Switching from guaiac to immunochemical faecal occult blood test increases participation and diagnostic yield of colorectal cancer screening

Jean-François Bretagne, Christine Piette, Mathilde Cosson, Gérard Durand, Astrid Lièvre

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SWITCHING FROM GUAIAC TO IMMUNOCHEMICAL FAECAL OCCULT BLOOD TEST INCREASES PARTICIPATION AND DIAGNOSTIC YIELD OF COLORECTAL CANCER SCREENING

Authors: Jean-François Bretagne[a,b], Christine Piette[b], Mathilde Cosson[b], Gérard Durand[b], Astrid Lièvre[a,b,c,d]

[a] Rennes 1 University, 35000 Rennes, France; [b] Association pour le Dépistage des Cancers en Ille-et-Vilaine, ADECI35, 35040 Rennes, France; [c] Department of Gastroenterology, CHU Pontchaillou, 2 rue Henri le Guilloux, 35033 Rennes, France; [d] INSERM UMR 1242, COSS "Chemistry, Oncogenesis, Stress Signaling," 35042 Rennes, France

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Corresponding author: JF Bretagne; phone: +33 607491311; E-mail: jf.bretagne@gmail.com

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ABSTRACT

Background

Compared with the guaiac-faecal occult blood test (gFOBT), faecal immunological tests (FIT) are considered to be more effective for colorectal cancer (CRC) screening. However, only scarce research has examined the outcomes of switching to FIT within a mature gFOBT-based CRC screening programme.

Methods

We reported a 15-year experience of biennial FOBT screening in a well-defined population of approximately one million inhabitants, including six gFOBT-based screening rounds and one round with FIT at the 30 μg Hb/g cut-off. The main outcome measures were screening participation, FOBT positivity and advanced neoplasia detection in each round.

Results

In this study, 647 676 screenings were performed in 228 716 different individuals, leading to 17 819 positives and 16 580 follow-up colonoscopies. Compared with the last gFOBT round, switching to FIT led to an increased participation of nearly 20 percentage points, and a fivefold increased detection of CRC and advanced adenoma among invitees (3-fold among attendees). The numbers needed to screen and scope to detect one advanced neoplasia declined from 221 to 66 and from 4.7 to 2.6, respectively.

Conclusions

The present population-based study demonstrated a dramatical increase in the diagnostic yield of advanced neoplasia by switching to FIT within a mature gFOBT-based CRC screening programme.

Keywords: colorectal cancer screening, guaiac faecal occult blood test, immunological faecal occult blood test, colonoscopy, colorectal cancer, adenoma, advanced adenoma

INTRODUCTION

Randomized controlled studies have shown that colorectal (CRC) screening using a guaiac-based faecal occult blood test (gFOBT) can significantly reduce mortality from CRC.[1] Therefore, French National Health Authorities launched CRC screening in France in 2003 using a gFOBT in average-risk people aged 50-74. The programme achieved national coverage in 2008, but mean participation was low compared to other countries.[2,3] In 2015, French National Health Authorities replaced gFOBT with a faecal immunological test (FIT) because of its higher sensitivity for CRC and cancer precursors[4] but also for its greater acceptance by populations in controlled studies.[5,6] However, in the literature, there is little data in regard to switching to FIT within mature gFOBT-based screening programmes. A pilot study within the national screening programme in England, which replaced the gFOBT with FIT over a 6-month period, reported an increased participation and improved outcomes with FIT compared to gFOBT, which was still running during the same period of time.[7] 'Ille-et-Vilaine' which was one of the first administrative areas in France to implement the national screening programme in 2003, has a 15-year (2003-2017) experience in CRC gFOBT-based screening, as well as the switch to FIT-based screening. Therefore, the aim of this study was to demonstrate increased participation in and improved outcomes of CRC screening following gFOBT replacement by FIT within a mature screening programme in a large population-based study.

POPULATION AND METHODS

Population and screening strategy

This study was conducted in the 'Ille-et-Vilaine' district in France. 'Ille-et-Vilaine' was one of the first administrative areas in France to implement the national CRC screening programme in 2003 using the biennial g-FOBT (Hemoccult II; Beckman Coulter Inc., Villepinte, France). CRC screening was proposed to individuals aged between 50 and 74 years with an average risk of CRC and no

contraindications for colonoscopy. Individuals with a personal or family history of CRC or adenoma, those with inflammatory bowel disease, and those who had undergone total colonoscopy in the previous five years were excluded from the mass screening programme. The gFOBT-based national screening programme, which was generalized in France in 2008, ran in France and therefore in 'Ille-et-Vilaine' until 2014. The shift from gFOBT to FIT occurred in 'Ille-et-Vilaine' in May 2015; the FIT selected by the French Health Authorities was the OC-Sensor™ test (Eiken, Tokyo, Japan).

Thus, in 'Ille-et-Vilaine', six rounds of gFOBT-based screening and one round of FIT-based screening were performed between 2003 and 2017. Regarding the first six rounds with gFOBT, two particularities should be mentioned. First, following National Health Authorities decisions regarding the replacement of the Hemoccult™ test by the FIT; therefore, the sixth round was shortened, and a gap of 6 months occurred between the end of screening using gFOBT and the start of FIT-based screening. Second, the third round in the district of 'Ille-et-Vilaine' was part of a published randomized controlled study involving three other districts that compared the performance of CRC screening with Hemoccult II™ and OC-Sensor™ tests.[8] In 'Ille-et-Vilaine', therefore, the performance of the third round with gFOBT should be interpreted with the knowledge that 28% of respondents to gFOBT during that round had the FIT performed simultaneously.

The screening strategy was similar for every screening round. An information brochure and an invitation letter were sent to each individual in the target population. People were invited to consult their general practitioners (GPs), who proposed the screening test to eligible subjects seen at their practice. GPs were also asked to state the exclusion criteria, at which point they provided each eligible individual with one screening test. The first 6 months of the screening round corresponded to the medical free-offer phase. A reminder letter including the screening test was sent 8 months later to non-respondents who were not excluded from participation by their GPs. Contrary to national guidelines related to gFOBT, the national FIT-based screening programme decided to discontinue the mailing of the test. However, in 'Ille-et-Vilaine', on the basis of the results of a randomized controlled

study that demonstrated the benefit to mailing the FIT test along with the reminder letter,[9] the screening centre was authorized by the regional health authorities to mail the FIT test with the second reminder letter after the first reminder letter to those in the target population who had not participated during the medical free-offer phase. Thus, we can conclude that the screening strategy and the implication of GPs were similar for gFOBT and FIT delivery in our district.

Participants were instructed to scrape different parts of the surface of their stool with the test probe and to return the test by mail to the central analysis centre in a prepaid envelope as soon as possible. No diet restriction was imposed. Two samples from each of three consecutive stools were required for the gFOBT test, while a single sampling tube was used for the FIT test. Tests were analysed by a single central laboratory without prior rehydration for the gFOBT test. The latter test was defined as positive when one to six square(s) was positive, while a cut-off of 30 µg of haemoglobin per gram of faeces (i.e., 150 ng of haemoglobin per millilitre of buffer) was used for the FIT positivity. The period of time between the accomplishment of the FIT and the dosage by the central laboratory should be less than seven days. The results were sent by mail to each individual, to their general practitioner and to the screening centre. All positives were recommended to undergo colonoscopy. Those with non-analysable tests were invited to redo testing, while those with negative tests were informed to participate again two years later until they were 74 years old.

