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Interval cancers in the Scottish Bowel Screening Programme

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SIGNIFICANCE OF THE STUDY

What is already known about this subject?

Interval cancers have been observed to occur in biennial gFOBT-based pilot colorectal cancer screening programmes in substantial numbers.

When compared with screen-detected cancers, interval cancers are more likely to arise in women and the right colon.

When compared with screen-detected cancers, more interval cancers are diagnosed at a more advanced stage, but not as advanced as cancers arising in non-participants.

What are the new findings?

In a fully rolled-out gFOBT screening programme, interval cancers account for around 50% of the cancers diagnosed in the screened population.

Although right-sided cancers are commoner in women, and are more likely to be interval cancers, the gender bias favouring screen-detection in men is independent of tumour site.

Although screen-detected colonic cancers are less advanced at diagnosis than interval cancers, this is not the case in the rectum.

How might it impact on clinical practice in the foreseeable future?

To achieve informed choice, the risk of interval cancer must be made explicit to the population offered screening for colorectal cancer.

Gender imbalance in screening needs to be addressed by considering the use of gender partitioned faecal haemoglobin cut-off concentrations.

Strategies are required to reduce the interval cancer rates and to improve the early detection of rectal cancer.

ABSTRACT

Objective To study the prevalence and the characteristics of interval cancers arising in the Scottish Bowel Screening Programme, and to compare them with screen-detected cancers and cancers in non-participants arising in the same time period.

Design Observational study done in the Scottish Bowel Screening Programme, consisting of biennial guaiac faecal occult blood testing (gFOBT) offered as the initial test to all between the ages of 50-74 years. All individuals (772,790) invited to participate in bowel screening in Scotland between 01/01/2007 and 31/05/2009 were studied by linking their screening records with confirmed colorectal cancer records in the Scottish Cancer Registry (SCR). Numbers and characteristics of screen-detected (SC), interval (IC) and non-participant (NPC) cancers were determined.

Results In the study period, there were 555 SC, 502 IC and 922 NPC. Overall, SC were diagnosed at an earlier stage than IC and NPC, screening preferentially detected cancers in males (as evidenced by the significant gender difference in the proportion of SC and IC), and this was independent of a different cancer site distribution in males and females. Although SC in the colon were less advanced than IC, this was not the case in the rectum.

Conclusion Colorectal IC account for around half of all cancers diagnosed in the screened population, indicating a test sensitivity of around 50% for gFOBT. It is clear that the sensitivity of gFOBT is less for women than for men: gFOBT screening may not be effective for rectal cancer.

INTRODUCTION

In the context of iterative cancer screening, the term “interval cancer” denotes a cancer that has been diagnosed after a negative screening test result in the interval before the participant has had an opportunity to repeat the test.[1] Thus, in colorectal cancer (CRC)

screening programmes that use biennial guaiac faecal occult blood testing (gFOBT) as the initial investigation, such as are currently in place across the United Kingdom, an interval cancer (IC) represents a cancer that has been diagnosed within two years of a negative test result.

While CRC may arise *de novo* in the interval between screening invitations, this is almost certainly a rare event, and, for the most part interval cancers (IC) are likely to be cancers that have been missed by the screening test, either at a non-invasive (adenoma) or an earlier invasive stage. The percentage of cancers arising in the screened population that are IC is therefore a key performance indicator of a population screening programme, since it provides a pragmatic index of test sensitivity, i.e., the ability of the test to detect CRC.

Despite this, relatively little is known about IC in CRC screening programmes. World-wide, the most commonly employed non-invasive CRC screening test involves the detection of haemoglobin in faeces, and this is predicated on the results of population-based trials of gFOBT, all of which demonstrated a reduction in disease-specific mortality with biennial screening.[2] However, these studies have little data on interval cancers, and there have been only two reports describing the pattern of IC occurrence in pilot studies of gFOBT screening, one from Scotland[3] and one from Catalonia,[4] and none from fully rolled out national programmes.

In Scotland, after a demonstration pilot[5] based on the Nottingham randomised trial[6] and running from 01/03/2000 to 31/05/2007 for individuals aged 50-69 years, CRC screening was rolled out across the country starting on 01/06/2007 and was offered to all those between the ages of 50 and 74 years. Here, the characteristics of IC arising in all individuals invited to participate in the Scottish Bowel Screening Programme between 01/06/2007 and 31/05/2009 and followed up until 30/11/2011 are reported. This interval was chosen to allow time for reliable identification of the interval cancers from the Scottish Cancer Registry and to ensure that complete data for CRC was available on the Registry. We also compare the IC

with the screen detected cancers (SC) and the cancers diagnosed in those who chose not to participate in screening during the same time period, termed non-participant cancers (NPC).

