Abbreviated title page:

Effect of fecal occult blood positivity on detection rates and positive predictive value of CT colonography when screening for colorectal neoplasia.

Manuscript type:

Original research

Key points:

1. Detection rates of colorectal cancer, advanced neoplasia and ≥6mm polyps at CT colonography increase with higher levels of fecal occult blood, with each additional positive FOBt window increasing the odds of advanced neoplasia by approximately 17%.
2. Positive predictive value of CT colonography for advanced neoplasia increases with greater fecal occult blood positivity, ranging from 66.7% to 88.1%.
3. The number of positive FOBt windows at initial screening does not affect the stage or location of cancers diagnosed by CT colonography.
4. CT colonography may be viable as an initial whole-colon test in otherwise low risk patients with small amounts of fecal occult blood.

Keywords:

Screening, Occult blood, CT colonography, Colorectal neoplasms

Introduction

Population screening programmes for colorectal cancer (CRC) vary worldwide[1], although the commonest approach is to test stool samples for small amounts of blood (or its degradation products) – fecal occult blood testing (FOBt)[2]. Meta-analysis of 4 randomized trials which enrolled over 300,000 participants estimated the reduction in CRC mortality at approximately 16%[3]. Individuals who test FOBt-positive require further testing to confirm or refute the presence of neoplasia: Approximately 50% will have CRC or adenoma(s)[4]. The main target lesion of screening is termed advanced neoplasia, corresponding to CRC or an “advanced adenoma” (which itself is defined as an adenoma measuring ≥10mm or demonstrating high-grade dysplasia or >20% villous histology)[5]. When screening with FOBt, it is common practice to use a test kit with two separate windows in which to place the stool sample and to repeat the test on three occasions, yielding six separate results[6]. A “positive test” may therefore vary from only a single window to all six being positive. This variability influences the positive predictive value (PPV) for CRC, which ranged from 1% to 6% in the Minnesota randomised trial of FOBt screening, increasing with each additional positive window[7]. More recent observational studies have confirmed this, although generally with higher rates of CRC for a given number of positive FOBt windows[8,9].

For most screenees, colonoscopy is the preferred test following positive FOBt, since it combines diagnosis with treatment by excision biopsy for smaller

cancers and adenomas. However, a proportion of screening participants are unable to undergo total colonoscopy due to frailty, refusal or technical failure. CT colonography (CTC) is a well-tolerated alternative, with sensitivity for ≥6mm adenomas or CRC estimated at 89% by meta-analysis[10]. CTC diagnostic yield of CRC and adenomas has rarely been reported following a positive FOBt result on a population level, with one retrospective observational study reporting detection rates of 4.5% for CRC and 13.9% for advanced adenomas in patients judged relatively unsuitable for colonoscopy[11]. These detection rates were approximately 50% lower than for colonoscopy, although whether this was due to selection bias (i.e. higher incidence of false positive FOBt in patients undergoing CTC) or lower sensitivity of CTC is unknown. Furthermore, the outcome of CTC according to the number of positive FOBt windows was not reported. We are not aware of any data regarding this for CTC. Here, we report detection rates of CRC and advanced neoplasia at CTC stratified by FOBt positivity.

Materials and Methods

A waiver to publish anonymized data was obtained from our institution's research office. Data were collated from the English national Bowel Cancer Screening Programme (BCSP)[4]. English residents aged 60-74 years are invited to complete and return a postal guaiac FOBt kit to one of five regional laboratories ("screening hubs"). Individuals testing positive are invited for consultation at one of 58 "screening centres". Positive FOBt results can be stratified by the number of positive windows. If the initial test kit shows 5-6

positive windows, the result is deemed a “strong positive” and further colonic testing is immediately recommended. Alternatively, if 1-4 windows are positive, the test is repeated twice: If either subsequent kit shows any positive windows, the patient is categorized as having a “weak positive” FOBt result overall (irrespective of the number of positive windows on the follow-up kits). In either case (weak or strong positive), consenting individuals are referred for colonoscopy: Those deemed unsuitable are either discharged from the programme or referred for CTC. Two consecutive kits, each with six negative windows, are required to “over-rule” an initial FOBt kit with 1-4 positive windows and obviate the need for further colonic testing.