Outcome measures and statistical analysis

The total population and the population aged from 50 to 74 years in the district were registered at the beginning of each round according to INSEE files.[10] The target population of the CRC screening programme was defined as the population aged from 50 to 74 years minus the excluded individuals.

Results of testing were classified as positive, negative or non-analysable. FOBT positivity was defined as the proportion of participants with a positive testing. Compliance to colonoscopy was assessed among individuals with positive testing. Colonoscopies were performed by gastroenterologists. The

proportion of completed colonoscopy and the rate of serious complications, such as colon perforation, were prospectively recorded. Colorectal neoplastic lesions (macroscopic features, size, location, and number of lesions) and their treatment were prospectively recorded in the database. Histopathology records were obtained from pathologists. Colonoscopy findings were classified according to the most advanced lesion: cancer, advanced adenoma, low-risk adenoma. Other colorectal lesions, such as hyperplastic or serrated polyps, were not considered in the current analysis. Advanced adenoma was defined as an adenoma of 10 mm or more in size or with high-grade dysplasia or intra-epithelial carcinoma. The villous component was not taken into account in the definition in accordance with recent French recommendations.[11] Cancers were classified according to the TNM classification system, with Tis corresponding to intra-mucosal carcinoma.[12] Cancers and advanced adenomas were analysed in a pooled group named 'advanced neoplasia', while advanced and low-risk adenomas were analysed in another pooled group named any 'adenoma'.

Crude positive predictive values (PPV) for cancer, advanced adenoma, low-risk adenoma, advanced neoplasia and any adenoma were defined as the number of participants with those lesions relative to all participants with positive testing and subsequent colonoscopy. The per-protocol analysis considered the neoplasia detection rates among screening participant (x1000 subjects), while intention-to-treat analysis considered the detection rates among the invited target population (x1000 subjects).

Screen-detected cancers were defined as cancers detected during screening. Interval cancers were cancers diagnosed within a two years-period following a negative test. Non-screen-detected cancers were cancers detected in non-participants within a two-year period following an invitation.

Analyses according to gender and age were performed for FOBT positivity rates and neoplasia detection rates. The number needed to screen (NNScreen) and the number needed to scope

(NNScope) to detect one case of advanced neoplasia were calculated with 95% confidence intervals (95% CI). Analyses according the rank of screening (first screening or subsequent screening) were performed for FOBT positivity, PPV for any kind of colorectal lesion, and also for NNScreen and NNScope calculation. Differences in screening outcomes between the FIT-based screening round (seventh round) and the last gFOBT round (sixth round) were calculated using a χ^2 test. Differences in screening outcomes between the first screening group and the subsequent screening group were calculated using a χ^2 test. All P values were two-sided and considered significant if < 0.05. All analyses were carried out with Epi Info™ 7.1.5 software.

RESULTS

Population

From 2003 to 2015, the total population in the district increased from 908 449 to 1 042 884 inhabitants (+ 14.8%, + 1.2% per year), while the population at age 50 to 74 years increased from 218 175 to 269 698 subjects (+ 23.6%, + 2% per year).[10] From the latter population, the rate of excluded individuals at each round progressively increased from 13.0% to 17.2% during the same period of time (Table 1). Most people were excluded because they had undergone total colonoscopy in the previous five years. Nevertheless, despite the increased exclusions, the target population for CRC screening continued to increase from 189 812 to 223 374 subjects between 2003 and 2015 (+ 17.7%). The mean age of the target population was 59 years at each round, while the sex ratio (males:females) was 0.91.

Participation rate

The participation rate for gFOBT-based screening was highest in the first round (51.0%) and then progressively decreased to 33.9% by the sixth round. The participation rate for FIT-based screening

(7^{th} round) rebounded to 53.4%. There was a significant increase in participation rate between the last round with gFOBT (round 6) and the first round with FIT (round 7) (+19.5%; $p<10^{-7}$). As already mentioned, the round 6 was shortened and the population and GPs were waiting for the FIT test, which may explain the lowest participation rate observed in this round. However, the increase in participation rate observed between round 5 and 7 remained highly significant (+12.3%; $p < 10^{-7}$). In each round, the participation rate was higher in women than men and increased with age (Table 1). The rebound observed with the switch to FIT was seen in all age groups with a particular benefit for the 50-54 and 70-74 age groups exceeding 50% and reaching almost 70%, respectively (Table 1). We estimated that the participation rate in the seventh round would have been equal to 36.6% without mailing the FIT with the reminder letter along.

gFOBT and FIT results

The gFOBT positivity rate was highest (2.59%) at the first round, and then slightly decreased with the exception of the 3^{rd} round (3.01%) during which FIT and gFOBT data were pooled for 28% of the gFOBT attendees. Using the 30 µg Hb/g cut-off, the FIT positivity rate was 4.26%. Regardless of the test used or the screening round, the FOBT positivity rate was markedly higher in men than in women. The positivity rate also increased according to age with both tests (Table 1). Most of the non-analysable tests were redone such that the final proportion of non-analysable tests remained low, though notably slightly higher with FIT because of exceeding the expiration date.

Colonoscopy findings

Compliance with colonoscopy following positive testing was constantly superior to 90%. In each round, the number of colonoscopies was higher in men than in women, despite lower participation to screening in men than in women. This difference was related to the higher positivity rate of testing in men and was particularly true for the FIT-based screening round, where 2741 colonoscopies were performed in men vs. 1934 colonoscopies in women (Table 2). In each round, the proportion of

complete colonoscopy was superior to 95% (Table 2). Reasons for incomplete colonoscopy have been previously published.[13] Among the 16 580 colonoscopies performed over 14 years, only 10 perforations occurred (perforation rate 0.60%).

The PPV for cancer was the highest (11.1%) in the first round and then progressively declined to 4.9% in the sixth round with gFOBT and then rebounded to 8.5% in the 7th FIT-based screening round (P<0.001) (Table 2). By contrast, the PPV for advanced adenoma did not change during the six g-FOBT-based screening rounds. However, following the switch to FIT, the PPV for advanced adenoma and advanced neoplasia increased significantly (P<10^{-7}) (Table 2). As a consequence of the concomitant decline of the PPV for cancer and decreased participation rate over the course of the six gFOBT-based screening rounds, the number of screen-detected cancers progressively decreased from 260 to 76 cases per round with gFOBT. By contrast, the number of screen-detected cancers was 395 with FIT screening. A similar increase was observed for the number of subjects with advanced adenoma (Table 2).

