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The Association between NSAID use and Colorectal Cancer Mortality: Results from the Women's Health Initiative

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Abstract

Background—Randomized trial evidence demonstrates that non-steroidal anti-inflammatory drug (NSAID) use, particularly long-term use, reduces the incidence of colorectal neoplasia. Recent data also suggests an inverse association between NSAID use and death due to colorectal cancer (CRC).

Methods—We examined the association between NSAID use and CRC mortality among 160,143 post-menopausal women enrolled in the Women's Health Initiative. Women provided details on medication use at baseline and three years after enrollment. Reported CRC cases were locally confirmed and centrally adjudicated; cause of death was determined according to centralized medical record and death certificate review. Cox regression was used to investigate the association between NSAID use and CRC mortality.

Results—Overall, NSAID use at baseline was not associated with CRC mortality (HR: 0.93; 95% CI 0.76, 1.14). However, women who reported NSAID use at both baseline and year-three experienced reductions in CRC mortality (HR: 0.72; 95% CI 0.54, 0.95) compared to non-users.

Conclusion—Results suggest that NSAID use is associated with lower CRC mortality among post-menopausal women who use these medications more consistently over time.

Impact—Our results support prolonged NSAID use in post-menopausal women for the prevention of poor CRC outcomes.

Keywords

colorectal cancer mortality; NSAIDs; WHI

INTRODUCTION

Inflammation plays a role in the initiation and promotion of colorectal tumors (1–4); data from randomized trials and large cohorts have consistently demonstrated that non-steroidal anti-inflammatory drug (NSAID) use reduces the risk of colorectal adenomas, invasive colorectal cancer (CRC), and disease recurrence (5–11). A meta-analysis including 2 randomized aspirin trials and 30 observational studies of NSAID use highlighted the

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importance of the duration of medication use (12); reductions in CRC incidence were greater for randomized treatment assignments ≥5 years, and reductions in observational studies were most pronounced with ≥10 years use.

Recent reports also indicate that NSAID use may play a role in case-fatality after CRC diagnosis (13–18). Meta-analyses of randomized aspirin trials demonstrated significant associations between lower CRC mortality, reduced frequency of metastatic disease, and aspirin use (19–21). However, the two largest trials included in the meta-analyses recruited only men. Furthermore, the literature to date is not conclusive on the role of non-aspirin NSAIDs in CRC mortality, and the relationship between NSAID use duration and colorectal carcinogenesis has not been thoroughly investigated for CRC mortality.

We investigated the association between NSAID use and CRC mortality in the Women's Health Initiative (WHI), a large, well-characterized cohort of post-menopausal women with available information on duration and amount of use for aspirin and non-aspirin NSAIDs.

METHODS

Study Sample

The WHI is comprised of 161,808 post-menopausal women, ages 50–79, enrolled from 40 clinical centers across the United States. Women participated in either a series of randomized clinical trials (CT) or an observational study (OS). Recruitment occurred between October 1, 1993, and December 31, 1998; details of recruitment have been published (22, 23). At enrollment, women provided written informed consent for participation. Human Subjects Review Committees at all participating institutions approved the WHI study protocol. For this analysis, women who reported a prior CRC at the time of study enrollment (n=946) or had no follow-up information (n=725) were excluded, leaving 160,143 eligible women.

Exposure Assessment

WHI participants attended baseline screening visits, during which they completed a series of self-administered questionnaires, collecting detailed information on demographics, family history of cancer, reproductive history, physical activity, and medical history. Physical measurements, including height and weight, were measured at baseline.

Participants were asked to bring prescription and over-the-counter medications used regularly (at least twice a week for the previous two weeks) to their clinic visit to facilitate completion of interviewer-administered questionnaires regarding current medication use (24). Women were asked the following questions regarding NSAIDs: 1) “Do you take aspirin pills or powders, for example, Anacin, Bufferin, and BC pain reliever?” 2) “Do you take ibuprofen tablets or capsules, for example, Advil, Motrin, or Nuprin?” 3) “Do you take Naprozyn, Naproxen, Aleve, Indocin, Clinorial, Feldene, or other anti-inflammatory pain pills?” A question inquiring about use of acetaminophen was included on the questionnaire; acetaminophen use was not classified as NSAID use. Women who indicated that they did take NSAIDs completed a medication questionnaire, providing information on the strength (milligrams) and duration (years) of use. A separate questionnaire was completed for each medication a woman reported currently using. Follow-up medication questionnaires were administered approximately three years after study enrollment.

