Low-Dose Aspirin Use and Performance of Immunochemical Fecal Occult Blood Tests

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Context Immunochemical fecal occult blood tests (iFOBTs) are potentially promising tools for colorectal cancer screening. Low-dose aspirin use, which increases the likelihood of gastrointestinal bleeding, is common in the target population for colorectal cancer screening.

Objective To assess the association of low-dose aspirin use with the performance of 2 quantitative iFOBTs in a large sample of patients undergoing colorectal cancer screening.

Design, Setting, and Participants Diagnostic study conducted from 2005 through 2009 at internal medicine and gastroenterology practices in southern Germany including 1979 patients (mean age, 62.1 years): 233 regular users of low-dose aspirin (167 men, 67 women) and 1746 who never used low-dose aspirin (809 men, 937 women).

Main Outcome Measures Sensitivity, specificity, positive and negative predictive values, and area under receiver operating characteristic (ROC) curves in detecting advanced colorectal neoplasms (colorectal cancer or advanced adenoma) with 2 quantitative iFOBTs.

Results Advanced neoplasms were found in 24 users (10.3%) and 181 nonusers (10.4%) of low-dose aspirin. At the cut point recommended by the manufacturer, sensitivities of the 2 tests were 70.8% (95% confidence interval [CI], 48.9%-87.4%) for users compared with 35.9% (95% CI, 28.9%-43.4%) for nonusers and 58.3% (95% CI, 36.6%-77.9%) for users compared with 32.0% (95% CI, 25.3%-39.4%) for nonusers (P=.001 and P=.01, respectively). Specificities were 85.7% (95% CI, 80.2%-90.1%) for users compared with 89.2% (95% CI, 87.6%-90.7%) for nonusers and 85.7% (95% CI, 80.2%-90.1%) for users compared with 91.1% (95% CI, 89.5%-92.4%) for nonusers (P=.13 and P=.01, respectively). The areas under the ROC curve were 0.79 (95% CI, 0.68-0.90) for users compared with 0.67 (95% CI, 0.62-0.71) for nonusers and 0.73 (95% CI, 0.62-0.85) for users compared with 0.65 (95% CI, 0.61-0.69) for nonusers (P=.05 and P=.17, respectively). Among men, who composed the majority of low-dose aspirin users, the areas under the ROC curve were 0.87 (95% CI, 0.76-0.98) for users compared with 0.68 (95% CI, 0.63-0.74) for nonusers and 0.81 (95% CI, 0.68-0.93) for users compared with 0.67 (95% CI, 0.61-0.72) for nonusers (P=.003 and P=.04, respectively).

Conclusion For 2 iFOBTs, use of low-dose aspirin compared with no aspirin was associated with a markedly higher sensitivity for detecting advanced colorectal neoplasms, with only a slightly lower specificity.

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performance of 2 quantitative iFOBTs in a large sample of women and men from the target population for CRC screening.

METHODS
Study Design and Population
Our analysis is based on updated data from the ongoing BLITZ study (Begleitender Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung), whose design has been described in detail in previous publications based on partly overlapping study populations and addressing different study questions.12-15 Briefly, participants of the German screening colonoscopy program are recruited in 20 gastroenterology practices in southern Germany and invited to provide blood and stool samples for the evaluation of novel CRC screening tests. Patients are informed about the study at a preparatory visit, typically about 1 week prior to colonoscopy. Patients willing to participate are given stool collection instructions and devices, including a small container (60 mL) for collecting a stool sample before bowel preparation for colonoscopy. Stool from 1 bowel movement is to be collected. No specific recommendations are given for dietary or medical restrictions. Participants are asked to keep the stool-filled container in a provided plastic bag in the freezer if possible or in the refrigerator otherwise.

Figure 1. Flow Diagram

**Other colorectal neoplasm** refers to nonadvanced adenomas (ie, neoplasm other than cancer or advanced adenoma). ELISA indicates enzyme-linked immunosorbent assay; FOBT, fecal occult blood test.
sure screening conditions and to minimize potential colonoscopy due to imperfect colonoscopy: visible rectal bleeding or previous positive FOBT result, history of inflammatory bowel disease, colonoscopy in the past 5 years, incomplete colonoscopy, and inadequate bowel preparation for colonoscopy. In addition, the following exclusions were made to minimize potential misclassification of findings at colonoscopy or of use of low-dose aspirin: participants with pseudopolyps or histologically undefined polyps at screening colonoscopy and participants reporting to use low-dose aspirin occasionally or regularly but not currently. Finally, we excluded participants who reported regular use of analgesics in order to prevent interference from effects of analgesic doses of aspirin or other NSAIDs, whose use may differ between users and nonusers of low-dose aspirin.