Data selection

Test results within the BCSP are recorded on a database termed the “Bowel Cancer Screening System” (BCSS). Using anonymised data from BCSS, we identified screenees undergoing CTC as their first colonic investigation following a positive FOBt between April 2006 and December 2013 inclusive. For each screenee, the following were extracted: (a) age, (b) sex, (c) screening centre attended, (d) screening hub processing the FOBt kit, (e) number of positive FOBt windows on the initial test kit (and, if required, any subsequent follow-up test kits for those with a weak positive initial result), (f) CTC result (including size, location and morphology of any polyp(s) diagnosed), (g) result of subsequent endoscopy (again including size, location and morphology of polyp(s) found), (h) histological type and degree of dysplasia of resected polyp(s) and (i) staging information for confirmed carcinomas. A proportion of the patients we selected (2731 of 4601, 59.4%)

have had their screening result published previously[11], although not stratified by FOBt status, which is the aim of the current study.

Statistical analysis

Data were collated using Microsoft Excel for Mac 2011 (Microsoft Corp, Redmond, WA, USA) and analyzed with R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). As histological endpoints, we analyzed the proportion of screenees with either histologically-confirmed cancer or advanced neoplasia according to the number of positive FOBt windows. For patients who returned more than one FOBt kit, we used the average number of positive windows across all FOBt kits, rounded to the nearest integer. Advanced neoplasia was defined as either CRC or an advanced adenoma (diameter ≥10mm, >20% villous features, and/or high-grade dysplasia[5]). We also analyzed the proportion of screenees with CRC or any polyp ≥6mm suspected at CTC as a radiological endpoint, to account for the fact that not all screenees with abnormal CTC will undergo confirmatory colonoscopy. Analyses used the most advanced lesion in a given individual for the histological endpoints and the largest lesion for the radiological endpoint. Per-patient positive predictive value (PPV) of CTC for advanced neoplasia was calculated as the number of screenees with advanced neoplasia divided by the number in whom CTC diagnosed a ≥6mm lesion (on the basis that this is the standard referral threshold for colonoscopy in the BCSP); binomial 95% confidence intervals were derived using the Wilson method[12].

To test whether detection rates were affected by the number of positive FOBt windows on the initial test kit, we performed multilevel binary logistic regression. The model accounted for the fact that screenees are grouped within screening centres, which themselves are grouped into screening hubs: Such clustering means there may be greater correlation between individuals within each group than those drawn from other groups. Separate models were built for the two histological endpoints and the radiological endpoint. The number of positive FOBt windows was entered as a screenee-level explanatory variable. For those screenees who required more than one FOBt kit (i.e. those testing weakly positive on their initial kit), we used the average number of positive FOBt windows across all screening kits returned, rounded to the nearest integer. Covariates were age and sex; screening centre and screening hub were entered as nested random effects terms[13]. Since the effect of FOBt positivity might not be linear, we also grouped the FOBt result into “weakly positive” (1-4 windows) and “strongly positive” (5-6 windows) as per current BCSP practice. Between-group comparisons were by the chi-squared test or Mann-Whitney U-test, as appropriate. Results were considered significant at the 5% threshold.

Results

Screenee characteristics and FOBt results

4601 screenees were included, 2109 females (45.8%) and 2492 males. Mean age was 66.7 years and was not significantly different between males (mean 66.8 years) and females (mean 66.7 years, p=0.33). The majority of

individuals who underwent CTC did so following a weakly positive result i.e. 1-4 positive windows (3788 of 4601 screenees, 82.3%). The most common FOBt result precipitating CTC was 2 positive windows (1423 of 4601 screenees, 30.9%) followed by a single positive window (1201 screenes, 26.1%). The proportion of individuals undergoing CTC who had tested weakly positive showed no significant variation by gender (females: 1749 of 2109, 82.9%; males: 2039 of 2492, 81.8%, p=0.35, Table 1). However, there was significant variation by screening hub, with the proportion of individuals testing weakly positive ranging from 78.9% (436 of 552 screenees) to 84.4% (1489 of 1765, p<0.004).