METHODS

When the Scottish Bowel Screening Programme (SBoSP) was rolled out to the rest of the country, the screening process differed from that employed in the pilot in two important respects. Firstly, the age range was extended form 50-69 years to 50-74 years. Secondly, instead of using a second gFOBT for a weak positive result (i.e. for those who had one to four of the six windows positive in the gFOBT), a qualitative faecal immunochemical test (FIT) (hema-screen SPECIFIC, Immunostics Inc, Ocean, NJ, USA) was employed.[7] This was based on work that had demonstrated improved performance of this novel two-tier reflex gFOBT/FIT screening algorithm in terms of fewer false positives.[8]

For the purposes of this report, the following definitions were employed: a screen-detected cancer (SC) was defined as a CRC diagnosed as a result of investigations (usually colonoscopy) carried out in response to a positive test result, an interval cancer (IC) was defined as a CRC diagnosed within two years of a negative test result and a non-participant cancer (NPC) was defined as a cancer arising in an individual who had been invited to participate in the SBoSP but had not done so. A missed cancer was defined as a CRC diagnosed within two years of a negative colonoscopy carried out in response to a positive test result and a miscellaneous cancer as a CRC diagnosed in an individual who either defaulted before a final test result was achieved, refused investigation after a positive test result, was found to be unfit for colonoscopy, was already undergoing investigations for symptoms, was admitted as an emergency, or died between screening investigations.

A right-sided (R) colonic cancer was defined as a cancer recorded as being between the caecum and the splenic flexure, a left-sided (L) colonic cancer as a cancer between (and including) the splenic flexure and the rectosigmoid junction and a rectal (RE) cancer as a cancer in the rectum or recto-sigmoid junction. There were also a small number of not

otherwise specified colonic cancers (NoSC), which are included in the analyses for completeness.

In order to categorise the CRC in the manner described above, all screening records were linked with confirmed CRC records in the Scottish Cancer Registry (SCR). This permitted the calculation of the time between the final test result being generated and the date that the CRC was diagnosed.

The stage at diagnosis of the CRCs was described using the Dukes' staging system and, although polyp cancers (cancers removed by polypectomy at colonoscopy) were identifiable in the SC group, such data were unavailable from the registry data. Thus, all polyp cancers were included in the "A" Dukes' category for the current analysis.

Socio-economic deprivation was estimated using the Scottish Index of Multiple Deprivation (SIMD), which is based on small area data zones each containing around 250 households which can be identified by postcode. Seven different aspects of deprivation are identified in the SIMD: employment, income, health, education, access to services, crime and housing. The index provides a relative ranking for each data zone and this is commonly divided into quintiles, with quintile 1 representing the most deprived, and 5 the least deprived.

The SCR utilises multiple sources and routine indicators of data quality indicate very nearly complete case ascertainment. A study of the year 1992 estimated completeness of ascertainment of 96.5% for all cancers and 98.5% for CRC.[9]

In all cases, the Chi-squared test was used to test the statistical significance of the distribution of the results.

RESULTS

Between 01/06/2007 and 31/05/2009, 772,790 screening invitations were issued and 417,354 final test results were obtained (an overall uptake of 54%). In this population, there

were 555 SC, 502 IC and 922 NPC diagnosed. Table 1 shows the complete breakdown of all the categories and the overall gender and stage distributions.

Tables 2-6 show the distribution of gender, stage, tumour site, age and deprivation categories in SC, IC and NPC. Table 2 shows a highly statistically significant difference in the gender distribution of SC compared to IC, with a greater preponderance of males in the SC than in the IC category. There were also more males than females amongst the NPC, and this was less pronounced than in the SC and more than in the IC groups. In Table 3, it can be seen that the stage distribution was more favourable in the SC group than in both the IC and NPC groups, and that the distribution in the IC group was more favourable than in the NPC group. The site distribution, shown in Table 4, indicates that R colon cancers were less common in the SC group than in either the IC or the NPC groups. The age distribution (Table 5) indicates a younger population in the NPC group than the SC group, but little difference between SC and IC or IC and NPC. In Table 6, it is demonstrated that there was a trend towards the more deprived end of the spectrum in the NPC group when compared to both SC and IC, but no difference between SC and IC groups.