Figure 1 depicts the increase of any kind of screen-detected lesions following FIT compared with gFOBT by per-protocol (x1000 screened individuals) or intention-to-treat analysis (x1000 target individuals). The benefit of FIT was already perceptible during the 3rd round with gFOBT because one-quarter attendees simultaneously had both tests performed. Regarding screen-detected advanced neoplasia, which is the major goal of screening, the per-protocol analysis demonstrated that the greater than threefold increase observed between the 6th and the 7th round was seen in both sexes and all classes of age (P<10^{-7}) (Fig. 2). By intention-to-treat analysis, a fivefold increased detection of CRC and advanced adenoma was seen among invitees (P<10^{-7}) (Fig. 2).

Screen- and non-screen detected cancers

The proportion of screen-detected, interval and non-screen-detected cancers among cancers diagnosed at each round in the target population is given in Figure 3. The proportion of screen-

detected cancers progressively declined over the course of the six gFOBT-based screening rounds, decreasing from 39.9% to 17.6%, whereas the proportion of interval cancers was relatively stable and the proportion of non-screen-detected cancers progressively increased from 42.1% to 67.7%. That tendency radically reversed with the FIT test; the proportion of screen-detected cancers was 61.8% and that of non-screen-detected cancers was 31.8%. With the FIT test, the proportion of interval cancers was only 6.4% ($P<10^{-7}$).

Screening output measures

Table 3 depicts the estimates of NNScreen and NNScope for detecting one advanced neoplasia. Both NNScreen and NNScope values progressively increased over the course of the six gFOBT-based screening rounds, except for the 3rd round, while FIT-based screening induced a dramatic decrease in both values for men and women. Indeed, by using FIT, NNScreen was 66 for detecting one advanced neoplasia, which corresponded to a 3.3-fold reduction compared to the value registered at the last gFOBT screening round ($P<10^{-7}$). NNScope was 2.6 for detecting one advanced neoplasia, which corresponded to a 1.8-fold reduction compared to the value registered at the previous round ($P<10^{-7}$). As expected, both NNScreen and NNScope values were higher in women than in men with any test (Table 3).

Role of screening rank

At each round, except at the first round naturally, the majority of tests that were done, were subsequent tests (70.9 to 83.7%). As expected, the proportion of positive testing was significantly higher for the first screening tests than for subsequent tests, both for gFOBT ($P<0.05$) and FIT ($P<0.01$) (Table 1). Regarding gFOBT, the PPV for advanced neoplasia was higher for the first screening test than for subsequent tests (4.4 to 7.3 percentage points, $P<0.01$). By contrast with the FIT, figures were similar regardless of the screening rank (Table 2). Within the first screening group however, the PPV for advanced neoplasia screened with FIT was significantly lower in individuals who

were invited for the first time than in those who had never participated before (30.6% and 40.8%, respectively, P<0.001). Similarly, if NNScreen and NNScope values were higher for the first screening gFOBT than subsequent gFOBT, the values were similar regardless of the rank of screening for the FIT (Table 3). When comparing figures between first tests and subsequent tests among all the gFOBT-based screening rounds, the third round was an exception. As already mentioned, one-quarter of attendees in the third round simultaneously had both tests performed, mostly in people with previous screening.

DISCUSSION

In this study, we presented a population-based experience in biennial FOBT-based CRC screening over a 15-year period, leading to a cumulative 647 676 screenings performed in 228 716 different individuals, 17 819 subjects with positive testing and 16 580 following colonoscopies resulting from a compliance to colonoscopy of 93%. Of course, the population in the district was not fixed during the seven rounds. Indeed, the total population progressively increased by 1.2% per year as the target population for CRC screening increased by 17.5% from 2003 to 2015. The long-term performance of screening programmes, including the switch of gFOBT to FIT in real life, has been not reported in the literature. Six biennial screening rounds with gFOBT were performed in the present study before shifting to FIT for the 7th round.

Our study demonstrated a slight but regular decline in participation rate during the first six rounds with gFOBT. The lowest rate, recorded in the 6th round, could be observed because the population and GPs were waiting for the FIT test, the launch of which was expected. The first benefit of the switch to FIT was the increased participation rate of nearly 20 percentage points compared with the last gFOBT-based screening round and 9.8 percentage points compared with the mean value for the 6 gFOBT-based rounds. The benefit of 12 percentage points previously reported in randomized

controlled studies,[5,6] was found in our study when comparing participation between the round 7 and the round 5 which best reflects the participation rate with gFOBT given the limitations of the 6th round underlined above. In the present study, the increased participation with FIT was observed for women and men and for all age groups with a notable benefit for the 50-54 and 70-74 age groups (52.5% and 67.6%, respectively). To understand the reasons for this increase in participation, we conducted a survey in previous non-responders to gFOBT who participated in FIT.[14] Among the test-related major determinants of FIT compliance was the perception that the test was less complicated than the previous test and that a unique stool sample was required. Among the non-test related major determinants of FIT compliance were the feeling of being more concerned and the perception that the GP was more convincing. We could hypothesize that GPs were more motivated to present the new test because it was more reliable but also simpler to realize. GPs were sensitized on these two points during the implementation of the FIT through a new national information and training campaign. As a result of FIT launching in France, 'Ille-et-Vilaine' was the district with the highest participation rate while the mean participation rate in France was only 33% in the 2016-2017 period.[15] However, the participation rate would have been 36% instead of 53% if mailing the test had not been allowed by health authorities as part of a pilot study in our district. Considered together with these results, National Health Authorities have just introduced substantial changes to the screening specifications now authorizing test delivery with the second reminder letter throughout the whole French territory.[16] In order to limit the additional costs however, we chosen for the ongoing 8th screening round not to mail the FIT to people who were previously non-responders despite invitation to at least three rounds.

The second benefit of the switch to FIT was the rebound in the diagnostic yield of advanced neoplasia, CRC and advanced adenomas. Indeed, the number of screen-detected cancers increased fivefold with FIT screening compared to the last gFOBT-based round, while a similar increase (x 5.5) was observed for the number of subjects with advanced adenoma. Thus, the detection rate of

advanced neoplasia per 1000 invitees increased fivefold. That benefit was not solely the consequence of the increased participation rate but also the increased detection rate among attendees as previously shown in controlled studies.[5,6] This result is all the more remarkable given that performance measures of repeat gFOBT screening had markedly decreased, as was also reported in other national gFOBT-based screening programmes.[17,18] The detection rate of advanced neoplasia among attendees increased more than threefold compared with the previous round and was observed in both sexes and all age groups. This benefit was the result of the increased PPV for cancer and advanced adenoma (rate difference 3.6% and 13.7%, respectively) and a testing positivity rate difference of +2.0% (almost twice as high) due to a higher test sensitivity. The benefit of FIT could not be attributed to the important proportion of first tests (28.1%) at the seventh round because the PPV for advanced neoplasia were similar for first and subsequent tests (Table 2).