Variation in detection rates and PPV according to gender and FOBt result

Histologically confirmed lesions

Overall, 228 participants were diagnosed with cancer (5.0%) and 836 (18.2%) with either cancer or advanced adenoma (i.e. advanced neoplasia). Males had higher rates of cancer than females (155 of 2492 males, 6.2% vs 73 of 2109 females, 3.5%; X^2=17.9, p<0.001). Rates of advanced neoplasia were also significantly higher in males (both p<0.001, Table 2).

Screenees with strongly positive FOBt had higher rates of cancer (78 of 813, 9.6%) and advanced neoplasia (195 of 813, 24.0%) than those with weakly positive FOBt (cancer: 150 of 3788, 4.0%, X^2=43.9, p<0.001; advanced

neoplasia: 641 of 3788, 16.9%, X^2=22.0, p<0.001; Table 2). Furthermore, there was a progressive increase in rates of cancer and advanced neoplasia as the number of positive FOBt windows increased (Table 2, Figure). These increases were statistically significant in the multilevel logistic regression model, with the odds ratio for the detection of advanced neoplasia being 1.17 (95%CI 1.12-1.23, p<0.001); i.e. for each additional positive FOBt window, the odds of advanced neoplasia increased by 1.17. This effect was even stronger for the detection of colorectal cancer (OR 1.41, 95%CI 1.31-1.52, p<0.001). When considering FOBt as either weakly or strongly positive, the odds ratio for a strongly positive result (versus a weakly positive test) was 1.56 (95%CI 1.29-1.87, p<0.0001) for advanced neoplasia and 2.56 (95%CI 2.21-2.96, p<0.0001) for colorectal cancer (Table 3).

Radiologically detected abnormality

Consistent with endpoints based on histological confirmation, the magnitude of FOBt positivity was significantly associated with the proportion of screenees harboring a ≥6mm lesion at CTC. Of the 813 individuals testing strongly positive, 243 (29.9%) had a ≥6mm lesion reported at CTC, compared to 883 of 3788 (23.3%) screenees who had tested weakly positive (X^2=16.8, p<0.001). This difference remained significant in the regression models, whether FOBt status was treated as a linear variable (OR 1.16, 95%CI 1.11-1.21, p<0.001) or categorized as strongly vs weakly positive (OR 1.42, 95%CI 1.19-1.68, p<0.001, Table 3).

Per-patient positive predictive value for advanced neoplasia (PPV) increased with stronger FOBt positivity. Overall, 1126 individuals had a ≥6mm lesion suspected at CTC and 836 had advanced neoplasia confirmed, a PPV of 74.2% (95%CI 71.6-76.7%). This figure was significantly greater for those with a strongly positive FOBt result (195 advanced neoplasms from 243 positive CTC examinations, 80.2%, 95%CI 74.8-84.8%) than a weakly positive FOBt (641 advanced neoplasms from 883 positive CTC examinations, 72.6%, 95%CI 70.0-75.4%, p=0.020, Figure). PPV was significantly higher in males (566 advanced neoplasms from 696 positive scans, 81.3%, 95%CI 78.3-84.0) than females (270 advanced neoplasms from 430 positive scans, 62.8%, 95%CI 58.1-67.2%, p<0.001).

Stage and location of cancers detected according to FOBt result

Of the 228 cancers detected, both staging and FOBt results were available for 164 (71.9%). Overall, the stage distribution of cancers detected following strongly- and weakly positive FOBt results were similar (Table 4). There was no evidence to suggest that Dukes' stage was related to either the strength of test positivity (p=0.30) or the number of positive windows, although numbers in each category were small (Table 4).

Locations of screen-detected cancers were available in 216 cases (95.6% of all cancers): 53 (23.5%) cancers were right-sided (proximal to the splenic flexure) and 163 (72.1%) were left-sided (at or distal to the splenic flexure). The median number of positive windows for patients with right-sided cancers was 4 out of a possible 6 (interquartile range 2 to 6); for those with left-sided

cancers it was 3 (interquartile range 2 to 5); this difference was not statistically significant (p=0.20).

