

Do Aspirin and Nonsteroidal Anti-inflammatory Drugs Cause False-Positive Fecal Occult Blood Test Results? A Prospective Study in a Cohort of Veterans

Charles J. Kahi, MD, Thomas F. Imperiale, MD

PURPOSE: To determine whether use of regular aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) is a risk factor for a false-positive fecal occult blood test result.

METHODS: Consecutive patients referred for colonoscopy for a positive fecal occult blood test result at a Veterans Affairs hospital were eligible. Patients with hematochezia, peptic ulcer disease, or unevaluated dyspepsia requiring antacids, or who used warfarin, were excluded. Regular aspirin and NSAID use was defined as at least one daily dose for at least 3 days per week. Colonoscopic findings unlikely to explain a positive test result alone were defined a priori as diverticulosis, hemorrhoids, or polyps <1.0 cm with no villous histology. Findings likely to explain a positive test result included cancer and advanced polyps.

RESULTS: The sample comprised 193 veterans with a mean

(\pm SD) age of 66 ± 10 years; 98% were male and 86% were white. No colonoscopic findings explained the positive fecal occult blood test result in 153 patients (79%). One hundred and thirty-five patients (70%) were regular aspirin or NSAID users, of whom 21% ($n = 29$) had findings to explain the positive test results, compared with 19% (11/58) of nonusers ($P = 0.7$). There was no relation between aspirin dose and colonoscopic findings unlikely to explain a positive test result. Multivariate analysis found no association between regular aspirin or NSAID use and a false-positive test result (odds ratio = 0.85; 95% confidence interval: 0.39 to 1.84).

CONCLUSION: Aspirin and NSAID use were not risk factors for a false-positive fecal occult blood test result in this study. *Am J Med.* 2004;117:837–841. ©2004 by Elsevier Inc.

Screening for colorectal cancer by testing for fecal occult blood has been shown to decrease the incidence of, and mortality from, colorectal cancer, and is recommended annually in persons aged 50 years or older (1–5). Several factors influence the accuracy of the test, particularly dietary and medication restriction at the time of specimen collection. Intake of red meat, poultry, fish, certain raw vegetables, and certain medications may result in false-positive test results (6), whereas ingestion of vitamin C may result in a false-negative test result.

There are few data to guide the decision about whether to restrict the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) during the collection of stool specimens for fecal occult blood testing. Studies addressing this issue have had results with uncertain validity and generalizability to clinical practice, owing to enrollment of young, healthy volunteers (7,8), use of unusually high

doses of aspirin for short periods of time (7,8), use of fecal occult blood assays that are rarely used in practice (8), or the lack of systematic correlation between positive results and colonic findings (9). Clinical guidelines reflect these uncertainties by stating that it is unclear whether low doses of aspirin cause false-positive test results, and that "... higher doses may cause problems" (10). The objective of this study was to determine whether regular use of aspirin or NSAIDs increases the risk of a false-positive fecal occult blood test result in a cohort of patients who are likely to be encountered in clinical practice.

METHODS

We conducted a prospective cohort study at the Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana, between February 2001 and December 2002. The study protocol was approved by the institutional review boards of Indiana University and Roudebush Veterans Affairs Medical Center, and all subjects gave written informed consent. Consecutive patients referred during the 22-month period for a colonoscopy to evaluate a positive fecal occult blood test result were eligible. Three stool specimens for testing with Hemoccult II (Smith-Kline Diagnostics, Palo Alto, California) were collected at home by patients as part of routine screening for colorectal cancer, and mailed or brought to the hospital for laboratory processing and interpretation in the physician's

From the Department of Medicine (CJK, TFI), Division of Gastroenterology and Hepatology, Indiana University Medical Center; Roudebush Veterans Affairs Medical Center (CJK, TFI); and The Regenstrief Institute, Inc. (TFI), Indianapolis, Indiana.

This study was supported in part by a National Institutes of Health grant (DK02756) to Dr. Imperiale.

Requests for reprints should be addressed to Charles J. Kahi, MD, Indiana University Medical Center, 550 N. University Boulevard, UH 4100, Indianapolis, Indiana 46202, or ckahi2@iupui.edu.

