



Durham E-Theses

The Impact and Limitations of the NHS Bowel Cancer Screening Programme in the North East of England

GILL, MICHAEL

How to cite:

GILL, MICHAEL (2013) *The Impact and Limitations of the NHS Bowel Cancer Screening Programme in the North East of England*, Durham theses, Durham University. Available at Durham E-Theses Online: <http://etheses.dur.ac.uk/8507/>

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in Durham E-Theses
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full Durham E-Theses policy](#) for further details.

Academic Support Office, Durham University, University Office, Old Elvet, Durham DH1 3HP
e-mail: e-theses.admin@dur.ac.uk Tel: +44 0191 334 6107
<http://etheses.dur.ac.uk>

The Impact and Limitations of the
NHS Bowel Cancer Screening
Programme in the North East of
England

Mr Michael Gill MBBS MRCS(Ed)

Submitted for the Degree of Doctor of Medicine

Abstract

This thesis analyses the impact of the NHS Bowel Cancer Screening Programme (BCSP) since its national implementation. A regional cancer registry (Northern Colorectal Cancer Audit Group, NORCCAG, database) and the regional BCSP database were combined to obtain the full screening history for all patients diagnosed with a colorectal cancer (CRC) in the North East of England, out of the population eligible for screening.

The CRCs in the screening population between April 2007 and March 2010 were identified and classified into four groups: control (diagnosed before first screening invite), screen-detected, interval (diagnosed between screening rounds, after a negative screening episode), and non-uptake (declined screening). Patient demographics, tumour characteristics and survival were compared between groups.

In all, 511 out of 1336 (38.2%) CRCs were controls; 825 (61.8%) were in individuals invited for screening of which 322 (39.0%) were screen-detected, 311 (37.7%) were in the non-uptake group, and 192 (23.3%) were interval cancers. Compared with the control and interval cancer group, the screen-detected group had a higher proportion of men, left colon tumours, and superior survival, implying the guaiac-based faecal occult blood test (FOBT) is more effective at detecting cancers in these groups. There was no difference in demographics, tumour location/stage, or survival between control and interval groups.

A cost-effectiveness analysis of altering the screening pathway by lowering the minimum criteria for an abnormal FOBT was performed and raises potential opportunities that the screening programme could develop in order to minimise on the number of missed cancers.

Bowel Cancer Screening In North East England: Impact and Shortcomings

Mr Michael Gill MBBS MRCS(Ed)

Doctorate of Medicine (MD)

...screening is an admirable method of combating disease, since it should help detect it in its early stages and enable it to be treated adequately before it obtains a firm hold on the community.

J. M. G. Wilson & G. Junger, Principles and Practice of Screening for Disease, World Health Organisation, Geneva, 1968.

Table of Contents

Chapter 1 Colorectal Cancer: Résumé of the Literature	1
1.1 Incidence.....	2
1.2 Epidemiology.....	2
1.2.1 Sex.....	2
1.2.2 Age.....	3
1.2.3 Family History.....	4
1.2.4 Socioeconomic Status.....	4
1.2.5 Smoking.....	5
1.2.6 Diet.....	5
1.2.7 Medication Use: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Aspirin and Statins	5
1.3 Genetics.....	6
1.3.1 Hereditary Cancer Syndromes.....	6
1.3.2 Lynch Syndrome (aka Hereditary Non-Polyposis Colorectal Cancer, HNPCC).....	7
1.3.3 Familial Adenomatous Polyposis, FAP.....	8
1.3.4 Adenoma-Carcinoma Sequence.....	8
1.3.5 Mismatch Repair Genes and Microsatellite Instability.....	9
1.3.6 BRAF/KRAS Mutations.....	10
1.3.7 CIMP (CpG island methylator phenotype) Status.....	10
1.4 Chapter Conclusion.....	11
Chapter 2 Screening: General Background	12
2.1 Screening Definition.....	13
2.2 Cervical Screening.....	13
2.3 Breast Screening.....	14
2.4 Chapter Conclusion.....	17
Chapter 3 Colorectal Cancer: Patient Presenting Features	18
3.1 Symptoms of Colorectal Cancer.....	19
3.2 Difficulties in Diagnosis.....	20
3.3 Distribution of Colorectal Cancers.....	23
3.3.1 Rectal Cancers.....	24
3.3.2 Cancers Distal to the Splenic Flexure.....	24
3.3.3 Cancers Proximal to the Splenic Flexure.....	25
3.4 Symptoms and Stage of Colorectal Cancer.....	25
3.5 Atypical Presentations of Colorectal Cancer.....	25
3.6 “Asymptomatic” Colorectal Cancers.....	27
3.7 Chapter Conclusion.....	29
Chapter 4 Investigation of Lower Gastrointestinal Symptoms	30
4.1 Introduction.....	31
4.2 Flexible Sigmoidoscopy.....	31
4.2.1 Screening with Flexible Sigmoidoscopy.....	32
4.3 Colonoscopy.....	35
4.3.1 Screening with Colonoscopy.....	35
4.4 Newer Types of Colonoscopy.....	36
4.4.1 Wide-Angle Colonoscopy.....	36
4.4.2 Chromoendoscopy.....	36
4.4.3 Narrow Band Colonoscopy.....	37
4.4.4 Autofluorescence Imaging.....	37
4.5 Chapter Conclusion.....	38
Chapter 5 The Faecal Occult Blood Test, FOBT	39
5.1 Background of the test.....	40
5.2 Screening with Faecal Occult Blood Tests.....	41

5.2.1 <i>The Nottingham Trial</i>	41
5.2.2 <i>The Funen Trial</i>	42
5.2.3 <i>Other FOBt trials</i>	43
5.3 Summary of Mass Population Studies	44
Chapter 6 Interval Cancers	49
6.1 Introduction	50
6.2 The Biology of Interval Cancers	50
6.3 Interval Cancers Related to Diagnostic Test Sensitivity	51
6.3.1 <i>Interval Colorectal Cancers Post Faecal Occult Blood Test</i>	51
6.3.2 <i>Interval Colorectal Cancers Post Colonoscopy</i>	52
6.4 Chapter Conclusion	55
Chapter 7 The UK Bowel Cancer Screening Pilot.....	56
7.1 Study Design	57
7.2 Faecal Occult Blood Test Results	58
7.3 Colonoscopy within the Pilot Study	59
7.4 Colonoscopy Results	61
7.5 Adverse Consequences of the Screening Pilot.....	63
7.6 Chapter Conclusion.....	64
Chapter 8 The NHS Bowel Cancer Screening Programme (BCSP)	65
8.1 Background	66
8.2 Aims & Objectives of the Screening Programme	66
8.3 The Screening Process	66
8.4 Bowel Cancer Screening In the North East of England	67
8.5 Data Storage	68
8.6 Data Items.....	68
8.7 Chapter Conclusion.....	71
Chapter 9 Northern Region Colorectal Cancer Audit Group (NORCCAG)	72
9.1 Background	73
9.2 Format of Audit Programme.....	73
9.2.1 <i>Audit Staff</i>	73
9.2.2 <i>Steering Group</i>	73
9.2.3 <i>Dataset</i>	74
9.2.4 <i>Data Capture</i>	75
9.2.5 <i>Data Quality</i>	75
9.2.5 <i>Data security</i>	75
9.2.6 <i>Data Confidentiality</i>	75
9.3 Chapter Conclusion	76
Chapter 10 Aims of the Project	77
10.1 Introduction	78
10.2 Colorectal Cancer Occurring in the Non-Uptake Group	79
10.3 Interval Cancers	80
10.4 Screen-Detected Cancers.....	80
10.5 Control Group	80
10.6 Chapter Conclusion	81
Chapter 11 Methods	82
11.1 Study Location	83
11.2 Regional Population Demographics	84
11.3 Study Population.....	88
11.4 Permissions	88
11.5 Ethics and Consent.....	91
11.6 Study Materials	92

11.7 Database Validation	92
11.8 Postcode Deprivation Data	93
11.9 Combining Databases	93
11.10 Classification of Data Items in SPSS	94
11.11 Classification of Study Group	94
11.12 Data Analysis.....	96
11.13 Medication Use Dataset.....	97
11.14 Chapter Conclusion	98
Chapter 12 How Effective is the Current Screening Programme in North East England?	99
12.1 Introduction	100
12.2 Uptake of Screening in North East England	100
12.3 Study Group	104
12.4 Control Group vs. Intervention Group	105
12.5 Chapter Conclusion	111
Chapter 13 The Impact of Screening Programme	112
13.1 The Impact of the Screening Programme	113
13.2 Screen-Detected Cancers.....	115
13.3 Chapter Conclusion	121
Chapter 14 Cancers Not Detected through the Screening Programme	122
14.1 Introduction	123
14.2 Non-Uptake Cancers	124
14.3 Interval Cancers	127
14.3.1 Interval Cancers with an Unclear First Test Result	130
14.4 Incident Screening Round Cancers	132
14.5 Chapter Conclusion	134
Chapter 15 The Effectiveness of the Faecal Occult Blood Test	136
15.1 The Effectiveness of the Faecal Occult Blood Test	137
15.2 Outcomes for Screen-Detected and Interval Cancer Groups by Dukes Stage	140
15.2.1 Outcomes for Dukes' A Cancers.....	141
15.2.2 Outcomes for Dukes' B Cancers	142
15.2.3 Outcomes for Dukes' C Cancers	143
15.2.4 Outcomes for Dukes' D Cancers.....	151
15.3 Interval Cancer Group vs. Control Group by Dukes Stage	152
15.4 Role of Medication Use on FOBt Positivity	156
15.5 Chapter Conclusion	158
Chapter 16 How Can the Screening Programme Be Improved?	159
16.1 Analysis of Window Positivity of First Returned FOBt Kit.....	160
16.2 Implications of Changing the Minimum Criteria for an Abnormal Test to 3/6 Positive Windows	172
16.3 Chapter Conclusion	177
Chapter 17 Discussion	178
17.1 Introduction	179
17.2 The Impact of the Screening Programme	179
17.3 Cancers in the Population who do not take up Screening	181
17.4 The Effectiveness of the Faecal Occult Blood Test	182
17.5 Outcomes of Screen and Interval Cancers by Dukes Stage.....	185
17.6 Medication Use in Screen-Detected and Interval cancer Groups.....	188
17.7 Altering the parameters of an abnormal FOBt Result.....	190
17.8 Limitations of Study	191
17.8.1 Database Accuracy and Completeness.....	191
17.8.2 Missing Cause of Deaths.....	193

17.8.3 Variable Patient Management between Hospital Trusts.....	194
17.8.4 Mix of Screening Rounds	194
Chapter 18 Conclusions and Areas for Future Research	196
18.1 Conclusion.....	197
18.2 Areas for Future Research	198
18.2.1 Cohort Study into Change to FOBt Result Classification	198
18.2.2 Histological Analysis of Post-FOBt Interval Cancers and Screen-detected Cancers.....	199
18.2.3 Qualitative Study with Interval Cancer Patients	200
18.3 Personal Reflection on this Research.....	200
References	202
Appendix 1 Database Variables Creation	211
Appendix 2 Sample Proforma.....	214
Appendix 3 1st Medication Request Letter	215
Appendix 4 2nd Medication Request Letter.....	216
Appendix 5 3rd Medication Request Letter	217
Publications and Presentations from this thesis.....	218

List of tables and Figures

Figure 1.1 Number and incidence rates of colorectal and anal cancer by age group.	4
Table 3.1 Sensitivity and specificity of symptoms in relation to a colorectal cancer.	20
Table 3.2 Causes of per rectal bleeding.....	21
Table 3.3 Likelihood and odds ratio of clinical features in the diagnosis of colorectal cancer.	22
Figure 3.1 Distribution of colorectal cancers.....	23
Table 3.4 Percentage Distribution over time of Colorectal Cancers in Northern Ireland.....	24
Table 3.5 Atypical presentation of a colorectal cancer	26
Figure 3.2 Phases of symptoms for a colorectal cancer	27
Figure 3.3 Distribution of Symptoms for Screen-detected Cancers in the English Screening Pilot.	28
Table 3.6 Symptom prevalence by Dukes Stage.....	29
Table 5.1 Methodology and uptake of FOBt screening.	46
Table 5.2 Number and incidence rate of colorectal cancer by study.	47
Table 5.3 Type of FOBt, positivity rate and predictive value for colorectal cancer and adenoma.	47
Table 5.4 Number and rate of deaths for each study.....	48
Table 7.1 Number & Percentage of Responders from Both Sites.....	57
Figure 7.1 Percentage of responders by demographic.....	58
Table 7.2 Number and percentage of uptake of colonoscopy by demographic.	60
Figure 7.2 Uptake of colonoscopy by demographic.	60
Table 7.3 Results following FOBt and colonoscopy	62
Figure 7.3 Stage of screen-detected tumours.	63
Figure 8.1 Outcomes after screening colonoscopy, Polyp surveillance guidelines.	67
Figure 8.2 Data obtained from regional BCSP database.....	69
Table 8.1 Data Items Collected within the Bowel Cancer Screening Database.....	70
Figure 9.1 Flow chart representing storage of data on NORCCAG database.	74
Figure 10.1 Classification of Study Groups	79
Figure 11.1 The North East of England	83
Figure 11.2 Percentage of population aged 65 and over, 2010 and 2030.....	84
Figure 11.3 Predicted total numbers of North East England population aged 60 to 74	85
Figure 11.4 Percentage of Lower Super Output Areas (LSOAs) In Each Region Falling In 'Most Deprived 20% Of LSOAs In England'	86
Table 11.1 Comparison of North East Social Indications against other English regions.....	87
Figure 11.5 Hospitals and Trusts within the North East Bowel Screening Hub.	90
Figure 11.6 Flow chart representation of allocation to each study group.	95
Figure 12.1 Overall number of FOB invites, their uptake and results	101
Figures 12.2 a and b. Numbers of SSP appointments post positive FOBt, total and per subject.....	102
Figure 12.3 Numbers of investigations, total and per subject.....	103
Figures 12.4 a & b. Numbers of SSP appointments post investigation, total and per subject.	104
Figure 12.5. Proportion of cancers by classification group.....	105
Table 12.1 Patient demographics and tumour details for control group and intervention group.	106
Table 12.2 Pearson Chi-Square Tests comparing control group vs. intervention group.	106
Figure 12.6 a & b. Survival curve comparing gender for control and intervention groups.	108

Figure 12.7 a & b. Survival curve comparing deprivation level for control group and intervention groups.	109
Figure 12.8 a & b. Survival curve comparing ASA grade for control group and intervention groups.	110
Table 12.3 Log Rank (Mantel-Cox) comparison of control group against intervention group for each variable	111
Table 13.1 Outcomes of the control and intervention groups.	113
Figure 13.1 Tumour stage proportions between groups.....	114
Figure 13.2 Kaplan-Meier survival curves for control group and intervention group.....	115
Figure 13.3 Proportion of cancers by classification group.....	116
Figure 13.4 Box plot of time from completion of FOBt to diagnosis for the screen-detected cancer group.	117
Table 13.2 Distribution of patient demographics, tumour characteristics and management of patients between control and screen-detected cancer group.....	118
Table 13.3 30-day mortality figures for each cancer group.....	119
Table 13.4 30 day mortality figures for each cancer group by level of operative intervention.	120
Table 13.5 Chi-squared figures and significance for each level of operative intervention .	120
Figure 13.5 Kaplan-Meier survival curves for control and screen-detected cancers.	121
Figure 14.1 Proportion of cancers by classification group.....	124
Figure 14.2 Types of Non-Uptake Cancers.....	125
Table 14.1 Distribution of patient demographics, tumour characteristics and management of patients between control and non-uptake groups.....	126
Figure 14.3 Kaplan-Meier survival curve comparing control against non-uptake groups...	127
Table 14.2 Distribution of patient demographics, tumour characteristics and management of patients between control and interval cancer groups	129
Figure 14.4 Kaplan-Meier survival curves for control and interval cancers.	130
Table 14.3 FOB results for interval and screen-detected cancers	131
Figure 14.5 Kaplan-Meier survival curve comparing control against non-uptake and interval cancer groups.....	132
Table 14.4 Stage and site of tumours by earlier test result.....	133
Figure 14.6 Horizontal organisation chart of the results of earlier FOB tests by group.	134
Table 15.1 Distribution of patient demographics, tumour characteristics and management of patients between screen-detected and interval cancer groups.....	138
Table 15.2 Proportions of screen and interval cancers by tumour site for men and women.	139
Table 15.3 Proportions of screen and interval cancers by gender for left and right-sided tumours.....	139
Figure 15.1 Kaplan-Meier survival curves for screen and interval cancer groups.....	140
Table 15.4 Demographics, tumour stage and location, and management for screen and interval Dukes' A cancers.....	141
Figure 15.2 Survival Curve for Screen and Interval Cancers of Dukes' A stage.	142
Figure 15.3 Kaplan-Meier curve for interval and screen-detected Dukes' B cancers.....	143
Table 15.5 Demographics, tumour details and outcome for interval and screen-detected Dukes' C cancers.	144
Figure 15.4 Kaplan-Meier curve for interval and screen-detected Dukes' C cancers.....	145
Table 15.6 Proportions of Dukes C1 and C2 for screen and interval cancers.....	146
Table 15.7 Mean number of positive lymph nodes and total nodes harvested for each Dukes C stage.	146
Table 15.8 Number and percentage of each Dukes C cancer with less than or greater than 12 lymph nodes harvested for screen and interval cancers.....	147

Figures 15.5 a & b Kaplan-Meier survival curves for Dukes' C1 and C2 cancers comparing interval vs. screen-detected groups.....	148
Table 15.9 Log Rank (Mantel-Cox) test for survival curve equality for Dukes' C1 and C2 cancers.	148
Figures 15.6 a & b. Kaplan-Meier survival curves for left and right sided cancers comparing interval vs. screen-detected groups.....	149
Table 15.10 Log Rank (Mantel-Cox) test for survival curve equality for left and right sided cancers.	149
Figures 15.7 a & b. Kaplan-Meier survival curves for male and female gender comparing interval vs. screen-detected groups.....	150
Table 15.11 Log Rank (Mantel-Cox) test for survival curve equality for male and female gender.	150
Table 15.12 Demographics, tumour details and outcome for interval and screen-detected Dukes' D cancers.	151
Figure 15.8 Kaplan-Meier curve for interval and screen-detected Dukes' D cancers.	152
Table 15.13 Tests of equality of survival distributions for interval vs. control cancer groups for each Dukes stage.....	153
Figure 15.9 Survival curve for interval and control cancers of Dukes Stage A.	154
Figure15.10 Survival curve for interval and control cancers of Dukes Stage B.	154
Figure15.11 Survival curve for interval and control cancers of Dukes Stage C.	155
Figure15.11 Survival curve for interval and control cancers of Dukes Stage D.	155
Table 15.14 Use of hormone antagonists at time and prior to carrying out FOBt.	156
Table 15.15 Use of Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs (NA-NSAID), Anti-Coagulants and Aspirin within two months of carrying out a FOBt.....	157
Table 16.1a Total number of individuals offered and taking up the FOB test and their results.....	161
Table 16.1b Outcomes after an unclear first test result by number of positive windows. .	162
Table 16.2 Number of cancers per number of positive windows for each cancer classification group.	163
Figure 16.1 Types of Non-Uptake by Positive Windows.....	164
Figure 16.2 Number of cancers in each group of positive first FOB test result.....	165
Figure 16.3 Outcomes of the first round of screening.....	167
Figure 16.4 Kaplan-Meier survival curves of screen-detected cancers with 1-4 & 5-6 windows positive on first FOBt against interval cancer group.	168
Table 16.3 Log rank (Mantel-Cox) test comparing groups of screen-detected cancers and interval cancers.	169
Figure 16.5 Kaplan-Meier survival curves of screen-detected cancers with 1-2, 3-4 & 5-6 windows positive on first FOBt against interval cancer group.	169
Table 16.4 Log rank (Mantel-Cox) test comparing groups of screen-detected cancers and interval cancers.	170
Table 16.5 Patient, tumour and management variables for each positive window on first FOBt and interval cancers, and Chi-squared comparisons.	171
Table 16.6 Outcomes after 1-4 positive windows on first FOBt in prevalent screening round.	173
Table 16.7 Minimum and maximum numbers of additional cancers detected by number of positive windows on first FOBt kit.	174
Table 16.8 Net costs of alteration to different minimum numbers of positive windows on first FOBt.	176

Statement of Copyright

The copyright of this thesis rests with the author, Michael Gill. No quotation from it should be published without the author's prior written consent and information derived from it should be acknowledged.