Discussion

CTC is intuitively attractive as an alternative to colonoscopy following positive FOBt, as it is highly sensitive and moderately specific for advanced neoplasia[10]. However, unselected use of CTC for FOBt-positive individuals (triaging those with normal results to routine screening, and those with positive CTC to colonoscopy) is unlikely to be cost-effective overall – the high prevalence of advanced neoplasia means that relatively few colonoscopies are avoided[14,15]. One cost-effectiveness study assessing CTC after positive FOBt[16] estimated only small savings (£776,283 over 10 years for 100,000 screening invitations), which would be significantly outweighed by the costs of implementing such large-scale CTC infrastructure and training. Accordingly, CTC is generally reserved for individuals who are unable or unwilling to undergo total colonoscopy after positive FOBt[17].

We found that screenees with an average of only one positive FOBt window had relatively low rates of cancer (30 of 1201 individuals, 2.5%) and advanced neoplasia (174 of 1201, 14.5%). Recent colonoscopic data from the English BCSP has confirmed that low levels of FOBt positivity are also associated with lower detection rates of CRC, confirming our result using CTC[18]. So, although CTC is a relatively ineffective follow-up colonic test when employed for all FOBt-positive patients, it is possible that in the scenario of very weak

positivity, CTC could become attractive because subsequent colonoscopic referral would be uncommon. CTC has been shown to boost compliance when targeted at FOBt-positive individuals who refuse colonoscopy[19] and in a randomised screening trial the compliance with CTC was significantly greater at 34% than that for colonoscopy (22%). In theory, such strategies might increase acceptability of the programme as a whole while also reducing overall costs. Health economic modeling studies or large prospective trials would be required to determine if substituting CTC for colonoscopy in screenes with small amounts of fecal occult blood is likely to be a net cost saving.

The positive predictive value (PPV) of CTC for advanced neoplasia also increased in line with the number of positive FOBt windows, presumably partly because cancers and large adenomas bleed more[20] and partly because of higher disease prevalence. The anatomical location of detected cancers (i.e. just over 70% left-sided) was very similar to that described in prior reports of FOBt screening[4,21]. We found there was no difference in FOBt-positivity for left- and right-sided cancers, contrasting with a colonoscopy report documenting greater FOBt-positivity for right-sided cancers[9]. There are many possible explanations for this, including differences in populations under investigation, variable sensitivity of CTC and colonoscopy for right- and left-sided lesions and underpowering due to the relatively small number of cancers included.

The main limitation of our study is the fact that the true disease status of screenees who underwent CTC alone is unknown, since those having negative CTC were not investigated further. Theoretically, any bias might be greater in screenees with weakly positive FOBt results, since they may have more subtle, early stage lesions, perhaps more easily missed by CTC. However, since our findings are consistent with the colonoscopy literature[7], it seems unlikely that this is the sole explanation for detection varying according to FOBt positivity. Nonetheless, given prior concerns regarding the low detection rate of CTC compared to colonoscopy in the English BCSP[11], we would caution against concluding that the true rate of cancer in those with a single FOBt-positive window is as low as reported here: We do not know the rate of missed cancers. Even so, irrespective of the absolute rates of cancer and advanced neoplasia, the fact that there is a considerably lower prevalence of these significant lesions in screenees with small amounts of FOBt positivity supports the hypothesis that specifically targeting CTC to these individuals may be beneficial; this area should be the subject of further study. An additional limitation is sample size: Although this is (to our knowledge) the largest reported series of CTC in FOBt-positive patients, the absolute number of cancers is relatively small at 228, meaning differences in cancer location or stage according to number of positive FOBt windows may be undetected due to low statistical power. Although data regarding FOBt status and location of cancers were almost complete, cancer staging information was frequently missing from the BCSP database. Finally, as with any central database, conclusions are dependent on the accuracy of the data

recorded: Although audit suggests accuracy of data input exceeds 90%, this may not be universal.

In summary, we found that both **the detection rate of CTC and its positive predictive value for advanced neoplasia increase in line with the number of positive windows in screenees testing positive for FOBt. In contrast, cancer stage and location were unrelated** to the magnitude of FOBt positivity. Future studies should consider the effect on compliance and screening cost-effectiveness of CTC for lower risk patients, who are relatively less likely to harbor advanced neoplasia.