Manuscript submitted December 11, 2003, and accepted in revised form May 20, 2004.

clinic. Patients who had a previous colonoscopy within the past 5 years; a history of hematochezia, active peptic ulcer disease, or other bleeding upper gastrointestinal lesion identified by endoscopy; unevaluated dyspepsia requiring acid-suppressive medications; unsatisfactory colonic preparation precluding full colonoscopy; or unclear exposure status (missing medical records along with cognitive impairment and no caretaker); or who used warfarin or an antiplatelet agent (e.g., clopidogrel); were excluded. Patients were blinded to the study hypothesis.

Protocol

Shortly after colonoscopy was scheduled, eligible patients were contacted by telephone by a research assistant and asked to participate in the study. Questionnaire items included a review of prescribed medications and diagnoses, use of over-the-counter aspirin and NSAIDs, and recall of instructions regarding specimen collection for testing (avoidance of certain foods, aspirin, and NSAIDs). In addition, patients were asked if they were taking aspirin or NSAIDs at the time the specimens were collected. Medical records were reviewed in parallel with the interview, and data regarding comorbid conditions and prescribed medications were abstracted and combined with the results of the interview. Patients underwent colonoscopy in the standard fashion. The endoscopists performing the procedure were staff gastroenterologists and fellow trainees rotating at the Roudebush Veterans Affairs Medical Center. All endoscopists were blinded to the questionnaire and medical record findings.

Exposure Status

Regular aspirin or NSAID use was defined as at least one daily dose for at least 3 days per week at the time of stool specimen collection, as determined by the interview, medical record review, or both. Conflicts between the medical record and questionnaire were resolved by reviewing pharmacy records. If aspirin or other NSAIDs were being filled regularly, then the patient was considered a user. Patients had to have taken the medication for at least 1 month before fecal occult blood testing. For aspirin, the dose was divided into ranges of 81 to 324 mg/d, 325 to 649 mg/d, and 650 to 1250 mg/d.

Outcome Measures

The primary outcome was the type of colorectal lesion found on colonoscopy that could explain a positive fecal occult blood test result. Findings unlikely to explain a positive test result were defined a priori as diverticulosis, hemorrhoids, polyps <1.0 cm with no villous histology, or normal findings. Findings likely to explain a positive hemoccult test result included cancer, polyps \geq 1.0 cm or with villous histology, right-sided vascular lesions, or right-sided colitis. A dose-response relation between

Table 1. Reasons for Exclusion of the 122 Patients

Exclusion Criterion	Number
Use of warfarin	34
Bleeding upper gastrointestinal lesion	28
Erosive or hemorrhagic gastropathy	10
Gastric or duodenal ulcer	7
Gastric cancer	2
Esophageal cancer	2
Erosive duodenopathy	2
Erosive esophagitis	2
Portal hypertensive gastropathy	2
Ampullary tumor	1
History of hematochezia	20
Colonoscopy within 5 years	11
Uninvestigated dyspepsia requiring medications	9
Use of clopidogrel	7
Unsatisfactory colonic preparation	7
Refusal to participate	4
Incomplete medical records with impaired cognition and no caregiver	2

daily aspirin dose and the risk of a false-positive hemoccult test result was also determined.

Statistical Analysis

Based on pilot data obtained by one of the investigators (TFI), we assumed a prevalence of regular aspirin use of 40% among patients with colorectal findings that explain a positive hemoccult test result, and of 60% among patients without such findings; using traditional values for a two-sided α (0.05) and β (0.2), these parameters require a sample size of 180. Descriptive statistics were used to identify demographic and clinical features of the cohort. The frequency of colorectal findings that could explain a positive test result was compared between aspirin or NSAID users and nonusers using chi-squared statistics and the Fisher exact test. Logistic regression was then used to adjust for variables potentially associated with the risk of (neoplastic) lesions that may cause a positive test result, including patient age, body mass index, family history of colorectal cancer, and use of acid-suppressive medications. A chi-squared test for trend was used to test for a dose-response relation between the dose of aspirin and the proportion of colorectal findings that would not explain a positive test result. Two-sided P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software, version 8.0 (Cary, North Carolina).