Acknowledgments

Firstly, I would like to thank my supervisor, Professor Mike Bramble. He has been extremely supportive throughout this research project. His invaluable guidance and enthusiasm for the subject gave me the incentive and reassurance that I was on the right track over these past two years.

To my co-supervisor, Professor Pali Hungin, thank you for mentorship and help in developing this thesis.

To my clinical supervisors, Miss Sarah Mills and Mr Mike Bradburn, thank you for your instruction for giving me the opportunity to carry out this project.

To Dr Colin Rees and Dr Tom Lee, thank you for helping me develop the project from its inception onwards, and for your aid in easing the cogs of the bowel cancer screening programme.

To Dorothy Simms and John Lovely of the Northern Region Colorectal Cancer Audit Group, and Colin Taylor of the regional Bowel Cancer Screening Programme hub, thank you for all your help in delivering the raw data from each database. This project literally could not have taken place without you.

To Professor James Mason and Dr Doug Wilson for their help with developing my statistical skills.

Finally, to my wife and son (who joined us halfway through the project), thank you for your unwavering support in all my endeavours. Your patience in listening to the minutiae of the project, whilst remaining interested, has truly helped me remain focussed on completing this work.

Chapter 1 Colorectal Cancer: Résumé of the Literature

1.1 Incidence

Colorectal cancer is a major public health problem. In 2007, there were around 17,100 new cases diagnosed in men and 14,400 in women making it the third most commonly diagnosed cancer in the United Kingdom (excluding non-melanoma skin cancers). Cancer Research UK estimates that men have a 1 in 16 risk and women a 1 in 20 lifetime risk of being diagnosed with bowel cancer. In 2008 around 13,300 people died from colorectal cancer giving it the second highest mortality rate in the UK.

Colorectal cancer incidence increases with increasing age of the patient. More than four out of every five new cases are diagnosed in people aged 60 and over. This peaks in the 70-79 age group in men and in the over 75's in women [1].

In 2008, 1.23 million new cases of colorectal cancer were diagnosed worldwide. Incidence rates vary with geographical location with the lowest incidence occurring in South Central Asia, and Middle African countries. The highest rates are in Europe, North America and Australasia [2].

1.2 Epidemiology

1.2.1 Sex

More than 100 people are diagnosed with colorectal cancer every day in the UK. Colorectal cancer affects more men than women, at a ratio of 1.56 over all ages (European age-standardised rates), affecting 70 men and 56 women per 100,000 population in the UK [2, 3].

This difference in frequency is mirrored when the disease is subdivided into colon cancer and rectal cancer. The crude rates of cases of colon cancer per 100,000 persons are 42 and 38, with the rates for rectal cancer being 28 and 19, for men and women respectively.

The rates of advanced neoplasia (a cancer or adenoma at least 10 mm in diameter, with high-grade dysplasia, villous or tubulovillous histologic characteristics, or any combination thereof) are also independently associated with male sex (adjusted odds ratio, 1.73; 95% confidence interval, 1.52 to 1.98; $p < 0.001$) [4].

1.2.2 Age

The rates of bowel cancer are linked with age, increasing as you get older. The vast majority of cases occur after the age of 60, a total of 84% of all new diagnoses. Figure 1.1 below shows the distribution of cases with age at diagnosis [2].

In the population aged 80 and over, the post-operative mortality is much higher than that of patients aged less than 65 (16% vs. 0.7%) [5]. The likelihood of an octogenarian being fit enough to survive a major bowel resection will be low, given their higher degree of frailty and co-morbidities [6]. By screening the population aged 60-74, with the long lag time between normal colonic mucosa and a colorectal carcinoma, it is hoped that the incidence of cancers in this elderly age group will decrease. However, as the mean age of the UK population becomes greater, there will be an increasing number of patients aged 75 and over who will be able to undergo the stress of a colorectal cancer resection. For these patients, survival rates have been shown to be acceptable regardless of age [6].

11.0% of cases in men and 10.4% of cases in women occur in the age group of 50-59 years (rate of 66.6 in men and 50.4 in women per 100,000 population). This age group has been included in several mass population studies and recommended as a possible starting point for screening, but was not included in the English bowel cancer screening programme due to resource constraints [7].

In the younger population (aged 40 and below), the incidence of colorectal cancer is rare, accounting for 2.3% of all cancers. However, this figure is increasing (from 1.4% in 1990-1999 to 3.0% from 2000-2009 in one UK study) [8]. Although predisposing factors such as inflammatory bowel disease and genetic cancer conditions (FAP and Lynch syndrome) make up a larger proportion of cancers than in the older age group (16%), sporadic tumours still comprise the majority of these cancers, with a family history of colorectal cancer being attributed to the rest (22.7%)[9].

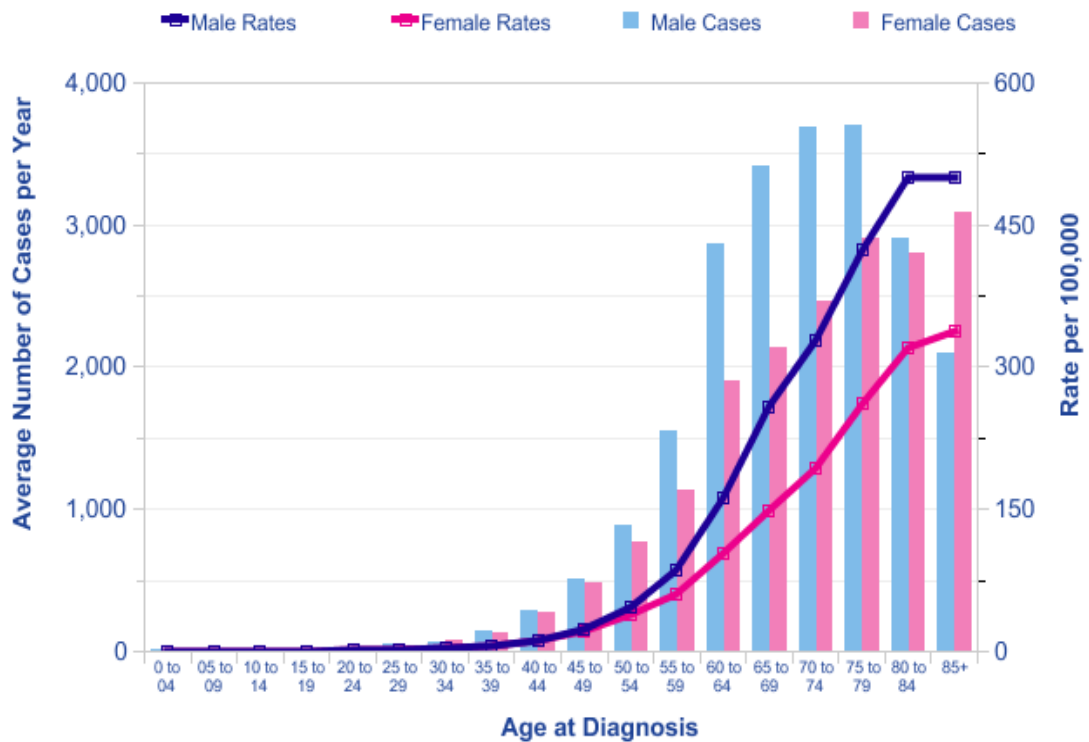


Figure 1.1 Number and incidence rates of colorectal and anal cancer by age group [2].

1.2.3 Family History

A family history of colorectal cancer is associated with a greater risk of developing a similar cancer. Approximately 20% of colorectal cancers, excluding hereditary conditions (such as Lynch Syndrome, and Familial Adenomatous Polyposis, FAP) or inflammatory bowel diseases are linked with a family history of the condition. Patients must have either one first-degree relative diagnosed with a colorectal cancer aged under 45, or two first-degree relatives of any age, to have an increased risk (16-25% for men, 10-15% for women)[10].

1.2.4 Socioeconomic Status

In men, there is a direct correlation between the incidence of colorectal cancer and level of social deprivation. In both the 1995-1999 and 2000-2004 time periods, there was a statistically significant ($p=0.02$ & $p=0.001$ respectively) drop in incidence when men move from lower to higher socioeconomic groups. Incidence rates were 11% higher in the most deprived groups compared to the most affluent. However, this variation is not observed for

women [11]. This could be due to a dietary influence and/or increased rates of smoking and alcohol use that are associated with lower socioeconomic groups.

1.2.5 Smoking

There is a well-established link between smoking and the risk of many different types of cancer, and this is also the case for colorectal cancer, although not as marked an effect as with some other cancers (e.g. lung).

A meta-analysis performed in 2008 and published in the Journal of the American Medical Association, JAMA, looked at 106 observational studies, from which a relative risk of 1.18 (95% confidence interval, 1.11-1.25) and an absolute risk increase of 10.8 cases per 100,000 person-years (95% confidence interval, 7.9-13.6) was derived. There was also a dose dependent increase in risk, with a greater chance of developing colorectal cancer, the greater the number of pack years of an individual (however, this was only statistically significant after 30 pack-years). From 17 cohort studies analysed, the pooled risk was 1.25. They also found that for both incidence and mortality, the effect was greater with rectal cancers compared with colon cancers [12].

1.2.6 Diet

In countries such as Japan where their residents diets have rapidly shifted from a “traditional” diet with steamed rice as the staple food, to “modernized” or “Westernised” with an excessive amount of protein and animal fat, there has been marked increase in the incidence of colorectal cancer [13]. For Japanese males (in two of the three regional registries), there has been greater than a 90% increase in incidence between 1963 and 2002 [14].

1.2.7 Medication Use: Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), Aspirin and Statins

For both rheumatoid (RA) and osteoarthritis (OA) patients, there is a significant decrease in the risk of developing a colorectal cancer. For RA patients, the standardized incidence ratio (SIR) for males is 0.87 (95% CI 0.7–1.1), and for females is 0.71 (95% CI 0.6–0.9). For OA patients, for males the SIR is 0.88 (95% CI 0.8 –1.0) and for females the SIR is 0.84 (95% CI 0.8–0.9) [15]. The reasons behind this are thought to be due to non-steroidal anti-inflammatory drug (NSAID) use.

Non-steroidal anti-inflammatory drugs are thought to decrease the risk of colorectal cancer by inducing programmed cell death, known as apoptosis, of cancer cells as well as inhibiting the production of prostaglandin, which is “known to promote tumour angiogenesis and cell proliferation” [16]. Shadman et al. (2009) found a 30% decrease in colorectal cancer risk (odds ratio 0.70, 95% confidence interval 0.56-0.88) in patients who had ever used NSAIDs, but only for those patients who were currently taking them.

Aspirin use is also associated with improved survival from colorectal cancer, after diagnosis. However, this was only statistically significant for those patients whose cancers overexpress the enzyme COX-2 compared with tumours with weak or absent expression (multivariate hazard ratio, 0.39 vs. 1.22) [17].

It is also associated with a reduced risk of colorectal cancer (pooled odds ratio 0.62, 95% CI 0.58-0.67, $p < 0.0001$) [18], a reduced risk of Dukes' D cancers (odds ratio 0.52, 95% CI 0.35-0.75, $p = 0.0006$), and of a reduced risk of developing distant metastases on follow up, after diagnosis (HR 0.26, 95% CI 0.11—0.57, $p = 0.0008$) [19]. As part of the CAPP2 randomised trial, 600mg of aspirin per day for an average of 25 months, produced a hazard ratio for colorectal cancer of 0.41 (95% CI 0.19-0.86, $p = 0.02$) against placebo [20].

There is some disagreement as to whether the use of statins (3-Hydroxy-3-methylglutaryl CoA reductase inhibitors) increases or decreases a patient's risk of colorectal cancer. A meta-analysis of the subject was performed in 2006 of which 27 randomized controlled trials of statin use were included. Criteria for inclusion were a mean duration of follow-up of at least 1 year, enrolment of a minimum of 100 patients, and reporting of data on either cancer incidence or cancer death. Out of 6662 incident cancers and 2407 cancer deaths, statins did not reduce the incidence of cancer (odds ratio, 1.02; 95% confidence interval, 0.97-1.07) or cancer deaths (odds ratio, 1.01; 95% confidence interval, 0.93-1.09) [21].

1.3 Genetics

1.3.1 Hereditary Cancer Syndromes

There are several genetic theories as to the cause of colorectal cancer. These originate from work done looking at the hereditary cancer syndromes, of which the most common are Lynch Syndrome (aka Hereditary Non-Polyposis Colorectal Cancer, HNPCC), and Familial Adenomatous Polyposis, FAP. It is through FAP investigation that the adenoma-carcinoma sequence was postulated for the development of colorectal cancers.

The Bowel Cancer Screening Programme's aim is not only to identify colorectal cancers at an early stage, but also to identify, remove and stage adenomatous polyps. This is to

prevent the postulated natural progression of colorectal adenomas into carcinomas, thereby decreasing the incidence rate and mortality from colorectal cancer. Adenoma progression to a carcinoma takes an average of 5.5 years for large polyps (>1cm) and up to 10 years for smaller polyps [22].

1.3.2 Lynch Syndrome (aka Hereditary Non-Polyposis Colorectal Cancer, HNPCC)

Lynch Syndrome is the most common of the hereditary colon cancer syndromes and accounts for between 1-6% of all cases of colorectal cancer [23]. Lynch Syndrome is an autosomal dominant condition and is thought to be due to mutations in five DNA mismatch repair genes; hMSH2, hMLH1 (most common), hPMS1, hPMS2 and hMSH6. In those persons who have mutations in both copies of the above genes, there is an ever increasing amount of DNA sequence errors. This is primarily in seen in segments of DNA containing multiple, short, repeated sequences known as a microsatellites [24]. 90% of colorectal cancers and 80% of colorectal adenomas display microsatellite instability (MSI) – the widespread expansion or contraction of these short sequences of DNA [25]. Those with the trait have an 80% lifetime risk of developing a colorectal cancer, which tends to develop at a younger age compared to sporadic cancers. Whilst the total number of colorectal polyps found in sufferers tends not to be greatly increased; the polyps are of a larger size and more dysplastic [26]. Lynch Syndrome is also associated with other types of cancer, most commonly endometrial cancer, but also ovarian, gastric, biliary and urinary tracts. Diagnosis of this condition was initially with the Amsterdam criteria [27, 28] and then with the Bethesda guidelines [29]. An overview of the current revised Bethesda guidelines are shown here:

1. Colorectal cancer diagnosed at age <50 years.
2. Synchronous or metachronous colorectal or other Lynch Syndrome associated tumours regardless of age.
3. Colorectal cancer diagnosed at age <60 years with histologic findings of infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation or medullary growth pattern.
4. Colorectal cancer in ≥ 1 first-degree relative(s) with a Lynch Syndrome tumour, with one of the cancers being diagnosed at age <50 years.
5. Colorectal cancer diagnosed in ≥ 2 first- or second-degree relatives with Lynch Syndrome tumours, regardless of age.

Known Lynch Syndrome patients undergo frequent colonoscopies starting from 10 years before their youngest known relative was diagnosed, to detect and to remove polyps, as well as diagnosing colorectal cancers. They are also offered screening for the other cancers associated with Lynch Syndrome, e.g. endometrial aspiration.

1.3.3 Familial Adenomatous Polyposis, FAP

Familial adenomatous polyposis syndrome, FAP, is also an autosomal dominant condition. It is characterised by the presence of over 100, sometimes over 1000 colorectal polyps. It accounts for approximately 1% of all cases of colorectal cancer.

It is caused by a mutation in the adenomatous polyposis, APC, gene, located on chromosome 5. This mutation causes uncontrolled growth of colorectal adenomas starting from a young age, mean of 16 yrs. These polyps are histologically identical to polyps found in non-FAP sufferers. It is from this knowledge that the theory of the adenoma-carcinoma sequence came about. 100% of patients with FAP will go on to develop colorectal cancer, where it is thought that the adenomas have an increasing amount of dysplasia over time before developing into adenocarcinoma cells.

Again, FAP is associated with other cancers such as papillary thyroid cancer, hepatoblastoma, and adrenal hyperplasia/carcinoma. Treatment for these patients is with prophylactic colectomy, normally performed during adolescence, as well as screening for the above associated cancers.

Mutations in the APC gene have also been suggested to have a role in the development of sporadic colorectal cancers. In up to 80% of sporadic cancers, somatic mutations of the APC gene are found. This would suggest their involvement in initiating tumourigenesis. [30].

1.3.4 Adenoma-Carcinoma Sequence

This is the theory that colorectal cancers will develop from a colorectal adenoma. Evidence for this hypothesis is described here.

Adenomas exhibit variation and differences (dysplasia) from normal mucosa in their cytological and architectural features. The degree of dysplasia they possess, ranges from mild to severe. Often seen are areas of focal severe dysplasia within an otherwise mildly/moderately dysplastic adenoma. The epidemiology of adenomas and carcinomas are significantly similar with correlating distributions by site, as well as a similar changing distribution with the populations' age. As with dysplastic adenomas, within 57% of early

colorectal cancers (T1, limited to the submucosa), the carcinoma can be seen adjacent to adenomatous tissue. In the small number of patients in which they have declined treatment for their adenoma, follow-up has shown that there is cancer at the same site as the adenoma. The importance of this sequence is that it is theoretically possible to prevent the development of a colorectal cancer by screening a population for adenomas and removing them, therefore preventing their progression. There are, however, descriptions of colorectal cancers appearing 'de novo', i.e. not from an adenoma, this can be seen in chronic inflammatory bowel disease, where a cancer can arise from "within a plaque of dysplastic epithelium showing villous change" [31].