Women were defined as users at baseline if they reported use of any NSAID on a baseline medication questionnaire. Women who reported NSAID use on a medication questionnaire completed approximately three years (2.5–3.5 years) after study enrollment were considered NSAID-users at year-three. If a woman did not report NSAID use on the baseline

questionnaire or at the time of the year-three follow-up questionnaire, she was considered a non-user at that time point.

Women who reported NSAID use on both the screening medication questionnaire and the year-three medication questionnaire were classified as `continued users'. Women who reported NSAID use at baseline but did not report use at year-three were considered `discontinued' users, whereas those who did not report NSAID use at baseline but did report use at year-three were considered `initiated' users.

Information from the completed baseline medication questionnaire detailing the medication strength (milligrams) and reported duration (years) was used to further investigate the association between NSAID use and CRC mortality. Because women could report use of multiple NSAIDs at baseline, only the maximum value of the variable of interest for each participant was considered in the analysis. For example, if a woman reported aspirin and ibuprofen use at baseline, only the duration value for the medication the woman reported using the longest was considered.

Outcome Assessment

WHI participants were followed for outcomes through March 2005. Women were then invited to participate in the WHI Extension Study; those who refused to participate were administratively censored at the end of 2005. As of August 2007, 115,400 women were enrolled in the Extension Study, with outcome follow-up continuing through 2010.

Disease outcomes were identified through annual medical updates. Reported cases of CRC were locally confirmed based on medical record review and centrally adjudicated; disease characteristics were coded according to Surveillance, Epidemiology, and End Results standards by specially trained staff (25). Cause of death was determined by centralized medical record and death certificate review at a WHI clinical center; regular linkages to the National Death Index were performed to ensure complete mortality ascertainment (26).

The primary outcome of interest in this investigation was mortality due to CRC. Time to CRC mortality was calculated as the time from study enrollment to the recorded date of death due to CRC. Among women who developed CRC, time to case-fatality was calculated as the time from diagnosis to date of death due to CRC. For all analyses, participants alive and free of the endpoint at the date of last follow-up were administratively censored. Women dying of causes other than CRC were administratively censored at their date of death.

Statistical Analysis

Cox regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between NSAID use at baseline and CRC mortality. Cox regression models included the following baseline covariates: age, body mass index (BMI), smoking, personal history of cardiovascular disease, diabetes, and ulcerative colitis, family history of CRC, receipt of colonoscopy, and study arm enrollment (CT vs. OS). Regression models that examined baseline medication strength or duration parameterized exposures based upon the quartile distribution among women reporting current use of the specified NSAID at baseline.

To examine extended NSAID use, regression models were evaluated comparing CRC mortality between women who were continued users and the following reference groups: 1) discontinued users, 2) initiated users, and 3) women who did not report use at either baseline or year-three. Models that considered NSAID use reported on the year-three medication questionnaire included only women who survived at least three years after study enrollment

(n=156,440). Cox regression models restricted to women who developed CRC were run for all comparisons outlined above to investigate the association between NSAID use and case-fatality. Results from case-fatality models are presented without adjustment for stage at diagnosis, given that stage may be in the causal pathway between NSAID use and CRC mortality. Exploratory models including stage were also run.

Exploratory analyses examined whether observed associations between NSAID use and CRC mortality differed by study arm (i.e. one OS strata and separate strata for each CT arm). Analyses also explored whether associations differed according to baseline BMI (< 25.0, 25.0–29.9, ≥ 30.0), or tumor site at diagnosis (proximal, distal/rectal). Because NSAIDs may play a greater role in altering colorectal carcinogenesis in the absence of other known risk factors, we examined associations according to whether women received a colonoscopy prior to baseline interview. The proportional hazards assumption was evaluated using Schoenfeld residuals for CRC mortality, with no violations observed.