It is noteworthy that our findings compare favourably with those of a screening-naïve population-based study using a 10 µg/g cut-off that reported a detection rate of 23 advanced neoplasia per 1000 subjects screened compared to 15.1% in the present study, while the positivity FIT rates were 7.9% and 4.2%, respectively.[19] By using the intermediate 20 µg/g cut-off, a pilot study conducted within the mature national gFOBT-based screening programme in England reported a testing positivity rate of 7.8% and a detection rate of cancer and advanced adenomas that had increased twofold and nearly fivefold, respectively.[7] The smaller increase recorded in the present study for advanced adenomas (3.3-fold) could be a natural consequence of the value chosen for the FIT cut-off but could also be related to the inclusive 60-74 age group or a weaker performance of the gFOBT in the English screening programme.[7] In a very large population-based cohort followed for six FIT-based rounds by using the same 20 µg/g cut-off, Zorzi et al. reported crude detection rates in the first screening round that were similar to the values recorded in the present study for cancer (3.3 vs. 3.3 per 1000 subjects screened) and slightly higher for advanced adenoma (15.9 vs. 11.8 per 1000 subjects screened) but the cumulative values over the six consecutive rounds were lower (1.77 for cancer and 10.7 for

advanced adenoma per 1000 subjects screened, respectively).[20] In that Italian study, the number needed to screen and number needed to scope to detect one case of advanced neoplasia were 80.4 and 3.1, respectively (52.0 and 2.7 at the first round), compared with 66 and 2.6 in the present study. However, the comparability between the two studies is limited by the fact that the analysis was restricted to subjects aged 50 to 64 in the Italian study.[20] Knowing that an increase in participation and in test positivity rates has implications for colonoscopy workload, it seems, therefore, that the 30 µg Hb/g cut-off chosen by the French Health Authorities is a good compromise between increasing performance outcomes and limiting the number of colonoscopies required. By using Markov models to compare different strategies in a general population of 100,000 individuals aged 50-74 over a 20-year period, Lejeune et al. demonstrated that the one-stool sample OC-Sensor with the 30 µg Hb/g cut-off was the most efficient strategy.[21] Goede et al. reported that, compared to the biennial gFOBT programme, switching to FIT at a high 200 ng/ml (40 µg/g) cut-off level could increase the health benefits of the Canadian CRC programme without considerably increasing colonoscopy demand.[22] The economic analysis of FIT screening in England, using data directly comparing FIT with gFOBT in the NHS screening programme, suggested recently that FIT was highly cost-effective at all thresholds considered, reaching 180 µg/g.[23]

The strengths of the present study are as follows: 1) the long-term experience with FOBT-based screening in a large well-defined population, including the switch to FIT, whose increased performance for the detection of cancers and advanced adenomas compared to gFOBT has been confirmed; 2) the quality metrics of the screening programme, notably for colonoscopy[24] including: a) the high rate for the compliance to colonoscopy following positive testing (93%), b) the high rate for complete colonoscopy (97%), c) the high rates for neoplasms detection despite inter-endoscopist variability demonstrated in organized screening programmes[25-27], and d) the low rate of colonoscopic perforation that was similar to rate of 0.6‰ recently reported in the English NHS bowel screening programme;[28] and 3) the prospective data recording for interval and non-screen-detected CRC, which

permitted us to demonstrate the reversal of the ratio between screen-detected and non-screen detected CRC by switching to FIT.

Our study also has some limitations: a) comparability with literature is limited for colonoscopic findings because we did not take into account villous component for the definition of advanced adenoma according to recent French recommendations.[11] Such an analysis leads to minimizing the rate of advanced adenoma and therefore of advanced neoplasia detected by colonoscopy in the present study. b) some characteristics of the target population, such as levels of deprivation, were not considered for analysis of contributors to screening participation other than age and gender.

To conclude, the present study demonstrated a dramatically increase in participation and improved outcomes of CRC screening with the FIT test introduced into a mature gFOBT-based screening programme. Furthermore, these findings seem to validate at the population level the choice of a 30 µg Hb/g cut-off for the OC-sensor test positivity, even if improving screening participation remains a challenge in France.

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Figure legends

Figure 1.

A) Prevalence of neoplasia detected among individuals (x 1000) invited to participate to the screening programme at each of the seven consecutive screening rounds.

B) Prevalence of neoplasia detected among screened individuals (x 1000) at each of the seven consecutive screening rounds.

Figure 2. Detection rates of advanced neoplasia among screened individuals (x 1000) at round 6 and 7.

A) Females

B) Males

Figure 3. Proportion of screen-detected, non-screen-detected and interval cancers among cancers diagnosed in the target population at each of the seven consecutive screening rounds.

Fig. 1 A

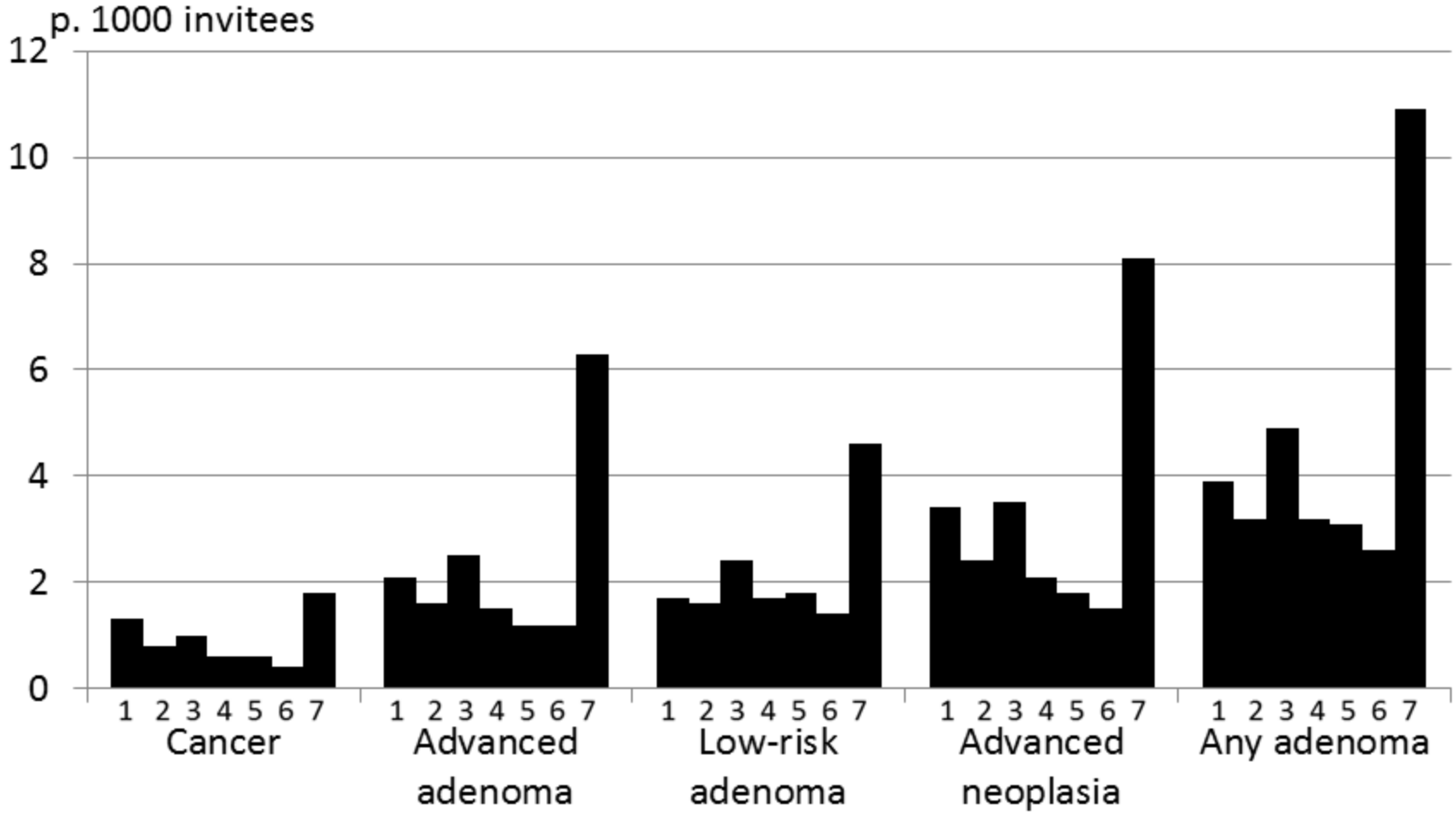
p. 1000 invitees
12
10
8
6
4
2
0
1 2 3 4 5 6 7
Cancer
1 2 3 4 5 6 7
Advanced adenoma
1 2 3 4 5 6 7
Low-risk adenoma
1 2 3 4 5 6 7
Advanced neoplasia
1 2 3 4 5 6 7
Any adenoma