Overall, when stage was examined by site, it was clear that RE and L colon cancers tended to present at an earlier stage than R colon cancers (Table 7) and that males had a lower proportion of R colon cancers that females (Table 8). There did not, however, appear to be any significant difference in stage at presentation between males and females (Table 9).

Since both stage and screen detection are therefore related to site, the stage at presentation was broken down by site and screening status (Table 10). This demonstrated that SC had a more favourable stage distribution than IC and NPC in both the R and L colons, but that there was no difference between IC and NPC. In the RE, however, there was no difference in the stage distribution between SC and IC, but both had a significantly more favourable distribution than NPC.

Additionally, since screen-detection was found to be related to both gender and site, SC and IC were broken down by site for males and females separately. This is shown in Table 11, which demonstrates that SC were more common in males for both R and L cancers, but not significantly so for RE.

DISCUSSION

This detailed study of cancers diagnosed in the population invited to participate in the SBoSP confirms that screen-detected cancers are diagnosed at an earlier stage than interval cancers and non-participant cancers, that screening preferentially detects cancers in males (as evidenced by the significant gender difference in the proportion of screen detected and interval cancers), that cancers in the right colon are less common in the screen-detected group, that right-sided colon cancers have a less favourable stage distribution than left-sided and that right-sided cancers are less commonly seen in males than females. In addition to confirming, in more detail, previous reports both by our group[3] and others[3,10], the results described here pose two important new questions. Firstly, since right-sidedness is associated with both poorer stage and a resistance to screen-detection, is early diagnosis by screening a function of the site of the tumour? Secondly, since right-sidedness is associated with female gender as well as a resistance to screen-detection, is the well-documented better sensitivity of gFOBT screening in males compared with females also related to tumour site?

We have been able to answer these questions from this analysis. It is clear that both right-sided and left-sided screen-detected colonic cancers do have a more favourable stage distribution than either interval cancers or non-participant cancers, indicating that the screening process does indeed identify earlier stage disease in the colon. In the rectum, however, this does not seem to be the case. The stage distribution was very similar in the screen-detected and the interval cancers, and both were more favourable than non-participant cancers.

It is interesting to speculate why this should be. Rectal cancer more often presents with rectal bleeding than colon cancer, and in the Nottingham trial of gFOBT screening, it was observed that, during the study, the stage at presentation of rectal cancer improved in the control group as well as in the group offered screening, but that this was not seen in colon cancer.[11] It can be hypothesised that this was caused by a halo effect of the screening programme which raised awareness of the significance of the presence of frank blood seen in faeces, both in those not offered screening, and amongst general practitioners. A similar argument may be applied to our findings; it is possible that those who had taken up the offer of screening had an already heightened awareness of the implications of rectal bleeding, so that when this occurred after a negative test result, they engaged with primary care promptly, whereas those who had not taken up the offer of screening were less likely to appreciate the importance of this symptom, either because they were less health conscious or because they had not been exposed to the messages delivered by engaging with the SBoSP.

We have also been able to show that screen-detection occurs more often in males than in females in both the right and the left colon. This may also be the case in the rectum, although this did not reach statistical significance. Thus the difference in sensitivity of gFOBT for CRC between males and females is not explained by the gender difference in tumour site. Why this difference in sensitivity should exist is not clear but, in an evaluation of quantitative faecal immunochemical testing (FIT) in a population in Scotland, we have shown that men tend to have significantly higher faecal haemoglobin concentrations than women.[12]This finding, although currently of obscure aetiology, may explain the differential sensitivity phenomenon.

Our findings with respect to age and deprivation are also worth comment. Firstly, the age of people diagnosed with screen-detected disease was slightly greater than those with CRC who had not participated in screening. This is in keeping with previous findings that uptake of screening and faecal haemoglobin concentrations tend to increase with age,[12] and this may have the effect of exaggerating the association between age and CRC risk. Secondly,

both the screen-detected and interval cancer groups exhibited a deprivation gradient, with more cancers being diagnosed in the less deprived categories, and this was not seen amongst the non-participants. This undoubtedly reflects the well-described deprivation gradient associated with screening uptake and the decrease of positive predictive value of gFOBT with increasing deprivation.[13]

CONCLUSIONS

In summary, this study is the first to address interval cancers in a rolled-out national population-based screening programme for colorectal cancer using gFOBT as the initial screening modality. It demonstrates that interval cancers make up a substantial proportion of cancers diagnosed in the screened population when a biennial gFOBT-based algorithm yielding a positivity of around 2% is used, and serves to reinforce current advice to participants not to regard a negative test result as a "certificate of health" and not to ignore symptoms. It is likely that the proportion of interval cancers will increase with time, as demonstrated in our previous study of three biennial pilot screening rounds,[5] but it is not yet clear at what level and when this proportion will plateau. In any event, moving into the future, an interval cancer rate of this magnitude is unlikely to be acceptable to the population being offered screening and efforts to overcome this problem constitute an essential component of screening research and development.

