First results of the Flemish colorectal cancer screening program : start-up-period late 2013

Sarah Hoeck[1,2], Sarah Pringels[3], Eliane Kellen[2,4], Koen Van Herck[2,5], Patrick Martens[2], Erik Van Limbergen[2,4], Julie Francart[3], Guido Van Hal[1,2]

(1) Research Group Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium ; (2) Centrum voor Kankeropsporing (Center for Cancer Detection), Brugge, Belgium ; (3) Belgian Cancer Registry, Brussels, Belgium ; (4) Leuven Center for Cancer Prevention, University Hospital Leuven, Belgium ; (5) Department of Public Health, Ghent University, Ghent, Belgium.

Abstract

***Background & study aims* : Investigation of the first participation rate and follow-up results of the Flemish colorectal cancer screening program.**

***Patients & methods* : In 2013 five age cohorts with an even age between 66 and 74 year old (n=243 335) were invited by mail to return a completed iFOBT. Participants who tested positive (≥75ng/ml) were referred to a follow-up colonoscopy.**

***Results* : Participation rate was 48.4% (n=117 774). Overall positivity rate was 10.1%, and 78.1% of those tested positive underwent a colonoscopy. The positive predictive value of colonoscopy for CRC was 8.2%, for advanced adenoma 16.9% and for non-advanced adenoma 36.5%.**

***Conclusion* : Based on the EU-guidelines 35% was expected as participation for a first screening round, thus a participation rate of 48.4% is more than acceptable for a first screening year. The high positivity rate can partly be explained by including only the older ages in the start-up-period and by the first year of mass screening in Flanders.** (Acta gastroenterol. belg., **2016**, 79, **421-428**).

Key words : colorectal cancer, screening, prevention, immunochemical faecal occult blood test (iFOBT), participation, Flanders.

Background

Colorectal cancer (CRC) has become an important public health problem in Europe due to its frequency, morbidity and mortality rates (1). CRC is the third most common newly diagnosed cancer in males (after lung cancer and prostate cancer) and the second in females (after breast cancer) and the second leading cause of cancer related mortality in the EU (2). Without screening the life-time average risk of CRC is 5-6% in Western populations (3). In Flanders (being the northern part of Belgium), 1806 deaths due to CRC and 5438 new cases of CRC were reported in 2012. CRC constituted 13.5% and 14.3% of all new cancer cases in men and women (2). Its high frequency and slow development from a well-known premalignant lesion makes CRC an ideal disease for screening (4). Repeated CRC screening increases the likelihood of early detection of (pre-)cancer, enhances the odds of cure, and reduces mortality from the disease.

The European guidelines recommend that men and women aged 50-74 years participate in CRC screening (5). In European countries where CRC annual or biennial screening was implemented using a fecal occult blood test (FOBT), mortality rates were reduced by 15-35% (6). Recent results for the 34 OECD (Organisation for Economic Co-operation and Development) countries demonstrated that between 2001 and 2006, five-year CRC survival improved from 58 to 61.3% (7). These improved CRC survival rates can be attributed to advances in the diagnosis and treatment of CRC, but also to the introduction of CRC screening. Approximately 53% of the decline in CRC incidence and mortality between 1975 and 2000 could be due to CRC screening, while treatment accounts for about 12% and changes in risk factors for about 35% of the total CRC incidence and mortality reduction (8).

The superiority of iFOBT over guaiac FOBT (gFOBT) has been recognized for many years (5,9), such as a higher sensitivity (10), better specificity for human hemoglobin (11), no diet or medication restrictions required, only one sample required and the quantitative nature of iFOBT results which makes it possible to adjust positivity rates (10,11-17). Replacement of gFOBT by iFOBT resulted in an increased CRC and adenoma detection rate in Western countries (12,18-19).

Repeated iFOBT screening will eventually have a larger impact on CRC related mortality than gFOBT screening (8,14). Furthermore, iFOBT narrows the gap in CRC screening uptake by sex, age and deprivation (17) and enhances overall participation (15,21). Since the European Guidelines in 2010 (8), no more countries have selected gFOBT for screening programs.