Fig. 1 B

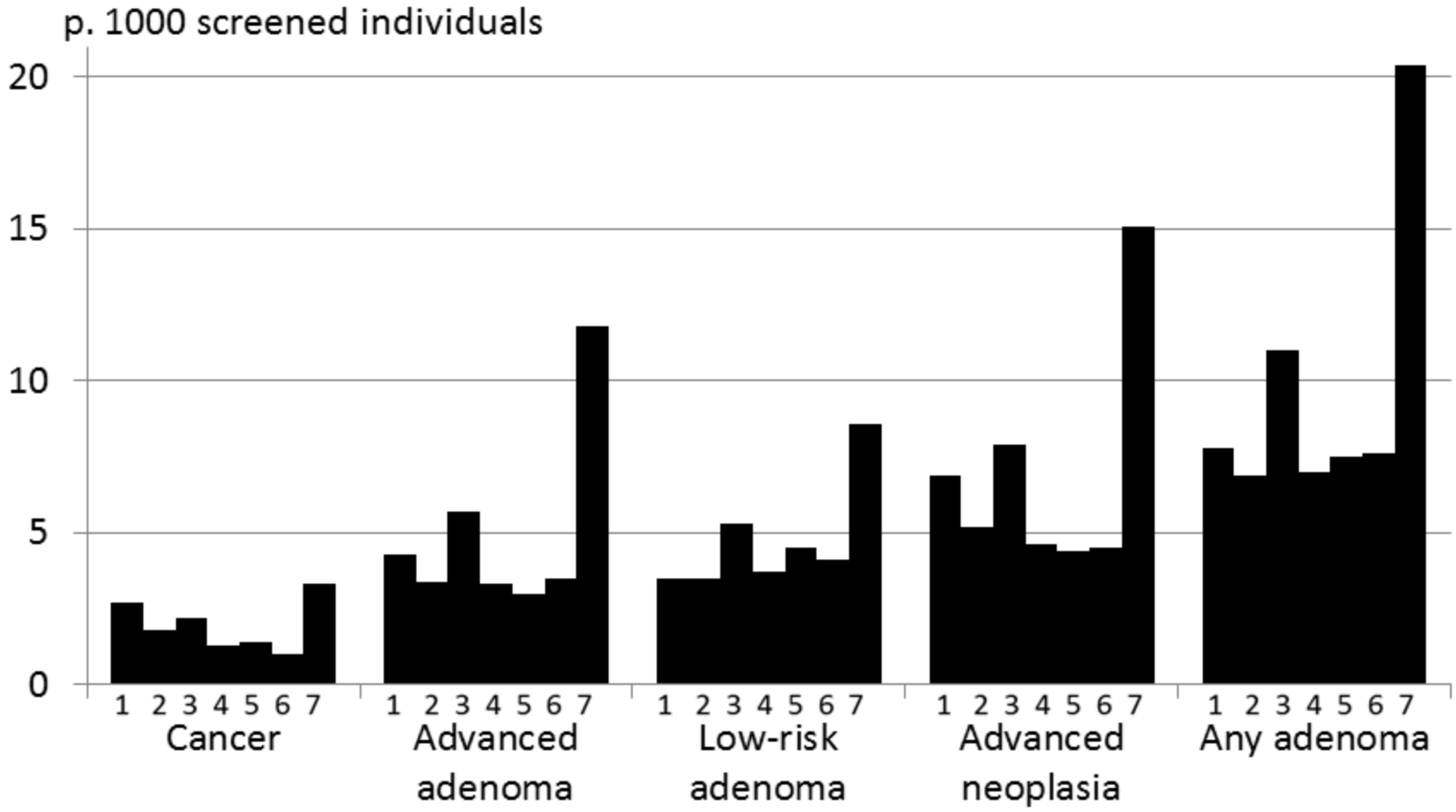
p. 1000 screened individuals
20
15
10
5
0
1 2 3 4 5 6 7
Cancer
1 2 3 4 5 6 7
Advanced adenoma
1 2 3 4 5 6 7
Low-risk adenoma
1 2 3 4 5 6 7
Advanced neoplasia
1 2 3 4 5 6 7
Any adenoma