1.3.5 Mismatch Repair Genes and Microsatellite Instability

Microsatellite instability has an important role in the pathogenesis of colorectal cancers. Its finding within a large proportion of 'interval bowel cancers', has been suggested as a possible indicator of fast growth of these tumours, giving an explanation as to why they are diagnosed after a recent examination of a patients large bowel. This will be discussed further in the section on interval cancers.

Mismatch repair, MMR, genes act to maintain the integrity of the genome by correcting DNA base pairing errors in newly replicated DNA. There are 7 MMR genes (MLH1, MLH3, PMS1, PMS2, MSH2, MSH3 and MSH6, spread over 5 chromosomes. When there is a defect in one these genes, repeated accumulation of errors spread across the genome, termed microsatellite instability, MSI.

Whilst an abnormality of a MSI is found in 90% of HNPCC cancers, it is also found in approximately 15% of non-familial colorectal cancers [32]. However, a Korean paper found that those patients whom had a colorectal cancer resected were not at greater risk of developing an adenoma or advanced adenoma at their follow up colonoscopies 1 and 3 years post operatively. By performing this review of the histology of these patients, they diagnosed 11.6% of patients who were found to have a high level microsatellite instability with Lynch Syndrome [33].

MSI instability has also been found to be a prognostic factor in colorectal cancer [34]. In a recent meta-analysis looking at whether MSI could be viewed as a predictive factor in effectiveness of chemotherapy, the authors "showed that there was no survival difference among MSI-High patients whether or not they received chemotherapy, whereas MSS patients had a better response to chemotherapy, suggesting that MSI could be considered as a predictive marker of chemoresistance" [35]. However, for those patients undergoing

chemotherapy for colorectal metastases, a similar meta-analysis showed no difference in response as to whether patients had MSI or not found as part of their cancers [36].

1.3.6 BRAF/KRAS Mutations

The Ras/Raf/MEK/ERK signalling pathway plays an important role in the regulation of cell proliferation, differentiation, and survival. An activating mutation in the RAF gene, BRAF, leads to unregulated cell growth and tumour proliferation. Mutations of the BRAF gene have been reported in 9.5–23.5% of all sporadic colon cancers and are strongly associated with microsatellite instability (MSI) in sporadic colon cancers [37]. In a study by Samowitz et al. “the BRAF mutation was seen in 5% (40 of 803) of microsatellite-stable tumours and 51.8% (43 of 83) of microsatellite-unstable tumours. In microsatellite-stable tumours, this mutation was related to poor survival” [38].

1.3.7 CIMP (CpG island methylator phenotype) Status

There is a third theory in the development of a colorectal cancer, along with APC/KRAS gene malformations and microsatellite instability. This is known as CpG island methylator phenotype, or CIMP, where abnormal DNA methylation leads to silencing of CpG rich genes causing the development of a colorectal cancer.

A study by Sanchez et al. looked at the prevalence of MSI, CIMP status as well as BRAF and KRAS mutations in colorectal cancer histology. They found that CIMP-High was found in 21.2% of tumours and MSI-High in 21.0%. The CIMP-H tumours tended to present in an older age group, 10 years later than CIMP-negative tumours.

MSI-H/CIMP-H tumours had a higher rate of BRAF mutation (72%) than the other groups ($p < 0.001$). 34.0% of microsatellite stable tumours had KRAS mutations compared with only 13 per cent of MSI-H tumours ($p < 0.001$) [39]. They did not find that CIMP status was linked to a worse outcome, as has been reported in other studies [40, 41].

1.4 Chapter Conclusion

In this chapter, the incidence of colorectal cancer has been discussed, broken down into differences between gender and age. Patient and environmental factors have been reviewed in their effect on the risk of developing a colorectal cancer. These include a family history of a cancer, smoking and alcohol consumption, diet, and certain medication use (non-steroidal anti-inflammatory drugs, aspirin, and statins).

Finally, the genetics of colorectal cancer development through the widely accepted adenocarcinoma sequence has been covered. The specific genetic mutations that increase the likelihood of developing a cancer are included (micro-satellite instability, CIMP status, mismatch repair genes and BRAF/KRAS mutations). These have particular importance as have been associated with the development of fast growing, interval colorectal cancers, which will be discussed in a later chapter.

Chapter 2 Screening: General Background

2.1 Screening Definition

The UK National Screening Committee defines screening as “a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition” [42].

In 1968, Wilson & Jungner put forward their criteria for a screening programme [43]:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Screening clinical trials are expensive and harder to carry out compared with standard trials. Patient recruitment is more challenging as subjects are healthy, asymptomatic individuals, of which large numbers are required, with a long lag time between intervention and outcome (predominantly disease specific mortality). A screening programme puts subjects at risk of complications from the test, or from the treatment of a screen detected condition. There are also risks of over-diagnosis, or false-negative results among each programme.

2.2 Cervical Screening

Cervical screening was the first screening programme that caused both an increase in the incidence of a condition, but also a decrease in its mortality rate. This was due to the fact that the screening test was able to pick up cancers that were “*in situ*” and therefore had an excellent prognosis following surgery [44].

The Papanicolaou (Pap) smear test was first described in 1943 and the test used in cancer detection centres across the United States. Cervical screening started in England in 1964, however it was not until the 1980's, when the screening interval was changed to every three years, and a national call and recall system was introduced, did the uptake rate increase significantly. In 1988, the coverage of the target age group was at 42%, however this rose to 85% in 1994 [45]. The introduction of the programme occurred despite there never being a randomised controlled trial comparing outcomes of a screened population against a non-screened population [46].

The cervical screening programme has been criticised due to the high rates of interval cancers secondary to inadequate sampling or reporting error. An Australian study reported an interval cancer rate of 13.2% of all cancers diagnosed, with only 7.7% of interval cancer slides re-reviewed that were deemed truly negative and of a high quality [47]. Within the NHS Cervical Screening Programme, the interval cancer rate for invasive cervical cancers was 45.2% in one UK region between 1985-1996, of which 49.1% were after negative cytology. On reviewing of the cytology of these slides, 41.1% were confirmed as negative, 11.0% were deemed inadequate, 17.0% were felt to be low-grade dyskaryosis, and 31.0% as high-grade dyskaryosis. The authors attribute these high rates due to “no rapid review or preview of negative smears; there was no external quality control; there were no standards for cytology reporting rates”. Initially, a certificate of competence for cytology screeners was not mandatory for qualified biomedical scientists. However, such measures have since been introduced [48].

2.3 Breast Screening

The NHS Breast Screening Programme began in 1988, employing single view mammography and inviting women aged 50–64 years for screening once every three years. By 2005, the programme changed to using two-view mammography with 1.3 million women aged 50–70 years screened annually. This number equates to approximately 75% of those invited. In the UK, it costs £75 million per year, or £45.50 per woman screened [49].

Possibly due to the halo effect, women with symptomatic breast cancer are typically presenting with smaller tumours than before 1988. Screening for breast cancer also has an impact on other treatment modalities with a substantially greater proportion of women with breast cancer receiving chemotherapy and/or hormonal therapy than before 1988.

Mammographic screening between the ages of 50 and 70 years reduces mortality from the malignancy. The International Agency for Research on Cancer (IARC) concluded that the

25% reduction in mortality seen in the trials of mammographic screening, based on an 'intention to treat' analysis, implies a reduction in breast cancer mortality of about 35% for women who are screened regularly. The current NHS breast screening programme diagnoses about 10,000 breast cancers annually and saves an estimated 1400 lives each year in England [50].

A Cochrane review published in 2009 reviewed breast cancer screening with mammography [51]. They identified and reviewed 8 randomised trials comparing mammographic screening with no mammographic screening. Out of these 8 trials, the authors judged that 3 were adequately randomised (Canada 1980, Malmö 1976 and UK age trial 1991), and 5 were suboptimally randomised but still included in the analysis [Göteborg 1982, New York 1963, Stockholm 1981, Two- County 1977 and the extension of the Malmö trial, MMST II 1978). The three adequately randomised trials did not find a statistically significant effect of mammographic screening on deaths ascribed to breast cancer, relative risk (RR) 0.93 (95% CI 0.79 to 1.09) after 7 years and RR 0.90 (95% CI 0.79 to 1.02) after 13 years. The four suboptimally randomised trials found a beneficial effect: RR 0.71 (95%CI 0.61 to 0.83) after 7 years and RR 0.75 (95% CI 0.67 to 0.83) after 13 years. The combined risk reduction for all seven trials was 0.81 (95% CI 0.72 to 0.90) after 7 years and 0.81 (95% CI 0.74 to 0.87) after 13 years. All-cause mortality was not significantly reduced.

Significantly more breast operations (mastectomies plus lumpectomies) were performed in the study groups than in the control groups: RR 1.31 (95% CI 1.22 to 1.42) for the two adequately randomised trials; RR 1.42 (95% CI 1.26 to 1.61) for the suboptimally randomised trials.

When data from 40,075 Norwegian women with invasive breast cancer were analysed, comparing mortality rates between the screened and non-screened group, against a historical non-screened group [52]. This showed a reduction in death rate of 7.2 deaths per 100,000 person-years in the screened group (RR 0.72, 95% CI 0.63 to 0.81, $p < 0.001$), and by 4.8 deaths per 100,000 person-years (RR 0.81, 95% CI 0.71 to 0.93, $p < 0.001$). The authors surmise that the reduction in mortality due to screening alone was 2.4 deaths per 100,000 person-years (1/3 of the total reduction). The introduction of multi-disciplinary teams in the management of patients with breast cancer between the historical and contemporary groups is suggested as being the predominant factor in the mortality reduction seen. In addition to this, new treatment modalities were introduced between groups, namely sentinel lymph node biopsies. From the editorial accompanying the above Norwegian paper, the impact of breast screening was outlined: "If you screen 2500 women over the

age of 50 for 10 years, then one breast cancer death might be avoided at the cost of 1000 false alarms and between five and 15 women being over-diagnosed and treated needlessly with surgery, radiotherapy, and chemotherapy” [53, 54]. In the UK, for women aged 40-55, the mortality risk reduction from breast cancer screening moves from 0.41% to 0.35%, a difference of 0.062%. Therefore, the number needed to be screened to avoid one death is 1610. At age 60, the number needed to be screened is still 259 to avoid one death [49].

No screening programme is without risks to those patients being screened. The main risk with any programme is likely to be the implications of a false positive result, including both physical and psychological effects. The Cochrane review reports that those women who had a false positive result were “twice as likely to suffer psychological consequences three years later than women who received a clear result after their last mammogram”. The authors conservatively estimate that the rate of overdiagnosis is 30% with more than 10% of these women experiencing marked psychological distress due their false positive result. Controversy around breast cancer screening revolves around early breast cancers and ductal carcinoma in situ (DCIS). Approximately 20% of screen detected cancers in the UK during 2009/2010 were DCIS [55]. There is a debate regarding how this should be managed, as this pre-malignant condition may never become an invasive cancer in the patient’s lifetime. Even if it does, low grade DCIS will only become a low grade invasive cancer, which again may not be attributable to a patient’s cause of death.

Jørgensen & Gøtzsche reviewed whether these risks described above are accurately represented on websites by interest groups [56]. They reviewed 13 websites from advocacy groups and 11 from government institutions, all of which whom recommended mammographic screening, and 3 from consumer organisations who questioned it ($p=0.0007$). They reviewed whether specific topics were covered in each of the websites, such as lifetime risk of developing breast cancer, survival rate, number needed to treat, overdiagnosis and overtreatment. The authors found that the websites from professional advocacy groups had poor information and was “severely biased in favour of screening”. The consumer organisation’s websites were “much more comprehensive and balanced”. In 2009, Baum et al. called upon the patient information leaflet “Breast Screening: the Facts” to be rewritten as the full risks and benefits were not accurately conveyed to the public [54].

The cost effectiveness of the Breast Cancer Screening Programme has been reviewed by Pharoah et al. [57]. They calculated that screening was associated with a cost of £20,800

per quality adjusted life year (QALY) gained. This equates to 9.2 days gained per person time survival. However, in only 45% of cases did the QALY gained of screening fall below NICE's cut-off level of £20,000, with 12% of cases screening being associated with a reduction on QALYs.

The Independent UK Panel on Breast Cancer Screening published their findings and recommendations in the Lancet in 2012 [58]. They primarily reviewed 11 randomised trials where on meta-analysis the relative risk of breast cancer specific mortality of screened individuals against controls was 0.80 (95% CI 0.73 to 0.89). It accepted that overdiagnosis did occur, but estimates as to its effect have been exaggerated in previous studies. However, they calculate that for every breast cancer death prevented through screening, there were three overdiagnosed cases identified and treated. This equates to a 1% chance of women aged 50-52 years having an overdiagnosed cancer during the next 20 years. Despite this, they conclude that the UK breast screening programme "confers significant benefit and should continue".

2.4 Chapter Conclusion

In this chapter, the background to screening has been discussed along with details of other screening programmes that are currently in use in the UK.

There has been recent controversy regarding breast and cervical screening. Breast screening has been shown to have a high rate of false positive results leading to significant emotional stress to individuals who undergo surgical treatment. Cervical screening suffers from a significant rate of false negatives, particularly for cervical cancer, due to several different parts of its screening programme where errors may occur.

The need for a robust screening tool that is easy to perform, with reliable and accurate results is crucial for an effective screening programme. It must be well accepted by the public, leading to a high uptake rate. Such a program must be evidence based, with proven outcomes on meta-analyses.

Chapter 3 Colorectal Cancer: Patient Presenting Features

3.1 Symptoms of Colorectal Cancer

Patients with a colorectal cancer may present to a healthcare professional with symptoms relating to the location of the lesion.

A large number of patients will be asymptomatic with their cancer, but, of those that are symptomatic, their related symptoms can be split into rectal, distal to the splenic flexure and proximal to the splenic flexure cancers. Early bowel cancers are unlikely to cause a patient symptoms, therefore the problems described below are more likely to be caused by more advanced colorectal cancers (Dukes C/D), in particular weight loss and iron deficiency anaemia [59].

Pre-screening, the frequencies of initial symptoms that patients have presented with due to a resectable colorectal cancer are shown below. Some patients may present with more than one symptom [60].

- Abdominal pain (including pain secondary to bowel obstruction or bowel perforation) – 44%
- Change in bowel habit – 43%
- Haematochezia or melaena – 40%
- Lethargy – 20%
- Anaemia without other gastrointestinal symptoms – 11%
- Weight Loss – 6%

The prognosis of patients who present with different symptoms has been reviewed by Steinberg et al. [61]. They showed that if you present with abdominal pain secondary to bowel obstruction then you have a significantly worse prognosis compared to presenting without an obstruction ($p=0.003$ for survival). This effect is stays true after correcting for age, gender and Dukes' stage. A similar result is seen with bowel perforation.

From the systematic review and meta-analysis by Ford et al., the table below shows both the sensitivity and specificity of individual symptoms that are caused by a colorectal cancer [62].

<i>Symptom</i>	<i>Sensitivity (95% CI)</i>	<i>Specificity (95% CI)</i>	<i>Positive likelihood ratio (95% CI)</i>	<i>Negative likelihood ratio (95% CI)</i>
Rectal bleeding	64% (55-73%)	52% (42-63%)	1.32 (1.19-1.47)	0.76 (0.66-0.87)
Change in bowel habit	41% (23-60%)	69% (58-78%)	1.29 (1.05-1.59)	0.82 (0.66-1.01)
Anaemia	17% (5.5-33%)	90% (87-92%)	1.43 (0.75-2.74)	0.96 (0.87-1.06)
Weight loss	22% (14-31%)	89% (81-95%)	1.96 (1.25-3.08)	0.91 (0.84-0.98)
Diarrhoea	19% (1-54%)	80% (63-93%)	0.74 (0.34-1.62)	0.98 (0.85-1.13)
Iron deficiency anaemia	23% (2-57%)	87% (83-91%)	1.38 (0.48-3.94)	0.88 (0.68-1.13)
Abdominal Mass	5% (2-9%)	97% (96-98%)	1.47 (0.68-3.19)	0.99 (0.95-1.02)
Dark red rectal bleeding	15% (3-34%)	96% (93-98%)	3.83 (2.62-5.61)	0.88 (0.75-1.04)

Table 3.1 Sensitivity and specificity of symptoms in relation to a colorectal cancer [62].

The table shows that the difficulties in diagnosis for primary care physicians as those symptoms with a high specificity for a colorectal cancer (an abdominal mass and dark red rectal bleeding), have a poor sensitivity (i.e. only a small proportion of colorectal cancers will present with these symptoms).

3.2 Difficulties in Diagnosis

Due the fact that symptoms relating to colorectal cancer are typically related to more advanced tumours, there is considerable difficulty in making a diagnosis of a cancer at an earlier stage. There are also other conditions that can cause the same symptoms as a

colorectal cancer, potentially delaying diagnosis. Using rectal bleeding as an example, its major causes in a Dutch general practice setting are shown in the following table:

<i>Causes of PR Bleeding</i>	<i>Frequency</i>
Haemorrhoids	55%
Anal fissure, perianal abscess	15%
Diverticulosis/diverticulitis	15%
Malignant neoplasm colon/rectum	4%
Chronic enteritis/colitis	2.5%

Table 3.2 Causes of per rectal bleeding [63]

The incidence of rectal bleeding is estimated to be: “20 per 100 people per year, the 'consultation incidence' in general practice approximately six per 1000 and the incidence of referral to a medical specialist is estimated to be about seven per 10,000 per year” [63]. In a population based cross-sectional study in Denmark out of a total of 13,777 randomly selected persons aged 20 years and older, 5.7% (CI 5.2% to 6.3%) reported blood in bowel movements within the preceding 12 months, emphasising the widespread prevalence of this cancer alarm symptom [64].

An analysis of a large primary care database carried out by Hamilton et al. reviewed the symptoms of patients with colorectal cancer in the two years preceding their diagnosis [65]. Between the years of 2001 and 2006 (i.e. pre-screening), 5,477 patients with colorectal cancer were matched against 38,314 controls.

Clinical Feature	Positive Likelihood Ratio (95% CI)	Odds Ratio (CI)
Symptoms		
Constipation	2.6 (2.4 to 2.7)	2.1 (1.9 to 2.3)
Diarrhoea	3.2 (3.0 to 3.4)	2.4 (2.1 to 2.7)
Change in bowel habit	5.5 (5.2 to 5.8)	14 (12 to 17)
Rectal bleeding	6.0 (5.7 to 6.3)	20 (17 to 23)
Weight loss		
5.0–9.9%	1.6 (1.4 to 1.8)	1.2 (0.99 to 1.5)
≥ 10%	2.9 (2.6 to 3.1)	2.5 (2.1 to 3.0)
Abdominal pain	3.5 (3.3 to 3.7)	3.9 (3.6 to 4.3)
Investigations		
Haemoglobin (g/dl)		
<12.0	4.4 (4.2 to 4.6)	
12.0–12.9		1.7 (1.5 to 1.9)
11.0–11.9		2.8 (2.4 to 3.2)
10.0–10.9		5.9 (4.8 to 7.2)
9.0–9.9		9.3 (7.1 to 12)
< 9.0		18 (14 to 25)
Mean red cell volume < 80 fl	2.8 (2.4 to 3.1)	6.5 (5.3 to 7.9)
Diagnoses and Risk Factors		
Irritable bowel syndrome	2.4 (2.1 to 2.8)	
Diabetes	1.2 (1.1 to 1.3)	
Obesity	1.0 (0.93 to 1.1)	

Table 3.3 Likelihood and odds ratio of clinical features in the diagnosis of colorectal cancer [65].

