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Risk stratification for colorectal neoplasia detection in the Flemish colorectal cancer screening programme

Wessel van de Veerdonk[a,*], Guido Van Hal[a,c], Marc Peeters[b,e], Isabel De Brabander[d], Geert Silversmit[d], Sarah Hoeck[a,c]

[a] Faculty of Medicine and Health Sciences, Department of Social Epidemiology and Health Policy, University of Antwerp, Belgium
[b] Department of Oncology, Antwerp University Hospital, Antwerp, Belgium
[c] Centre for Cancer Detection, Bruges, Antwerp, Belgium
[d] Belgian Cancer Registry, Brussels, Belgium
[e] Molecular Imaging, Pathology, Radiotherapy & Oncology (MIPRO), University of Antwerp, Belgium

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ABSTRACT

Background: The quantitative faecal immunochemical test (FIT) detects pre-cancerous lesions and colorectal cancer (CRC). Current CRC screening programmes are based upon a binary FIT result. This study evaluates the possibility of personalised risk prediction, based on FIT, age and gender to gain more insight into improving discrimination between normal outcomes, pre-cancerous lesions, carcinoma in situ and CRC working towards a more tailored screening approach.

Methods: In this retrospective study, from October 2013 until July 2016, data from 57,421 participants who underwent a colonoscopy after a positive FIT in the Flemish CRC screening programme were analysed using a multinomial multivariable logistic regression model.

Results: A significant difference in risk of detecting neoplasia was found between the established risk profiles based on the combination of the quantitative FIT, age and gender. The odds for detecting CRC in men aged 74, with a FIT result of ≥1000 ng/ml, was higher by a factor of 58.43 than that for women aged 56, with a FIT result of 75 ng/ml.

Conclusion: A large difference in risk with regard to the detection of colorectal neoplasia was found, based on demographics of the population. For some participants, the chance of finding no anomalies was more than 60%. Including additional variables in a prediction model could further increase discrimination between outcomes and practicality.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in Europe [1]. With an increasing annual estimated incidence of 345,000 cases and a decreasing annual mortality of 152,000 cases, Europe accounts for 25% of the colorectal cancers worldwide [2]. In Flanders (a Belgian region) there is a CRC mortality level of 1800 people each year [3]. Most CRCs develop from polyps over the course of 10 to 15 years, since the growth of CRC is slow [4]. Regular screening aims to reduce CRC incidence and mortality through early detection and treatment of pre-cancerous lesions and CRC [5].

Several countries with population-based CRC screening use a faecal immunochemical test (FIT) to detect (occult) blood in the stool, which is an indicator for the presence of (pre-)cancerous lesions and CRC [6]. In Flanders, a regional screening programme was implemented in October 2013 [7], and has been evaluated to be a cost effective approach [8]. Current practice uses the FIT result in a binary way, which selects participants who require follow up by colonoscopy. In Flanders, a FIT cut-off discrimination of < /≥75 ng/ml is used [9]. Different countries use different cut-off values, for example, the Netherlands uses < / ≥275 ng/ml [10].

This current practice does not exploit the full potential of the FIT. There is room for improvement since in Flanders ~27% of the participants with a positive FIT (≥75 ng/ml) have a negative colonoscopy afterwards. In addition, 20% of the participants who have a positive FIT are not followed up by colonoscopy within 6 months [9]. Haemoglobin levels differ between colonoscopy findings and some determinants are independently associated with the occurrence of CRC, apart from the

* Corresponding author at: University of Antwerp, CDE, D.R.226, Universiteitsplein 1, 2610, Antwerp, Belgium.
E-mail address: Wessel.vandeVeerdonk@uantwerpen.be (W. van de Veerdonk).

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Table 1
Study population demographics, FIT results and colonoscopy findings.

Colonoscopy findings	N	Women	56–59y ♀&♂	60–64y ♀&♂	65–69y ♀&♂	70–74y ♀&♂	FIT results ng/ml Median (Interquartile range)
Normal or non-cancerous lesions	24,362	50.5%	18%	26%	27%	29%	180 (106–379)
Pre-cancerous lesions	26,074	34.5%	15%	28%	27%	30%	231.5 (127–573)
Carcinoma in situ	3,413	33.9%	14%	26%	30%	30%	437 (189–1000)
Colorectal Cancer	3,423	34.4%	11%	23%	29%	37%	922 (288–1000)
No colonoscopy follow-up	14,634	39%	15%	23%	29%	33%	222 (121–763)

FIT result [11,12]. Known predictors of CRC are older age [11,12], male gender, obesity [13,14], smoking [14], alcohol intake [15–18], inflammatory bowel disease [14], red and processed meat intake [14], prior screening results and family history of CRC or adenoma [14,19,20]. Considering that faecal haemoglobin level results are not easily transferable across countries and regions for CRC screening [21] and life style data are not always transferable between countries, Flanders cannot improve its screening programme accuracy based on foreign data. Therefore, to investigate the benefits of tailored screening approaches a study on Flemish regional data is necessary.