**Laboratory Analyses**

The stool samples were thawed within a median 4 days after arrival at the central laboratory. Fecal occult blood levels were measured by 2 automated, enzyme-linked immunosorbent assay (ELISA)–based iFOBTs according to the manufacturer’s instructions (RIDASCREEN Haemoglobin, and RIDASCREEN Haemo-/Haptoglobin Complex; r-biopharm, Bensheim, Germany) following the same procedures as in clinical use. The lower detection limit and the cut point for test positivity given by the manufacturer are 0.42 µg and 2 µg per g of stool, respectively. The tests were performed by technicians who were blind to the results of colonoscopy.

**Statistical Analyses**

Characteristics of the study population and findings at screening colonoscopy, which served as diagnostic reference standard, were described according to use of low-dose aspirin. Analyses of sensitivity; specificity; positive and negative predictive values; and likelihood ratios for detecting any colorectal neoplasm (cancer or adenoma), any advanced neoplasm (cancer or advanced adenoma), defined as adenoma with at least 1 of the following features: 1 cm or more in size, tubulovillous or villous components, or high-grade dysplasia), or any advanced neoplasm 1 cm or more in diameter were first calculated according to use of low-dose aspirin at the cut point given by the manufacturer (2 µg/g of stool). Differences in indicators of test performance between users and nonusers of low-dose aspirin were tested for statistical significance by 2-sided tests at an α level of .05. We did not adjust for multiple testing.

Additional analyses of sensitivity and specificity for detecting advanced neoplasms were carried out at various cut points for test positivity (ranging from 1 to 8 µg/g of stool) and graphically displayed by use of low-dose aspirin. This range of cut points includes the cut point given by the manufacturer (2 µg/g) as well as cut points yielding specificities well above 90%; ie, levels that are commonly considered a prerequisite for population-based screening. Furthermore, receiver operating characteristic (ROC) curves, displaying sensitivity along with the false-positive rate (1–specificity) for detecting advanced neoplasms at various cut points were constructed by use of low-dose aspirin, and the area under the curve with 95% confidence intervals (CIs) was calculated as an indicator of test performance in the groups compared.

To account for possible sex differences in test performance, which were strongly suggested by previous analyses, we carried out additional sex-specific analyses of test performance by use of low-dose aspirin. However, given that almost 3 of 4 users of low-dose aspirin were men, and the numbers of women using low-dose aspirin were too small to estimate group-specific test performance with reasonable precision, results are shown for men only. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

**RESULTS**

Overall, 3077 participants in screening colonoscopy were recruited between 2005 and December 2009. After we applied the exclusion criteria outlined in the “Methods” section (Figure 1), 1979 participants were...
Table 2. Performance of the Quantitative Fecal Hemoglobin Test and Hemoglobin-Haptoglobin Test for Detecting Colorectal Neoplasms According to the Use of Low-Dose Aspirin in the Entire Study Population and in Men*  