It is also interesting that rectal cancer is diagnosed at roughly the same stage in the group accepting screening regardless of whether or not the gFOBT result is positive or negative, suggesting that an alternative strategy may be required to detect rectal cancer more effectively through screening.

Finally, women are at a disadvantage in colorectal cancer screening employing gFOBT, both because they are at higher risk of right-sided cancers, which are less likely to generate a positive test result, and because they are inherently less likely to have a positive test result with CRC at any site.

The solution to these issues may be multifactorial, and a screening programme that offers both faecal testing for the presence of blood and endoscopy of the rectum and distal colon may pay dividends.[14] equally important, however, is the advent of the use of automated quantitative faecal immunochemical test (FIT) analysis which offers a much more flexible approach to CRC screening. Using this technology, it is possible to set the cut-off faecal haemoglobin (f-Hb) concentration to suit colonoscopy capacity and to take account of gender and age differences in f-Hb concentrations[12]. In addition, it is plausible that decreasing the cut-off used so as to increase the sensitivity while extending the screening interval to offset the increase in colonoscopy demand or determining the screening interval on the basis of the index f-Hb could improve the performance of a screening programme.

Contributors

RJCS conceived the study, prepared the first draft of the manuscript, and is the guarantor for the study. GS, JL and DHB provided data, performed the statistical analyses, participated in the analysis of results, and contributed to the writing of the manuscript. FAC directed the pathological and histological examination of lesions found at colonoscopy, participated in analysis of results, and contributed to the writing of the manuscript. CGF directed the FOBT analyses, participated in analysis of results, and contributed to the writing of the manuscript.

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Competing interests

CGF has acted as a consultant for Immunostics Inc., Mode Diagnostics and Kyowa-Medex Co. ltd, and has received support for travel from Alpha Labs Ltd. All other authors declare no competing interests.

Ethics approval

Not required.

Data sharing

Data sharing should be discussed with Professor RJC Steele, corresponding author.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Table 1 Overall distribution of cancers

Cancer category	%	n
Screen detected cancer	**25.7**	555
Interval cancers	**23.2**	502
Missed cancers	**0.5**	12
Miscellaneous cancers	**7.9**	170
Non-participant cancers	**42.7**	922
Total		**2161**

Gender	%	n
Males	**59.2**	1279
Females	**40.8**	882

Stage	%	(n)
A	**20.5**	442
B	**24.9**	539
C	**27.7**	599
D	**16.5**	356
Unknown (UK)	**10.4**	225

Table 2 Distribution of screen-detected (SC), interval (IC) and non-participant (NPC) cancers by gender

Gender	SC		IC		NPC	
	%	(n)	%	(n)	%	(n)
Male	**64.7**	(359)	**52.8**	(265)	**59.7**	(550)
Female	**35.3**	(196)	**47.2**	(237)	**40.3**	(372)
Total		555		502		922

SC vs IC: $\chi 2 = 15.42$ $p<0.0001$

IC vs NPC: $\chi 2 = 6.26$ $p=0.0123$

SC vs NPC: $\chi 2 = 3.71$ $p=0.0542$

Table 3 Distribution of screen-detected (SC), interval (IC) and non-participant (NPC) cancers by stage

Stage	SC		IC		NPC	
	%	(n)	%	(n)	%	(n)
A	**33.9**	(188)	**18.7**	(94)	**11.3**	(104)
B	**25.6**	(142)	**25.5**	(128)	**25.3**	(233)
C	**25.2**	(140)	**28.5**	(143)	**29.3**	(270)
D	**6.3**	(35)	**18.9**	(95)	**21.5**	(199)
UK	**9**	(50)	**8.4**	(42)	**12.6**	(116)
Total		555		502		922