At this time, the number of predictors available in Flanders is limited. This study will explore the implications of an approach where quantitative FIT, combined with age and gender in screening follow-up, is associated with an increased discrimination between predicted probabilities of detecting pre-cancerous lesions, adenocarcinoma in situ (CIS) or CRC. This approach will be explored in participants who have been positively screened by the FIT within the Flemish CRC screening programme.

2. Methods

2.1. Study population of the Flemish CRC screening programme

In the Flemish region, CRC screening was initiated from October 2013 onwards and all eligible persons, aged 56–74 years were invited by letter to perform a FIT. Persons who were not eligible for screening were those who had had a FIT in the past two years, had undergone a colonoscopy, had had a CRC diagnosis in the past ten years or persons who had had their colorectum fully removed. Data on exclusions were provided by the Belgian Cancer Registry (BCR). People who communicated that they did not want to participate were excluded by the Centre for Cancer Detection (CfCD).

2.2. Data sources

The data for this study was obtained from the BCR. The BCR is legally authorized to collect all data on new cancer diagnoses, resulting in a national population-based cancer registry. In addition, the laboratories for anatomical pathology are obliged to provide the BCR with all test results of colon specimens, regardless of the diagnosis. The BCR completes this Cyto-Histopathology register (CHP) with population-based reimbursement data from the Health Insurance Companies (HIC). The BCR couples these data with screening data available at the CfCD, in accordance with the latest data security guidelines and quality indicators.

2.3. Definitions

Colonoscopies were performed by gastroenterologists within routine practice and without specific guidelines or quality control. Individual colonoscopy findings were categorised as: normal or non-cancerous lesions (negative colonoscopy, inflammation, non-specific polyps, hyperplastic polyps etc.), pre-cancerous lesions (adenomas (sessile, serrated, tubular) with low-grade dysplasia and with/without a villous component), adenocarcinoma in situ (with high grade dysplasia) and (invasive) CRC. Detected CRCs were classified using the TNM classification system, where CIS is considered as TNM stage 0 [22]. CIS is included to make a distinction between TNO 0 and ≥ 1 possible.

This categorisation was chosen over the classical non-advanced adenoma, advanced adenoma and CRC due to several reasons. Firstly, normal or non-cancerous lesions are used as a reference in the prediction model over the non-advanced adenoma, as we intend to also predict the detection of pre-cancerous lesions what would only be possible with this categorisation. Secondly, there is no colonoscopy register in Belgium, resulting in the lack of data on the size and number of lesions. It is therefore not possible to classify according to the classical approach.

Individuals with more than one lesion were classified according to the most advanced finding observed within 6 months after FIT. Four groups were established from the colonoscopy findings, as shown in Table 1. Risk factors considered were: age (56–74 years), gender and quantitative FIT results (75 ng/ml up to ≥1000 ng/ml). FIT results of 1000 ng/ml and more are considered as ≥1000 because results above 1000 ng/ml cannot be specifically quantified.

2.4. Faecal immunochemical test for haemoglobin

In Flanders, the FIT results are reported as nanograms of blood per millilitre of faeces (ng/ml). Internationally, the micrograms of haemoglobin per gram faeces (μg/gr) is oftentimes used. For generalisability regarding the OC-sensor (FIT) results, a valid conversion is possible namely: (ng/ml result/25)*5. The FIT uses antibodies specific for human haemoglobin and detects blood by immunoassay. FIT analysis measures the quantity of antibody bound to haemoglobin using a variety of methods. The analysis of the FIT is done by using the OC-Sensor Diana™ (Eiken Chemical, Tokyo, Japan). The range of the results extends from 50 ng/ml to ≥1000 ng/ml. The haemoglobin value of 75 ng/ml was used as a positivity threshold. The quality control of both the FIT test and the rest of the screening programme is reported elsewhere [9].

2.5. Statistical analyses

The FIT variable is non-normally distributed and is therefore approached as non-parametric for descriptive purposes, thus medians and interquartile ranges (IQR) are used. Differences in the median FIT result between colonoscopy findings was tested using the Kruskal-Wallis test, while pairwise differences were evaluated with a Pearson's chi-squared test. Multivariable multinomial logistic regression analysis was used to obtain insight into the association between the variables (age, gender, FIT) and the presence or absence of pre-cancerous lesions, CIS or CRC compared to the reference standard. The model's reference standard is the group of women (normal or non-cancerous lesions), age 56 with a FIT result of 75 ng/ml, since this group is most likely least at risk. Based on the reference standard, odds ratios (OR) and 95% confidence intervals (CI) are calculated. Predicted probabilities are calculated