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcome</th>
<th>Low-Dose Aspirin</th>
<th>Hemoglobin Test</th>
<th>Hemoglobin-Haptoglobin Test</th>
<th>P Value</th>
<th>Low-Dose Aspirin</th>
<th>Hemoglobin Test</th>
<th>Hemoglobin-Haptoglobin Test</th>
<th>P Value</th>
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<td></td>
<td>All Participants</td>
<td>+15.4</td>
<td>.003</td>
<td>+14.6</td>
<td>.003</td>
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<tr>
<td>Sensitivity</td>
<td>Any neoplasm</td>
<td>31/81 (38.3)</td>
<td>121/529 (22.9)</td>
<td>27/81 (33.3)</td>
<td>99/529 (18.7)</td>
<td>14.6</td>
<td>.003</td>
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<tr>
<td></td>
<td>95% CI</td>
<td>27.7-49.7</td>
<td>19.4-26.7</td>
<td>23.2-44.7</td>
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<td>Advanced neoplasm</td>
<td>+34.9</td>
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<td>No./total No. (%)</td>
<td>17/24 (70.8)</td>
<td>65/181 (35.9)</td>
<td>14/24 (58.3)</td>
<td>58/181 (32.0)</td>
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<td>.003</td>
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<td>53/120 (44.2)</td>
<td>12/19 (63.2)</td>
<td>48/120 (40.0)</td>
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<td>Specificity</td>
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<td>No./total No. (%)</td>
<td>179/209 (85.7)</td>
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<td>PPV</td>
<td>Advanced neoplasm</td>
<td>+8.4</td>
<td>.25</td>
<td>+2.5</td>
<td>.74</td>
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<td>No./total No. (%)</td>
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<td>65/234 (27.8)</td>
<td>14/44 (31.9)</td>
<td>58/198 (29.3)</td>
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<td>27.9-48.3</td>
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<td>LR+</td>
<td>Advanced neoplasm</td>
<td>4.94</td>
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<td>4.06</td>
<td>3.69</td>
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<tr>
<td></td>
<td>LR−</td>
<td>Advanced neoplasm</td>
<td>0.34</td>
<td>0.72</td>
<td>0.49</td>
<td>0.75</td>
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<td></td>
<td>PE</td>
<td>0.18-0.57</td>
<td>0.29-0.71</td>
<td>0.19-0.71</td>
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<tr>
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<td>95% CI</td>
<td>0.29-0.71</td>
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Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PE, point estimate; PPV, positive predictive value.

*Results for the cut point recommended by the manufacturer (2 µg/g of stool).

**Difference in percentage points between users and nonusers of low-dose aspirin.

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included in this analysis. Among these, 233 (12%) were current regular users of low-dose aspirin and 1746 had never used low-dose aspirin.

TABLE 1 lists characteristics of the study population according to use of low-dose aspirin. Users of low-dose aspirin were on average older than nonusers (mean age, 65.4 vs 61.7 years; \( P < .001 \)). The majority of low-dose aspirin users (167/233, 72%) were men compared with 46% of nonusers. Despite higher age and higher proportion of men among low-dose aspirin users, prevalence of neoplasms was similar in both groups.

Performance of the quantitative tests when using the cut point recommended by the manufacturer (2 \( \mu \)g/g of stool) is shown for users and nonusers of low-dose aspirin in TABLE 2. Sensitivity of both tests for detecting any neoplasm was substantially higher among users than among nonusers (\( P = .003 \) for both tests). Differences were even larger for advanced neoplasms, especially for the hemoglobin test, with sensitivity of 70.8% among users compared with 35.9% among nonusers (\( P = .001 \)). Specificity with respect to detection of advanced neoplasms was slightly lower among users than among nonusers, the difference being statistically significant for the hemoglobin-haptoglobin test only (\( P = .01 \)). Both positive and negative predictive values were higher among users than among nonusers, but differences between both groups were not statistically significant. In sex-specific analyses for men, advantages in sensitivity for users of low-dose aspirin were even more pronounced, with differences of up to 46.4 percentage points for advanced neoplasms for the hemoglobin test. Sensitivity of this test for detecting large neoplasms exceeded 90% among users of low-dose aspirin. Furthermore, clear advantages in negative predictive values were seen among men using low-dose aspirin compared with men not using low-dose aspirin.

As shown in FIGURE 2, the major advantage in sensitivity among users of low-dose aspirin compared with nonusers in detecting advanced neoplasms was observed for both iFOBTs across a wide range of relevant cut points. With the exception of very high cut points, sensitivity was consistently higher by approximately 30 percentage points among users than among nonusers of low-dose aspirin, whereas specificity was up to approximately 5 percentage points lower. As expected, sensitivity decreased, and specificity increased with increasing cut points. Among men, increases in sensitivity for users of aspirin were more pronounced across a range of cut points up to 6 \( \mu \)g per gram of stool for the hemoglobin test, and differences in specificity of the hemoglobin test between users and nonusers of low-dose aspirin were generally small.