From 2008 until 2011 a pilot study was performed to assess the implementation of a population based CRC screening with iFOBT in three regions in the province

Correspondence to : Sarah Hoeck, Ph.D., Department of Epidemiology and Scoial Medicine, University of Antwerp, Campus Drie Eiken, Universiteitsplein 1 - 2610 Wilrijk, Belgium.
E-mail: sarah.hoeck@uantwerpen.be

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of Antwerp (Flemish region in Belgium). In this pilot study, 19 542 asymptomatic individuals aged 50-74 were invited by two invitation strategies. Participation in the mail-group (invitation containing the iFOBT directly) was significantly higher than in the GP-group (inviting people through their GP) (52.3% vs 27.7%) (22). After this pilot study a population-based CRC screening program based on a biennial iFOBT invitation by mail has been implemented throughout Flanders since October 2013.

This paper reports on (i) the participation rate, and (ii) on the positive results and follow-up results after colonoscopy for the first round of CRC screening in the start-up period 2013.

Methods

Population

We report on the startup phase of the first round of a CRC population-based screening program in Flanders. Because of the short start-up-period between October and December 2013, only the Flemish residents aged 66, 68, 70, 72 and 74 years (n=243 335) were invited by the Center for Cancer Detection to participate in the CRC program.

People who were not eligible for screening were excluded from being invited as much as possible based on data of the Belgian Cancer Registry and the Belgian Health Insurance. The exclusion criteria were: people who had performed a stool test (iFOBT and gFOBT) in the past two years or had undergone a colonoscopy in the past ten years, people who had CRC in the past ten years and people who had their colorectum removed.

Invitation strategy

Prospective participants were sent an invitation with an iFOBT kit (OC Sensor, Eiken Chemical Co., Tokyo, Japan) by mail and were asked to return a completed stool test in a postage-paid return envelope with preprinted laboratory address. Each invitation contained an invitation letter, an information leaflet with general information about the CRC screening program, a reply form, kit instructions and an immunochemical FOBT with collection paper. The iFOBT-kit and the analyses in the laboratory were free of charge. Non-participants received a reminder letter (without iFOBT-kit) after 8 weeks.

iFOBT and follow-up colonoscopy

iFOBT samples were used for measurement of occult blood in the faeces and were processed using an automated reading technique (OC-sensor Diana, Tokyo, Japan) allowing quantitative measurement of the human haemoglobin content expressed in ng/ml (23).

Research indicated that a cut-off level in the range of 75-100 ng/ml is preferred to have an appropriate balance between sensitivity and cost-effectiveness (24). The cut-off value for a positive test was set at 75 ng of haemoglobin per ml of stool. Studies are in favor of 1-sample OC Sensor (25). The participants and their GP received the result by mail within 14 calendar days after the analysis. Those with a positive iFOBT result were advised to plan a colonoscopy (not free of charge). During colonoscopy, all observed adenomas were removed if feasible, and biopsied if necessary. Participants with a negative colonoscopy after positive iFOBT do not require an iFOBT screening for 10 years. Previous studies indicate that these people have a strongly reduced risk of CRC compared with people who have never undergone colonoscopy (26). This is consistent with the 'polyp dwell time' which is estimated to be on average at least 10 years (27). Histological results of biopsies or removed lesions during colonoscopy were registered by the Belgian Cancer Registry (BCR). Location and histology were registered for at least the most severe diagnosis of each patient.

Data collection and analyses

BCR collects data on all new cancer cases diagnosed in Belgium since 2004 (Flanders since 1999). Data are collected from the oncological care programs and pathology laboratories. Since 2010 the BCR also collects all anatomopathological test results in the context of early detection of colorectal, cervical and breast cancer from the pathology network. These databases are supplemented with reimbursement data from the Health Insurance and provided to the BCR by the Intermutualistic Agency.

The overall participation rate was assessed by the total number of iFOBT-analyses (performed in 2013 or in 2014 until 30th of June 2014) for all individuals invited in 2013. Participation rates before the reminder were calculated separately.

