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

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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.

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 account 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 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 Insurances. 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 a 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 Insurances 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.

[Insert 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.

[Insert Figure 1]

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.

[Insert Table 2]

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.

[Insert Table 3]

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.

[Insert Table 4]

Discussion

The minimum acceptable ~~recommended~~ uptake of 45% ~~(in any following round~~) - set by the European Guidelines ~~to keep the program cost-effective~~ [5,28] was already achieved in this start-up-period (~~overall participation~~ 48.4%). ~~And, for a first round t~~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 ~~implementation across Flanders resulted in an overall participation rate~~ is close to that in the pilot study. ~~The intensity of local communication about the pilot in the three regions, mainly organized by the local authorities and the GPs, could explain the difference in participation rate. Despite various awareness-raising initiatives, more general campaign is needed to improve knowledge about the CRC program in all regions. The participation rate in 2013 in two of the three regions from the pilot study (Vosselaar and Schilde) was significantly higher than the Flemish average uptake of 48.4% in the start up period 2013 (54.4% and 52.9%, respectively, p<0.01). Only in Borgerhout it is lower (36.1% in the pilot as compared to 48.4%). The uptake in the start-up in 2013 in Borgerhout and Schilde is higher than in the pilot (36.1% as compared to 32.8% and 52.9% as compared to 48.5%). The opposite holds true for Vosselaar (54.5% as compared to 57.3%).~~

~~Opportunistic screening by GPs is embedded for some years in Flanders, and in a setting where opportunistic screening exists for some time, the participation rate of an organized~~

~~program may differ markedly from those in a setting were no such opportunistic screening exists [32]. No Flemish data are published to support this assumption.~~

~~As indicated by others [33] the~~ Participation increases ~~significantly~~ by direct mailing of a FOBT [33, 22], ~~the pilot study in Antwerp confirmed this finding (uptake of 52.3% in mail group vs. 27.7% in GP group) [22]~~ and by ~~Research also indicates that~~ sending reminder letters ~~increase participation~~ [21, 34-37]. ~~In the Flemish program a large amount of tests (11.4% of total invited population) was returned following the reminder.~~ Without the reminder (additional 11.4% uptake), the EU minimum ~~participation requirement~~ uptake of 35% ~~set in the EU Guidelines~~ for a first round ~~(35%)~~ would still have been achieved in the Flemish program. ~~However, the desirable uptake of 45% in any following round would not have been achieved.~~

~~A GP's signature on the invitation letter or direct recommendation by the GP could enhance participation [36, 38], although other studies reveal no significant difference in uptake in CRC screening [39]. If the current pilot study in the Flemish breast cancer screening program with a GP's signature confirms an improved participation, this A GP's signature on the invitation could be adopted in the CRC screening program as well.~~

Participation among men was slightly higher compared with women (49.0% vs. 47.8%, p<0.01) which is in contrast with other studies [40-42]. However, the ~~data on~~ uptake in 2014 ~~report a significant~~ is higher ~~participation~~ among women (52.0% vs. 48.6%, total uptake 2014 50.3%). Gender disparity emphasizes that awareness interventions targeting ~~the needs of~~ subgroups might be more effective than a whole population approach [43]. As indicated in other studies [44-46], 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).

~~Further research is needed to determine current barriers to CRC screening in Flanders.~~

The iFOBT positivity rate ~~was~~ of 10.1% ~~and~~ is higher compared with other studies ~~using immunochemical tests~~ [63]. ~~It is known that~~ Positivity rates and adenoma detection rates are higher in first screening rounds and among first-time participants [64, 65]. ~~Future rounds would yield fewer advanced adenomas compared with baseline screening [65].~~ Moreover, in the start-up-period only the people of 66-68-70-72-74 years old were invited and positivity

rates are higher among the elderly participants [65]. In the first year of CRC screening in the Netherlands - where eldery persons ~~of 63-65-67-75 and 76 years old~~ were invited - a positivity rate of 12.2% was registered ~~(Sentinel, cut off 88 ng/ml)~~ [66]. ~~Furthermore~~ And, although mentioned in the leaflet, it cannot be excluded that some subjects ~~attended the screening~~ participate with ~~the presence of~~ symptoms for CRC [67], ~~although it is explicitly mentioned in the leaflet not to participate when having symptoms~~ or with a ~~when having~~ higher risk of CRC. ~~The iFOBT positivity rate in Flanders was higher among men (12.5%) compared with women (7.8%).~~