SC vs IC: $\chi 2 = 57.97$ $p<0.0001$

IC vs NPC: $\chi 2 = 19.35$ $p=0.0007$

SC vs NPC: $\chi 2 = 146.50$ $p<0.0001$

Table 4 Distribution of screen-detected (SC), interval (IC) and non-participant (NPC) cancers by site

Site	SC		IC		NPC	
	%	(n)	%	(n)	%	(n)
R	**27.9**	(155)	**39.2**	(197)	**36.0**	(332)
L	**37.7**	(209)	**23.7**	(119)	**25.0**	(230)
NSC	**3.2**	(18)	**4.8**	(24)	**5.4**	(50)
RE	**31.2**	(173)	**32.3**	(162)	**33.6**	(310)
Total		555		502		922

SC vs IC: $\chi 2 = 28.33$ $p<0.0001$

IC vs NPC: $\chi 2 = 1.56$ $p=0.6694$

SC vs NPC: $\chi 2 = 29.91$ $p<0.0001$

Table 5 Distribution of screen-detected (SC), interval (IC) and non-participant (NPC) cancers by age group

Age	SC		IC		NPC	
	%	(n)	%	(n)	%	(n)
50 - 54	**8.3**	(46)	**10.2**	(51)	**12.7**	(117)
55 - 59	**12.2**	(68)	**12.5**	(63)	**13.1**	(121)
60 - 64	**18.6**	(103)	**21.5**	(108)	**19.9**	(183)
65 - 69	**26.8**	(149)	**22.7**	(114)	**18**	(166)
70 - 74	**34.1**	(189)	**33.1**	(166)	**36.3**	(335)
Total		555		502		922

SC vs IC: $\chi 2 = 4.07$ $p=0.3969$

IC vs NPC: $\chi 2 = 6.93$ $p=0.1394$

SC vs NPC: $\chi 2 = 19.79$ $p=0.0006$

Table 6 Distribution of screen-detected (SC) , interval (IC) and non-participant (NPC) cancers by deprivation category (Depcat) (1- most deprived, 5 – least deprived)

Depcat	SC		IC		NPC	
	%	(n)	%	(n)	%	(n)
1	**12.4**	(69)	**11.5**	(58)	**17**	(157)
2	**19.3**	(107)	**15.3**	(77)	**23.4**	(216)
3	**19.5**	(108)	**22.3**	(112)	**20.2**	(186)
4	**25.1**	(139)	**24.2**	(121)	**20.6**	(190)
5	**23.7**	(132)	**26.7**	(134)	**18.8**	(173)
Total		555		502		922

SC vs IC: $\chi 2 = 4.53$ p=0.3387

IC vs NPC: $\chi 2 = 28.80$ p<0.0001

SC vs NPC: $\chi 2 = 14.89$ p=0. 0075

Table 7 Overall relationship between tumour site and stage (R – right colon **L** – left colon **NoSC** – not otherwise specified colon **RE** – rectal including recto-sigmoid)

Stage	R		L		NoSC		RE	
	%	(n)	%	(n)	%	(n)	%	(n)
A	**13.4**	(98)	**23.4**	(145)	**18.4**	(18)	**25.5**	(181)
B	**31.7**	(233)	**26.7**	(165)	**16.4**	(16)	**17.6**	(125)
C	**31.6**	(232)	**24.9**	(154)	**21.4**	(21)	**27.1**	(192)
D	**17.2**	(126)	**15.8**	(98)	**31.6**	(31)	**14.2**	(101)
UK	**6.1**	(45)	**9.2**	(57)	**12.2**	(12)	**15.6**	(111)
Total		734		619		98		710

$\chi^2 = 118.61$ DoF = 12 p<0.0001

Table 8 Overall relationship between tumour site and gender (R – right colon **L** – left colon **NoSC** – not otherwise specified colon **RE** – rectal including recto-sigmoid)

Site	M		F	
	%	(n)	%	(n)
R	**29.3**	(375)	**40.7**	(359)
L	**28.9**	(370)	**28.2**	(249)
NoSC	**4.4**	(56)	**4.8**	(42)
RE	**37.4**	(478)	**26.3**	(232)
Total		1279		882

$\chi^2 = 39.64$ $p<0.0001$

Table 9 Overall relationship between tumour stage and gender

Stage	Male		Female	
	%	(n)	%	(n)
A	**22**	(281)	**18.3**	(161)
B	**25**	(320)	**24.8**	(219)
C	**25.7**	(328)	**30.7**	(271)
D	**16.8**	(215)	**16**	(141)
UK	**10.5**	(135)	**10.2**	(90)
Total		1279		882