The positivity rate was calculated as the number of participants with a positive iFOBT (≥75 ng/ml) relative to all completed iFOBT. The detection rate for CRC or adenoma was calculated as the number of positive iFOBT with cancer or advanced adenoma relative to the total number of participants. The positive predictive value (PPV) of the iFOBT was calculated as the number of true positives relative to the total number of positive iFOBTs followed up with colonoscopy. The number needed to scope to find one true positive was calculated as the number of participants with a positive iFOBT followed by colonoscopy relative to the number of true positives. True positives are defined as positive iFOBTs that are followed by a colonoscopy by which at least one colorectal lesion was detected.

Tubular and serrated adenoma with low-grade dysplasia were counted as non-advanced adenoma whereas adenoma with a villous component and/or high-grade dysplasia were counted as advanced adenoma. There were no data available on the size or the amount of villous components in an adenoma.

Results

Participation rate and program coverage

The total Flemish population aged 56-74 year olds included 1 339 841 individuals. The start-up-period only included the people of 66, 68, 70, 72 and 74 years old, resulting in a total of 243 335 individuals who met the selection criteria and who were invited to participate. 117 774 returned a completed iFOBT, resulting in an overall participation rate of 48.4% (47.8% for women, 49.0% for men, p<0.01). In the age category of 66-70 years 50.7% participated whereas in the age category of 71-74 years only 44.9% participated (p<0.01). Overall participation before the reminder letter was 37.0%. Thus, the minimum acceptable uptake of 35% in a first round set by the EU guidelines (42) was already achieved. Of the 117 774, 11 886 (10.1%) had a positive iFOBT (≥75 ng/ml). The overall percentage of technical recalls was low (0.001%). 18.4% of non-participants (n=23 090) had informed the Center of Cancer Detection they were not willing to participate. The characteristics of the total population, the invited population and the participants are summarized in Table 1.

Figure 1 shows the amount of participants, refusals and non-responders. Almost 20% of the non-responders who received a reminder letter after 8 weeks, still participated. Finally, a total of 42% of the invited people in 2013 were non-responders.

Follow-up results

Follow-up results are summarized in Table 2. Although all participants with a positive iFOBT were recommended to have a full colonoscopy, only 78% were registered with a full colonoscopy. 4.6% performed a second stool test instead of a colonoscopy. For 14.4% no follow-up data were registered.

The differences in the adherence to full colonoscopy are summarized in Table 3. A significantly higher proportion of full colonoscopies was registered among women as compared to men (78.3% vs. 76.9%, p=0.046). There are no significant differences in full colonoscopy according to age and province.

Outcomes with iFOBT and colonoscopy

Table 4 summarizes the colonoscopy findings. The positive predictive value of colonoscopy for non-advanced adenoma was 36.5%, for advanced adenoma 16.9% and for invasive cancer 8.2%. The number needed to scope to find one person with non-advanced adenoma was 2.7, for advanced adenoma 5.9 and to find one person with CRC 12.2.

Table 1. — **Characteristics of the participants (absolute numbers and percentages)**

Population	**Absolute numbers**	**Percentage of total**
Total target population (Flanders, 56-74y)	1 339 841	100
Non eligible population*	286,903	21.4
Eligible population	1 052 938	78.6
Invited population**	**243 335**	**18.2**
Total of participants (on invited population)	117 767	48.4
Reminder		
Before reminder	90 003	37.0
After reminder	27 764	11.4
Sex***		
Female	59 992	47.8
Male	57 775	49.0
Age group***		
65-69 years	57 729	51.3
70-74 years	60 038	45.9
Province***		
Antwerp	31 885	49.0
East Flanders	26 475	47.7
West Flanders	23 865	46.5
Limburg	17 631	56.0
Flemish Brabant	17 911	44.8
Total of positive iFOBT§	11 886	10.1
Sex***		
Female	4 681	7.8
Male	7 205	12.5
Age group***		
66-69 years	7 844	9.7
70-74 years	4 042	11.1