Fig. 2 A

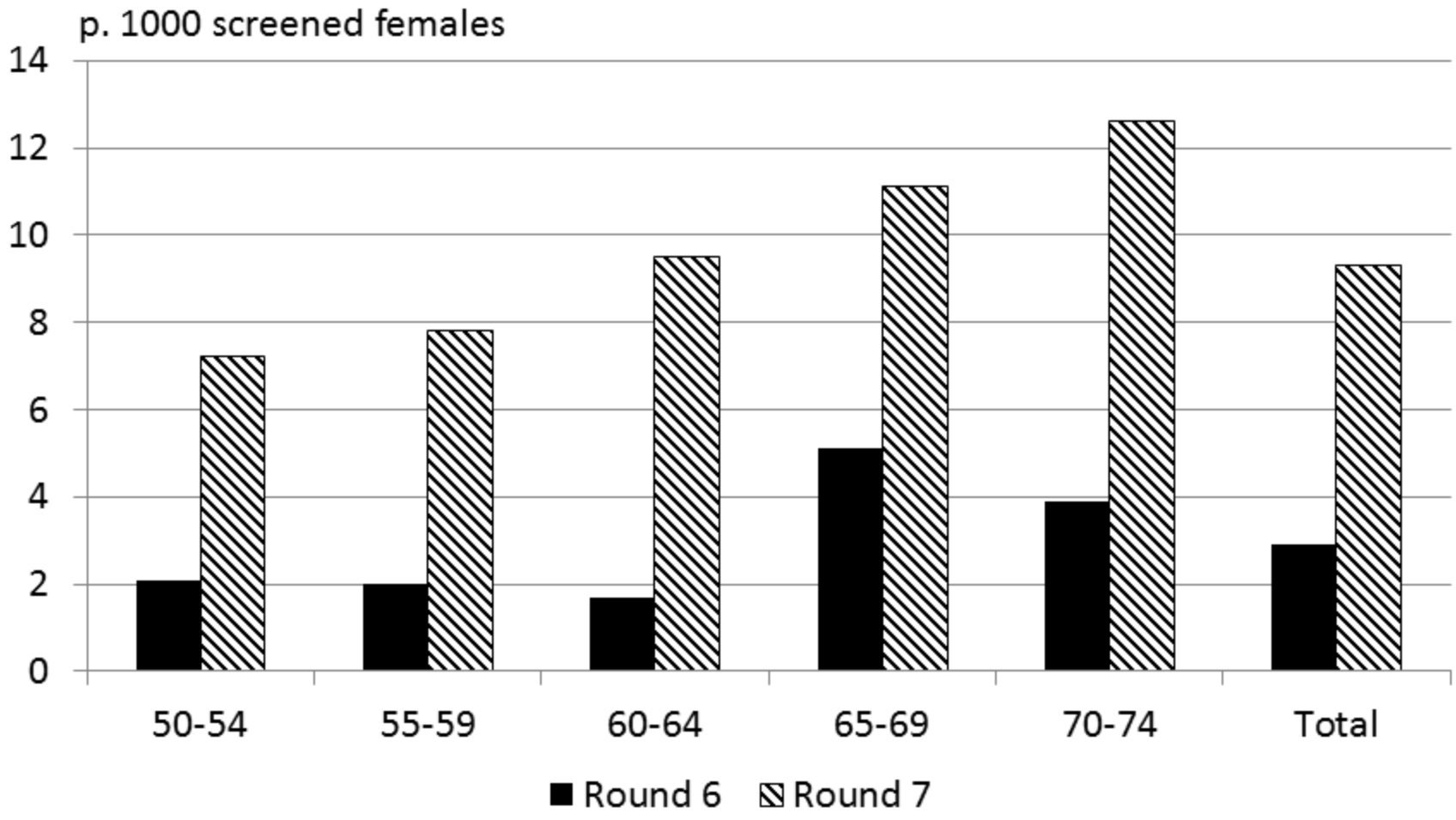
p. 1000 screened females
14
12
10
8
6
4
2
0
50-54
55-59
60-64
65-69
70-74
Total
Round 6
Round 7

Fig. 2 B

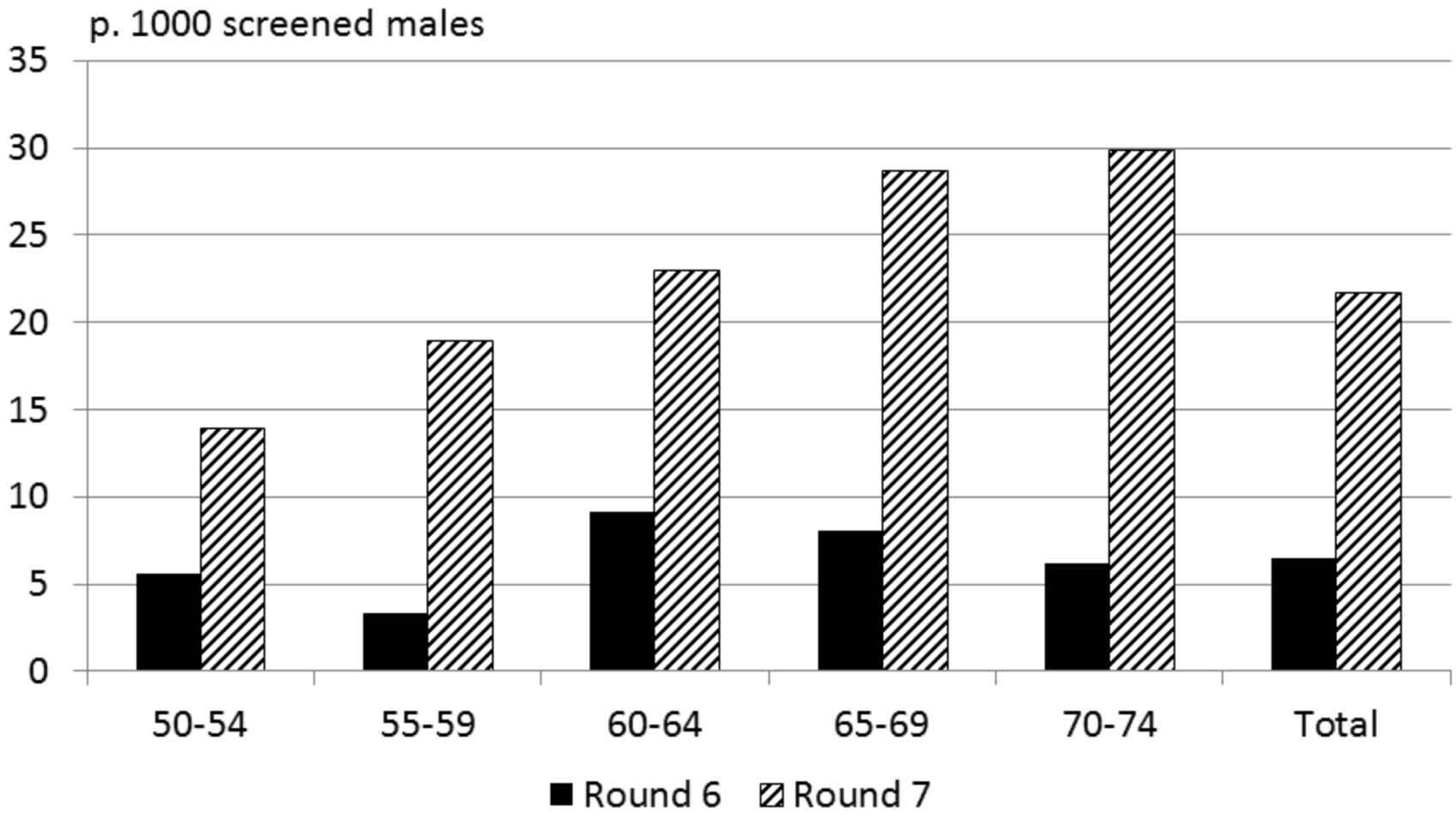
p. 1000 screened males
35
30
25
20
15
10
5
0
50-54
55-59
60-64
65-69
70-74
Total
Round 6
Round 7