$\chi^2 = 8.67$ $p=0.069$

Table 10 Relationship between site, screening status and stage (**RS** – right colon screen-detected **RI** – right colon interval **RNP** - right colon non-participant **LS** – Left colon screen-detected **LI** – left colon interval **LNP** – left colon non-participant **NoSCS** – not otherwise specified colon screen detected **NoSCI** – not otherwise specified colon interval **NoSCNP** – not otherwise specified colon non-participant **ReS** – Rectal screen-detected **ReI** – rectal interval **ReNP** – Rectal non-participant)

	RS		**RI**		**RNP**		**LS**		**LI**		**LNP**		**NoSCS**		**NoSCI**		**NoSCNS**		**ReS**		**ReI**		**ReNP**	
	%	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)	**%**	(n)
A	**25.2**	(39)	**9.7**	(19)	**8.8**	(29)	**37.7**	(79)	**17.7**	(21)	**12.1**	(28)	**38.8**	(7)	**8.3**	(2)	**12.0**	(6)	**36.4**	(63)	**32.1**	(52)	**13.2**	(41)
B	**41.3**	(64)	**29.4**	(58)	**29.8**	(99)	**21.1**	(44)	**29.4**	(35)	**29.6**	(68)	**16.7**	(3)	**25.0**	(6)	**14.0**	(7)	**17.9**	(31)	**17.8**	(29)	**19.0**	(59)
C	**27.1**	(42)	**31.5**	(62)	**32.2**	(107)	**22**	(46)	**31.1**	(37)	**26.1**	(60)	**27.8**	(5)	**29.2**	(7)	**18.0**	(9)	**27.2**	(47)	**22.8**	(37)	**30.4**	(94)
D	**4.5**	(7)	**22.8**	(45)	**20.8**	(69)	**9.1**	(19)	**16.8**	(20)	**22.6**	(52)	**–**		**29.2**	(7)	**42.0**	(21)	**5.2**	(9)	**14.3**	(23)	**18.4**	(57)
UK	**1.9**	(3)	**6.6**	(13)	**8.4**	(28)	**10.1**	(21)	**5.0**	(6)	**9.6**	(22)	**16.7**	(3)	**8.3**	(2)	**14.0**	(7)	**13.3**	(23)	**13.0**	(21)	**19.0**	(59)
Total		155		197		332		209		119		230		18		24		50		173		162		310

RS vs RI: $\chi 2 = 40.62$ p<0.0001 **LS vs LI:** $\chi 2 = 20.88$ p=0.0011 **NoSCS vs NoSCI:** $\chi^2 = 10.67$ p=0.0305 **ReS vs ReI:** $\chi 2 = 8.173$ p=0.0854

RI vs RNP: $\chi 2 = 0.92$ p=0.9215 **LI vs LNP:** $\chi 2 = 5.66$ p=0.2260 **NoSCI vs NoSCNP:** $\chi^2 = 3.39$ p=0.4951 **ReI vs ReNP**: $\chi 2 = 24.87$ p=0.0001

RS vs RNP: $\chi 2 = 50.41$ p<0.0001 **LS vs LNP:** $\chi 2 = 13.31$ p<0.0099 N**oSCS vs NoSCNP:** $\chi 2 = 13.31$ p=0.0099 **ReS vs ReNP:** $\chi 2 = 44.46$ p<0.0001

Table 11 Relationship between gender and site broken down by screening status (**R** – right colon **L** – left colon **NoSC** – not otherwise specified colon **RE** – rectal including recto-sigmoid **MS** – male screen-detected **MI** – male interval **FS** – female screen-detected **FI** – female interval)

	R		**L**		**NoSC**		**RE**	
	%	(n)	%	(n)	%	(n)	%	(n)
MS	**49.4**	(88)	**70.7**	(140)	**35.7**	(10)	**55**	(121)
MI	**50.6**	(90)	**29.3**	(58)	**64.3**	(18)	**45**	(99)
Total		178		198		28		220
FS	**38.5**	(67)	**53.1**	(69)	**57.1**	(8)	**45.2**	(52)
FI	**61.5**	(107)	**46.9**	(61)	**42.9**	(6)	**54.8**	(63)
Total		174		130		14		115
	$\chi^2 = 4.27$ p=0.0388		$\chi^2 = 10.55$ p=0.0012		$\chi^2 = 1.75$ p=0.1859		$\chi^2 = 2.89$ p=0.0889	