Figure Legend

Figure: Left vertical axis: Percentage of screenees with cancer (triangle) or advanced neoplasia (circle). Right vertical axis: Postive predictive value of CTC for advanced neoplasia (diamond)

Acknowledgements

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References

1. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. Int. J. Cancer 2012;**130**(12):2961-73 doi: 10.1002/ijc.26310published Online First: Epub Date]|.

2. Benson VS, Patnick J, Davies AK, et al. Colorectal cancer screening: a comparison of 35 initiatives in 17 countries. Int. J. Cancer 2008;**122**(6):1357-67 doi: 10.1002/ijc.23273published Online First: Epub Date]|.

3. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007(1) doi: 10.1002/14651858.CD001216.pub2published Online First: Epub Date]|.

4. Logan RFA, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut 2012;**61**(10):1439-46 doi: 10.1136/gutjnl-2011-300843published Online First: Epub Date]|.

5. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. Gastrointestinal endoscopy clinics of North America 2002;**12**(1):1-9

6. Segnan N, Patnick J, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. Secondary European guidelines for quality assurance in colorectal cancer screening and diagnosis. 2012 2012. http://bookshop.europa.eu/en/european-guidelines-for-quality-assurance-in-colorectal-cancer-screening-and-diagnosis-pbND3210390/downloads/ND-32-10-390-EN-C/ND3210390ENC_002.pdf;pgid=lq1Ekni0.1lSR0OOK4MycO9B0000Z

33aOyCA;sid=c1hlNUHRPTVlORIfAvv7kiP0Pjt7R0YCdYs=?FileName=ND3210390ENC_002.pdf&SKU=ND3210390ENC_PDF&CatalogueNumber=ND-32-10-390-EN-C.

7. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;**343**(22):1603-7 doi: 10.1056/NEJM200011303432203published Online First: Epub Date]|.

8. Weller D, Moss S, Butler P, et al. English Pilot of Bowel Cancer Screening: an evaluation of the second round, 2006.

9. Lee TJ, Clifford GM, Rajasekhar P, et al. High yield of colorectal neoplasia detected by colonoscopy following a positive faecal occult blood test in the NHS Bowel Cancer Screening Programme. J Med Screen 2011;**18**(2):82-6 doi: 10.1258/jms.2011.011032published Online First: Epub Date]|.

10. Plumb AA, Halligan S, Pendse DA, et al. Sensitivity and specificity of CT colonography for the detection of colonic neoplasia after positive faecal occult blood testing: systematic review and meta-analysis. Eur Radiol 2014 doi: 10.1007/s00330-014-3106-0published Online First: Epub Date]|.

11. Plumb AA, Halligan S, Nickerson C, et al. Use of CT colonography in the English Bowel Cancer Screening Programme. Gut 2013 doi: 10.1136/gutjnl-2013-304697published Online First: Epub Date]|.

12. Wilson E. Probable inference, the law of succession, and statistical inference. Journal of the American Statistical Association 1927;**22**(158):209-12

13. lme4: Linear mixed-effects models using Eigen and S4 [program]. 1.0-5 version, 2013.

14. Liedenbaum MH, de Vries AH, van Rijn AF, et al. CT colonography with limited bowel preparation for the detection of colorectal neoplasia in an FOBT positive screening population. Abdominal Imaging 2010;**35**(6):661-68 doi: 10.1007/s00261-009-9586-8published Online First: Epub Date]|.

15. Liedenbaum MH, van Rijn AF, de Vries AH, et al. Using CT colonography as a triage technique after a positive faecal occult blood test in colorectal cancer screening. Gut 2009;**58**(9):1242-49 doi: 10.1136/gut.2009.176867published Online First: Epub Date]|.
16. Sweet A, Lee D, Gairy K, et al. The impact of CT colonography for colorectal cancer screening on the UK NHS: costs, healthcare resources and health outcomes. Appl Health Econ Health Policy 2011;**9**(1):51-64 doi: 10.2165/11588110-000000000-00000published Online First: Epub Date]|.
17. Spada C, Stoker J, Alarcon O, et al. Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline. Endoscopy 2014;**46**(10):897-915 doi: 10.1055/s-0034-1378092published Online First: Epub Date]|.
18. Geraghty J, Butler P, Seaman H, et al. Optimising faecal occult blood screening:retrospective analysis of NHS Bowel Cancer Screening data to improve the screening algorithm. Br J Cancer 2014;**111**(11):2156-62 doi: 10.1038/bjc.2014.480published Online First: Epub Date]|.
19. Sali L, Grazzini G, Ventura L, et al. Computed tomographic colonography in subjects with positive faecal occult blood test refusing optical colonoscopy. Dig Liver Dis 2013;**45**(4):285-89 doi: 10.1016/j.dld.2012.11.008published Online First: Epub Date]|.
20. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007;**146**(4):244-55
21. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;**348**(9040):1472-77 doi: 10.1016/S0140-6736(96)03386-7published Online First: Epub Date]|.