~~The PPV for CRC was 8.2%, for advanced adenomas 16.9% and for non-advanced adenomas 36.5%. Overall, the positive predictive value for advanced adenoma and CRC was 25.1%.~~ 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) ~~in the Flemish program~~ exceeds the EU-range of 19.6%-40.3% ~~as set by the European guidelines~~ [28]. ~~However, this range is based on the results of population-based studies.~~ Because the PPV's are calculated for different categories of adenoma which were not always clearly defined, it is ~~even more~~ difficult to compare international results.

The detection rate for invasive CRC (6.6‰) ~~was 6.6‰, which~~ is higher than reported by others [20, 106], 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 years old and 2.3‰ in a population of 70-74 years old (first round, gFOBT ~~screening~~) [68]. In the Netherlands ~~contrary,~~ a detection rate of 7‰ for CRC, and 34‰ for advanced adenoma was found ~~in the Netherlands~~ [66]. 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, ~~in the start-up period of the Flemish program only~~ invited persons were 66 years and older~~, 68, 70, 72 and 74 years old were invited~~ compared with 50 or even 40 years ~~and older while~~ in the studies referred to in the European guidelines~~, screening started at 50 or even at 40 years~~ [28]. Since

the incidence of colorectal adenoma and cancer increases with age, this partially explains the higher values for adenoma in the Flemish program.

Three aspects need further monitoring: compliance for follow-up ~~colonoscopy~~ is one critical aspect ~~of a CRC screening program~~ to assure the effectiveness of ~~the~~ a CRC screening program [31]. The rather low follow-up with full colonoscopy (78%) is therefore a particular concern. 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, 45, 66, 69-71]. However, in 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 ~~rates~~ for follow-up colonoscopy [54]. In ~~the Flemish CRC program~~ 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 ~~have hampered colonoscopy~~ decrease compliance, although almost completely reimbursement by the Health Insurances. ~~Research indicates that~~ Non-compliance to follow-up ~~colonoscopy~~ 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 [72]. Further investigation is needed to detect determinants of compliance to follow-up colonoscopy ~~after positive iFOBT~~. Overall, 78% of participants with positive iFOBT had a full colonoscopy and only 1.2% an incomplete colonoscopy. However, these numbers are based on ~~the~~ data given by the specialists to reimburse their medical activities.

~~It is possible that incomplete colonoscopies were partly registered as full colonoscopy (which is higher reimbursed than incomplete colonoscopies), and that the actual amount of incomplete colonoscopies might be higher than registered. However, no data are currently available to prove this assumption. 14.2% of participants with a positive iFOBT had no registered follow-up whatsoever and 4.6% had a second stool test as follow-up. Further research is needed to investigate how the lack of and inappropriate follow-up could be reduced.~~ Secondly, the time interval from a positive iFOBT to a colonoscopy is another crucial indicator: ~~in a CRC screening program. The EU guidelines indicate that it is acceptable that~~ 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 ~~according to~~ this ~~advised time~~ interval. ~~The~~ Prolonged waiting times could be explained by the large amount of invitations in the short start-up period ~~(October – December)~~ and the relatively high iFOBT positivity rate among first time and elderly participants. ~~Waiting times are monitored.~~ ~~A~~ Prolonged waiting times ~~for colonoscopy~~ have not been associated with an increase in late-stage-cancers, but ~~it is~~ are associated with higher levels of anxiety [73]. Further research is needed to investigate how the time interval could be decreased.