The positive predictive value (PPV) rises with age, especially after the age of 60, as well as with male sex. The highest values are for rectal bleeding and change in bowel habit. For men over 60 years, rectal bleeding PPVs ranged from 2.4% to 4.5%, with women being 2-3%. Constipation, diarrhoea, abdominal pain and weight loss all have low positive predictive values of less than 1.5%. This study shows that most colorectal cancers present

with low risk symptoms, with the chance of these symptoms being due to a colorectal cancer being very low.

3.3 Distribution of Colorectal Cancers

Figure 3.1 shows the distribution of colorectal cancers in the UK between 2007 and 2009. It should be noted that approximately 60% of tumours diagnosed are distal to the splenic flexure. This is likely to have implications in the presentation of the majority of patients, and also the ability of a screening test to detect these cancers.

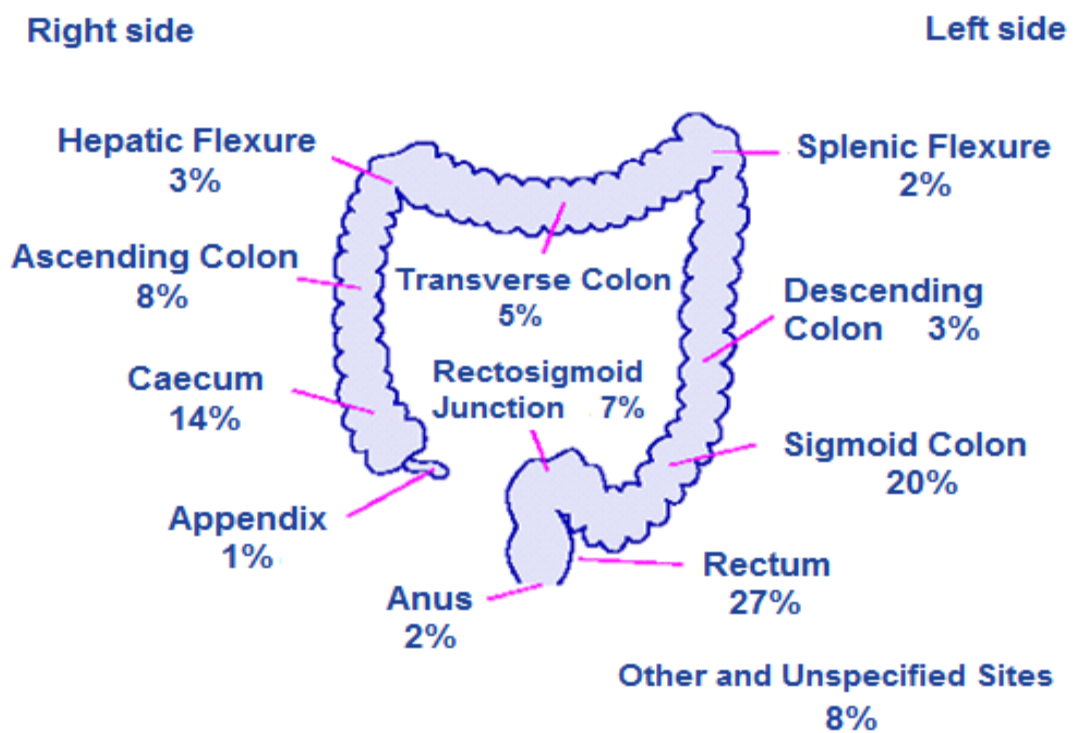


Figure 3.1 Distribution of colorectal cancers [2]

However, there has been a change over time towards more proximal, right-sided cancers as shown in the table below.

<i>Site</i>	<i>% CRC/site 1976–78</i>	<i>% CRC/site 1990–97</i>
<i>Proximal To Splenic Flexure</i>	<i>23.6</i>	<i>36.7</i>
<i>Distal To Splenic Flexure</i>	<i>27.2</i>	<i>27.1</i>
<i>Rectal</i>	<i>44.4</i>	<i>31.9</i>
<i>Unknown</i>	<i>4.8</i>	<i>3.5</i>
<i>Multiple</i>	<i>0.0</i>	<i>0.8</i>

Table 3.4 Percentage Distribution over time of Colorectal Cancers in Northern Ireland [66].

This change in distribution may be due to changes in dietary habits, physical activity, or other lifestyle factors as well as increased diagnostic activities affecting most age groups among women [67].

Rabeneck et al. performed a review of population-based cancer registries in the United States comparing the incidence of both right and left-sided colorectal cancers between 1978 and 1998. They found that although there seems to be an increase in the proportion of right-sided cancers compared to left, this is actually because the incidence of left-sided cancers is decreasing. For right-sided cancers in whites, the age adjusted incidence rate during 1978-1980 was 15.1 per 100,000, moving to 15.0 per 100,000 during 1996-1998. In left-sided cancers in whites, the age-adjusted incidence rate during 1978-1980 was 15.6 per 100,000 which fell to 12.6 per 100,000 during 1996-1998 [68].

3.3.1 Rectal Cancers

Patients will present with symptoms such as rectal bleeding that can be bright red in colour for rectal cancers, to a darker red for slightly more proximal lesions.

They may have some obstructive symptoms such as change in their bowel habit towards constipation or the feeling of incomplete emptying after they have opened their bowels. Occasionally, they may present to an emergency department with a complete bowel obstruction, not being able to pass flatus or open their bowels.

3.3.2 Cancers Distal to the Splenic Flexure

Bleeding is a more prominent feature, although it may be of a darker red colour compared to rectal cancers. A change in bowel habit towards constipation is more likely [69].

3.3.3 Cancers Proximal to the Splenic Flexure

Again, patients may present with a change in their bowel habit, although this may be more towards diarrhoea. This is because faeces are more liquid in the proximal colon and are therefore less likely to be associated with obstructive symptoms. If these patients do present with an obstruction, vomiting may be more of a prominent feature. A palpable abdominal mass has a greater association with proximal cancers. For all colorectal cancers, patients will have symptoms common to all cancers such as weight loss, decreased appetite, malaise, etc. Patients may have been found to be anaemic, often incidentally, which may represent blood loss from their cancer.

Caecal and ascending colon tumours have a greater daily blood loss than tumours at other sites. The geometric mean levels of blood loss for caecal and ascending colon cancers are 9.3 ml/day, 1.5 ml/day for transverse and descending colon, 1.9 ml/day for sigmoid colon, and 1.8 ml/day for rectum. Blood loss is independent of the stage of the cancer [70].

3.4 Symptoms and Stage of Colorectal Cancer

Although one might expect duration of a patient's symptoms to be longer in more advanced cancers, this has been shown not to be the case. In a review of 194 patients with colorectal cancer and their presenting symptoms, there was no association ($p=0.94$) between the duration of symptoms and the stage of cancer. Some patients with Dukes' Stage A cancers had had symptoms for 2 years whereas; some patients with Stage D cancers had had symptoms for less than 2 weeks. Majumdar found no evidence of confounding of the duration-stage relationship by any one symptom [69].

3.5 Atypical Presentations of Colorectal Cancer

9.2% of colorectal cancers present with metastases at time of diagnosis [2]. These patients may present with symptoms relating to the location of the spread of disease. Colorectal cancers spread via the lymphatic system to local and regional lymph nodes, haematogenous spread via the portal system to first the liver, then lungs, bone and brain. Symptoms caused by this spread may be right upper quadrant pain due to liver capsule stretch from a liver metastases, or bone pain [60].

Rarely, colorectal cancers can present with an infectious disease related to either the complications of the cancer or its spread. The table below summarises possible diagnoses:

<i>Intra-Abdominal Infections</i>		Peritonitis
		Abscesses (abdominal wall, retroperitoneal hepatic, perinephric, appendiceal)
		Urinary tract infections and sepsis due to colovesical fistulae
<i>Extra-Abdominal Infections</i>	<i>Due to Spread of Organisms along Intra-Abdominal Tissue Planes</i>	Non-traumatic crepitant cellulitis
		Non-traumatic myonecrosis
		Empyema
		Sepsis due to bowel flora
		Meningitis
		Suppurative thyroiditis
	<i>Due to Presumed Bacteraemia from a Necrotic Tumour</i>	Endocarditis
		Pericarditis
		Pulmonary microabscesses
		Septic arthritis
		"Metastatic" non-traumatic myonecrosis
		Fever of unknown origin

Table 3.5 Atypical presentation of a colorectal cancer [71]

3.6 “Asymptomatic” Colorectal Cancers

The natural history of colorectal cancers is such that they go through different symptom phases:

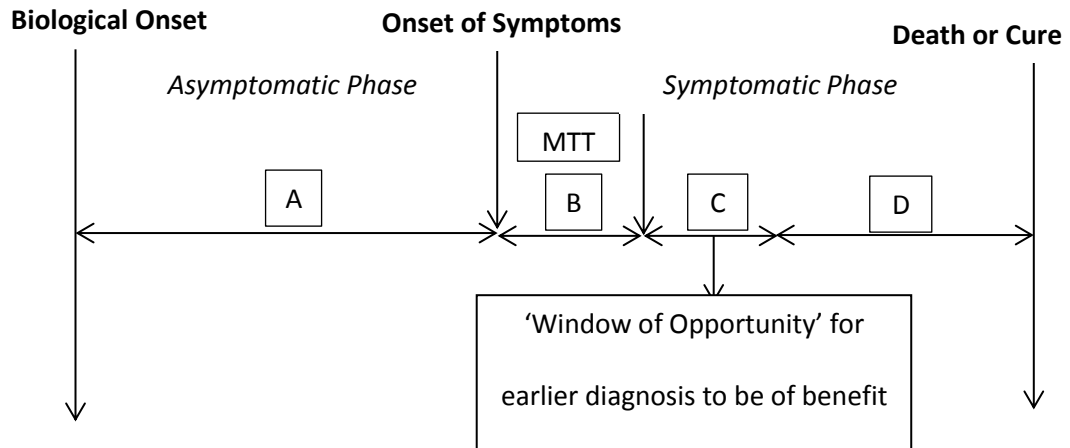


Figure 3.2 Phases of symptoms for a colorectal cancer. MTT, minimum time to treatment that can be achieved after onset of symptoms; A, asymptomatic phase; B, time between onset of symptoms and earliest possible treatment; C, early symptomatic phase; D, late symptomatic phase [72].

In the NHS, processes have been put in place to try and reduce the minimum time to treatment, ranging from health promotion campaigns to raise awareness of the symptoms of colorectal cancer, to increasing the speed that patients can be seen and treated once a referral from their general practitioner has been made. The authors state that at present, there are average delays of between 4-9 months, which has not significantly changed over the last 60 years.

The above phases do not seem to correlate with the stage of disease. Early colorectal cancers can present with significant symptoms and, conversely, advanced cancers can remain relatively ‘asymptomatic’ [73].

As mentioned with regards to rectal bleeding, only a small percentage of the population with this symptom will present to their general practitioner, and then even a smaller percentage will be referred to secondary care. Within screening programmes, all patients who undergo the relevant examinations are deemed to be asymptomatic for the disease that is being screened for. There is an assumption that patients within the appropriate age group will have sought the advice of their relevant health care professional regarding any

symptoms they may be having, and subsequently undergo further tests to confirm or exclude a particular disease.

Harmston et al. reviewed questionnaires regarding any symptoms suffered by 200 patients who were diagnosed with a colorectal cancer as part of the English arm of the Bowel Cancer Screening Programme pilot study [74]. They found that 70% of patients had significant symptoms (change in bowel habit, rectal bleeding, and peri-anal symptoms). The distributions of these are shown in the graph below (Figure 3.3). 59% of patients had two or more symptoms.

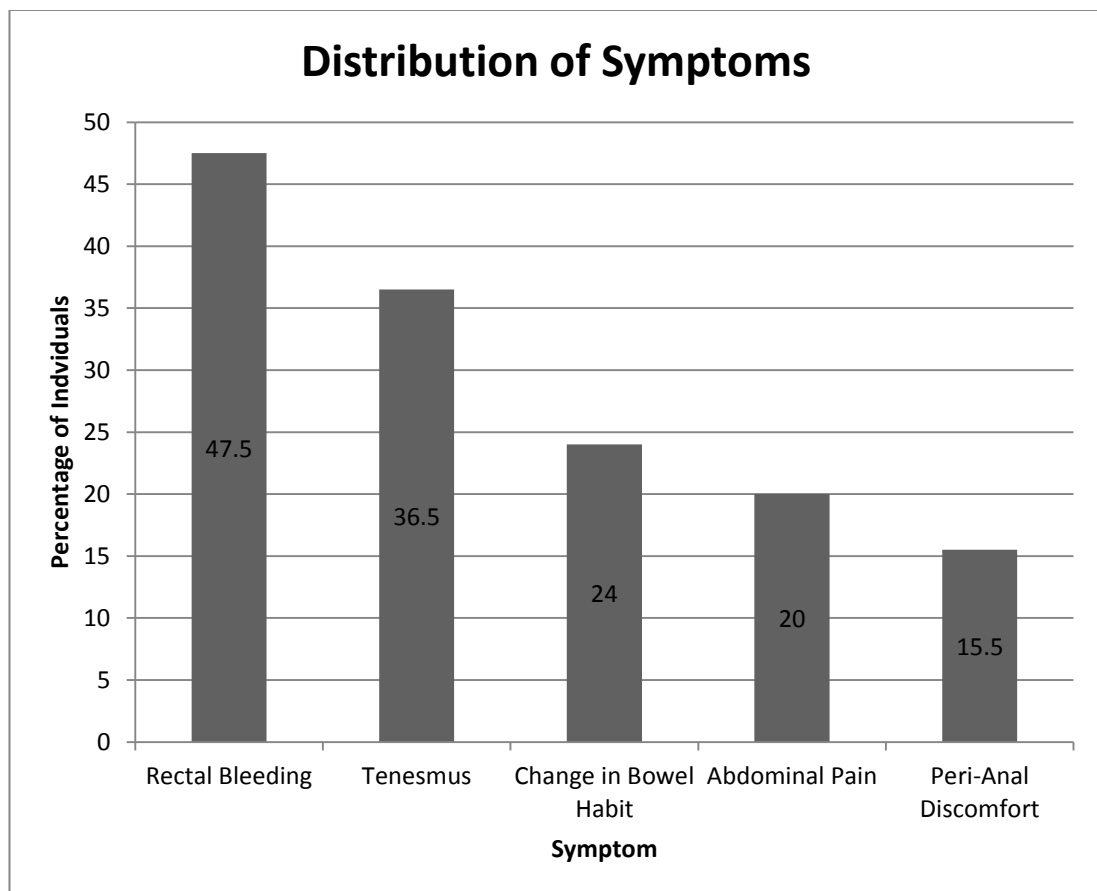


Figure 3.3 Distribution of Symptoms for Screen-detected Cancers in the English Screening Pilot [74].

Interestingly, a large proportion of “early” cancers had these significant symptoms as shown in the table below.

	<i>Rectal Bleeding</i>	<i>Change in Bowel Habit</i>	<i>Tenesmus</i>	<i>Peri-Anal Symptoms</i>	<i>Abdominal Pain</i>	<i>Urgency</i>
Dukes A	59.6%	28%	35%	14%	24.5%	47.4%
Dukes B	35.7%	24.2%	31.4%	14.3%	18.6%	27.1%
Dukes C1	50%	22.5%	43.5%	16%	19.4%	35.4%
Dukes C2	45.4%	9.1%	36.4%	27.3%	9.1%	63.6%

Table 3.6 Symptom prevalence by Dukes Stage [74].

The difficulty in drawing conclusions from this is that the authors do not state whether there was any other pathology that was concurrent with the patients' cancer that might be contributing to their symptoms, e.g. haemorrhoids with the symptom of rectal bleeding.

A similar review of the Scottish arm of the national colorectal cancer screening pilot was performed where all those patients with positive faecal occult blood tests completed a symptom questionnaire. Although lower gastro-intestinal symptoms were common among the patient group (78% of 563 participants had one or more symptoms), there were no significant associations found between any of these symptoms and the findings on colonoscopy. Likewise, the total number of symptoms was not predictive of neoplasia (colorectal adenoma or carcinoma) [75].

3.7 Chapter Conclusion

As described in the section above, the diagnosis of a colorectal cancer is a challenging one. For those patients who do have a colorectal cancer, any possible symptoms attributed to it can be vague or absent. Symptoms that are potentially attributable to a cancer can also be caused by a range of benign gastro-intestinal pathologies. Even for those patients who do have a colorectal cancer and are symptomatic with this, a large proportion will not seek medical advice, instead undergoing screening examinations. It is unclear at what point this group of patients would eventually seek the advice of their general practitioner, in the absence of a screening programme, or whether they would continue to manage their symptoms by themselves.

The NHS Bowel Cancer Screening Programme helps to identify the population with a colorectal cancer in which they are asymptomatic with their cancer, or have symptoms but have not actively sought medical attention.

Chapter 4 Investigation of Lower Gastrointestinal Symptoms

4.1 Introduction

Investigation for a suspected colorectal cancer can take the form of many different types of investigation. These are now usually endoscopic, such as a flexible sigmoidoscopy and colonoscopy, with the majority of patients requiring no further investigation. Other tests are radiological, such as a CT scan or occasionally a plain abdominal X-Ray for patients presenting with abdominal pain. Increasingly, stool and blood tests precipitate large bowel investigations with the increasing public awareness of bowel cancer. Given the range of investigations, there have been a number of studies that have looked into using each of these as possible screening tests for colorectal cancer. This section describes each of the examinations and gives an overview of the important literature regarding screening studies using either each of them alone or in combination with other tests.

The “History” of the nature of the patients’ problem will first be taken by their healthcare professional. This will involve enquiring into the severity and duration of each individual symptom, focusing on any “alarm” symptoms that might be caused by a colorectal cancer. A physical examination should be carried out, including a digital rectal examination. This is to look for a palpable abdominal or rectal mass which greatly increases the suspicion of a cancer. Appropriate blood tests should be carried out, in particular looking for iron-deficiency anaemia. This is due to occult blood loss from colorectal neoplasia which causes iron deficiency that is sufficiently severe to diminish erythropoiesis and cause the development of anaemia [76].

Each hospital NHS Trust will have referral guidelines for those with gastro-intestinal symptoms. These may be based upon the National Institute for Clinical Excellence guidelines published in 2004 [77], however these have been criticised for being “too restrictive and ... intended partly to ration limited diagnostic resources”, when an analysis of the predictive value of colorectal cancer related symptoms is performed [78].