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Figure 1
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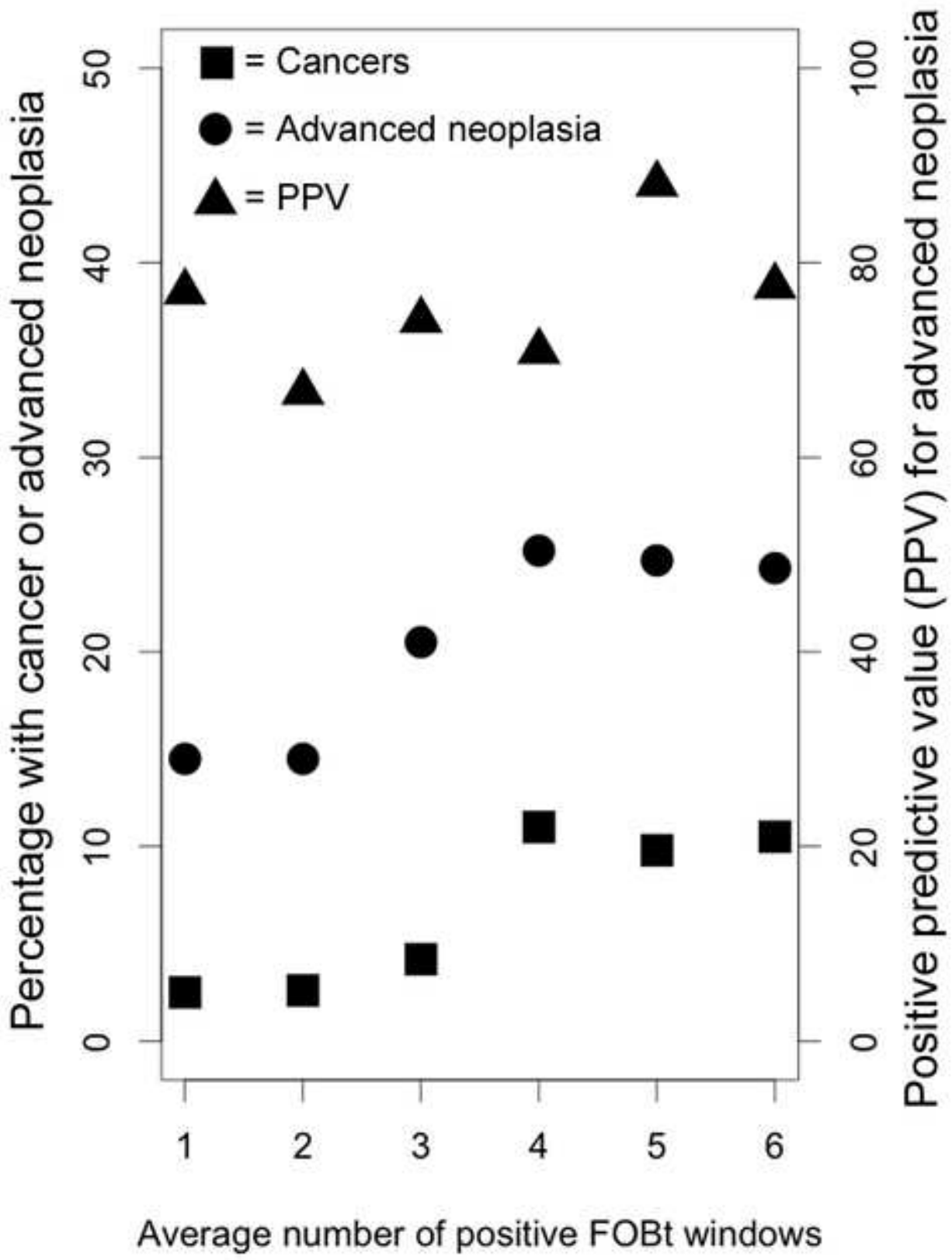