*non-eligible population: people who have had a stool test in the past 2 years, CRC or a colonoscopy in the past ten years, and people with full colectomy were not invited. ** in the start-up-period of late 2013 only the people of 66, 68, 70, 72 and 74 year olds were invited to participate. ***Chi square, p<0.01

Discussion

The minimum acceptable uptake of 45% (in any following round) - set by the European Guidelines (5,28) was already achieved in this start-up-period (48.4%). In fact, the EU Guidelines require only 35% for a first round (28). Other participation rates, using iFOBT, vary considerably among countries, within a range of 15 to 64% (13,22,29-31). The first participation rate of the Flemish program is close to that in the pilot study. Participation increases by direct mailing of a FOBT (22,32), and by sending reminder letters (21,33-36). Without the effect of the reminder (additional 11.4% uptake), the EU minimum uptake of 35% for a first round would still have been achieved.

Participation among men was slightly higher compared with women (49.0% vs. 47.8%, p<0.01) which is in contrast with other studies (37-39). However, the uptake in 2014 is higher among women (52.0% vs. 48.6%, total

Table 2. — **Follow-up after positive iFOBT (until 12 months after the positive iFOBT)***

Follow-up	n	%
Patients with full colonoscopy	9 254	77.9
Patients with an incomplete colonoscopy	138	1.2
Virtual colonoscopy	24	0.2
Second stool test (iFOBT or gFOBT)	550	4.6
Surgical operation colon**	18	0.1
Medical imaging***	185	1.6
No follow-up****	1 718	14.4
Total participants with a positive iFOBT	**11 886**	**100**

* In case of multiple follow-up procedures, only the most relevant procedure was taken into account: full colonoscopy > incomplete colonoscopy > virtual colonoscopy > second stool test > surgical operation colon > medical imaging. ** No prior colonoscopy registered at 30th June 2015. *** These reimbursement data for medical imaging are not specific for the colorectum but refer to larger or multiple topographical places. Therefore, it cannot be excluded that the medical imaging was performed for another organ (e.g. stomach, small intestines,…). **** No follow-up data available at 30th June 2015

Table 3. — **Full colonoscopy as follow-up according to sex, age and province (%)**

	Full colonoscopy (n=9 254)
Sex*	
Female	78.3%
Male	76.9%
Age group**	
66 year	78%
68 year	78.4%
70 year	77.6%
72 year	76.8%
74 year	75.9%
Province***	
Antwerp	77.2%
East Flanders	79%
West Flanders	76.3%
Limburg	76.7%
Flemish Brabant	78%

* Chi square, p=0.046. ** Chi square, p=0.248. *** Chi square, p=0.147

uptake 2014 50.3%). As indicated in other studies (40-42), participation was higher in the lowest age category 65-69 years (51.3%) compared with age category 70-74 years (45.9%) (p<0.01).

The iFOBT positivity rate of 10.1% is higher compared with other studies (43). Positivity rates and adenoma detection rates are higher in first screening rounds and among first-time participants (44,45). Moreover, in the start-up-period only the people of 66-68-70-72-74 year olds were invited and positivity rates are higher among the older participants (45). In the first year of CRC screening in the Netherlands - where elderly persons were invited - a positivity rate of 12.2% was registered (Sentinel, cut-off 88 ng/ml) (46). And, although mentioned in the leaflet, it cannot be excluded that some subjects participate with symptoms for CRC (47), or with a higher risk of CRC.

While the PPV for CRC (8.2%) falls within the predicted range based on population-based programs (4.5%-8.6%, first round), the PPV for adenoma (53.4%, advanced and non-advanced together) exceeds the EU-range of 19.6%-40.3% (28). Because the PPV's are calculated for different categories of adenoma which were not always clearly defined, it is difficult to compare international results.

