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Impact of age- and gender-specific cut-off values for the fecal immunochemical test for hemoglobin in colorectal cancer screening

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ABSTRACT

Background: There is no information on the impact of age and gender on the diagnostic yield of different positivity thresholds for the fecal immunochemical test for hemoglobin (FIT).
Objectives: To evaluate the performance of this test at distinct positivity cut-offs in a population-based colorectal cancer (CRC) screening program.
Methods: CRC detection rate (DR), and analysis of resources were evaluated retrospectively, at different cut-offs of FIT (20, 25, 30, 35 and 40 μg Hb/g) respect to a reference value (15 μg Hb/g), according to age and gender, in a screening population of 10,611 participants of the ColonPrev study (Quintero. NEJM 2013).
Results: At the reference cut-off value, 36 CRC and 252 advanced adenomas (AA) were diagnosed. Increasing the cut-off in women ≤60 years decreases colonoscopies performed by 44.5% without modifying the CRC (DR). Same CRC DR was observed in men ≤60 years and women >60 years increasing cut-off at 25–30 μg Hb/g. In men >60 years, all increases in the cut-off affected the CRC DR, especially when the cut-off was increased from 35 to 40 μg Hb/g (CRC miss rate 25%).
Conclusions: To improve the performance of FIT in CRC screening programs, FIT cut-offs could be individualized by age and gender.

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1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in developed regions [1]. Evidence from several studies has shown that screening is effective and cost-effective for CRC prevention in average-risk populations [2,3]. Standard strategies for CRC screening are fecal occult blood testing, flexible sigmoidoscopy and colonoscopy [4–8].

CRC screening based on the guaiac fecal occult blood test (gFOBT) is effective in reducing CRC mortality [6,7]. The fecal immunochemical test for hemoglobin (FIT) is based on the detection of human hemoglobin by identifying specific antibodies and, therefore, is more specific for lower gastrointestinal bleeding. Previous studies have shown that FIT is superior to other fecal occult blood tests, not only because it has a higher detection rate and is associated with earlier diagnosis of CRC [9–15], but also because it improves attendance and adherence, which are essential factors in any screening program [14]. FIT screening has been reported to be more effective clinically and in terms of cost compared with gFOBT screening [16]. Moreover, compared with the gFOBT, FIT has some advantages, such as automated analysis, ease of performance (only one sample is needed), and the absence of dietary requirements and medication restrictions. Moreover, quantitative FIT allows definition of the cut-off value indicating referral for colonoscopy [17]. The cut-off can be set to a desired sensitivity or specificity, which also raises the possibility of generating a multivariate risk score [18,19].

There is evidence that fecal hemoglobin concentrations are related to the type of bowel lesion [17,20,21], as well as to age and gender [22–25]. These findings indicate a need for more tailored screening strategies [17,23]. Moreover, recent studies have shown that certain subgroups had a higher rate of false positive and negative FIT results. In this sense, false positive results lead to unnecessary colonoscopies and costs [26–28].

The prevalence of CRC and advanced adenomas (AA), or both (i.e. advanced neoplasia [AN]) is associated with male gender and aging [29]. The prevalence of AA and CRC are higher in men than in women (8% vs. 4.3% for AA, 1.4% vs. 0.6% for CRC, respectively) [29]. A study carried out in Austria in 44,350 individuals undergoing screening showed that the prevalence of AA, as well as the number needed to scope (NTS), were similar between men aged 45–49 years and women aged 55–59 years [30]. However, there is no recommendation to adapt positivity thresholds in CRC screening by gender or age group.

In European CRC screening programs, FIT is performed using different cut-off values [31]. The ColonPrev study, a population-based, multicenter, nationwide, randomized controlled trial designed to assess the efficacy of one-time colonoscopy versus biennial FIT in reducing CRC mortality at 10 years, has recently published the interim baseline results [32]. In that study, individuals in the FIT arm were invited to colonoscopy if FIT was ≥75 ng/mL of hemoglobin (Hb) or 15 μg Hb/g faeces [33].

Several studies have evaluated the impact of different positivity cut-off values [34–41] and some have indicated the advisability of using distinct values in men and women [14,25]. However, until now, similar FIT screening regimens have been applied in men and women, despite evident gender differences in the prevalence of neoplasms. To our knowledge, no previous study has assessed the impact of different age-and gender-specific cut-off values. For this purpose, a nested analysis of the ColonPrev data was carried out to evaluate the diagnostic yield of distinct positivity cut-offs (≥20, ≥25, ≥30, ≥35 and ≥40 μg Hb/g faeces in comparison with the ≥15 μg Hb/g faeces, the reference value), depending on age and gender, in a cohort of asymptomatic average-risk individuals.

2. Materials and methods

2.1. Study design

The current analysis was performed within the ColonPrev study, a population-based, multicenter, nationwide, randomized controlled trial designed to compare the efficacy of one-time colonoscopy and biennial FIT in reducing CRC-related mortality (*ClinicalTrials.gov* NCT00906997) [32]. Asymptomatic men and women aged between 50 and 69 years were randomly allocated to receive either colonoscopy or biennial FIT. Individuals were randomized before invitation with the use of a computer-generated allocation algorithm on the basis of a randomized blocks method. Participants were sent a preinvitation letter containing information on CRC screening and the rationale for the study. Two weeks later, an invitation letter was sent indicating each participant's study-group assignment. Persons who agreed to participate in the study received an appointment at the local screening office, where they completed the questionnaire. The study design allowed for crossover between the two study groups. Exclusion criteria included a personal history of CRC, adenoma, or inflammatory bowel disease; a family history of hereditary or familial colorectal cancer; a severe coexisting illness; and previous colectomy. Persons were also temporarily excluded if they had undergone fecal occult blood testing in the previous 2 years, or sigmoidoscopy or colonoscopy within the previous 5 years, or if they had symptoms requiring additional workup. This study was based on 10,611 individuals allocated to the FIT arm (Fig. 1).

2.2. FIT strategy

The FIT strategy consisted of taking a single sample with the automated quantitative OC-sensor^{TM} (Eiken Chemical Co, Tokyo, Japan). Patients with ≥75 ng of Hb per milliliter of buffer solution (or 15 μg Hb/g faeces) were invited for colonoscopy. The quality assurance program for the whole process (i.e. recruitment, FIT measurements and colonoscopy) has been described elsewhere [32].

All colonoscopies were performed by experienced endoscopists (individual experience >200 colonoscopies per year) and the findings were documented in a standardized report form. Adenomas ≥10 mm or with villous architecture, high-grade dysplasia, or intramucosal carcinoma (pTis) were classified as AA. Invasive cancer was defined as the presence of malignant cells beyond the muscularis mucosa. AN was defined as advanced adenoma or invasive cancer. Patients were classified according to the most advanced adenoma observed. The location of the neoplasm was established with respect to the splenic flexure. The proximal colon was defined as the cecum, ascending colon, and transverse colon (including the splenic flexure).

2.3. Data analysis

The positivity rate (PR) was defined as the proportion of positive FIT tests among participants who returned samples. The detection rate (DR) was calculated as the number of CRC or AA detected per 100 individuals screened. The number needed to screen (NNS) was calculated as the number of FIT required to detect one case of CRC or AA. The NTS was calculated as the number of colonoscopies needed to find one case of AA or CRC. The positive predictive value (PPV) was defined as the number of individuals positive for CRC or AA relative to the total number of positive individuals who underwent colonoscopy. The PR, DR, PPV were calculated and described as percentages with 95% confidence intervals (95% confidence interval [CI]).

The miss rate was defined as the proportion of CRC or AA missed relative to the number of CRC or AA detected with the