Fig. 3

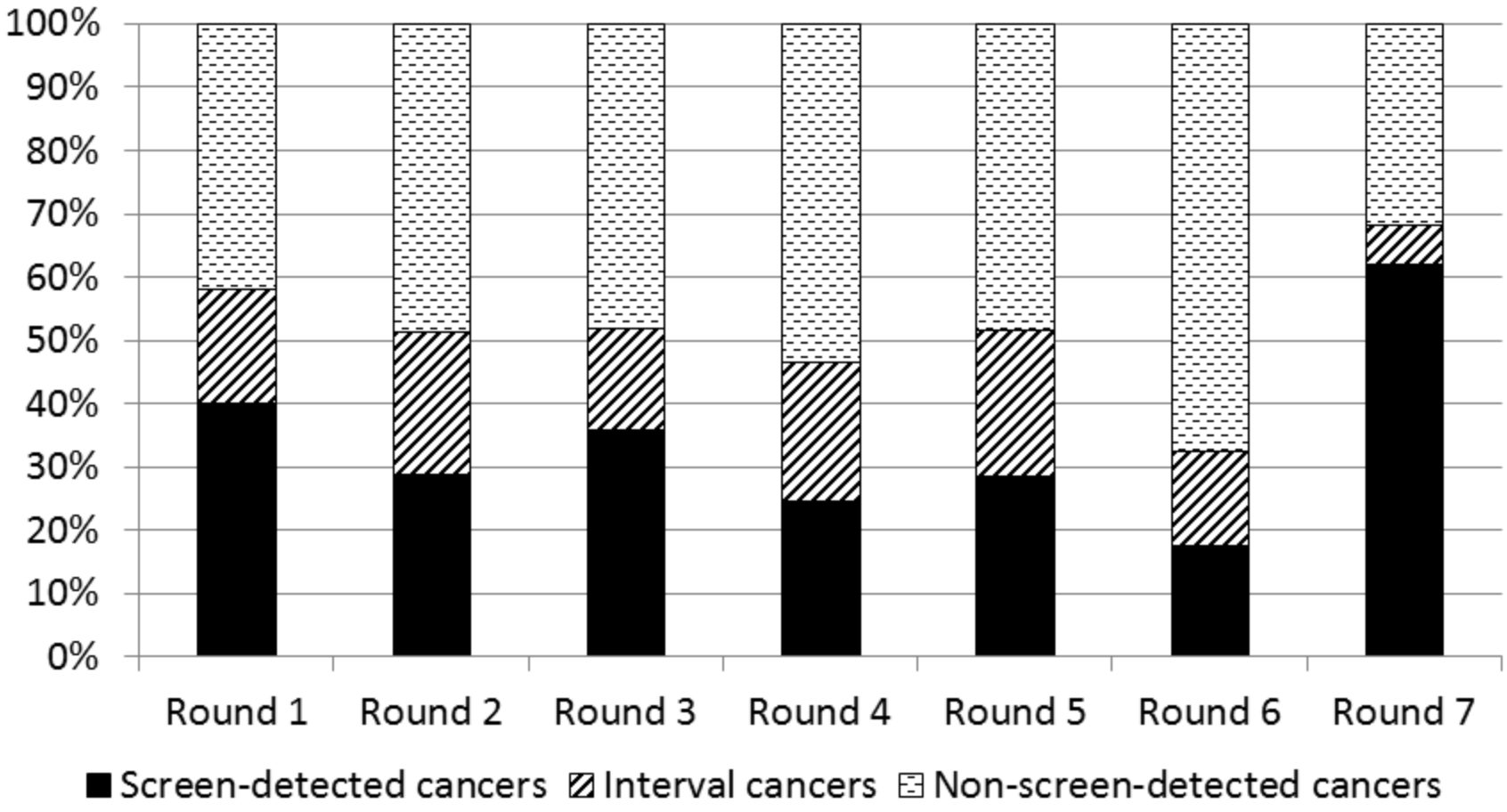
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Round 1
Round 2
Round 3
Round 4
Round 5
Round 6
Round 7
Screen-detected cancers
Interval cancers
Non-screen-detected cancers

Table 1. Demographic data, participation rates and testing positivity rates at each of the seven screening rounds.

	Round 1 2003-2005	**Round 2** 2005-2007	**Round 3** 2007-2009	**Round 4** 2009-2011	**Round 5** 2010-2012	**Round 6** 2012-2014	**Round 7** 2015-2017	**Comparison between rounds 6 and 7** **P values**
Total population at the start of the round (Million inhabitants)	0.908	0.924	0.955	0.976	0.996	1.019	1.042	
Population aged from 50 to 74 years n	218 175	226 175	232 920	241 089	249 573	258 994	269 698	
Exclusions n %	28 363 13.0	30 854 13.6	32 929 14.1	35 971 14.9	37 462 15.0	44 454 17.2	46 324 17.2	
Target population	189 812	195 321	199 991	205 118	212 112	214 540	223 374	
Males n %	90 330 47.6	93 562 47.9	95 037 47.5	97 522 47.5	101 200 47.7	102 651 47.8	107 010 47.9	
Females n %	99 482 52.4	101 759 52.1	104 954 52.5	107 596 52.5	110 912 52.3	111 889 52.2	116 364 52.1	
Population participating in the screening program								

Total n	96 829	89 285	89 138	93 429	87 127	72 642	119 233	
%	51.0	45.7	44.6	45.5	41.1	33.9	53.4	$<10^{-7}$
Males n	43 273	40 651	40 565	42 656	39 466	33 010	55 394	
%	47.9	43.4	42.7	43.7	39.0	32.2	51.8	$<10^{-7}$
Females n	53 556	48 634	48 573	50 772	47 660	39 632	63 839	
%	53.8	47.8	46.3	47.2	43.0	35.4	54.9	$<10^{-7}$
Participation rate according to age, %								
50-54	45.1	37.8	38.8	41.6	32.9	29.0	52.5	
55-59	52.3	44.4	41.0	40.7	38.2	28.9	46.9	
60-64	56.7	52.4	50.6	49.7	43.5	33.9	51.5	$<10^{-7}$
65-69	56.5	52.6	51.6	52.8	52.1	40.8	56.5	
70-74	48.1	47.9	47.1	48.7	47.3	45.6	67.6	
Distribution of attendees according to screening rank								
First screening, n	96829	25993	22669	21009	14232	14456	33454	
%	100	29.1	25.4	22.5	16.3	19.9	28.1	
Subsequent screening, n	0	63292	66469	72420	72895	58186	85779	
%	0	70.9	74.6	77.5	83.7	80.1	71.9	
Negative testing								
n	93 716	86 833	85 909	90 951	84 638	69 175	112 521	
%	96.8	97.3	96.4	97.3	97.1	95.2	94.4	

Positive testing								
n	2505	2039	2681	1936	1926	1651	5081	
%	2.59	2.28	3.01	2.07	2.21	2.27	4.26	$<10^{-7}$
Positive testing according to gender								
Males %	3.02	2.63	3.54	2.34	2.36	2.53	5.36	$<10^{-7}$
Females %	2.24	1.99	2.56	1.85	2.09	2.06	3.30	$<10^{-7}$
Positive testing according to age, %								
50-54	1.96	1.96	2.53	1.86	1.84	2.08	3.59	
55-59	2.23	2.02	2.61	1.93	2.04	1.88	3.91	
60-64	2.93	2.15	3.02	2.16	2.29	2.38	4.31	$<10^{-7}$
65-69	2.78	2.59	3.29	2.22	2.37	2.47	4.72	
70-74	3.49	2.96	4.05	2.34	2.69	2.68	5.28	
Positive testing according to screening rank								
First screening , n	2505	665	674	496	367	363	1528	
%	2.59	2.56	2.97	2.36	2.58	2.51	4.57	
Subsequent screening, n	NA	1374	2007	1440	1559	1288	3553	
%		2.17	3.02	1.99	2.14	2.21	4.14	
Non-								

analysable tests n %	608 0.63	413 0.46	548 0.61	542 0.58	563 0.65	1816 2.50	1631 1.37	
Proportion of tests which were redone among non-analysable tests, %	83.9	87.3	85.9	84.6	85.0	75.9	80.0	

Table 2. Colonoscopy characteristics and findings in the seven screening rounds.

