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Prescription drugs associated with false-positive results when using faecal immunochemical tests for colorectal cancer screening

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ABSTRACT

Background: The most common side effect in population screening programmes is a false-positive result which leads to unnecessary risks and costs.
Aims: To identify factors associated with false-positive results in a colorectal cancer screening programme with the faecal immunochemical test (FIT).
Methods: Cross-sectional study of 472 participants with a positive FIT who underwent colonoscopy for confirmation of diagnosis between 2013 and 2014. A false-positive result was defined as having a positive FIT (≥20 μg haemoglobin per gram of faeces) and follow-up colonoscopy without intermediate/high-risk lesions or cancer.
Results: Women showed a two-fold increased likelihood of a false-positive result compared with men (adjusted OR, 2.3; 95%CI, 1.5–3.4), but no female-specific factor was identified. The other variables associated with a false-positive result were successive screening (adjusted OR, 1.5; 95%CI, 1.0–2.2), anal disorders (adjusted OR, 3.1; 95%CI, 2.1–4.5) and the use of proton pump inhibitors (adjusted OR, 1.8; 95%CI, 1.1–2.9). Successive screening and proton pump inhibitor use were associated with FP in men. None of the other drugs were related to a false-positive FIT.
Conclusion: Concurrent use of proton pump inhibitors at the time of FIT might increase the likelihood of a false-positive result. Further investigation is needed to determine whether discontinuing them could decrease the false-positive rate.

1. Introduction

Early detection can play an important role in reducing colorectal cancer (CRC) mortality. In fact, compelling and consistent evidence from randomised controlled trials and observational studies shows that appropriate use of faecal occult blood testing, flexible sigmoidoscopy and screening colonoscopy can reduce mortality from CRC [1–3]. Faecal occult blood testing has traditionally been implemented in most developed countries as the preferable method for CRC screening, but more recently the guaiac faecal occult blood test has been substituted with the faecal immunochemical test (FIT) because of its higher sensitivity and specificity, better patient adherence, and lack of need for dietary restriction before testing. However, the FIT also has potential downsides. The most common adverse effect is the high rate of false-positive (FP) results that can lead to unnecessary colonoscopies, thus increasing extra healthcare costs and avoidable patient risk.

There are few published studies that have analysed the factors associated with FP results in faecal occult blood testing for CRC [4,5]. Our group reported the FP results from CRC screening in Catalonia (Spain) between 2000 and 2010 for the guaiac faecal occult blood test [6]. At that time, we found a FP rate of 55.2%, with female

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sex, first screening round of the programme, successive screening and diagnosis of haemorrhoids or anal fissure to be significantly associated with a FP result.

Our previous research emphasised the need to determine whether women have more FP results because of an inherently lower pre-test probability of developing CRC or because they have gender-specific risk factors (differential prescription drugs). Regardless of gender, it would also be interesting to explore other factors associated with FP results. For instance, drugs with potential haemorrhagic risk may increase the FP rate, and some studies have already shown that antiplatelet agents (APAs) [7–9], oral anticoagulants (OACs) [8–11] and/or non-steroidal anti-inflammatory drugs (NSAIDs) [5] can affect FIT results. Therefore, other drugs associated with gastrointestinal bleeding, such as selective serotonin reuptake inhibitors (SSRIs) which affect platelet aggregation [12] and proton pump inhibitors (PPIs) which may cause haemorrhage in the lower gastrointestinal tract [13–17], could affect the FP rate. In this study, we aimed to identify factors associated with FP results in a FIT-based CRC screening programme, with special attention given to prescription drugs.

2. Methods

2.1. Screening procedure

Briefly, in 2000, a biennial screening programme was launched by the Catalan Institute of Oncology. Since 2010, the OC-Sensor (Eiken Chemical Co., Japan), with a cut-off of faecal haemoglobin (Hb) of ≥20 μg Hb/g faeces (≥100 ng Hb/mL buffer), has been used in this programme. A detailed description of the FIT performance is provided elsewhere [18,19]. Diagnostic colonoscopies after a positive FIT result were performed by experienced endoscopists, with patients under conscious sedation. The target population (n = 77,150) included all men and women aged 50–69 years from l'Hospitalet de Llobregat and Vilafranca del Penedès (Barcelona, Catalonia, Spain).