Table 1 – Demographics and overall FOBt result for included participants

	Average number of positive FOBt windows							Overall		Total (any positive FOBt result)
Number of screened individuals	**1**	**2**	**3**	**4**	**5**	**6**	**Unknown**	**Weakly positive (1-4 windows)**	**Strongly positive (5 or 6 windows)**	
Males (% of all males)	667 (26.8)	734 (29.5)	394 (15.8)	162 (6.5)	210 (8.4)	317 (12.7)	8 (0.32)	2039 (81.8)	453 (18.2)	2492
Females (% of all females)	534 (25.3)	689 (32.7)	318 (15.1)	147 (7.0)	178 (8.4)	238 (11.3)	5 (0.24)	1749 (82.9)	360 (17.1)	2109
Both sexes (% of total)	1201 (26.1)	1423 (30.9)	712 (15.5)	309 (6.7)	388 (8.4)	555 (12.1)	13 (0.28)	3788 (82.3)	813 (17.7)	4601

Table 2 – Detection rates of cancer, advanced neoplasia, ≥6mm radiologically-suspected lesions and per-patient positive predictive value (PPV) according to gender and average number of positive FOBt windows. Percentages use the number of screenees of the relevant gender and FOBt result as the denominator (see Table 1).

	Average number of positive FOBt windows						Overall		Total (any positive FOBt result)
	1	2	3	4	5	6	Weakly positive (1-4 windows)	Strongly positive (5 or 6 windows)	
Both sexes									
Cancer (%)	30 (2.5)	37 (2.6)	30 (4.2)	34 (11.0)	38 (9.8)	58 (10.5)	150 (4.0)	78 (9.6)	228 (5.0)
Advanced neoplasia (%)	174 (14.5)	206 (14.5)	146 (20.5)	78 (25.2)	96 (24.7)	135 (24.3)	641 (16.9)	195 (24.0)	836 (18.2)
Any radiology lesion ≥6mm (%)	226 (18.8)	309 (21.7)	197 (27.7)	110 (35.6)	109 (28.1)	174 (31.4)	883 (23.3)	243 (29.9)	1126 (24.5)
PPV for advanced neoplasia (95% CI)	77.0 (71.1-82.0)	66.7 (61.2-71.7)	74.1 (67.6-80.0)	70.9 (61.8-78.6)	88.1 (80.6-92.9)	77.6 (70.8-83.1)	72.6 (70.0-75.4)	80.2 (74.8-84.8)	74.2 (71.6-76.7)
Males									
Cancer (%)	24 (3.6)	19 (2.6)	19 (4.8)	22 (13.6)	24 (11.4)	46 (14.5)	98 (4.8)	57 (12.6)	155 (6.2)
Advanced neoplasia (%)	125 (18.7)	133 (18.1)	97 (24.6)	45 (27.8)	63 (30.0)	102 (32.2)	426 (20.9)	140 (30.9)	566 (22.7)
Any radiology lesion ≥6mm (%)	140 (21.0)	182 (24.8)	128 (32.5)	59 (36.4)	68 (32.4)	118 (37.2)	536 (26.3)	160 (35.3)	696 (27.9)
PPV for advanced neoplasia (95%CI)	89.3 (83.1-93.4)	73.1 (66.2-79.0)	75.8 (67.7-82.4)	76.3 (64.0-85.3)	92.6 (83.9-96.8)	86.4 (79.1-91.5)	79.5 (75.9-82.7)	87.5 (81.5-91.8)	81.3 (78.3-84.0)
Females									
Cancer (%)	6 (1.1)	18 (2.6)	11 (3.5)	12 (8.2)	14 (7.9)	12 (5.0)	52 (3.0)	21 (5.8)	73 (3.5)
Advanced neoplasia (%)	49 (9.2)	73 (10.6)	49 (15.4)	33 (22.4)	33 (18.5)	33 (13.9)	215 (12.3)	55 (15.3)	270 (12.8)
Any	86	127	69	51	41	56	347	83	430