	Round 1 2003-2005	**Round 2** 2005-2007	**Round 3** 2007-2009	**Round 4** 2009-2011	**Round 5** 2010-2012	**Round 6** 2012-2014	**Round 7** 2015-2017	**Comparison between rounds 6 and 7** **P values**
Compliance to colonoscopy among individuals with positive testing, %	93.3	92.6	94.4	93.8	93.4	93.0	91.6	
Colonoscopy								
Total, n	2 337	1 888	2 531	1 815	1 798	1 536	4 675	
Males, n	1 217	985	1 363	936	863	771	2 741	
Females, n	1 120	903	1 168	879	935	765	1 934	
Distribution of colonoscopies according to screening rank								
First screening, n	2337	603	636	458	337	339	1 370	
Subsequent screening, n	0	1 285	1 895	1 357	1 461	1 197	3 305	
Proportion of complete colonoscopy, %	96.1	96.9	97.9	96.9	95.9	97.4	97.9	
Complication rate: perforation, %	1.3	1.1	0.0	0.6	0.6	0.7	0.4	
Individuals with cancer								
Total, n	260	164	199	121	121	76	395	
First screening, n	260	56	44	37	32	18	117	

Subsequent screening , n	0	108	155	84	89	58	278	
PPV for cancer, %								
Total	11.1	8.7	7.9	6.7	6.7	4.9	8.5	
First screening	11.1	9.3	6.9	8.1	9.5	5.3	8.5	<0.001
Subsequent screening	NA	8.4	8.2	6.2	6.1	4.8	8.4	
Individuals with advanced adenoma								
Total, n	412	304	507	305	263	253	1 411	
First screening, n	412	111	115	87	58	74	408	
Subsequent screening , n	0	193	392	218	205	179	1 003	
PPV for advanced adenoma, %								
Total	17.6	16.1	20.0	16.8	14.6	16.5	30.2	$<10^{-7}$
First screening	17.6	18.4	18.1	19.0	17.2	21.8	29.8	
Subsequent screening	NA	15.0	20.7	16.1	14.0	15.0	30.3	
Individuals with low-risk adenoma								
Total, n	341	310	473	347	388	299	1 033	
First screening, n	341	105	105	79	61	48	278	
Subsequent screening , n	0	205	368	268	327	251	755	
PPV for low-risk adenoma, %								
Total	14.6	16.4	18.7	19.1	21.6	19.5	22.1	<0.03
First screening	14.6	17.4	16.5	17.2	18.1	14.2	20.3	
Subsequent								

screening	NA	16.0	19.4	19.7	22.4	21.0	22.8	
Individuals with advanced neoplasia								
Total, n	672	468	706	426	384	329	1 806	
First screening, n	672	167	159	124	90	92	525	
Subsequent screening , n	NA	301	547	302	294	237	1 281	
PPV for advanced neoplasia, %								
Total	28.8	24.8	27.9	23.5	21.4	21.4	38.7	$<10^{-7}$
First screening	28.8	27.7	25.0	27.1	26.7	27.1	38.3	
Subsequent screening	NA	23.3	28.9	22.3	20.1	19.8	38.8	
Individuals with any adenoma								
Total, n	753	614	980	652	651	552	2 444	
First screening, n	753	216	220	166	119	122	686	
Subsequent screening , n	0	398	760	486	532	430	1 758	
PPV for any adenoma, %								
Total	32.2	32.5	38.7	35.9	36.2	35.9	52.3	$<10^{-7}$
First screening	32.2	35.8	34.6	36.2	35.3	36.0	50.1	
Subsequent screening	NA	31.0	40.1	35.8	36.4	35.9	53.2	

PPV: positive predictive value NA: not applicable

Table 3. Estimates of the number needed to screen and number needed to scope for detecting one advanced neoplasia

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	Round 7	**Comparison between rounds 6 and 7 P values**
NNScreen								
Total n (95% CI)	144 (134;156)	191 (175;210)	126 118;136	219 (200;242)	227 (206;252)	221 (199;247)	66 (63;69)	$<10^{-7}$
Males n (95% CI)	97 (89;107)	132 (118;148	85 (78;93)	146 (131;165)	169 (150;193)	154 (135;177)	46 (44;49)	$<10^{-7}$
Females n (95% CI)	238 (211;274)	306 (265;362)	212 (188;244)	379 (324;456)	318 (274;378)	348 (294;426)	107 (99;116)	$<10^{-7}$
First screening, n (95% CI)	144 (134;156)	156 (135;183)	143 (123;169)	169 (144;205)	158 (131;199)	157 (131;197)	64 (59;70)	$<10^{-7}$
Subsequent Screening, n (95% CI)	NA	210 (189;237)	122 (112;132)	240 (216;270)	248 (223;280)	246 (218;281)	67 (64;71)	$<10^{-7}$
NNScope								
Total n (95% CI)	3.5 (3.3;3.7)	4.0 (3.7;4.4)	3.6 (3.4;3.8)	4.3 (3.9;4.6)	4.7 (4.3;5.1)	4.7 (4.3;5.2)	2.6 (2.5;2.7)	$<10^{-7}$
Males n (95% CI)	2.7 (2.5;2.9)	3.2 (2.9;3.5)	2.9 (2.7;3.1)	3.2 (2.9;3.5)	3.7 (3.3;4.1)	3.6 (3.2;4.0)	2.3 (2.2;2.4)	$<10^{-7}$
Females n	5.0	5.7	5.1	6.6	6.2	6.7	3.2	$<10^{-7}$

(95% CI)	(4.5;5.6)	(5.0;6.6)	(4.6;5.8)	(5.7;7.8)	(5.4;7.3)	(5.7;8.1)	(3.0;3.5)	
First screening, n	3.5	3.6	4.0	3.7	3.7	3.7	2.6	$<10^{-7}$
(95% CI)	(3.3;3.7)	(3.2;4.1)	(3.5;4.6)	(3.2;4.3)	(3.2;4.5)	(3.1;4.5)	(2.4;2.8)	
Previous screening, n	NA	4.3	3.5	4.5	5.0	5.0	2.6	$<10^{-7}$
(95% CI)		(3.9;4.7)	(3.2;3.7)	(4.1;5.0)	(4.5;5.5)	(4.5;5.7)	(2.5;2.7)	

NNScreen: number needed to screen; NNScope: number needed to scope

NA: not applicable