Sensitivity Analyses

We restricted investigation of the association between continued NSAID use and CRC mortality to women not diagnosed with CRC prior to year-three (n=1,559 CRC cases; 343 CRC deaths). To account for women who were ill at baseline potentially using NSAIDs at higher rates, we conducted sensitivity analyses restricted to participants who did not die (from any cause) within the first year after enrollment (n=159,385). Less than 5% of observed deaths (492 of 15,068) were due to CRC. Because NSAID use may be associated with multiple causes of death, censoring women who died from non-CRC causes may be informative. To address this potential bias, we estimated the cause-specific hazard of mortality using a *proportional risk model* (27). This model generated an estimate for the association between NSIAD use and CRC-specific mortality *in the presence of mortality from other causes*, in contrast to the Cox model, which estimated the association between NSAID use and CRC-specific mortality *without* directly accounting for death due to other causes.

RESULTS

After an average follow-up of 11 years, 2,119 women developed CRC. Of the 15, 608 women who died during follow-up, CRC was the cause of death for 492. Approximately 36% of CRC cases reported current use of any NSAID at baseline (Table 1). Nearly half the women using NSAIDs at baseline reported <3 years of use, while 19% reported ≥10 years of use. Approximately 55% of baseline NSAID-users reported use of aspirin, and 10% of baseline users reported use of both aspirin and non-aspirin NSAIDs (n=5,883).

CRC Mortality

There was no overall association between NSAID use at baseline and CRC mortality (Table 2). However, women who reported continued use (both baseline and year-three use) experienced a significant reduction in CRC mortality (HR: 0.72; 95% CI 0.54,0.95) compared to *all* non-continuous users, including women who either initiated use after baseline or who discontinued their baseline use prior year-three. Women who were non-users at both baseline and year-three were more likely to be true non-users; compared to continued NSAID-users, women who consistently reported no NSAID use experienced 45% higher rates of CRC mortality (HR: 1.45; 95% CI 1.08–1.85).

Results demonstrated marginal evidence of an inverse, duration-dependent relationship (Table 3), of lower CRC mortality with increasing durations of NSAID use reported at baseline (*P*-trend=0.12). Use for ≥10 years was associated with lower CRC mortality (HR:

0.64; 95% CI 0.40,1.01) compared to no baseline use. Among the baseline NSAID-users, each quartile increase in the duration of use was associated with a 14% reduction in the risk of CRC mortality (HR: 0.86; 95% CI 0.75,1.00).

Effect estimates for baseline and continued aspirin use were similar to those reported for use of any NSAID. In contrast, estimates for non-aspirin NSAID use were not consistent with an association with CRC mortality. This may be attributable to differing patterns of usage according to NSAID type. Approximately 25% of women using aspirin at baseline reported ≥10 years of use, compared to only 11% of non-aspirin NSAID-users. We examined each medication type with adjustment for the other; effect estimates for baseline use remained null for both types. However, continued aspirin use was marginally associated with lower CRC mortality (HR: 0.72; 95% CI 0.51,1.03), while independent results for continued non-aspirin NSAID use were null (HR: 0.86; 95% CI 0.56,1.31).

CRC Case-Fatality

We found no association between NSAID use and case-fatality after CRC diagnosis, regardless of NSAID type (Table 4) or amount of use (data not shown). Results accounting for stage did not differ from those reported.

Explratory analyses revealed no suggestion of heterogeneity in the association of NSAID use with CRC mortality according to study arm enrollment, BMI, tumor site at diagnosis, or receipt of colonoscopy (data not shown). Results of the sensitivity analysis excluding women who died within the first year after study enrollment did not differ in direction or magnitude from those reported. When we removed women from our analyses who were diagnosed with CRC prior to year-three, continued NSAID use remained associated with lower CRC mortality (HR: 0.73; 95% CI 0.54,1.00); baseline use was not significantly associated with CRC mortality, although the result was more consistent with a reduction in mortality risk (HR: 0.80; 95% CI 0.62,1.02).

Results from the proportional risk model were consistent with those reported; continued NSAID use was significantly associated with a lower risk of CRC mortality, even in the presence of other causes of death (HR: 0.87; 95% CI 0.83,0.91).

DISCUSSION

Results suggested that NSAID use, particularly aspirin use, is associated with lower CRC mortality among post-menopausal women who use these medications for longer durations and more consistently over time. Women who reported NSAID use ≥10 years at baseline experienced 36% lower CRC mortality than non-users at baseline, and women who reported use at baseline and year-three had 28% lower CRC mortality than women reporting inconsistent NSAID use.