If the suspicion of a colorectal cancer is high, a “two-week” referral to secondary care is sent. The patient may then be seen in either an outpatient clinic or go straight for further investigations as listed below.

4.2 Flexible Sigmoidoscopy

This is a form of endoscopic examination of the large bowel. The procedure involves using an endoscope to visualise the large bowel from the rectum up to the splenic flexure (proximal descending colon). It differs from a colonoscopy in that the endoscopist does not

examine the whole length of the large bowel, visualising approximately 60cm from the anal verge.

Patients must undergo bowel preparation, either in the form of an enema or oral laxative, prior to the procedure to better visualise the bowel, as well as not eating or drinking for several hours prior to the procedure. Each hospital trust may have slight differences in the advice given prior to the procedure. The advantages of a flexible sigmoidoscopy over a colonoscopy are that it is better tolerated, safer, less painful, quicker, and has a lower complication rate. Sedation is not routinely given for a flexible sigmoidoscopy.

As discussed in Chapter 3, there is much discussion as to how best to identify those patients presenting to their general practitioner who have a colorectal cancer. Once a referral has been made to a colorectal clinic for a suspected cancer, there is further debate as to which choice of investigation should be used.

Thompson et al., attempted to identify which patients would be better suited having a flexible sigmoidoscopy, and which patient should have their whole colon visualised [79]. Of 15,363 patients analysed, 94.1% had one or more symptoms suggestive of a colorectal cancer (rectal bleeding, change in bowel habit, abdominal pain, iron deficiency anaemia or an abdominal mass). 98.9% of patients underwent a flexible sigmoidoscopy, of which 34.8% were then referred for whole colon imaging. Of the 946 patients that were diagnosed with a colorectal cancer, 86.2% had a rectal or sigmoid cancer. In 922 (97.5%) patients, this was diagnosed by flexible sigmoidoscopy (788) or subsequent whole colon imaging (134). There were 24 (2.5%) missed cancers. The authors conclude that only 0.2% of patients who present to a surgical outpatient clinic with symptoms of rectal bleeding, change in bowel habit, or abdominal pain without iron deficiency anaemia or abdominal mass, will have a cancer proximal to the sigmoid colon. If flexible sigmoidoscopy is negative, and the patient does not have anaemia, abdominal mass, severe symptoms or other significant factors on flexible sigmoidoscopy, then the residual risk of a colorectal cancer is less than an asymptomatic patient who has not had a flexible sigmoidoscopy.

The authors suggest a referral pathway that incorporates the fact that 95% of colorectal cancers will be detected by flexible sigmoidoscopy in patients without iron deficiency anaemia or an abdominal mass.

4.2.1 Screening with Flexible Sigmoidoscopy

Given the above benefits over colonoscopy, there have been a number of studies which use flexible sigmoidoscopy to screen for colorectal cancers.

A multi-centre randomised controlled trial based in England sent questionnaires to 368,142 men and women aged 55-64 years to establish their interest in a one-off flexible sigmoidoscopy screening examination [80]. This was on the background of two pilot studies [81]. 194,726 (52.9%) responded positively, of which 170,432 were randomised into the intervention group or control group at a ratio of 1:2. Participants were invited for a colonoscopy if they were found to have any of the following at flexible sigmoidoscopy: 1cm or larger polyp; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease; or 20 or more hyperplastic polyps above the distal rectum. Of the 57,237 allocated to the screening group, 40,674 (71.1%) attended their offered flexible sigmoidoscopy. 95% of patients were discharged after a negative exam with 2,131 (5.2%) of patients being referred for a colonoscopy, with the remainder entering a surveillance programme. There were 706 colorectal adenocarcinomas identified in the intervention group and 1,818 in the control group. After 11 years of follow up, there was a significant reduction in all site CRC incidence (HR 0.67, 95% CI 0.60-0.76), although this reduction was only significant for distal cancers. All-cause mortality was unchanged between the intervention screened group and control group; however, there was a significant reduction in verified deaths attributable to CRC (HR 0.56, 95% CI 0.45-0.69). The authors conclude that flexible sigmoidoscopy screening is a safe and practical test and, when offered only once to people between ages 55 and 64 years, confers a substantial and long lasting protection from colorectal cancer.

In a separate UK based study, when flexible sigmoidoscopy screening was offered as a service rather than as part of a research study, uptake remained high at 67%. The authors give the reasons that the examination was taken up well "because the entire study population was invited without the two-stage invitation procedure". As may be expected, "people living in more socioeconomically deprived areas were more likely to decline the offer of screening or not respond to the invitation" [82].

A large, population based randomised controlled trial from Norway, compared the incidence and mortality from colorectal cancer in patients aged between 55-64 [83]. The age range was chosen to maximise ability of the study to show the desired primary endpoint, due to the relative population size and colorectal cancer incidence at this range. Out of 13,823 people invited for a one-off flexible sigmoidoscopy, half were additionally asked to undergo an immunochemical FOB test. Of the 13,653 people eligible for screening, 8,846 underwent an examination, giving an attendance rate of 64.8% (67% with exclusion of those not examined owing to exclusion criteria). In total, 33 out of 71 colorectal cancers

were screen-detected, giving a significant 59% reduction in incidence of total colorectal cancer and 76% reduced incidence of rectosigmoid cancer among attenders, per protocol analysis (an analysis prone to selection bias). However, whilst there was a reduction in 6 year mortality (27% from total colorectal cancer and 37% from rectosigmoid cancer), this was not significant on statistical analysis. Interval cancers were found to have equivalent outcomes to the control group.

As part of the SCORE (Screening for COLon REctum) one-off Italian flexible sigmoidoscopy screening trial, of the 17,148 subjects assigned to the intervention group of a one-off flexible sigmoidoscopy, followed by a colonoscopy for any patient found to have large distal polyps (>5 mm), three or more adenomas, one adenoma with villous component greater than 20%, a high-grade dysplastic polyp, inadequate bowel preparation harbouring at least one polyp, and for those found to have invasive CRC [84]. It is important to note that the criteria for referral for a colonoscopy in the Norwegian and Italian trials were at a lower threshold than the UK RCT, and hence their colonoscopy rates were higher. 9,911 (57.8%) subjects were examined by flexible sigmoidoscopy. Of these, 9,387 (94.71%) subjects were discharged, 55 (0.55%) were referred for surgery (43 CRCs, 10 large adenomas, and two perforations: one during flexible sigmoidoscopy and one during total colonoscopy), 395 (4.0%) were referred for a subsequent surveillance colonoscopy, whereas the remaining 74 (0.74%) did not comply with the recommended colonoscopy assessment. 54 subjects were detected with 57 CRCs (44 in the rectum and sigmoid colon, four in the descending colon, and nine in the proximal colon). In an intention-to-treat analysis, the authors report an 18% reduction in CRC incidence in the intervention group, with an improved stage profile of the cancers and adenomas detected. However, there was still an interval cancer rate. Of 126 subjects diagnosed with a colorectal cancer that were screened, 54 (42.8%) of these were identified at the flexible sigmoidoscopy. This means that over half of cancers were not detected due to this screening intervention, which includes 32.4% of distal colon cancers, over the median 10.5 year follow up period. Although there was no difference found in the incidence of proximal cancers between those screened and not screened, the authors do not state when precisely these non-screen-detected cancers (for both proximal and distal lesions) were diagnosed in the intervention group. Therefore, we do not know whether the proportion of cancers were present at the time of the intervention, in the population that had no polyps that necessitated a subsequent colonoscopy.

4.3 Colonoscopy

A colonoscopy is an endoscopic examination of the entire length of the large bowel. Patients must undergo bowel preparation in order to establish adequate views of the bowel wall. During the procedure, patients often require either, or a combination of, intravenous analgesia and intravenous sedation, or inhaled analgesia (e.g. entonox, a 50/50 mix of nitrous oxide and oxygen). A colonoscopy naturally takes longer than a flexible sigmoidoscopy and has a higher (albeit low) complication rate. If a suspected cancer is found, the lesion can be tattooed endoscopically to aid identification of the lesion at operation. This tattooing is becoming increasingly important with the increase in laparoscopic bowel resections, as the surgeon can no longer manually feel for the lesion within the bowel. Colonoscopy itself is poor at identifying locations of lesions, with up to 21% being incorrectly recorded [85].

4.3.1 Screening with Colonoscopy

There has been much discussion regarding the frequency that a colonoscopy should be carried out. Lansdorp-Vogelaar et al., attempted to individualise the frequency of examination by sex and race of the population. Their proposed individualisation is to have white men undergo 4 screenings from age 53 to 74 years every 7 years; black men: 5 screenings from age 47 to 75 years every 7 years; white women: 4 screenings from age 53 to 77 years every 8 years and black women: 5 screenings from age 47 to 75 years every 7 years. However, when compared with their current local 8-yearly guidelines, there are only 0.0002 additional life-years gained, at \$9.09 lower costs per person [86].

Whilst Imeriale et al. [87] suggested a 5 year interval for colonoscopy screening, Singh et al. believe that this should be extended to 10 years following a negative colonoscopy with the standardised incidence ratio for colorectal cancer being 0.28 (95% CI, 0.09-0.65) at 10 years [88].

A study published by from the EPAGE (European Panel on the Appropriateness of Gastrointestinal Endoscopy) group, involved 561 colonoscopies that were performed for screening purposes, i.e. asymptomatic patients with a range of increase in risk for colorectal cancer, over a range of ages. Of these screening colonoscopies, 336 (59.9%) were for indications that were uncertain appropriateness with 80 (14.3%) being performed for inappropriate indications. 74 (13.2%) patients were diagnosed with colorectal neoplasia including 4 (0.7%) cancers and 70 (12.5%) adenomatous polyps [89].

4.4 Newer Types of Colonoscopy

The standard colonoscopy examination involves using a white light colonoscope. This uses air insufflation with a fibre-optic image being transmitted to a video monitor, viewed by the endoscopist. In order to improve the detection rate for colorectal neoplasia, newer methods of examination using endoscopic techniques are being evaluated. Below is an overview of these techniques, and the evidence to support their use.

4.4.1 Wide-Angle Colonoscopy

This type of colonoscopy uses a high definition (HD), wide angle endoscopy in the detection of colorectal neoplasia. A randomised controlled trial of 390 patients comparing HD, wide angle colonoscopy vs. standard colonoscopy was carried out by Tribonias et al., with the primary outcome of polyp detection [90]. The HD, wide angle colonoscopy group was found have a superior rate of all type and size polyp detection (SC 1.31 ± 1.90 ; HD 1.76 ± 2.31 ; $p=0.03$) and of polyps <5mm in size (SC 0.10 ± 0.36 ; HD 0.25 ± 0.61 ; $p=0.003$). No differences in detection were found between medium (5-10mm) size or large (>10mm) size polyps.

4.4.2 Chromoendoscopy

Chromoendoscopy or chromocolonoscopy is a type of lower gastro-intestinal endoscopic examination which is aimed at, in particular, increasing the identification of flat or depressed neoplasia, deemed harder to detect with conventional methods. Chromoendoscopy works by spraying a dye (indigocarmine) at the bowel wall in an attempt to better identify lesions. Kahi et al. [91] compared high-definition chromocolonoscopy versus high-definition white light colonoscopy for patients referred for screening colonoscopies. Out of 660 patients randomised into two groups, the number of patients with at least one adenoma (55.5% vs. 48.4, $p=0.07$), and the number of adenomas per patient (1.3 ± 2.4 vs. 1.1 ± 1.8 , $p=0.07$) were marginally higher in the chromocolonoscopy group. There were no significant differences in the number of advanced adenomas per patient ($p=0.3$) or the number of advanced adenomas <10mm per patient ($p=0.4$). Chromocolonoscopy detected significantly more flat adenomas per patient ($p=0.01$), adenomas <5mm in diameter per patient ($p=0.03$), and non-neoplastic lesions per patient ($p<0.0001$). The main problem with this technique is that it is labour intensive and time-consuming [92].

A Cochrane review of chromocolonoscopy of four studies all carried out prior to Kahi et al.'s, concluded that this technique will yield positive results for significantly more patients with at least one neoplastic lesion (OR 1.61, 95% CI 1.24-2.09) and significantly more patients with three or more neoplastic lesions (OR 2.55, 95% CI 1.49-4.36) [93]. They criticised the studies for not publishing their results of biopsies that proved to be of normal colonic tissue, hence making estimates of the specificity of the technique impossible. They suggest that this technique may have the most marked benefit for patients with inflammatory bowel disease and Lynch Syndrome.

4.4.3 Narrow Band Colonoscopy

Narrow band imaging uses a narrowed light source with wave lengths centred at 415nm (blue) and 540nm (green). Light at these wavelengths penetrates through the mucosa and submucosa and is absorbed by haemoglobin thereby enhancing the appearance of microvessels. The theory that lesions have a greater level of angiogenesis means that they should be more easily detectable, regardless of their shape.

In a tandem colonoscopy study using narrow band imaging versus the standard white light colonoscopy, there was a miss rate in 17 of 135 patients (12.6%) in the narrow band imaging group versus 17 of 141 (12.1%) in the white light group [94]. All missed neoplasms were tubular adenomas with 78% of these ≤ 5 mm. The authors felt that their high detection rate of neoplasms (49% of patients) was the reason that there was no difference seen between the two imaging modalities.

The DISCARD (Detect InSpect ChAracterise Resect and Discard) study used high-definition white light colonoscopy, followed by narrow-band imaging (without magnification or chromoendoscopy) to compare whether these modalities could accurately assess polyp characterisation, and hence follow up period, against histological assessment [95]. In polyps < 10 mm in size, 186 out of 198 adenomas (sensitivity 0.94, 95% CI 0.90-0.97) were accurately diagnosed, along with 55 of 62 hyperplastic polyps (0.89, 95% CI 0.78-0.95). The implications of the use of these techniques may mean savings in both time and cost by avoiding histological examination of a large number of these polyps.

4.4.4 Autofluorescence Imaging

A similar technique to narrow band imaging, except different wavelengths are used: ultraviolet (< 400 nm) or short visible light (mostly blue) to produce autofluorescence light.

The autofluorescence of neoplastic mucosa differs from that of normal colonic mucosa and so appears a different colour when the above light is shined upon it [92].

4.5 Chapter Conclusion

Flexible sigmoidoscopy and colonoscopy play pivotal roles in the current diagnosis of colorectal cancers. Despite an effective screening programme, there will always be patients who present through their general practitioner with symptoms attributable to a colorectal cancer, which are investigated with the above tools. This chapter has covered the evidence behind screening with flexible sigmoidoscopy, and the debate on the time intervals for repeat colonoscopies.

Newer forms of colonoscopy, including chromoendoscopy and narrow band imaging, have been discussed. These techniques may have a role to play in diagnosis and management of small polyps found on either screening or non-screening colonoscopies.

Chapter 5 The Faecal Occult Blood Test, FOBt

5.1 Background of the test

The test is a dehydrated, guaiac acid faecal occult blood test (FOBT). The test was developed after the finding by Van Deen that gum guaiac, a natural resin extracted from the wood of *Guaiacum officinale*, can detect occult blood. Guaiac had previously been used from the early 1500's as a treatment for syphilis, a treatment that continued until the early 19th Century [96].

The test is based on the properties of guaiac to turn to a blue-coloured compound when oxidised by hydrogen peroxide. The haem portion of haemoglobin, if present in the faecal specimen, has peroxidase activity which catalyses the oxidation of alpha guaiaconic acid (active component of the guaiac paper) by hydrogen peroxide (active component of the developer) to form a highly conjugated blue quinone compound [97].

Patients are sent three tests per kit and are given the following instructions with the test:

- For accurate test results, apply samples from bowel movements collected on **three different days** to slide.
- Do not collect sample if blood is visible in your stool or urine (e.g., menstruation, active haemorrhoids, urinary tract infection). **Contact your doctor.**
- For the most accurate test results collect each stool sample before contact with the toilet bowl water. You may use any clean, dry container.
- Return completed slides to your doctor or laboratory no later than 14 days after your first sample collection.
- Protect slides from heat, light, and volatile chemicals (e.g., ammonia, bleach, bromine, iodine and household cleaners).
- Remove toilet bowl cleaners from toilet tank and flush twice before proceeding.

They are given the following information regarding medication:

- For **seven** days before and during the stool collection period, **avoid** non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen or aspirin (more than one adult aspirin a day).
- For **three** days before and during the stool collection period, **avoid** vitamin C in excess of 250 mg a day from supplements, and citrus fruits and juices.

They are given the following information regarding diet:

- For **three** days before and during stool collection period, **avoid** red meats (beef, lamb and liver).
- Eat a well-balanced diet including fibre such as bran cereals, fruits and vegetables.

5.2 Screening with Faecal Occult Blood Tests

There are four main mass population-based screening studies that have used faecal occult blood tests to screen a population with the aim of diagnosing early, pre-symptomatic colorectal cancer. These were based in Nottingham in the UK, Funen in Denmark, Minnesota in the USA and, Goteborg in Sweden. The features of each of these are described below.

5.2.1 The Nottingham Trial

The Nottingham trial began in 1981 with subjects aged between 45-74 (identified by GP records) being randomly assigned to test and control groups, continuing to 1991. Subjects allocated to the intervention arm were offered biennial faecal occult blood tests. These tests were guaiac-based and un-rehydrated. The results of the trial was published over several papers [98-101], culminating in a paper showing follow up results over a median of 19.5 years (1,296,712 person-years in intervention group, 1,296,614 person-years in control group) [102].

In the preliminary phases of the trial, the Hemoccult test was shown to give false positive results secondary to dietary intake. Foods that contain natural peroxidase activity, such as broccoli, cauliflower, banana, and parsnip, as well as red meat (beef, lamb, black pudding) that contains animal haemoglobin can cause a positive reaction. Dietary restrictions, as well as repeating weakly positive tests were introduced following a study of repeating a selection of positive tests within the Nottingham pilot study with dietary restrictions [103]. The subjects who had a repeat negative test were asked to repeat a FOB test after three months and then endoscopically investigated if it was positive. Out of 31 positive tests, there were 4 cancers and 20 adenomas detected. This emphasised the need for regular and repeated testing due to the intermittent nature of polyps/cancers bleeding.

By the end of the allocation period, 152,850 subjects had undergone between three and five screening rounds. The trial methodology was altered as time and resources progressed. At the beginning of the study, no dietary restrictions (apart from vitamin C tablets) were imposed. Those with a positive FOB test were invited for an outpatient appointment, flexible sigmoidoscopy and double contrast barium enema.

In 1983, a cohort in the same age group was sent the FOB test, as well as an immunological FOB test. Those with a positive test, either FOBt or iFOBt, were investigated as above.

In 1984, those who completed the Hemoccult test from the first cohort were offered rescreening by a repeat FOB test. Those with a positive result were offered a repeat

examination with flexible sigmoidoscopy and barium enema, and were also asked to complete a 6-day Hemocult test with dietary restrictions.