RESULTS

Between February 2001 and December 2002, 315 patients underwent colonoscopy for evaluation of a positive fecal

Table 2. Characteristics of Colonoscopy Findings (n = 193)

Characteristic	Number (%)
Findings likely to explain a positive fecal occult blood test result	
Large polyps (≥ 1.0 cm)	
Hyperplastic	2 (1)
Tubular adenoma	21 (11)
Tubulovillous adenoma	6 (3)
Cancer	3 (2)
Right-sided vascular lesions	5 (3)
Right-sided colitis	3 (2)
Findings unlikely to explain a positive fecal occult blood test result*	
Diverticular disease	
Left-sided	69 (36)
Left- and right-sided	25 (13)
Hemorrhoids (large or moderate)	50 (26)
Small polyps (<1.0 cm)	
Hyperplastic	19 (10)
Tubular adenoma	59 (31)

* Sum of percentages exceeds 100% because some patients had more than one finding.

occult blood test result. Of these, 122 met the exclusion criteria (Table 1), leaving 193 for enrollment in the study. The mean (\pm SD) age of the 193 patients was 66 ± 10 years (range, 35 to 93 years); 98% (n = 189) were male and 86% (n = 154) were white. The hemoccult test was done as part of screening for colorectal cancer in 184 patients (95%), and for screening and evaluation of additional symptoms (e.g., abdominal pain, diarrhea, weight loss) in the remaining patients.

Colonoscopy Results

The cecum was reached in 189 (98%) of 193 procedures. The quality of preparation was rated as fair in 52 (27%), good in 104 (54%), and excellent in 35 (18%). One hundred and fifty-three patients (79%) had no colonoscopic findings to explain the positive hemoccult test result, whereas 40 patients (21%) had findings explaining the positive test result (Table 2).

Interview and Medical Record Review

Telephone interviews were obtained on 114 patients (59%); 26 (23%) of these patients reported that they restricted their diet appropriately (in particular, avoided red meat) at the time of stool specimen collection. Of the 193 patients, 135 (70%) were taking regular aspirin, NSAIDs, or both at the time of stool specimen collection, and 58 (30%) were nonusers. Regular aspirin or NSAID users tended to be older (mean age, 67 ± 10 years vs. 64 ± 11 years, $P = 0.04$) and have coronary artery disease (41% vs. 14%, $P = 0.0003$) than nonusers. There were no other significant differences in demographic characteristics or in the number and type of comorbid conditions between users and nonusers ($P > 0.05$).

Primary and Secondary Outcomes

Twenty-nine (21%; 95% confidence interval [CI]: 14% to 28%) of the 135 regular aspirin or NSAID users had colonic findings that could explain the positive fecal occult blood test result as compared with 11 (19%; 95% CI: 9% to 29%) of the 58 patients using neither agent regularly (absolute difference, 2%; 95% CI: -10% to 14%; $P = 0.7$). Among regular aspirin users, there was no relation between the dose of aspirin and the likelihood of colonic findings unlikely to explain a positive hemoccult test result (Figure). In analyses that adjusted for age, body mass

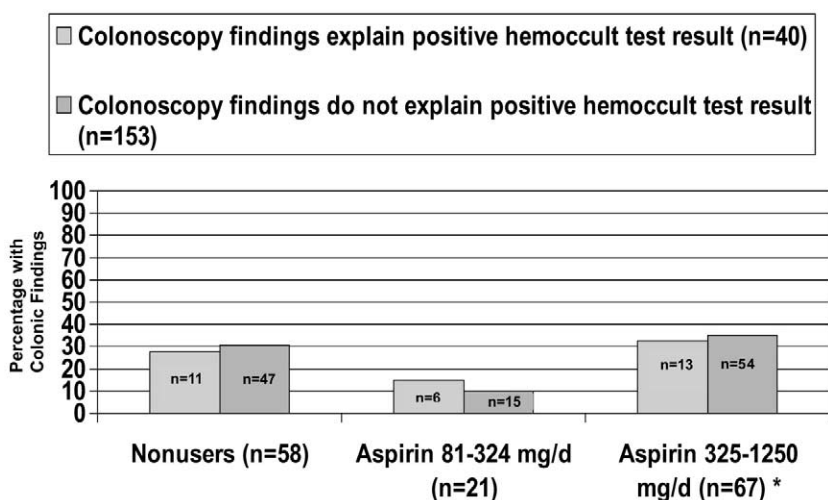


Figure. Percentage of patients with colonic findings that do or do not explain a positive hemoccult test result, by user status and daily aspirin dose. *The 325- to 649-mg/d and 650- to 1250-mg/d categories were combined owing to the small number of patients in the highest category (n = 3). $P = 0.6$ (chi-squared test for trend).

index, family history of colorectal cancer, and use of a proton pump inhibitor or histamine-2 receptor antagonist, there was no association between regular aspirin or NSAID use and colonic findings unlikely to explain a positive test result (odds ratio = 0.85; 95% CI: 0.39 to 1.84).