The detection rate for invasive CRC (6.6‰) is higher than reported by others (20,48), but falls within the range of 1.8-9.5‰ (28). The detection rate for advanced adenoma was 13.6‰ and 29.8‰ for non-advanced adenoma. Ontario reports a detection rate for CRC of 1.8‰ in a population of 65-69 year olds and 2.3‰ in a population of 70-74 year olds (first round, gFOBT) (48). In the Netherlands, a detection rate of 7‰ for CRC, and 34‰ for advanced adenoma was found (46). The variability in detection rates and PPV for adenoma could be explained by different categorization in non-advanced and advanced adenoma. In addition, it is often not clear whether the advanced and non-advanced adenoma were taken together to calculate PPV or detection rates of 'adenoma'. Nevertheless, the first results for the PPV and detection rate for adenoma in the Flemish program are relatively high. As mentioned above, the age groups that were invited first could explain the higher values for adenoma in the Flemish program.

Three aspects need further monitoring: compliance for follow-up is one critical aspect to assure the effectiveness of a CRC screening program (31). The proportion with full colonoscopy (78%) is therefore a particular concern. Indeed, 14.2% of participants with a positive iFOBT had no follow-up whatsoever and 4.6% had a second stool test as follow-up. The health benefit of the start-up-period could increase with higher compliance to follow-up colonoscopy. Other studies report compliance rates between 72 and 92% (22, 31, 41, 46, 49-51). However, in

Table 4. — **Colonoscopy findings (absolute numbers and percentages/promilles)**

Colonoscopy findings	Male	Female	Total
Non advanced adenoma			
N	2 359	1 166	3 525
PPV	40.6%	30.3%	36.5%
Detection rate (95% CI)	40.7‰ (39.5-41.9‰)	19.2‰ (18.4-20.1‰)	29.8‰ (29.0-30.5‰)
Number needed to scope	2.5	3.3	2.7
Advanced adenoma			
N	1 076	535	1 611
PPV	18.8%	14.2%	16.9%
Detection rate (95% CI)	18.4‰ (17.2-19.5‰)	8.8‰ (8.1-9.7‰)	13.6‰ (12.9-14.2‰)
Number needed to scope	5.3	7.1	5.9
Invasive cancers			
N	563	234	797
PPV	9.6%	6.1%	8.2%
Detection rate (95% CI)	9.6‰ (9.0-10.2‰)	3.7‰ (3.4-4.1‰)	6.6‰ (6.3-6.9‰)
Number needed to scope	10.5	16.4	12.2
Other lesions*			
N	414	364	778
Detection rate (95% CI)	7.1‰ (6.6-7.6‰)	5.9‰ (5.5-6.4‰)	6.5‰ (6.2-6.9‰)
Total			
False positives	2.2% (n=129)	2.3% (n=143)	2.2% (n=272)
PPV for adenoma and cancer	68.9%	50.6%	61.5%
Total detection rate of the screening	68.7‰	31.8‰	49.9‰
program for adenoma and cancer (95% CI)	(65.7-71.6‰)	(29.9-33.8‰)	(48.-51.7‰)
Number needed to scope to find 1 adenoma or cancer	1.5	2.0	1.6

* Lesions other than adenoma or cancer ,e.g. inflammation, diverticulum, hyperplastic polyps

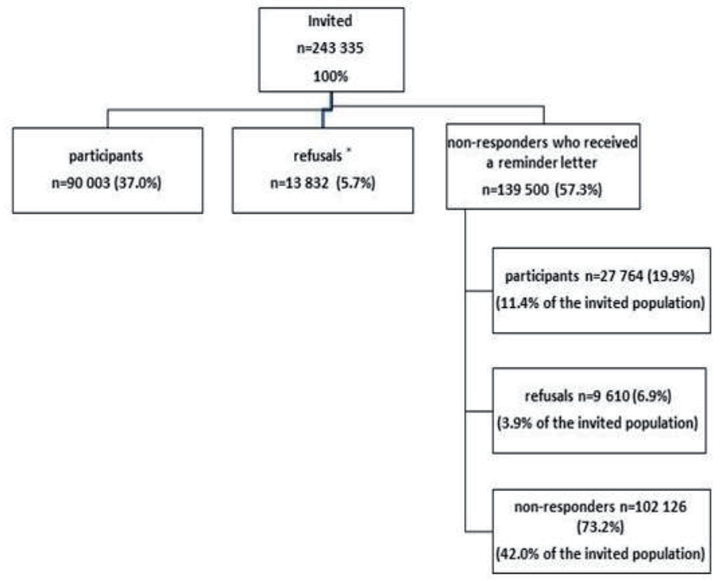

Fig. 1. — Participants, refusals and non-responders before and after reminder letter (absolute numbers and percentage of total)
* contacted the screening center: not being eligible or not willing to participate