Our observation of an association with long-term use is consistent with evidence from prior studies. Significant reductions in CRC incidence were observed in the Nurses' Health Study and the Health Professional's Follow-up Study only after 10 years and 6–10 years of aspirin use, respectively (9, 10). Recent meta-analyses of randomized trials have cited greatest benefit against CRC mortality for aspirin treatment durations of at least 5 to 7.5 years (19, 21). Of interest is our observation that the highest quartile of usage reported among these women was ≥6 years of use; three quarters of the baseline NSAID use was <6 years, which may have been inadequate to observe an overall reduction in CRC mortality.

Although no trend was observed between CRC mortality and increasing NSAID medication strength, compared to non-users at baseline, women in the highest quartile (>325 mg)

experienced significantly lower CRC mortality. No substantive differences were observed according to aspirin strength in the recent meta-analysis including aspirin treatments ranging from 30–1,200mg, although there was a suggestion of a lesser effect for 30mg aspirin (19). Observational studies investigating CRC case-fatality have not reported on associations according to medication strength; however, the one prior study that reported no association between aspirin use and CRC case-fatality investigated only lower-dose (75mg) aspirin (28).

No association between CRC incidence and aspirin use was observed in a prior study among women enrolled in the WHI OS (29). The average duration of aspirin use in that report was only 1.7 years, which may have been inadequate to confer any risk reduction. Potentially more important was the short duration of follow-up: 631 CRC cases were reported, with an average follow-up of 6.4 years. Data from randomized trials for CRC incidence demonstrated that a latency period of approximately 10 years was necessary to realize the benefit of aspirin (12, 21). Finally, we found some evidence that NSAIDs may play a more complicated role for cases diagnosed recently after baseline; removal of these cases resulted in less conservative estimates of the effect of baseline use on CRC mortality. The earlier WHI report observed an increased risk of CRC occurring in the first year after study enrollment in NSAID-users; inclusion of these cases thus could have precluded the detection of an overall reduction in risk.

Despite detecting an association between CRC and longer, more consistent NSAID use, we were not able to detect an overall association between NSAID use at baseline and CRC mortality. This may be attributed to limitations in measuring medication exposures in this study sample. First, the referent group of non-users was comprised of women who were not using at the specified time point (i.e. baseline); however, these women may have used NSAIDs at other time points. Nearly 20% of non-users at baseline reported use at year-three, and women were not asked about former NSAID use during screening visits, increasing the possibility for “unexposed” women to have some degree of exposure history. Second, a major limitation was the inability to assess NSAID use at a comparable time for all cases. For example, reported use at baseline for a woman diagnosed within the first three years may have constituted current use relative to diagnosis, but for women diagnosed five years after enrollment, baseline use may have represented former use. Finally, we were unable to account for treatment in the case-fatality analysis. Stage at diagnosis often predicts treatment, and we were able to consider analyses that accounted for stage. The examination of detailed treatment information could shed light on potential pharmaceutical interactions that may impact upon patient prognosis.

Despite limitations, our results demonstrated a biologically plausible effect. The primary targets of these medications are the prostaglandin synthases, particularly COX-2 (30–32); even low doses of aspirin (81mg) have been demonstrated to alter COX-2 levels in colorectal tissue (33). The role of COX-2 in promoting colorectal neoplasia has been well documented; over-expression in colorectal tumors has been observed in multiple studies (34, 35), and COX-2 expression has been linked to the size and prognosis of initiated colorectal tumors (36–38). COX-2-mediated inflammatory signaling facilitates the initiation and promotion of fatal CRC through mechanisms including adaption to a hypoxic tumor microenvironment (39), alteration of cellular apoptotic mechanisms (40), and promotion of metastasis through changes in cellular motility (41) and angiogenesis (42, 43). An increasing amount of NSAID exposure over many years could be expected to alter COX-2 expression, and thereby colorectal tumor initiation and promotion.

The WHI study represents a large and well-characterized cohort of post-menopausal women. Available data allowed us to investigate various durations and medication strengths of aspirin and non-aspirin NSAID use in relation to CRC mortality. Our results add to the

current literature, supporting an association between lower rates of CRC mortality and prolonged NSAID use, particularly longer and more consistent aspirin use, in post-menopausal women.