“Worst-Case Scenario” Analysis

Of the 114 patients who were interviewed, 80 (70%) reported regular aspirin or NSAID use; this was confirmed by the medical record in 57 (70%). Among the remaining 79 patients who were not interviewed, 44 (56%) were found to be regular aspirin or NSAID users by medical record. The remaining 35 patients were considered nonusers for the primary analysis, since 101 (75%) of the 135 aspirin or NSAID users were detected by medical record. However, the absence of an interview limited detection of over-the-counter use of aspirin and NSAIDs in this group. A “worst-case scenario” analysis was performed to test whether this uncertainty would affect the main findings. Assuming that all 35 patients were regular aspirin or NSAID users, there would have been 170 regular users and 23 nonusers. Among these 35 patients, 5 had colonic findings that could explain a positive hemoccult test result. Reassigning these 5 patients (the worst-case scenario) would lead to 34 (20%) of 170 regular users having colonoscopic findings explaining a positive test result, compared with 6 (26%) of 23 nonusers (absolute difference, 6%; 95% CI: -25% to 13%; $P = 0.6$).

DISCUSSION

Screening for colorectal cancer by testing for fecal occult blood entails many decisions about the techniques for collection and processing, including identifying persons who should be screened, the type of test to be used, the frequency of screening, whether to rehydrate samples during slide development, and dietary and medication restrictions during the collection process (11,12). Each decision, although seemingly mundane, can substantially affect the benefit of and effort involved in the screening process (11). The extent to which false-positive and false-negative test results occur in clinical practice is not known, but the effects on the benefit, cost, and effort of screening may be substantial. Previous studies addressing whether aspirin and NSAIDs cause false-positive fecal occult test results have had several limitations. In one randomized crossover study of 68 healthy volunteers (median age, 40 years), aspirin (975 mg administered three times daily) increased fecal hemoglobin levels to 2.0 mg/g stool (the presumed upper limit of normal) in all subjects (8). However, the study sample was relatively young and healthy, and the dose used was higher than that recommended for primary and secondary prophylaxis.

One of the best data on the effects of aspirin and NSAIDs on fecal occult test results come from a prospec-

tive crossover trial conducted by Greenberg and colleagues (9). In that study, fecal occult blood loss was measured in 100 adults aged 40 years or older. Twelve patients had positive results by Hemoccult II testing while ingesting aspirin. Of 17 patients with a positive result by either HemoQuant (Mayo Medical Laboratories, Rochester, Minnesota) or Hemoccult II testing, only 7 (41%) underwent full colonoscopy and no lesions were found, leading the authors to conclude that aspirin did not cause false-positive test results. One limitation of that study was that not all subjects with a positive test result had colonoscopy to exclude a colonic source of occult bleeding; hence, it is not clear whether aspirin ingestion affects the risk of a false-positive test result (13).

Our study systematically correlated colonoscopic findings with intake of aspirin and NSAIDs at the time of specimen collection for occult blood testing. The results have relevance and generalizability to clinical practice, as the study involved persons who take aspirin for primary or secondary prophylaxis of cardiovascular or cerebrovascular disease and who use NSAIDs for arthritis and other chronic conditions. We found no difference in the prevalence of colonoscopic findings that would potentially explain a positive fecal occult blood test result between regular aspirin or NSAID users and nonusers, even after adjusting for factors that affect the risk of a lesion that would account for a positive result (e.g., advanced colorectal neoplasia, peptic ulcer disease, esophagitis). These factors included age, body mass index, family history of colorectal cancer, and use of proton pump inhibitors or histamine-2 receptor antagonists. The dose of aspirin did not affect the likelihood of a colonoscopy with findings that would not explain a positive test result.