radiology lesion ≥6mm (%)	(16.1)	(18.4)	(21.7)	(34.7)	(23.0)	(23.5)	(19.8)	(23.1)	(20.4)
PPV for advanced neoplasia (95%CI)	57.0 (46.4-66.9)	57.5 (48.8-65.7)	71.0 (59.4-80.0)	64.7 (51.0-76.4)	80.5 (66.0-90.0)	58.9 (45.9-70.8)	62.0 (56.7-66.9)	66.3 (55.6-75.5)	62.8 (58.1-67.2)

Table 3 – Factors associated with diagnosis of cancer, advanced neoplasia and any ≥6mm radiologically-diagnosed lesion following a positive FOBt result, derived by logistic regression and expressed as odds ratios.

	Cancer (95%CI)	**p**	**Advanced neoplasia (95%CI)**	**p**	**Any ≥6mm radiology lesion (95%CI)**	**p**
Considering the FOBt result as a linear variable (i.e. 1 to 6 positive windows)						
Age (per year increase)	1.06 (1.03-1.09)	<0.001	1.03 (1.01-1.05)	<0.001	1.04 (1.03-1.06	<0.001
Male sex (vs female)	1.82 (1.37-2.43)	<0.001	2.00 (1.71-2.35)	<0.001	1.52 (1.32-1.74)	<0.001
Number of positive FOBt windows (per additional positive window)	1.41 (1.31-1.52)	<0.001	1.17 (1.12-1.23)	<0.001	1.16 (1.11-1.21)	<0.001
Considering the FOBt result as a binary variable (i.e. weakly or strongly positive)						
Age (per year increase)	1.06 (1.03-1.09)	<0.001	1.03 (1.01-1.05)	<0.001	1.04 (1.03-1.06)	<0.001
Male sex (vs female)	1.83 (1.37-2.43)	<0.001	2.00 (1.70-2.34)	<0.001	1.52 (1.32-1.74)	<0.001
Strongly positive FOBt result (vs weakly positive)	2.56 (2.21-2.96)	<0.001	1.56 (1.29-1.87)	<0.001	1.42 (1.19-1.68)	<0.001

Table 4 – Number (percentage) of patients with cancer of each Duke's stage, according to degree of FOBt positivity. Percentages use the total number of patients with a given FOBt result as the denominator.

	Average number of positive FOBt windows						**Overall FOBt result**		**Total**
Duke's stage	**1**	**2**	**3**	**4**	**5**	**6**	**Weakly positive**	**Strongly positive**	
A	9	9	6	9	11	8	37	15	52
(%)	(26.5)	(24.3)	(20.0)	(26.5)	(28.9)	(13.8)	(24.7)	(19.2)	(22.8)
B	7	8	7	9	9	21	36	25	61
(%)	(20.6)	(21.6)	(23.3)	(26.5)	(23.7)	(36.2)	(24.0)	(32.1)	(26.8)
C	3	8	6	7	4	12	26	14	40
(%)	(8.8)	(21.6)	(20.0)	(20.6)	(11.5)	(20.7)	(17.3)	(17.9)	(17.5)
D	2	0	0	2	2	5	5	6	11
(%)	(5.9)	(0.0)	(0.0)	(5.9)	(5.3)	(8.6)	(3.3)	(7.7)	(4.8)
Missing	10	12	11	7	12	12	46	18	64
(%)	(29.4)	(32.4)	(36.7)	(20.6)	(31.6)	(20.7)	(30.7)	(23.1)	(28.1)
Total	31	37	30	34	38	58	150	78	228
(%)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)

Highlights:

1. Detection rates at CTC increase with higher levels of fecal occult blood (FOB)
2. Positive predictive value of CTC increases with greater FOB positivity
3. Stage and location of cancers are not affected by magnitude of FOB positivity.
4. CTC may be valuable for otherwise low-risk patients with small amounts of FOB.