151,975 subjects were suitable for analysis after a median follow-up of 19.5 years (range 0.0-28.4 years, IQR 10.2). 76,056 subjects were in the intervention arm and 75,919 in the control arm. The uptake was 59.6% of at least one screening test with 38.2% completing all FOB tests offered. FOBt positivity was 2.3%. In the intervention arm, of a total of 2,279 colorectal cancers diagnosed, there were 236 (10.4%) screen-detected cancers (83 after first invitation - 51% Dukes' A, 21 in later invitation - 29% Dukes' A, and 132 at re-screen - 37% Dukes' A), 959 (42.1%) cancers in non-responders (8% Dukes' A) and, 1,037 (45.5%) interval cancers. Of the interval cancers, 173 were diagnosed between screening rounds within two years, with 864 being diagnosed after two years. This is likely the reason for the high rate of interval cancer. There were 2,354 cancers diagnosed with the control arm, of which 11% were Dukes' A. 314 of 2279 (14%) cancers diagnosed in the intervention arm were of Dukes' Stage A.

In addition to cancer detection, a total of 2,291 adenomas were removed at colonoscopy in the intervention arm with 1,484 from the control arm. 615 of the screen-detected adenomas were greater than 10mm in size.

The absolute reduction in mortality from CRC was 1.66 per 1000 persons, meaning 602 persons (95% CI 339-2648) who need to be invited for screening for an average of 6 years to prevent one death over 20 years.

5.2.2 The Funen Trial

Between August 1985 and September 1986, 30,970 individuals aged between 45 and 74 years of age were offered the un-rehydrated Hemocult FOBt, along with 30,968 controls [104]. They were all inhabitants in the county of Funen, Denmark. Of these, 20,695 (67%) completed the test. There were 215 patients with positive tests, all of whom were invited to undergo a colonoscopy examination. Of the 209 patients who underwent subsequent examination, 123 cases of colorectal neoplasia (37 carcinomas and 86 adenomas) were found. Only 8 individuals had no colorectal pathological findings. The authors included diagnoses of diverticulosis and haemorrhoids as a positive colonoscopic finding, although accept that these may not have been the cause for a positive FOBt.

There were 9 cases of interval colorectal cancer, following a negative FOB test. In the control group colorectal neoplasia was diagnosed in 76 persons. The cancers within the screening group had a large proportion of Dukes' A cancers compared to the control group

(19 vs. 2). There were 11 vs. 19 Dukes B cancers in the screening and control groups respectively. There was a greater proportion of more advanced cancer which had distant spread in diagnosis in the control group versus the screening group (8 vs. 2).

In 1996, Krongborg et al. published the results of the follow up study from their pilot study described above [105]. Having excluded those individuals from the pilot study, they randomised 137,485 persons aged 45-74 into a screening group (30,967 persons), control group (30,966 persons) and un-enrolled group (75,552). Only the control and intervention group were followed up. The authors estimated that a study and control group of size 30,000 subjects in each was sufficient to give an adequate power in detecting a significant reduction in CRC mortality by 25%. The un-enrolled group represented the excess population not required as part of the study, but would have potentially been eligible for inclusion. 20,672 (67%) submitted an un-rehydrated Hemoccult test (having restricted their diet) from the first screening round, >90% completed repeat biennial tests. There were a total of 481 cancers in the screening group identified (120 following positive FOB test, 18 before invitation for test, 195 in non-responders and 148 interval cancers), with 483 in the control group. There was a total of 413 adenomas ≥ 10 mm in the screening group versus 174 in the control group. As with the Nottingham study, the colorectal cancers were of a significantly earlier stage in the screening group (Dukes A – 22 vs. 11%, $p < 0.01$). The overall cumulative survival in patients with colorectal cancer was significantly higher in the screening group versus the control group ($p < 0.01$), with a reduction of 18% in colorectal cancer mortality. The mortality rate from CRC (including complications from treatment) was 0.89 per 1000 person-years in the control group, and 0.73 in the screening group. 249 of 6303 deaths (4.0%) were due to CRC in the control group, with 205 of 6228 deaths (3.3%) in the screening group.

5.2.3 Other FOBt trials

There have been numerous other trials looking at faecal occult blood tests. The Minnesota study showed a reduction in cumulative 18 year colorectal cancer mortality by 33% in the annual FOB screening group compared to the control group (rate ratio: 0.67; 95% CI 0.51–0.83) and a 21% reduction in the biennial FOB screening group (rate ratio: 0.79; 95% CI 0.62–0.97) [106]. A criticism of this study is that subjects volunteered for the study, meaning it is not a true population-based screening study.

Another notable study is Faivre et al.'s from Burgundy, France [107, 108]. A population based-study between 1988 and 1998 including 91,199 individuals aged 45-74, who

underwent biennial FOB tests. They showed a 33% reduction in colorectal cancer mortality in those who underwent at least one round of screening test versus the control group (mortality ratio: 0.67, 95% CI 0.56-0.81). In the whole screening group, colorectal cancer mortality was significantly lower than the control group (mortality ratio: 0.84, 95% CI 0.71–0.99).

Other studies have also shown a reduction in mortality due to the use of an annual or biennial FOB test [109, 110]. Meta-analyses of the studies from Nottingham, Funen, Minnesota and Burgundy showed an overall reduction in mortality due to colorectal cancer of 14-16% [111, 112]. A Cochrane review [113] from 2008 reviewed the Nottingham, Funen, Minnesota and Goteborg trials [114, 115]. They found a combined relative risk reduction of 16% of colorectal cancer mortality (relative risk 0.84, 95% CI 0.78-0.90). There was a 25% relative risk reduction (relative risk 0.74, 95% CI 0.66-0.84) in those who underwent at least one round of the screening test.

However, in a paper by Autier et al., the effect on colorectal cancer mortality due to only the FOB screening test was reviewed, i.e. not including the interval cancers mortality rates from the screening arm as a whole [116]. By doing this, the absolute reduction in mortality decreases from 16% to 12% and is no longer statistically significant ($p > 0.05$). The authors state that this effect is disease awareness of colorectal cancer. However, I would argue that this effect should be considered part of the screening programme. With the primary aim of the screening test to identify colorectal cancers and adenomas at an earlier stage so that they can be treated, if this means that a population of patients presents out with a screening programme and are subsequently diagnosed with a colorectal cancer, then the endpoint is still the same. This is reflected in the fact that 47% of interval cancers in the Nottingham study are of Dukes A or B (compared with 44% of controls).

The cost-effectiveness for introducing a biennial FOB test in terms of the Disability adjusted life years (DALYs) and the years of life lost (YLLs) averted was reviewed in Australia, and deemed to be suitable for introduction [117].

The risks associated with the Nottingham randomised controlled trial was reviewed by Robinson et al. [118]. There were seven (0.5%) complications of the colonoscopy, of which 6 required surgical intervention. There were 5 deaths within 30 days of surgery for a screen-detected cancer, but no post 30 day cancer related deaths post-surgery.

5.3 Summary of Mass Population Studies

A difficulty in interpreting the differing mass population studies is the different methodology and screening tests that have been used by the groups involved. Tables 5.1 and 5.2 below summarises the screening methodology for each of the four main trials, as well as the incidence of colorectal cancer in each group. Table 5.3 shows the positivity of the FOBt and its calculated sensitivity.

These tables have been adapted from the Cochrane review (published in 2008 and updated in 2011) [113], with results from the median 19.5 year follow up from Nottingham added [102].

Study	Country	Screen Frequency	Age Range (yr)	Length of Follow-Up (yr)	No. of Screening Rounds	Attending First Screening (%)	At Least One Round (%)
Funen [105]	Denmark	Biennial	45–75	17	9	66.8	NR
Goteborg [110]	Sweden	Biennial	60–64	15.5	2	63.0	70.0
Minnesota [119]	U.S.	Annual/ Biennial	50–80	18	11 (A) 6 (B)	NR	75.0 (A) 78.0 (B)
Nottingham [102]	U.K.	Biennial	45–74	19.5	6	53.4	59.6

Table 5.1 Methodology and uptake of FOBT screening. A = annual screening; B = biennial screening; NR = not reported.

Study	No. of CRC Cases		Incidence Rate of CRC Cases	
	Screening Group	Control Group	Screening Group (py)	Control Group (py)
Funen [105]	889/30,967	874/30,966	2.06/1,000	2.02/1,000
Goteborg [110]	252/34,144	300/34,164	NR	NR
Minnesota [119]	852/31,157	507/15,394	32–33/1,000	39/1,000
Nottingham [102]	2,279/76,056	2,354/75,919	1.77/1000	1.83/1000

Table 5.2 Number and incidence rate of colorectal cancer by study. NR = not reported.

Study	Rehydration	Positivity Rate (%)	Sensitivity (%)	Positive Predictive Value (CRC) (%)	Positive Predictive Value (Adenoma) (%)
Funen [105]	No	0.8–3.8	55.0	5.2–18.7	14.6–38.3
Goteborg [110]	Yes	1.7–14.3	82.0	NR	NR
	No	1.9	NR	NR	NR
Minnesota [119]	Yes	3.9–15.4	92.2	0.9–6.1	6.0–11.0
	No	1.4–5.3	80.8	5.6	NR
Nottingham [102]	No	1.2–2.7	57.2	9.9–17.1	42.8–54.5

Table 5.3 Type of FOBT, positivity rate and predictive value for colorectal cancer and adenoma.

Table 5.4 below shows the number and rate of mortality related to colorectal cancer. When all-cause mortality was reviewed in the Nottingham study, no significant difference was found between intervention and control group.

Study	No. of CRC Deaths		Mortality Rate		Mortality Reduction (%)
	Screening Group	Control Group	Screening Group (py)	Control Group (py)	
Funen [105]	363/30,967	431/30,966	0.84/1,000	1.00/1,000	16
Goteborg [110]	252/34,144	300/34,146	NR	NR	16
Minnesota (A) [119]	121/15,570	177/15,394	0.67/1,000	1.00/1,000	33
Minnesota (B) [119]	148/15,587		0.79/1,000		21
Nottingham [102]	1,176/76,056	1,300/75,919	0.91/1000	1.00/1000	13 (18*)

Table 5.4 Number and rate of deaths for each study. A = annual screening; B = biennial screening; NR = not reported; py = person years. *when adjusted for non-compliers of screening.

As described in Chapter 1, risk factors in the development of a colorectal cancer are also risk factors for many other conditions such as ischaemic heart disease and other types of cancer. Therefore, with the extended follow up data published on the Nottingham study, it is unsurprising that equivalent all-cause mortality rates were found.

Chapter 6 Interval Cancers

6.1 Introduction

Interval cancers can be classified into two groups:

1. A cancer relating to the biology of the cancer.

This group represents cancers that are aggressive in their growth, going through the adenoma-carcinoma sequence at an accelerated rate. It has been postulated that this may be due to the genetic make-up of this group of tumours.

2. A cancer relating to a false negative diagnostic test.

This type of interval cancer is related to the sensitivity of a test, i.e. the proportion of false negative test results. Within colorectal cancer screening, there are relatively large numbers of false negative faecal occult blood tests, due to the poor sensitivity of the test. There has also been research published on post colonoscopy interval cancers.

With regards to colorectal cancer, an interval cancer may belong to one, or both categories. Both of these groups will be discussed in this chapter.

6.2 The Biology of Interval Cancers

As discussed in Chapter 1, there are a series of genetic abnormalities that are associated with colorectal cancer development.

Microsatellite instability (MSI) is thought to play a key role in the pathogenesis of colorectal cancers. Lesions with MSI are associated with interval colorectal cancers. The reasons for this are multifactorial. The lesions themselves are associated with rapid growth, and therefore may develop between examination procedures [120]. Also, these lesions are more frequently found in the right colon, and are of a serrated sessile structure, making them harder to detect at colonoscopy [121]. Hawkins et al. compared benign polyps from cancer resection specimens in patients with and without microsatellite instability (n=29 in each group). They found that individuals with cancers showing MSI were more likely to have at least one serrated polyp than the control group (OR 4.0, 95% CI 1.1-14.2; p=0.03), but the frequency of non-serrated adenomas was the same in both groups (p=0.52) [122]. Sawhney et al. compared 51 interval cancer specimens against 112 non-interval cancers. They reported that 30.4% (95% CI 19.0%–44.9%) of interval cancers displayed MSI vs.

10.3% (95% CI 5.5%–18.1%) of non-interval cancers ($p=0.003$). After adjusting for age, subjects with an interval cancer were 3.7 times more likely (95% CI 1.5-9.1) to show MSI than non-interval cancers. The association between MSI and interval cancers was found to be more pronounced in the distal colon, despite a greater proportion of interval cancers being found in the proximal colon (61% vs. 40%, $p=0.02$). The authors found no difference in stage of interval cancers, with their survival rates being similar.

CIMP gene markers have been implicated in the development of interval bowel cancers. In a study by Arain et al., the CIMP status of interval bowel cancers (which they defined as those which had developed within 5 years of a negative colonoscopy), was compared against the CIMP status in matched non-interval colorectal cancers. The interval cancers were significantly more proximal, smaller, had similar 5-yr survival rates, but showed no variation in stage. 57% vs. 33% were found to be positive for CIMP ($p=0.004$). They also showed that the interval cancers were significantly more likely to have microsatellite instability (29% vs. 11%, $p=0.004$) [123].

6.3 Interval Cancers Related to Diagnostic Test Sensitivity

6.3.1 Interval Colorectal Cancers Post Faecal Occult Blood Test

In a review of the Nottingham, Funen and Minnesota trials, an attempt to evaluate the sensitivity of the Hemoccult test was made [124]. The authors took into account the natural progression of a small adenoma to a large adenoma, then from a preclinical cancer of varying stage to a clinical cancer of varying stage. The sensitivity of the test is 33% if it is assumed that this is the same for all stages of cancer; 13% for Dukes' A cancers to 66% for Dukes' D cancers if it is assumed that the sensitivity varies according with cancer stage, and 51% versus 19% when clinical stage versus earlier stage is assumed. With an estimated pre-clinical cancer duration of 6.7 years, the highest sensitivity, with the best 'goodness-of-fit' is within an average of 2.5 years before diagnosis, where the sensitivity becomes 50%. The sensitivity of the test also seems to become greater with age (up to age 72 for men and 75 for women) [125].

The above shows that it is likely that the majority of interval cancers are related to the overall poor sensitivity of the guaiac based faecal occult blood test. By rehydrating the test, its sensitivity improves. However, this leads to a greater proportion of false positive results, which will require extra resources (in both time and money) to cope with the increase in

screening colonoscopy. A more detailed description of interval cancers, as part of this study and related studies, is included in the discussion.

6.3.2 Interval Colorectal Cancers Post Colonoscopy

Colonoscopy is termed the gold standard for detecting neoplastic lesions. The reasons for missing neoplasia that is present at time of test (i.e. a false negative) can be split into two groups. These are either because of performing an incomplete procedure, i.e. not intubating the caecum; or by not visibly seeing/treating a lesion within the reach of the colonoscope.

To determine factors that might influence a colonoscopy being carried out that does not reach the caecum, a population-based study performed in Ontario, Canada reviewed all incomplete colonoscopies. Out of 331,608 colonoscopies, 43,483 (13.1%) were incomplete. The statistically significant variables for incomplete procedures were older age group (odds ratio [OR] 1.20 per 10-year increment; 95% CI 1.18–1.22), female gender (OR 1.35; 95% CI 1.30–1.39), a history of prior abdominal surgery (OR 1.07; 95% CI 1.05–1.09), or pelvic surgery (OR 1.04; 95% CI 1.01–1.06). Those procedures that were performed in a private office setting were 3 times more likely to be incomplete (OR 3.57; 95% CI 2.55–4.98). For patients undergoing a colonoscopy in an academic centre, the completion rate for high volume endoscopists (5th quintile, 641-1569 procedures) was the same, no matter what speciality (internal medicine, surgery, gastroenterology) [126].

As mentioned, even when the endoscopist visualises the whole colon, there is still a false negative rate. A review of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database of 57,839 patients aged ≥ 69 years, diagnosed with a colorectal cancer between 1994 and 2005, showed that the 7.2% had undergone a prior colonoscopy between 6 to 36 months earlier. Predictors of interval cancers were found to be proximal colon location (distal colon: OR 0.42, 95% CI 0.39-0.46; rectum: OR 0.47, 95% CI 0.42-0.53), greater patient comorbidity (OR 1.89, 95% CI 1.68-2.14 for 3 comorbidities), a previous diagnosis of diverticulosis (OR 6.00, 95% CI 5.57-6.46), and previous polypectomy (OR 1.74, 95% CI 1.62-1.87). Risk factors at the endoscopist level included a lower polypectomy rate (OR 0.70, 95% CI 0.63-0.78 for the highest quartile), higher colonoscopy volume (OR, 1.27, 95% CI 1.13-1.43), and specialty other than gastroenterology (colorectal surgery: OR, 1.45, 95% CI 1.16-1.83; general surgery: OR 1.42, 95% CI 1.24-1.62; internal medicine: OR 1.38, 95% CI 1.17-1.63; family practice: OR 1.16, 95% CI 1.00-1.35). Although patients with a previous diagnosis of carcinoma in situ were excluded from the analysis, there was no mention as to

the proportion of patients who underwent a polypectomy for a dysplastic lesion at their index colonoscopy. Given that a previous polypectomy was seen as a risk factor for the development of an interval cancer, and the inclusion of patients who underwent a colonoscopy up to three years prior to diagnosis, it is likely that there may be a proportion of patients who had high risk polyps removed, and had their cancer diagnosed at the planned surveillance colonoscopy. Their definition of an interval cancer therefore appears flawed. The study should have excluded any patients whose index colonoscopy had any degree of abnormality.

A study as part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Group repeated a flexible sigmoidoscopy 3 years after a negative examination [127]. Of 11,583 individuals without a polypoid mass or lesion on initial examination, 9,317 (80.4%) returned. The mean age was 65.7 years with 61.6% being men. Of these 9,317, 1,292 (13.9%) had a repeat flexible sigmoidoscopy where a polyp or mass was detected. 64.4% had 1 abnormal lesion (polyp or mass) identified, 19.7% had 2, 7.8% had 3, and 8.1% had 4 or more abnormal lesions found. The largest polyp size, estimated by the endoscopist, was at least 1 cm in 5.5%, between 0.5 and 0.9 cm in 21.6%, and 0.5 cm or smaller in 73.0%. In the distal colon, 292 (3.1%) of 9317 had an adenoma or cancer with 78 (0.8%) being classed as an advanced adenoma or cancer. 847 participants underwent a colonoscopy following their abnormal flexible sigmoidoscopy which increased the yield of advanced adenoma and cancer to 4.1% and 1.3% respectively.

This study raises the question as to whether some of these lesions were new lesions or whether they had been missed on the initial examination. Whilst it is possible that these are new lesions, other studies where a “tandem colonoscopy” has been carried out have shown that it is possible to miss lesions.