The participation rate in the most recent screening round was 40.6%. Subjects were excluded according to the following criteria: gastrointestinal symptoms, personal history of CRC, family history of CRC, prior adenomas, inflammatory bowel disease, criteria for hereditary CRC syndromes, colonoscopy within the previous five years or faecal occult haemoglobin test within the last two years, terminal disease and severe disabling conditions.

2.2. Study subjects

We included participants with a positive FIT result who underwent total colonoscopy between January 2014 and July 2014 and who answered a phone questionnaire administered by a nurse or a medical doctor (n = 472). A FP result was defined as a positive FIT result (≥20 μg Hb/g) followed by a colonoscopy result without either intermediate/high-risk lesions or CRC. According to "European guidelines for quality assurance in CRC" [20], intermediate-risk lesions were defined as 3–4 tubular adenomas measuring <10 mm with low-grade dysplasia or as ≥1 adenoma measuring 10–19 mm, while high-risk lesions were defined as ≥5 adenomas or ≥1 adenoma measuring ≥20 mm. All the participants with a FP result were followed until April 2016 to identify if a follow-up colonoscopy, upper gastrointestinal endoscopy or capsule endoscopy explained the FP result by FIT. The study protocol was approved by the ethics committee of our institution (PR138/12), and we obtained oral informed consent before the phone interview.

2.3. Data collection

The CRC screening programme information system allowed recording: sex, age (divided into 50–59 years and 60–69 years), blood Hb concentration and screening variables (number of individual participations, faecal Hb concentration and colonoscopy findings). Anaemia was defined according to WHO recommendations (men Hb < 130 g/L; women Hb < 120 g/L) [21], and the Hb concentrations were obtained from the routine blood analyses carried before the colonoscopy.

Level of education (less than primary education; at least secondary education) and clinical data (age at menopause, gastrointestinal diseases associated with bleeding (haemorrhoids, anal fissures, peptic ulcers, hiatus hernias and oesophageal varices) were gathered through a retrospective questionnaire. Information about the prescribed medication was self-reported in the questionnaire and extracted from the computerised Catalan healthcare database (SAP, Institut Català de la Salut). We analysed prescription information for the following drugs: PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole), NSAIDs (all cyclooxygenase 1 and 2 inhibitors), APAs (acetylsalicylic acid, triflusal, clopidogrel, prasugrel, ticagrelor, ticlopidine and cilostazol), OACs (acenocoumarol, warfarin, dabigatran, apixaban and rivaroxaban) and SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline).

2.4. Data analysis

Multivariate logistic regression models were performed to identify variables associated with the FP results. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated. We also computed models stratified by sex and examined interactions between the different covariates. Statistical analysis was carried out using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Participant characteristics

The overall proportion of FP results was 53.8% (n = 254), although this figure would have decreased to 37.7% (n = 178) had low-risk adenomas been included in the definition of a positive colonoscopy. Table 1 summarises the sociodemographic, screening and clinical characteristics of the participants. It was notable that there were more male participants in our study, because men had more positive results by FIT testing. The overall average response rate to the questionnaire was 76.6% (472 of 616 subjects), which corresponded to 74.0% (95%CI, 69.5–78.5) for men and 80.4% (95%CI, 75.5–85.3) for women. Moreover, only 11.2% of subjects had anaemia, and the mean blood Hb was 142.5 g/L (standard deviation: ±17.3 g/L). The median faecal Hb concentration was significantly higher among men than among women (p = 0.049), but there were no differences by age (p = 0.22). The median faecal Hb for a FP result was 48 μg Hb/g (95%CI, 40.34–55.26) and 64 μg Hb/g (95%CI, 53.76–74.64) for a true-positive result (p = 0.0004); however, the range of faecal Hb values was similar in both groups, with no predictive ability (area under the receiver operator characteristics curve, 0.6; 95%CI, 0.5–0.6).

3.2. Factors associated with FP results

Rescreening was a risk factor associated with FP results, though it was borderline significant in the multivariate analysis (adjusted OR, 1.5; 95%CI, 1.0–2.3). Women were two-fold more likely to have a FP result compared with men (adjusted OR, 2.3; 95%CI, 1.5–3.4).

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