ROC curves for detecting advanced neoplasms are shown for both iFOBTs in FIGURE 3. Apart from very high cut points yielding very high levels of specificity, test performance was substantially better among low-dose aspirin users than among nonusers. The areas under the ROC curve according to low-dose aspirin use were as follows: for all participants, hemoglobin test, 0.79 (95% CI, 0.68-0.90) for users and 0.67 (95% CI, 0.62-0.71) for nonusers (\( P = .05 \) for difference), hemoglobin-haptoglobin test, 0.73 (95% CI, 0.62-0.85) for users and 0.65 (95% CI, 0.61-0.69) for nonusers (\( P = .17 \) for difference); for men, hemoglobin test, 0.87 (95% CI, 0.76-0.98) for users and 0.68 (95% CI, 0.63-0.74) for nonusers (\( P = .003 \) for difference), hemoglobin-haptoglobin test, 0.81 (95% CI, 0.68-0.93) for users and 0.67 (95% CI, 0.61-0.72) for nonusers (\( P = .04 \)), respectively.

**COMMENT**

We provide a detailed comparison of the diagnostic performance of 2 quantitative iFOBTs among users and nonusers of low-dose aspirin in the target population for CRC screening. For both tests, sensitivity was markedly higher, while specificity was slightly lower...
among users of low-dose aspirin compared with nonusers. These patterns were consistent across a broad range of relevant cut points for test positivity. ROC analyses revealed sensitivity to be mostly much higher at comparable levels of specificity, with substantially larger areas under the curve among users of low-dose aspirin.

Previous work regarding the potential association of low-dose aspirin use and performance of FOBTs has mainly focused on concerns about hampered specificity due to increased risk of bleeding from insignificant colonic lesions or from upper gastrointestinal blood loss. In a recent study among patients who underwent colonoscopy because of positive results from guaiac-based FOBTs in a US Veterans Affairs medical center, the positive predictive value for detecting advanced colorectal neoplasms was significantly lower for users of low-dose aspirin than for controls, prompting the investigators to request that this medication be stopped prior to stool collection. Increased rates of positive results from guaiac-based FOBTs among aspirin users had previously been reported in several small studies, but given the lack of colonoscopy control, it was unclear to what extent these findings reflected enhanced sensitivity for detecting colorectal neoplasms or higher false-positive rates. In another study from a Veterans Affairs hospital investigating a guaiac-based FOBT, aspirin and NSAID use were not risk factors for false-positive test results.

From a theoretical point of view, the effect of low-dose aspirin use on the positivity rate of FOBTs is expected to be different for guaiac-based and immunochemical tests. While guaiac-based tests react to the pseudoperoxidase activity of the heme moiety of hemoglobin, which is relatively stable in the gastrointestinal tract, the immunochemical tests react to globin, which is degraded through proteases during its passage through the gastrointestinal tract. A study from Japan showed iFOBT to be inadequate as means for detecting upper digestive tract diseases. To our knowledge, only 1 recent study has assessed the association of aspirin use and performance of a quantitative iFOBT for detecting colorectal neoplasms. In this study from Israel evaluating the performance of an iFOBT with the OC-MICRO automated instrument (Eiken Chemical, Tokyo, Japan) among 1221 ambulatory patients undergoing colonoscopy for various reasons, sensitivity for detecting advanced neoplasms was tentatively increased by 15 to 20 percentage points, and specificity was not affected among users of aspirin or NSAIDs. The results for the iFOBTs used in our study, which was conducted in a screening setting and specifically focused on low-dose aspirin, are in line with and extend these findings and support conclusions that there is no need to stop low-dose aspirin use prior to undergoing iFOBT.

On the contrary, our results may even raise the provocative suggestion of whether temporary use of low-dose aspirin might be considered to enhance performance of iFOBTs.
our study and the study by Levi et al, \(^\text{10}\) sensitivity for detecting advanced neoplasms of 60% to 70% might be achieved at a specificity of approximately 90% with the use of low-dose aspirin. These levels of sensitivity exceed those observed for other established stool or blood tests and might come close to the sensitivity of sigmoidoscopy, keeping in mind that the latter detects neoplasms in the distal colon only. \(^\text{22,23}\) Of course, potential benefits in test performance would have to be weighed against potential adverse effects (in particular, increased risk of upper gastrointestinal bleeding) and any adverse impact on adherence and costs. However, costs of low-dose aspirin are very low. Likewise, adverse effects of short-term use of low-dose aspirin would be expected to be low and would probably be outweighed by benefits in terms of cardiovascular protection. \(^\text{56}\) In particular, risk of severe complications would appear to be low when compared with possible complications from endoscopic screening. \(^\text{26,27}\) Furthermore, for levels of sensitivity that were observed among users of low-dose aspirin with respect to advanced colorectal neoplasms, it might be an option to extend screening intervals from 1 year to several years, assuming that missed advanced neoplasms would be expected to be predominantly small \(^\text{28}\) and their progression to CRC would often take many years. \(^\text{27}\) Although recommending use of low-dose aspirin in CRC screening with iFOBTs would certainly be premature at this point, our results should encourage further research to this end, ideally including randomized intervention studies to assess benefits and possible harms at the highest possible level of evidence.