In a bid to determine the sensitivity of a colonoscopy examination, tandem colonoscopy studies have been performed. In a study by Hixson et al., subjects underwent two back-to-back colonoscopies [128]. At the first colonoscopy, all polyps/tumours were removed or biopsied. The colonoscopy was then repeated by a second examiner, who attempted to identify all lesions ≥ 1 cm in size. Any lesions identified on the 2nd colonoscopy that had not been seen on the first exam were deemed ‘missed’. Out of 90 patients, there were 63 lesions ≥ 1 cm, none of which were missed (95% CI 0%-4.6%). 58 of the polyps were found to be neoplastic, with 5 being hyperplastic. As would be expected, 37 (63.8%) of the neoplastic polyps were distal to the splenic flexure. There were 163 neoplastic polyps ≤ 9 mm in size of which 14.7% were missed on initial examination. The authors do not

comment as to the location of the missed polyps. As the likelihood of a polyp being malignant increases with its size, the authors conclude that colonoscopy is an extremely effective tool at identifying larger lesions, but repeat colonoscopies should be carried out for patients with multiple smaller polyps.

A similar back-to-back study of 183 colonoscopies, with varying patient positions and endoscopists for the 2nd exam, showed a miss rate of 27% for adenomas ≤ 5 mm, 13% for adenomas 6-9mm, and 6% for adenomas ≥ 1 cm. Right-sided adenomas were missed more frequently than left (27% vs. 21%), although not significantly [129]. However, a separate study has shown that right sided tumours are more likely to be missed compared to left sided tumours [130], of which the risk of missing a metachronous non-advanced (Ptrend<0.001) and advanced (Ptrend<0.07) adenomas was associated with patients with a higher BMI [131].

The possible reasons for missing a colorectal cancer have been looked at by identifying interval cancers within a colonoscopy screening programme. A paper published in the New England Journal of Medicine in 2010, used a multivariate Cox proportional-hazards regression model to evaluate the influence of particular quality indicators for colonoscopy on the risk of interval cancer [132]. They looked at 50,148 subjects from the National Colorectal Cancer Screening Program in Poland for the period from October 2000 through to December 2004. The study looked at the adenoma detection rate for each of the 186 endoscopists, as well as their caecal intubation rate, and whether they were statistically significant in the rate of interval cancers. There were 42 interval cancers diagnosed, of which two independent risk factors for interval colorectal cancer were identified: the endoscopists rate of adenoma detection ($p=0.008$) and the subject's age ($p=0.005$). The rate of caecal intubation was not significantly associated with the risk of interval colorectal cancer ($p=0.50$), as has been previously thought. An individual rate of adenoma detection below 20.0% was significantly associated with an increased risk of interval colorectal cancer, as compared with a detection rate of 20.0% or more ($p=0.02$). Older patients (≥ 60) within the study were also associated with a greater risk of developing an interval cancer.

The Polyp Prevention Trial (PPT) from the United States, found an incidence rate of interval cancer following colonoscopy being 1.2/1000 person-years of observation. A history of an advanced adenoma was the only factor significantly associated with the risk of an interval cancer ($p=0.04$) [133].

There is an on-going debate as to when, or even if, a colonoscopy should be repeated after a completely negative examination. A study by Brenner et al. found that in 593 patients

after a mean of 11.9 years post negative colonoscopy (no cancers or adenomas identified), no subsequent cancers were detected. The rate of advanced adenoma (defined as presence of adenoma with at least 1 of the following features: >1 cm in size, tubulovillous or villous components, high-grade dysplasia) was 0.38, 0.34, 0.38, and 0.53 among participants with a negative colonoscopy conducted 1-5, 6-10, 11-15, and >16 years previously respectively [134]. In a paper by the same group of health professionals, they suggest that those patients who have a negative screening colonoscopy may not need a repeat exam for a minimum of 20 years [135].

Imperiale et al. performed a repeat colonoscopy on 1256 participants aged ≥ 50 years old that had a negative colonoscopy 5.34 ± 1.34 years (mean \pm 1SD) previously. At this repeat colonoscopy, no cancers were found (95% confidence interval, 0 to 0.24%). One or more adenomas were found in 201 persons (16.0%) with a total of 19 advanced adenomas (of which 10 (52.6%) were distal to the splenic flexure), were found in 16 persons (1.3%). The authors conclude that a 5 year rescreening interval is supported by this paper, however, they did not include in their analysis a number of patients whom had a repeat colonoscopy outside of the study in which neoplasia was found. These patients will have increased the total percentage of neoplasia detected [87].

6.4 Chapter Conclusion

Interval cancers in any form of screening programme or cancer diagnosis test are crucial to review in detail. The causes as to why a cancer is not detected at the time of the test allow for both a better understanding of the condition and how it develops over time, as well as identifying possible areas for improvement of the test, to minimise on future missed cancers.

Public opinion and confidence behind the medical profession relies on having robust examinations with high sensitivities. As discussed above, there are possible genetic and test factors that influence whether a colorectal cancer is missed by the screening programme. Given the relatively low sensitivity of the guaiac FOBt, compared to the high sensitivity of a colonoscopy, it is expected that the majority of interval cancers will be after a normal FOBt.

Chapter 7 The UK Bowel Cancer Screening Pilot

7.1 Study Design

The UK bowel cancer screening pilot study began in 2000 and was based in Tayside, Grampian and Fife in Scotland and the West Midlands in England. Screening began at the Scottish site on 31st March 2000 and at the English site 6th September 2000 with a total of 486,355 people offered screening at the two sites by the time of its completion after 2 years.

The pilot had a similar format to that of the randomised controlled trials with FOBt kits sent out to all patients in the age group 50-69 on a two yearly basis. After a positive result, patients were sent out an appointment with a screening nurse where they were offered a colonoscopy examination.

Results from the 2nd year of the study are summarised below [136].

Demographic	Responders, n (%)
None	259402 (56.8)
England	105878 (58.6)
Scotland	153524 (55.4)
Male	118617 (52.1)
Female	140785 (61.4)
Male: <55 yrs	33104 (47.2)
Male: 55-59 yrs	30779 (51.2)
Male: 60-64 yrs	26992 (55.0)
Male: ≥65 yrs	27742 (57.3)
Female: <55 yrs	38964 (58.2)
Female: 55-59 yrs	37054 (62.6)
Female: 60-64 yrs	32105 (64.9)
Female: ≥65 yrs	32662 (61.7)

Table 7.1 Number & Percentage of Responders from Both Sites

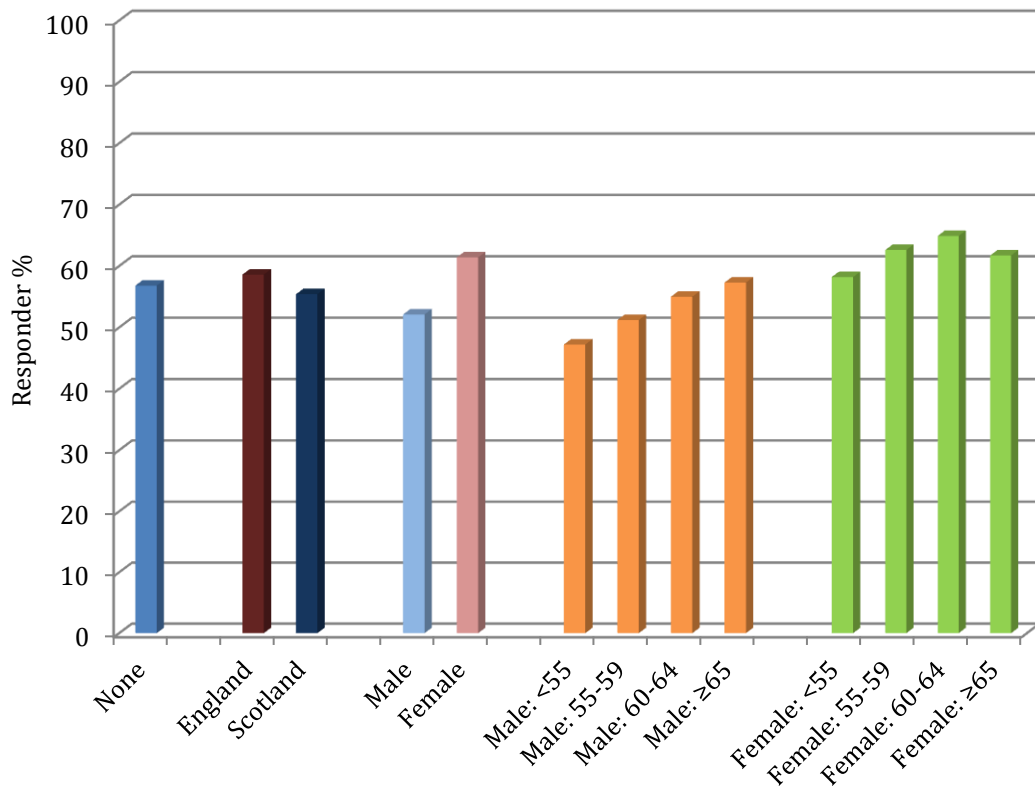


Figure 7.1 Percentage of responders by demographic.

These values represent a similar number to those seen in the Nottingham trial.

7.2 Faecal Occult Blood Test Results

The pilot study group sent a questionnaire to a sample of the population from each of the following groups: Phase 1 non-responders, Phase 1 negatives, Phase 3 negatives, FOBt positives, and cancer positives. The different phases represent the repeat FOBt after inconclusive initial tests.

The results from all the groups combined were that 40% didn't carry out any exercise, 20% were current smokers, 60% obese/overweight according to their body mass index (BMI) and 40-50% had a low fibre intake.

FOBt non-responders were: more likely to be current cigarette smokers than all responder groups, more likely to report a low fibre intake than phase 1 negatives and were more likely to perceive that bowel cancer would lead to death and pain, would limit their social and personal relationships and put their financial security at risk. They were less likely than all other groups to report knowing someone with bowel cancer or a family history of bowel

cancer and were less likely to believe that the FOBt would give them peace of mind and reduce the chances of dying from bowel cancer.

FOBt positives and cancer positives were more likely than all other groups to report a blood relative with bowel cancer.

The study group analysed each responder based on their deprivation index. They found that people who were from more deprived areas were less likely to take up FOBt, saw themselves at higher risk of developing bowel cancer, perceived bowel cancer as more serious (in terms of physical pain and damage to financial security), and had a low perceived ability to complete the kit. The authors suggest that non-completion of the FOBt may be an avoidance response to the fear of a positive result. These viewpoints were mirrored for the younger age groups. Non-completion in the younger age group was thought to be due to constipation, lack of time and storage problems, which were more commonly reported.

7.3 Colonoscopy within the Pilot Study

Uptake of colonoscopy amongst FOBt positives was 82.2%. Only 1.5% did not undergo colonoscopy because they were deemed medically unfit. Of the 16.3% that did not attend (DNA), 20% were under therapy or polyp follow-up, 8% had had a recent endoscopy, 2% had no colon and 6% intended to have a private colonoscopy. Correcting for these gives an alternative estimate of colonoscopy uptake of 87%.

The DNA rate was higher in England (20.8%) than in Scotland (14.0%), higher amongst all ethnic minorities (over 25%) and amongst those from areas of higher deprivation.

From similar surveys performed as with the FOB test, people undergoing colonoscopy in England were more likely to have consulted a clinic nurse, whilst those in Scotland were more likely to have consulted their GP.

Perceptions of the colonoscopy experience amongst attendees were very positive. More than 90% of people attending colonoscopy felt they had adequate information about the meaning of their FOBt result and the colonoscopy procedure prior to attendance.

Demographic	Colonoscopy Uptake, n (%)
England	1227 (77.5)
Scotland	2463 (84.3)
Male	2272 (82.2)
Female	1418 (81.4)
Male: < 55 yrs	436 (80.3)
Male: 55-59 yrs	524 (84.5)
Male: 60-64 yrs	610 (84.0)
Male: ≥ 65 yrs	702 (80.3)
Female: <55 yrs	278 (85.8)
Female: 55-59 yrs	321 (80.9)
Female: 60-64 yrs	362 (80.4)
Female: ≥ 65 yrs	457 (79.9)

Table 7.2 Number and percentage of uptake of colonoscopy by demographic.

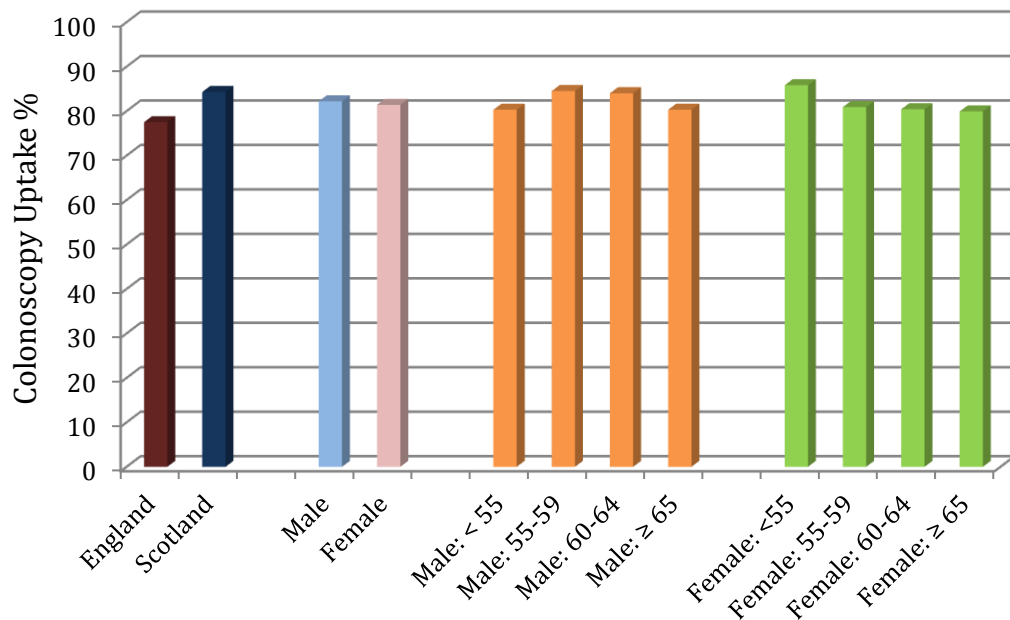


Figure 7.2 Uptake of colonoscopy by demographic.

7.4 Colonoscopy Results

Abnormalities were classified as:

- Non-malignant adenoma
 - polyp where lack of malignancy is confirmed by pathology data
- Malignancy
 - polyp cancer which is known from pathology data to have been completely removed
- Invasive colorectal cancer
 - all other cancers whose removal is incomplete or not known
- Neoplasia
 - sum of all three categories above

Subjects with more than one polyp and/or cancer were classified according to their most severe condition. The overall neoplasia rates in those with a positive FOB test result was 402 per 1,000.

		Neoplasia of subjects completing FOB testing, n (%)		Neoplasia of subjects testing positive, n (%)		Neoplasia of subjects with colonoscopy performed, n (%)	
		<i>England</i>	<i>Scotland</i>	<i>England</i>	<i>Scotland</i>	<i>England</i>	<i>Scotland</i>
Age (years)	<55	91 (0.32)	174 (0.43)	91 (29.45)	174 (31.18)	91 (37.60)	174 (36.86)
	55-59	121 (0.41)	248 (0.70)	121 (34.28)	248 (37.35)	121 (43.84)	248 (43.59)
	60-64	183 (0.75)	315 (0.98)	183 (40.94)	315 (43.21)	183 (53.20)	315 (50.16)
	≥65	209 (0.94)	442 (1.24)	209 (44.00)	442 (45.52)	209 (57.26)	442 (55.67)
Gender	<i>Male</i>	399 (0.82)	822 (1.27)	399 (42.18)	822 (45.24)	399 (53.77)	822 (53.73)
	<i>Female</i>	205 (0.37)	357 (0.45)	205 (32.13)	357 (32.31)	205 (42.27)	357 (38.26)
Deprivation Category	1/2	147 (0.49)	246 (0.76)	147 (40.27)	246 (44.57)	147 (52.50)	246 (51.14)
	3	102 (0.51)	217 (0.68)	102 (39.08)	217 (36.59)	102 (47.44)	217 (42.38)
	4	195 (0.67)	239 (0.87)	195 (42.58)	239 (40.17)	195 (53.87)	239 (46.77)
	5	67 (0.62)	93 (0.91)	67 (30.45)	93 (36.61)	67 (40.61)	93 (45.37)
	6/7	83 (0.68)	62 (0.86)	83 (33.33)	62 (32.29)	83 (45.60)	62 (41.89)

Table 7.3 Results following FOBt and colonoscopy

Over half of the cancers that were found within the pilot screening programme were of an early stage (up to and including Dukes B) as shown in the pie chart below.

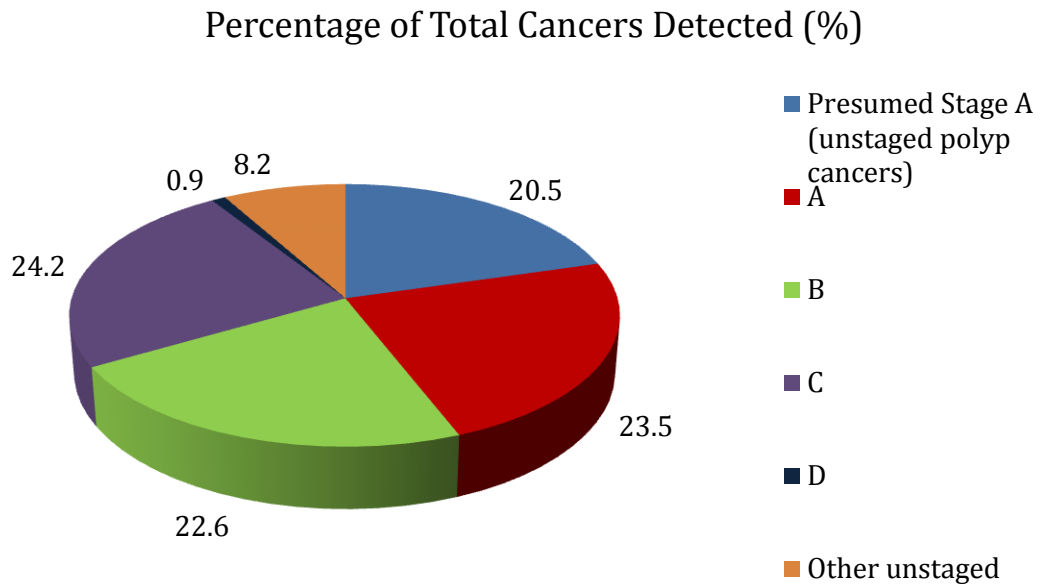


Figure 7.3 Stage of screen-detected tumours.

