Single dose aspirin affects fecal immunohistochemical test sensitivity in detecting advanced colorectal neoplasms: Truth or expectation?

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Colorectal cancer (CRC) accounts for approximately 860,000 global deaths each year (1). A large amount of these deaths could have potentially been prevented by the use of accurate screening strategies. Randomized clinical trials conducted previously on this subject have indicated that screening for CRC using guaiac-based, chemical fecal occult blood tests (FOBTs) is effective in reducing the cancer's incidence and mortality (2-4). However, newer fecal immunochemical tests (FITs) for hemoglobin (Hb) have been found to have better diagnostic accuracy than guaiac-based FOBTs and now being broadly recommended for CRC screening (5).

It has been proven that detecting advanced adenomas in addition to CRCs could make a major contribution to the effectiveness of FIT-based CRC screening (6). Although FITs detect most of (70%-80%) the CRCs with high (>90%) specificity, they are able to identify only a small proportion of advanced adenomas (approximately 20%-30%) (7). Since the sensitivity rates of FITs are low, repeated applications are required to enhance the detection rates of advanced adenomas (6). This repeated FIT testing can result in higher costs, which is why new studies are needed to find alternative methods to improve the sensitivity of the first FIT testing.

Ameliorating the sensitivity without decreasing the specificity could improve the performance of FIT for CRC screening. For this purpose, a recently published article in *JAMA,* entitled "Effect of a single aspirin dose prior to fecal immunochemical testing on test sensitivity for detecting advanced colorectal neoplasms: A randomized clinical trial," hypothesized that the antiplatelet effect of aspirin could improve the test characteristics of FIT by provoking microscopic bleeding from polyps or a malignancy. The researchers performed FIT in 2424 participants, aged between 40-80 years old. Participants who made routine visits to 1 of 18 trial centers in Germany from June 2013 to November 2016 to obtain a precolonoscopy date were included in the study. The researchers administered a single 300-mg oral aspirin dose two days before stool sampling (all fecal samples were collected before the initiation of large bowel preparation for colonoscopy). Excluded individuals were those who had a history of CRC, had overt or FOBT-detected rectal bleeding, or reported the recent use of aspirin, antithrombotic drugs, or other nonsteroidal anti-inflammatory agents. Patients who did not receive the colonoscopy or appropriate drugs, or did not complete the trial, were also excluded. Finally, 2134 participants were randomized to the aspirin group and the placebo group (1075: aspirin group and 1059: placebo group). All the participants underwent a colonoscopy (78% for primary screening and 22% for diagnostic purposes). The primary end-point of this randomized, placebo-controlled, double-blinded study was to determine the sensitivity of a quantitative FIT at two predefined cut-offs (10.2 µg Hb/g and 17 µg Hb/g of stool) for detecting advanced neoplasms. Advanced neoplasms were defined as the presence of either CRC or advanced adenomas that were either was 1 cm or larger in size, had tubulo-villous or villous components, or high-grade dysplasia. Secondary outcomes included additional test characteristics of both the quantitative and qualitative FITs (threshold value: 10.2 mg Hb/g of stool), gender-specific test characteristics of both FITs, and serious adverse events. The majority of participants (93.6%) were between 45-74 years old, with a mean age of 59.6

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years. The proportions of men and women were similar. Advanced neoplasms were identified in 224 participants (10.5%), including 8 participants (0.4%) with CRC and 216 participants (10.1%) with advanced adenomas. Sensitivity was 40.2% in the aspirin group and 30.4% in the placebo group (p=0.14) at a cut-off value 10.2-µg Hb/g stool, and 28.6% in the aspirin and 22.5% in the placebo group (p=0.32) at cut-off value 17-µg Hb/g stool. So, there was no statically significant difference in the sensitivity of FIT at both two predefined cut-offs on detecting advanced neoplasms between the aspirin group and the placebo group. The specificity of the quantitative FIT (10.2-µg Hb/g stool cut-off) was 82.2% in the intervention group and 88.7% in the control group (p<0.001), and 91.7% and 94.8% at cut-off value of 17-µg Hb/g of stool, respectively (p=0.008). Therefore, the specificity of the quantitative FIT was significantly lower in the aspirin group at two predefined cut-offs. In the qualitative test, the sensitivity was significantly higher (by 12.7 percentage points) in the intervention group than it was in the control group (34.7% vs 22.0%, respectively, p=0.048), but the specificity was significantly lower (by 8.0 percentage points) in the intervention group (83.8% vs. 91.8%) than it was in the control group (p<0.001). Further, no significant differences were seen in the PPVs and NPVs. Among the male subgroup, sensitivities were higher but specificities were lower in the intervention group than in the control group. In contrast, among women, the sensitivity was similar, but specificity was lower in the intervention group than in the control group. P-values for the interaction effects between sex and intervention ranged between 0.08-0.49, and all the values were not statistically significant. Two serious adverse events in the aspirin group (acute appendicitis and acute suppurative cholangitis accompanied by acute kidney injury) were detected, but all the participants recovered completely.

FIT plays an important role in the screening of colorectal cancers because of its simplicity and affordability. However, ongoing research is being conducted to enhance the detection rates of FIT because of its low sensitivity (8). Administration of a single dose aspirin prior to FIT, compared with the placebo, did not significantly increase the test sensitivity for detecting advanced colorectal neoplasms at two predefined cut-offs in the quantitative FIT in this study.

An observational study in 2010 by Brenner et al. demonstrated significantly increased sensitivity of 2 other FITs (RIDASCREEN Hemo-/Haptoglobin Complex) in detecting advanced neoplasms in users of low-dose aspirin among men, but not among women. However, this study compared regular daily use of low-dose aspirin with nonuse in a nonrandomized design. Besides, this study evaluated FIT at a much lower hemoglobin threshold of 2 mg Hb/g (9).

The antithrombotic effects of aspirin seem to be stronger in men than in women, and further sex differences in platelet number, function, and responsiveness to aspirin have been reported (10). Also, the longer colonic transit time of feces and higher prevalence of constipation among women might favor intracolonic hemoglobin degradation, especially in the case of bleeding from proximal neoplasms (11). Therefore, adequately powered studies are needed to evaluate potential sex differences and reasons for differential effects of aspirin on FIT sensitivity. Another observational study from Israel also found substantially higher sensitivity of another FIT (OC-Micro) among users of aspirin or nonsteroidal anti-inflammatory drugs (12). Considered together, the results from these observational studies and this trial suggest that further research is needed to assess if low-dose aspirin affects the FIT test performance, perhaps by conducting larger and more well-powered trials.

As shown in this study, aspirin can decrease the specificity of FIT by increasing false-positive results, and can cause anxiety regarding the "probably missed" lesions after a negative colonoscopy. This may, therefore, lead to more surveillance after the incidental detection of nonadvanced adenomas or additional testing for other causes of occult bleeding, such as capsule endoscopy or esophagogastroduodenoscopy (13,14). Thus, future studies are needed to better understand alternate explanations and outcomes of individuals with a false-positive FIT results. Other important questions regarding the aspirin dose, optimal timing of aspirin intake, and fecal sampling may also be answered in future studies. In this study, a 300-mg single dose aspirin was used to achieve an appropriate hemorrhagic effect. Perhaps an equivalent or better effect might be achieved with single or multiple tablets (taken over several days) containing lower doses of aspirin, which should be explored in further researches.

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