A number of specific strengths and limitations of our study deserve careful discussion. Strengths include the prospective design, large overall sample size, and conduction among the target population for screening. Furthermore, colonoscopy was performed and available to serve as the reference standard for all participants. Despite the overall large sample size, the number of participants with advanced neoplasms was limited, especially in the relatively small group of users of low-dose aspirin, leading to broad CIs around some of the estimates of test performance.

Information on use of low-dose aspirin was based on self-reports, which may be inaccurate. \(^\text{28}\) However, our questionnaire specifically queried low-dose aspirin use and was completed by study participants mostly at their homes, and the high proportion of exact specification of the drug and corresponding dose makes us confident that data on its use were accurate (even though there is potential for misclassification due to low adherence in drug intake). As an additional precaution, we excluded from the analysis participants for whom current regular use of low-dose aspirin was uncertain.

Use of low-dose aspirin is known to be related to a number of factors that by themselves might affect test performance, such as sex and age. \(^\text{15}\) Nevertheless, differences in test performance according to use of low-dose aspirin were even stronger among men, who composed the majority of low-dose aspirin users in our study. However, the small numbers of neoplasms in the low-dose aspirin group prohibited meaningful analyses for other subgroups, such as women, certain age groups, or subgroups defined by other risk factors (eg, family history, obesity, and smoking) as well as more comprehensive control for potential confounding by multivariate analyses.

Even though colonoscopy is the most reliable method available to date for assessing presence of colorectal neoplasms, it is not perfect, \(^\text{26}\) and missed adenomas at colonoscopy might have led to some overestimation of false-positive rates of the FOBTs, despite the high levels of training and quality control established in the German screening colonoscopy program. Data were collected from multiple endoscopists and histopathological laboratories in our study, leaving more room for heterogeneity in ratings than in a single-center study.

Despite its limitations, our study strongly suggests that use of low-dose aspirin does not hamper testing for fecal occult blood by immunochemical tests. On the contrary, our findings raise the hypothesis that test performance may be enhanced by temporary use of low-dose aspirin, a hypothesis that needs replication in larger samples and followed up in further research, ideally including randomized trials and different types of FOBTs.

**Author Contributions:** Dr Brenner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brenner, Haug. Acquisition of data: Brenner, Tao. Analysis and interpretation of data: Brenner. Drafting of the manuscript: Brenner. Critical revision of the manuscript for important intellectual content: Tao, Haug. Statistical analysis: Brenner. Obtained funding: Brenner. Administrative, technical, or material support: Haug. Study supervision: Brenner.

**Financial Disclosures:** Dr Brenner reported that the German Cancer Research Center received a grant from Eiken Chemical to evaluate an immunochemical fecal occult blood test (iFOBT) that was not included in this analysis. Dr Brenner also reported that a patent application was filed at the European Patent Office for the combination of low-dose aspirin use and iFOBTs in early detection of colorectal neoplasms. No other disclosures were reported.

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**Role of the Sponsors:** The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

**Additional Contributions:** We gratefully acknowledge the excellent cooperation from physicians conducting screening colonoscopies during patient recruitment (who received compensation of €10 [US $14] per recruited patient). Isabel Lerch and Sabrina Hundt, PhD (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg), assisted with data collection, monitoring, and documentation; they did not receive additional compensation besides salary. Labor Limbach (Heidelberg) assisted with test performance, for which it did not receive compensation.

**REFERENCES**


2. Levin B, Lieberman DA, McFarland B, et al; American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Ra-
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diology Colon Cancer Committee. Screening and surveill-
17. RIDASCREEN Haemoglobin information.

Justice . . . will not be a powerful spring of action unless it extend[s] to the whole creation.

—Mary Wollstonecraft (1759-1797)