Thirdly, ~~The EU recommends population-based CRC screening with~~ quality assurance of the entire screening process [28] ~~which~~ is critical to ensure that the benefits of screening outweigh the harms and to improve the effectiveness ~~of CRC screening programs~~ [73-74]. The follow-up colonoscopy has to be performed according to high-quality standards, especially regarding detection rates and safety [75]. ~~If participants with a negative colonoscopy are temporally excluded from the CRC screening program, no lesions may have been overlooked.~~ ~~Studies indicate that~~ Approximately half of interval CRC is related to the quality of the colonoscopy [176-77] and the adenoma detection rate ~~(ADR)~~ is directly related to ~~the risk of~~ interval cancers [78]. Quality assurance programs monitoring the specialists performances are still lacking in Belgium, although ~~the Flemish authority has given this issue~~ the political priority. There are not yet data available on interval CRC and a thorough evaluation of the effectiveness of a CRC screening program will be measurable over at least 4 to 10 years [79].

While the acceptability of iFOBT ~~has been reported to be as~~ is high ~~as~~ (83%) [47], screening promotion messages may increase participation and knowledge [48]. Research indicates ~~that patient reported~~ different barriers to CRC screening ~~were~~: e.g. not willing to handle ~~their~~ stool, not wanting to keep ~~the~~ stool on a card in the house and a concern about posting ~~their~~ samples in the mail [49-50]. However, these studies concern stool sampling with gFOBT, which is ~~known to be~~ less user-friendly. The Flemish pilot study indicated that iFOBT is ~~proves to be~~ feasible and there does not seem to be a 'stool taboo' ~~in Flanders~~ [51]. Other barriers to CRC screening may be cancer fatalism and cancer fear [52-54]. More frequent health visits [55], the feeling of having adequate time with their healthcare provider [56] and being involved in medical decision-making [57] result in higher uptakes ~~of CRC screening~~,

while ~~individuals with a~~ present time orientation ~~have been shown to be are~~ and being less concerned about making decisions to prevent future health problems result in lower uptakes of CRC screening. ~~results in lower uptakes for CRC screening~~ [58]. ~~Further research is needed to investigate determinants of non-participation in the Flemish CRC program in upcoming years.~~ There seems to be a social gradient ~~in CRC screening participation, throughout the total~~ CRC screening pathway. Lower socioeconomic groups are less likely to participate ~~in screening, less likely~~ to undergo a follow-up colonoscopy and ~~less likely~~ to have cancer identified as a result of a positive test [59]. Furthermore, a social gradient in survival following the diagnosis of CRC exists [60]. A lower preventive [61] and specialist care use [62] among lower SE~~socio-economic~~ groups is documented ~~in Belgium~~, including Flanders ~~the Flemish region~~. ~~but~~ Determinants of non-participation and SE differences in CRC screening in Flanders have yet to be explored ~~in future research~~.

Conclusion

This article reports the results of the start-up-period of the Flemish CRC screening program ~~from October until December 2013~~. The overall participation rate ~~was~~ (48.4%) ~~which is higher than expected for a start-up screening program, and~~ is even acceptable according to EU Guidelines without the additional uptake of 11.4% after the reminder. ~~Participation among men was slightly higher compared with women (49.0% vs. 47.8%) and was higher in the lowest age category 65-69y (51.3%) compared with age category 70-74 (45.9%).~~ The relatively high iFOBT positivity rate ~~was relatively high~~ (10.1%)~~, but~~ can be explained by the first-time participants and the older ages ~~(66-68-70-72-74)~~ that were invited. The ~~positive predictive value~~ 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 ~~after a positive iFOBT~~ (78%) ~~was 78%~~ and lack of follow-up (14.2%) ~~for 14.2%~~ of the participants with positive iFOBT need to be explored ~~no follow-up was registered. It is of critical importance to improve correct follow-up colonoscopy after a positive iFOBT in Flanders. Although participation rates in this start-up-period are promising, an uptake of 60% has to~~

~~be achieved by 2020. Barriers to participate and to undergo a follow-up colonoscopy need to be explored~~ in order to strengthen the Flemish CRC screening program in the future.

Conflicts of interest

None to be declared.

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