotes colorectal cancer in mice (43). However, our data suggested that the benefit of NSAIDs is attenuated, rather than enhanced as expected, among obese people. It is possible that larger dose, higher frequency, and longer duration of NSAID use are needed to reduce the elevated colorectal cancer risk among individuals with higher BMI.

Our study suggested that only aspirin, rather than nonaspirin NSAIDs, interacted with BMI or smoking on colorectal cancer risk, which may be partially explained by unique mechanisms of actions of aspirin that are not shared by other NSAIDs. Low-dose aspirin has shown to be associated with lower risk of colorectal cancer in randomized trials, suggesting the antiplatelet effect of

aspirin may also play a role in the inhibition of colorectal tumor cells (1). In addition, aspirin can also acetylate COX-2 to synthesize antitumorigenic "aspirin-triggered lipoxin" (ATL), which is anti-inflammatory and inhibits carcinoma cell proliferation (44). The generation of ATL by aspirin was also observed at low, antiplatelet doses of aspirin in a small intervention study of healthy humans (45).

Our study has several strengths. First, we had larger sample size and therefore greater statistical power for interaction analyses than prior studies. Second, we had detailed assessment for most of the colorectal cancer risk factors from all participating studies, a characteristic not seen in previous meta-analyses, which allowed us to perform systematic analyses on potential effect modification. In addition, we were able to adjust for potential confounders in all the analyses, whereas meta-analyses using published data have had limited control for confounding. Furthermore, we used an iterative harmonization process on all the environmental variables across all participating studies to reduce the level of heterogeneity and the impact of outliers.

There are also limitations. As all the environmental factors were assessed via questionnaires and varied across studies, there may be measurement errors in the main NSAID exposures and the covariates. For example, the definition of "regular use of NSAIDs" varied across studies, ranging from current use to $\geq$4 days/week for $\geq$1 year. However, despite these differences, there was minimal evidence of heterogeneity across studies in the interaction analyses. Secondly, the main associations of NSAIDs on colorectal cancer were stronger in case–control studies than nested case–control studies from cohort studies. This stronger main effect in case–control studies could be due to more accurate exposure assessment of NSAID use in these studies, compared with that in cohort studies where NSAID use may have started or been discontinued in the long-term period between exposure assessment and colorectal cancer diagnosis, leading to attenuation of the association. In addition, there might have been recall bias in the case–control studies, which could have spuriously exaggerated the effect of NSAIDs on colorectal cancer risk. Compared with the meta-analysis of randomized trials of aspirin and colorectal cancer risk (1), our results for case–control studies were stronger and those from cohort studies were weaker, with an almost identical overall estimate. Case–control studies may also be more susceptible to selection bias in that the response of participants may be jointly influenced by NSAID use, colorectal cancer status, and effect modifier status. However, the odds ratios for our results of interaction of smoking with aspirin use and of BMI with any NSAID use showed no evidence of heterogeneity between study types. We did not have information on the indicators for NSAIDs use nor the contraindications for use, such as ulcers, so the possibility for unadjusted confounding remains. Furthermore, all the participants were of European ancestry; therefore, our results may not be applicable to other race/ethnicity groups. Lastly, we acknowledge that the observed interactions were of borderline statistical significance, and we did not adjust for multiple testing in the analysis.

To our knowledge, this is the largest study to systematically analyze the interactions between NSAID use and other risk factors in relation to colorectal cancer risk. Regular use of NSAIDs, including both aspirin and nonaspirin NSAIDs was statistically significantly protective against colorectal cancer risk in almost all subgroups. We observed stronger associations between aspirin and colorectal cancer risk among nonsmokers than among smokers. We also found a suggestive interaction between any NSAID use and BMI on colorectal cancer risk, primarily driven by aspirin. Our results suggested that aspirin may have different effects on colorectal cancer prevention within the general population, depending on other colorectal cancer risk factors. The beneficial effects of use of aspirin on colorectal cancer risk appears to be attenuated, rather than enhanced, among those with greater colorectal cancer risk due to obesity and heavy smoking, making it unlikely that these groups would benefit from use of aspirin for the prevention of colorectal cancer. Our results warrant further evaluation on both validation of observed interactions and risk–benefit evaluation of aspirin use in colorectal cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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