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Table 1

Characteristics of Study Sample, by NSAID use at Baseline

	Total Study Sample (n=160,143)		Women *not* currently using NSAIDs at baseline (n=103,100)		Women currently using NSAIDs at baseline (n=57,043)	
	N	%	N	%	N	%
Enrollment Status						
Any Clinical Trial	67,822	42.35	44,106	42.78	23,716	41.58
Observational Study	92,321	57.65	58,994	57.22	33,327	58.42
Age at Baseline (years)						
50–54	21,398	13.36	15,399	15.81	5,999	10.52
55–59	31,741	19.82	21,999	21.34	9,742	17.08
60–69	71,902	44.90	45,268	43.91	26.634	46.69
70–79	35,102	21.92	20,434	19.82	14,668	25.71
Body Mass Index at Baseline (kg/m^2)						
<25.0	55,788	35.14	38,340	37.53	17,448	30.84
25.0–29.9	55,144	34.74	35,447	34.70	19,697	34.81
≥30.0	47,805	30.12	28,367	27.77	19,438	34.35
Smoking History						
No	80,616	50.75	52,703	51.55	27,913	49.30
Yes	78,234	49.25	49,529	48.45	28,705	50.70
Duration (years)[a] ≤9	18,154	23.20	11,881	23.99	6,273	21.85
10–19	16,366	20.92	10,560	21.32	5,806	20.23
20–29	16,468	21.05	10,448	21.09	6,020	20.97
30–39	14,036	17.94	8,622	17.41	5,414	18.86
40+	10,330	13.20	6,169	12.56	4,161	14.50
History of Diabetes						
No	150,560	94.08	97,607	94.73	52,953	92.90
Yes	9,475	5.92	5,428	5.27	4,047	7.10
History of Cardiovascular Disease						
No	124,099	82.18	83,044	85.58	41,055	76.07
Yes	26,905	17.82	13,991	14.42	12,914	23.93

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	Total Study Sample (n=160,143)		Women *not* currently using NSAIDs at baseline (n=103,100)		Women currently using NSAIDs at baseline (n=57,043)	
	N	%	N	%	N	%
History of Ulcerative Colitis						
No	156,289	98.90	100,442	98.85	55,847	98.98
Yes	1,742	1.10	1,166	1.15	576	1.02
Colonoscopy Received in Prior Five Years [b]						
No	29,059	37.18	18,054	37.34	11,005	36.93
Yes	49,097	62.82	30,302	62.66	18,795	63.07
Family History of Colorectal Cancer						
No	121,962	83.46	78,809	83.65	43,153	83.13
Yes	24,163	16.54	15,405	16.35	8,758	16.87

[a] Numbers and percentages for duration calculated among women reporting positive smoking history

[b] Numbers and percentages calculated among women reporting ever receiving a colonoscopy

Table 2

Hazard Ratios for Colorectal Cancer Mortality and NSAID Use, by NSAID type

	Any NSAID			Aspirin			Non-Aspirin NSAID		
	Total /Events	**HR**	**95% CI**	**Total/Events**	**HR**	**95% CI**	**Total/Events**	**HR**	**95% CI**
Current Use at Baseline									
No	103,100/319	1.00	Referent	128,538/391	1.00	Referent	128,822/406	1.00	Referent
Yes	57,043/173	0.93	0.76,1.14	31,605/101	0.92	0.72,1.16	31,321/86	0.91	0.71,1.16
Continued Use [a]									
No[b]	127,786/355	1.00	Referent	140,336/384	1.00	Referent	145,948/396	1.00	Referent
Yes	28,654/66	0.72	0.54,0.95	16,104/37	0.72	0.51,1.03	10,492/25	0.86	0.56,1.31
Continued Use [c]		1.00	Referent		1.00	Referent		1.00	Referent
Discontinued Use	27,026/83	1.55	1.11,2.18	14,721/49	1.58	1.01,2.47	20,109/50	1.11	0.67,1.84
Initiated Use	20,395/52	1.07	0.72,1.60	17,318/45	1.07	0.67,1.72	10,083/22	0.88	0.48,1.62
None	80,365/220	1.45	1.08,1.95	108,297/290	1.44	1.00,2.06	115,756/324	1.23	0.80,1.89