Our study has several limitations. First, we defined colonoscopic findings that would explain a positive test result based on literature review and consensus that contained little high-quality evidence. However, the tests were primarily developed for the detection of advanced neoplasia (cancer, large polyps, or polyps with villous histology), and bleeding from diverticular disease and hemorrhoids is more likely to manifest as hematochezia that patients would see with the naked eye and report with careful questioning, as opposed to an isolated positive test result. Such lesions were considered to be unlikely to explain a positive fecal occult blood test result alone. Second, patients with a history of unevaluated dyspepsia requiring medications for symptomatic relief were excluded. Such patients are at increased risk of an upper gastrointestinal tract lesion, evaluation for which should ideally include an upper endoscopy in addition to a colonoscopy for investigation of a positive fecal occult blood test result (12). Third, we administered questionnaires primarily to identify patients taking over-the-counter aspirin or

NSAIDs without knowledge of their physicians. As we were able to contact only 59% of subjects before their colonoscopy, we may have underestimated the true prevalence of regular aspirin or NSAID use. However, 75% of aspirin and NSAID use was detected by reviewing the medical record. Furthermore, assuming that patients in whom over-the-counter use could not be excluded were all regular users did not affect the results. Fourth, nearly all of the patients were men. However, there are no reasons to believe that the rate of false-positive test results is different in women older than 50 years who take aspirin or other NSAIDs regularly. Fifth, although the study was adequately powered for the primary outcome, it is possible that the small sample size in the subgroup analysis precluded the detection of a dose-response relation between aspirin dose and the risk of a false-positive test result (type II error). The consistency of the proportions for lesions that would and would not explain a positive test result in the three aspirin dose ranges mitigates this possibility to some extent. Sixth, the assay used was the Hemoccult II test; whether the results would apply to other fecal occult tests, particularly immunochemical tests, is not known. Finally, most patients had no colonic findings that explained a positive hemoccult test result. Part of the explanation may be that most patients were not instructed, or did not recall being instructed, on proper dietary restrictions at the time of sample collection. Although our study was not specifically designed to address cost-effectiveness, the number of procedures that may have been done for an improperly collected fecal occult blood specimen may have been substantial.

In conclusion, aspirin and NSAID use were not risk factors for a false-positive fecal occult blood test result in this study. Our findings suggest that these medications need not be restricted at the time of specimen collection for fecal occult blood testing.

ACKNOWLEDGMENT

We thank Beverly Musick, MS, and Addie Mitchell for data management, and Faouzi Azzouz, MS, for statistical analysis.

REFERENCES

1. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med.* 2000;343:1603–1607.
2. Scholefield JH, Moss S, Sufi F, et al. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut.* 2002;50:840–844.
3. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med.* 1993;328:1365–1371.
4. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult blood test. *Lancet.* 1996; 348:1467–1471.
5. Jorgensen OD, Kronborg O, Fenger C. A randomized study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut.* 2002;50:29–32.
6. Van Dam J, Bond JH, Sivak MV Jr. Fecal occult blood screening for colorectal cancer. *Arch Intern Med.* 1995;155:2389–2402.
7. Savon JJ, Allen ML, DiMarino AJ Jr, et al. Gastrointestinal blood loss with low dose (325 mg) plain and enteric-coated aspirin administration. *Am J Gastroenterol.* 1995;90:581–585.
8. Fleming JL, Ahlquist DA, McGill DB, et al. Influence of aspirin and ethanol on fecal blood levels as determined by using the HemoQuant assay. *Mayo Clin Proc.* 1987;62:159–163.
9. Greenberg PD, Cello JP, Rockey DC. Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. *Am J Med.* 1996;100:598–604.
10. American College of Physicians. Suggested technique for fecal occult blood testing and interpretation in colorectal cancer screening. *Ann Intern Med.* 1997;126:808–810.
11. Ransohoff DF, Lang CA. Screening for colorectal cancer with the fecal occult blood test: a background paper. American College of Physicians. *Ann Intern Med.* 1997;126:811–822.
12. Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med.* 1999; 341:38–46.
13. Marks RD. Aspirin use and fecal occult blood testing. *Am J Med.* 1996;100:596–597.