some countries, e.g. Finland, Spain and the Netherlands, a pre-booked appointment for colonoscopy is provided in the result letter, which can increase compliance for follow-up colonoscopy (52). In Flanders, participants with a positive iFOBT can be referred for colonoscopy by a GP or can directly make an appointment with a gastroenterologist of their choice. The cost of a consultation with a GP for referral and the cost of the colonoscopy may decrease compliance, although there is almost complete reimbursement by the Health Insurances. Non-compliance to follow-up is related to problems with scheduling a colonoscopy and finding transport, while fear of embarrassment, pain and injury seem not significantly linked with non-compliance (53). Further investigation is needed to detect determinants of compliance to follow-up colonoscopy. Secondly, the time interval from a positive iFOBT to a colonoscopy is another crucial indicator: 90% (desirable 95%) of participants should undergo a follow-up colonoscopy within 31 calendar days after receiving the positive test result (EU guidelines). In the Flemish start-up-period only 35% had a colonoscopy within this interval. Prolonged waiting times could be explained by the large amount of invitations in the short start-up period and the relatively high iFOBT positivity rate among first time and elderly participants. Prolonged waiting times have not been associated with an increase in late-stage-cancers, but are associated with higher levels of anxiety (54). Further research is needed to investigate how the time interval could be decreased.

Thirdly, quality assurance of the entire screening process (28) is critical to ensure that the benefits of screening outweigh the harms and to improve the effectiveness (54-55). The follow-up colonoscopy has to be performed according to high-quality standards, especially regarding detection rates and safety (56). Approximately half of interval CRC is related to the quality of the colonoscopy (57-58) and the adenoma detection rate is directly related to interval cancers (59). Quality assurance programs monitoring the specialists performances are still lacking in Belgium, although a political priority. There are not yet data available on interval CRC and a thorough evaluation of the effectiveness of the CRC screening program will be measurable over at least 4 to 10 years (60).

While the acceptability of iFOBT is high (83%) (61), screening promotion messages may increase participation and knowledge (62). Research indicates different barriers to CRC screening: e.g. not willing to handle stool, not wanting to keep stool on a card in the house and a concern about posting samples in the mail (63, 64). However, these studies concern stool sampling with gFOBT, which is less user-friendly. The Flemish pilot study indicated that iFOBT is feasible and there does not seem to be a 'stool taboo' (65). Other barriers to CRC screening may be cancer fatalism and cancer fear (52, 66,-67,). More frequent health visits (68), and being involved in medical decision-making (69) result in higher uptakes, while present time orientation and being less concerned about making decisions to prevent future health problems result in lower uptakes of CRC screening (70). There seems to be a social gradient throughout the CRC screening pathway. Lower socioeconomic groups are less likely to participate, to undergo a follow-up colonoscopy and to have cancer identified as a result of a positive test (71). Furthermore, a social gradient in survival following the diagnosis of CRC exists (72). A lower preventive and specialist care use among lower SE groups is documented, including Flanders (73,74). Determinants of non-participation and SE differences in CRC screening in Flanders have yet to be explored.

Conclusion

This article reports the results of the start-up-period of the Flemish CRC screening program. The overall participation rate (48.4%) meets EU Guidelines even without the additional uptake of 11.4% after the reminder. The relatively high iFOBT positivity rate (10.1%) can be explained by the first-time participants and the older age groups who were invited. The PPV for CRC was 8.2%, for advanced adenomas 16.9% and for non-advanced adenomas 36.5%. The determinants of low compliance of follow-up colonoscopy (78%) and lack of follow-up (14.2%) of the participants with positive iFOBT need to be explored in order to further strengthen the Flemish CRC screening program in the future.

Conflicts of interest

None to be declared.

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