Models include all variables from Table 1

[a] All comparisons reported for continued users are restricted to women who survived at least three years after enrollment (n=156,440)

[b] No: Combines women with discontinued use, initiated use, and no reported use at both time points

[c] Exposure group definitions:

Continued Use: Women who reported use at both baseline and year-three

Discontinued Use: Women who reported use at baseline but did not report use at year-three

Initiated Use: Women who did not report use at baseline but did report use at year-three

None: Women who did not report use at either baseline or at year-three

Table 3

Hazard Ratios for Colorectal Cancer Mortality and Baseline NSAID Use

	Any NSAID			Aspirin			Non-Aspirin NSAID			
	Total/Events	**HR[a]**	**95% CI**	**Total/Events**		**HR**	**95% CI**	**Total/Events**		**HR**	**95% CI**
Duration of Use in Years											
None		1.00	Referent		None	1.00	Referent		None	1.00	Referent
<1year	12,605/43	1.12	0.80,1.56	5,163/16	<1year	0.92	0.54,1.57	5,250/19	<6months	1.37	0.86,2.17
1≤years<3	15,757/57	1.06	0.78,1.44	8,738/39	1≤years<3	1.27	0.89,1.81	5,811/19	0.5≤years<2	1.01	0.61,1.67
3≤years<6	13,834/34	0.82	0.57,1.17	9,760/27	3≤years<9	0.87	0.58,1.29	7,198/16	2≤years<5	0.78	0.47,1.31
6+years	14,847/39	0.75	0.52,1.08	7,944/19	9+years	0.59	0.34,1.00	7,179/18	5+years	0.89	0.55,1.45
P-trend=0.12[b]											
Strength in Milligrams											
None		1.00	Referent		None	1.00	Referent		None	1.00	Referent
<200mg	10,466/31	0.84	0.56,1.25	421/1	<81mg[c]	--	--	3,296/6	<200mg	0.64	0.29,1.44
200–324.9mg	13,719/50	1.29	0.95,1.75	6,563/23	81mg	0.97	0.62,1.53	10,070/37	200mg	1.34	0.95,1.90
325mg	20,180/66	0.95	0.71,1.26	20,173/66	325mg	0.96	0.72,1.26	7,691/18	201–500mg	0.80	0.49,1.31
>325mg	12,678/26	0.61	0.39,0.94	3,134/6	>325mg	0.52	0.22,1.27	4,381/11	>500mg	0.78	0.40,1.51
P-trend=0.20[b]											

Covariate adjustment identical to Table 2

[a] HR estimates from regression models with each quartile treated as a categorical variable and `no use' reported at baseline as the consistent referent group

[b] P-trend calculated for **any NSAID use** from reqression model with quartiles treated as ordinal variables and `no use' reported at baseline as the zero category

[c] Numbers too small to estimate stable HR

Table 4

Hazard Ratios for Colorectal Cancer Case-Fatality and NSAID Use, by NSAID Type

	Any NSAID Use			Aspirin Use			Non-Aspirin NSAID Use		
	Total/Events	**HR**	**95% CI**	**Total/Events**	**HR**	**95% CI**	**Total/Events**	**HR**	**95% CI**
Current Use at Baseline									
No	1,418/319	1.00	Referent	1,702/391	1.00	Referent	1,835/420	1.00	Referent
Yes	701/173	1.16	0.93,1.44	417/101	1.04	0.80,1.35	284/72	1.24	0.93,1.65
Continued Use									
No	1,713/355	1.00	Referent	1,826/384	1.00	Referent	2,060/475	1.00	Referent
Yes	320/66	1.00	0.74,1.35	207/37	0.86	0.59,1.25	59/17	1.29	0.70,2.37
Continued Use		1.00	Referent		1.00	Referent		1.00	Referent
Discontinued Use	352/83	1.15	0.80,1.66	193/49	1.45	0.89,2.35	225/55	0.85	0.41,1.74
Initiated Use	287/52	0.83	0.55,1.28	232/45	1.09	0.66,1.80	109/19	0.60	0.25,1.45
None	1,074/220	1.01	0.73,1.40	1,401/290	1.15	0.78,1.69	1,726/401	0.80	0.43,1.47

Covariate adjustment and exposure definitions identical to Table 2