7.5 Adverse Consequences of the Screening Pilot

Out of 3600 people who underwent a colonoscopy examination as part of the pilot screening programme the number of adverse effects are as follows:

- 10 (0.28%) patients were admitted overnight for post-procedure bleeding or abdominal pain, and then discharged the next day
- 13 (0.36%) patients re-admitted for bleeding or abdominal pain
- 2 (0.06%) patients suffered a bowel perforation
- 1 (0.03%) patient in England died post colonoscopy (although this was not attributed to the colonoscopy itself, but their co-morbidities)
- 3 (0.08%) patients died post-surgery on their cancers picked up by the screening colonoscopy (secondary to their ischaemic heart disease)

These complication rates are similar to those in the published literature regarding colonoscopy [137].

7.6 Chapter Conclusion

In this Chapter, the pilot bowel cancer screening programme has been reviewed. Uptake of the FOBt, its positivity levels, and cancer detection rates are equivalent to that seen in the mass population trials. The pilot study added key information regarding the population who do not take up the screening test, along with adverse consequences of the screening programme. It also demonstrated equivalent results from Scotland, which had not been part of any FOBt screening studies. This finding is key to the initiation of a nationwide programme.

Chapter 8 The NHS Bowel Cancer Screening Programme (BCSP)

8.1 Background

The bowel cancer screening programme formally began in April 2006. This followed UK and Scandinavian research undertaken in Nottingham and Funen in the 1980's (which is discussed in Chapter 5) and then based on a pilot service in Coventry, Warwickshire and Scotland. The planned roll out of a screening programme was due to be phased region by region over a three year period, with the entire eligible UK population covered by 2009.

8.2 Aims & Objectives of the Screening Programme

Taken from the NHS BCSP guidebook [138], the aims and objectives of the programme are to:

- identify and invite eligible men and women for screening
- enable people to make an informed choice about whether or not to participate in the screening programme
- provide clear information quickly to people with either normal or abnormal FOBt results
- diagnose a significant proportion of cancers at an early stage
- minimise anxiety among participants in the programme
- make the best use of screening resources
- maintain minimum standards of screening and continually strive for excellence
- involve and give feedback to the population covered by the programme
- develop the staff who deliver the screening service
- continue research into screening for and diagnosis and treatment of colorectal cancer.

8.3 The Screening Process

The NHS BCSP offers a guaiac based faecal occult blood test, FOBt, to all men and women aged between 60 and 69 every two years. Initially, anyone aged over 69 could request a FOBt kit. From February 2010, the age group was extended up to 75.

Each FOBt kit has six samples within it. If a participant has six negative samples, the test is deemed negative, and a repeat kit will be issued in two years time. If the result is unclear, classed as one to four positive samples, then either one or two complete repeat kits are then sent to the patient. A second unclear or abnormal test kit and the episode is deemed a

positive result. If two subsequent test kits both have zero of six positive windows, the episode is classed as negative and the patient re-invited for screening in two years time. If five or six samples are positive, either on initial or repeat test, the test is deemed positive and the patient is invited to attend a nurse led clinic.

At this appointment, the screening nurse discusses the abnormal test result and its implications. They will complete a medical history assessment and make a decision regarding the suitability for the patient to undergo a colonoscopy. At that session, the screening nurse can make the appointment for the patient to return for the colonoscopy examination. If there are concerns about the fitness of a patient to undergo a colonoscopy, they are referred to a screening colonoscopist. These patients will alternatively be offered a CT colonography examination in these circumstances.

From the colonoscopy, the possible results are as follows:

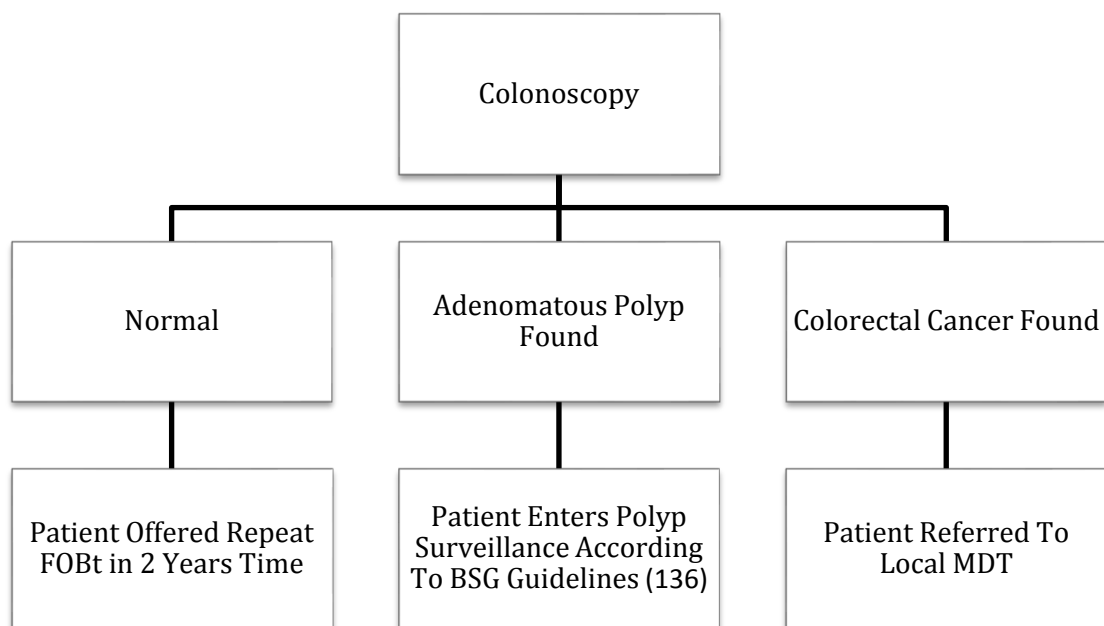


Figure 8.1 Outcomes after screening colonoscopy, Polyp surveillance guidelines [139].

8.4 Bowel Cancer Screening In the North East of England

Bowel cancer screening using the FOBT began in February 2007, with full uptake in the region by April 2008. There are four programme hubs from which the screening programme within their catchment area is co-ordinated. These hubs are Tees, South of Tyne, North of Tyne and County Durham & Darlington. Within the programme hubs are 12

primary care trusts: Hartlepool, North Tees, Middlesbrough, Redcar & Cleveland, County Durham, Gateshead, South Tyneside, Sunderland, Darlington, Newcastle, North Tyneside, and Northumberland Care Trust.

Each hub is responsible for issuing and monitoring screening invitations, including despatching test kits, issuing results and arranging screening nurse practitioner appointments.

8.5 Data Storage

Data is stored on a central database that can be accessed on a regional and national level. There is a service level agreement between the NHS Cancer Screening Programme and NHS Connecting for Health Service Management for the support and infrastructure of IT systems within the programme. A web based data recording system is used, with access via the Open Exeter system [140]. All data items except invite and FOBt data are primarily entered by the screening nurse practitioners.

8.6 Data Items

Table 8.1 shows a summary of all the data that is stored on the BCSP database. From this dataset, data obtained from the regional database was split into four categories as shown in the below figure:

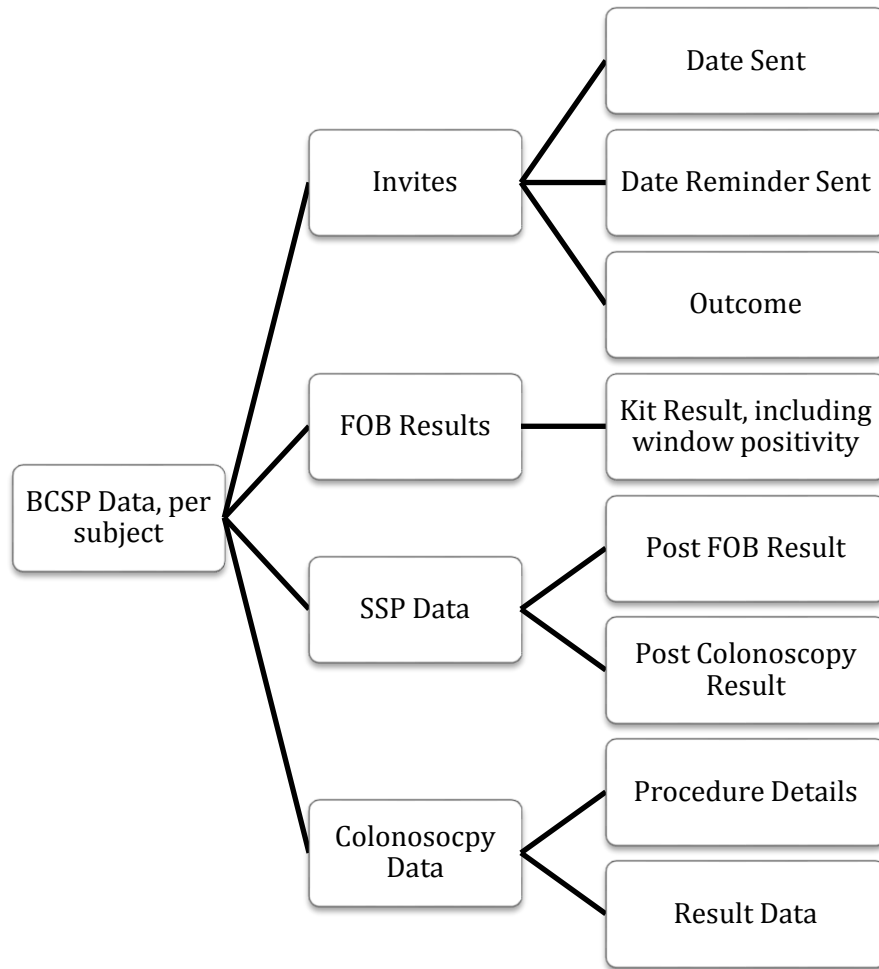


Figure 8.2 Data obtained from regional BCSP database.

Also obtained were the overall numbers of invites sent and uptake of an offered FOBT, the proportion of each FOBT result, the uptake of SSP appointments and uptake of a screening colonoscopy within the study time period.

Data Headings	Data Items			
<i>Patient Demographics</i>	Gender ASA Grade	Drinks Alcohol Smoking	Allergy	Cause Of Death
<i>Screening</i>	Reason for Cease/Change			
<i>Episode</i>	Status	Closure	Type	Recall Method
<i>Communications</i>	Communication Records			
<i>Test Kit</i>	Episode Type Individual Window Result	Spoilt Reason	Overall Result	Technical Failure Reason
<i>Practitioner Clinic</i>	Appointment Type Attendance? Information Given	Symptom Confirmation Symptom Type Decision to Proceed	Medical History Confirmation Cancellation Reason Healthy Eating And Symptom	General Health Fit For Colonoscopy MDT Outcome
<i>Diagnostic Test</i>	Type Diagnostic Test Result Distant metastases Bone Distant metastases Liver Distant metastases Lung Distant metastases Other	Final Pre-treatment TNM category Radiology Complication Radiology Diagnosis Radiology Fail Reason Radiology Location	Result CT Scan Result Endoanal Ultrasound Result 1 st MRI Scan T Stage Result 1 st MRI Scan N Stage Result 2 nd MRI Scan T Stage First MRI Scan Margin Threatened	Colonoscope Inserted Colonoscope Extent Fail Reason Complication Early Complication Late Result
<i>Neoplasia</i>	Histology ICD10 Cancer Type Cancer Differentiation Lymphovascular Invasion Cancer Location Polyp Carcinoma Polyp Type	Polyp Class Polyp Dysplasia Polyp Excision Complete Polyp Location Polyp Lymphovascular Invasion Polyp Stalk Invasion Polyp Sub Type	Polyp Therapy Device Polyp Therapy Modality Polyp Therapy Success Modified Dukes Staging T Category Pathological N Category Pathological M Category Pathological Excision Margin	Circumferential Margins Excision Margin Positivity Of Cut Colon Or Rectum Margin Perforation Or Serosal Involvement Synchronous Cancer Sites Cancer Therapy Modality Cancer Therapy Success
<i>Procedure</i>	Primary Procedure Name OPCS	Procedure Type	Stoma Procedure	Reason No Surgery Performed
<i>Chemotherapy</i>	Chemotherapy Trial	Teletherapy Trial		
<i>Colonoscopy Quality Assurance</i>	Bowel Prep Comfort Exam Comfort Recovery	Evaluation Extent	Outcome Retro	Sedation Exam Sedation Recovery
<i>Patient Discharge</i>	Type	Confirmed Follow Up		

Table 8.1 Data Items Collected within the Bowel Cancer Screening Database

8.7 Chapter Conclusion

The NHS Bowel Cancer Screening Programme aimed to repeat the benefits found in the preliminary studies and pilot programme. It has a comprehensive data collection system, predominantly collected by screening nurse practitioners. This chapter summarises the screening process and data items that will be used in this study's analysis.

Chapter 9 Northern Region Colorectal Cancer Audit Group (NORCCAG)

9.1 Background

The Northern Region Colorectal Cancer Audit Group, NORCCAG, was started in 1997 by a group of colorectal surgeons, oncologists and pathologists from the region. The stated aim was “to improve the treatment, care and outcome of patients with colorectal cancer” [141]. It is currently funded by the strategic health authority and employs an audit co-ordinator and an audit clerk. There is IT support from an external company, Xentec, who are experienced in medical databases. Attached to the group currently are two clinical research fellows.

It primarily acts as a data collection and analysis group for all colorectal cancers known to the gastrointestinal multi-disciplinary team meeting in the Northern Region of England. This area stretches from Wansbeck General Hospital in Northumberland down to the Friarage Hospital in North Yorkshire, and from South Tyneside across to Carlisle Hospital in the North West, a population of approximately 3.1million. It covers one cancer network (North of England Cancer Network), encompassing 9 Trusts, 11 MDT’s and 17 District General Hospitals.

Prior to 2005, NORCCAG collected the data of approximately 1400 patients with colorectal cancer per annum. This number has increased to around 1800 per annum with a change of data collection. All data from submitted surgical, pathological and oncological forms are collated by the audit team. All deaths are flagged by the Office of National Statistics to the audit group.

9.2 Format of Audit Programme

9.2.1 Audit Staff

There are 2 full-time audit co-ordinators who visit MDTs, co-ordinate data submissions and review case notes. They maintain the database and ensure data quality through both external & internal data validation, assist with data analysis and feedback outcomes to units on request through presentations. Outcomes are also presented to the Cancer Network and the Regional Chapter of the Association of Coloproctology.

9.2.2 Steering Group

A multidisciplinary steering group oversees the management of the audit and consists of a chairman, 2 secretaries, a surgical representative from each of the 17 participating

hospitals, pathologists, clinical and medical oncologists, medical gastroenterologists and clinical geneticists. Advice from other specialists is co-opted as required. This group is large as the essence of the audit is that it is organised by the audit participants.

9.2.3 Dataset

The NORCCAG dataset was previously divided into 3 subsets, collected on separate forms;

- **Patient Management Form;** demographics, waiting times & staging investigation data items. Completed by the NORCCAG staff, previously with the support of some MDTs.
- **Surgical Form;** operative data items. Completed by the operating surgeon or the NORCCAG staff from the operation note.
- **Pathology Form;** pathology data items. Completed by the reporting pathologist or the NORCCAG staff from the pathology report.

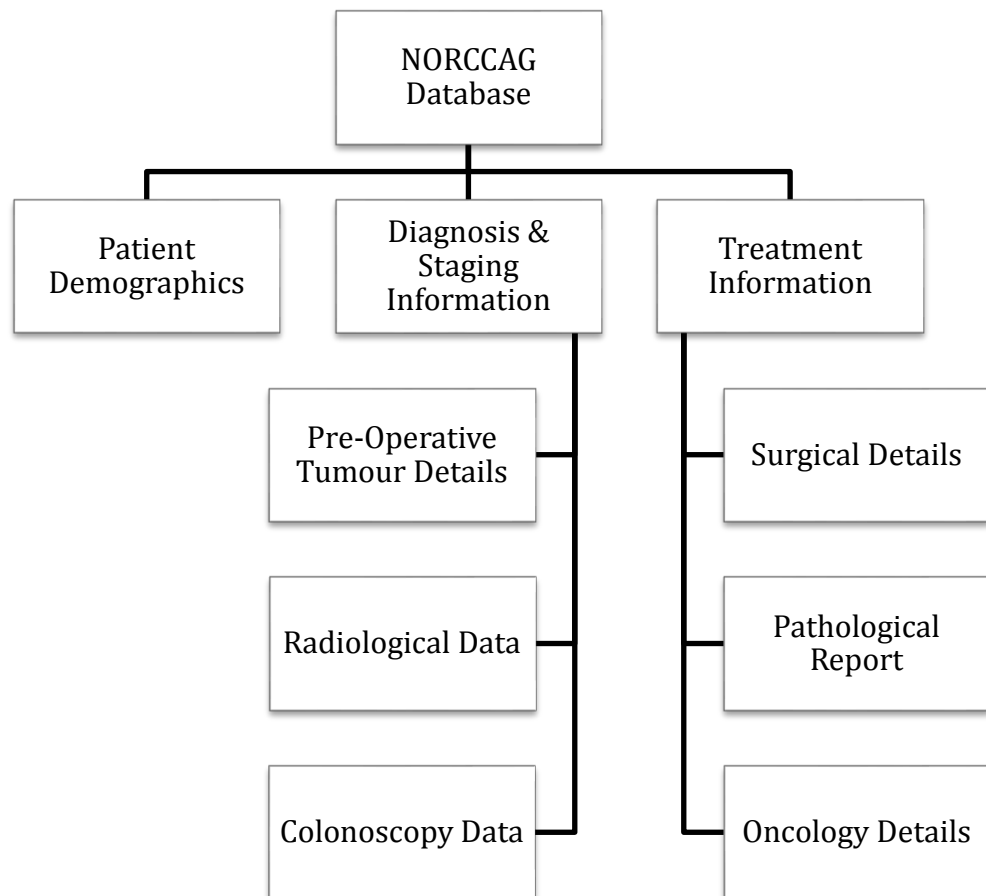


Figure 9.1 Flow chart representing storage of data on NORCCAG database.

During 2009/10, the database was revised and updated to include newer data items on liver and lung resection and to ensure consistency of data items and data definitions with those of the NBOCAP dataset.

9.2.4 Data Capture

In previous years, data capture has been entirely reliant on case note review. Whilst this is a robust method, the difficulty inherent in obtaining paper notes has been a major obstacle and resulted in an increasing retrospective dataset, due in part to the limited resources of the group. In 2006, NORCCAG's role changed with colorectal cancer data recording being relinquished to each individual trust. Data submitted to the National Bowel Cancer Audit Project (NBOCAP) was downloaded and imported into the NORCCAG database. From here it could be validated for accuracy and completeness. NORCCAG continues to aid some trusts in collecting and submitting data by reviewing data upload files and assisting with filling in missing data items. It also provides a training role to audit clerks in each trust.

9.2.5 Data Quality

The NORCCAG staff are experienced with colorectal cancer data items and trained to extract information from clinical notes and systems. There is rigorous internal and external data validation to ensure data quality.

9.2.5 Data security

The audit co-ordinators and the chairman of the Steering Group are responsible for data security and maintaining confidentiality. Ethical approval for the project was obtained from the Multi-Centre Research Ethics Committee in August 1999. The Caldicott Guardians in all 17 hospitals have approved NORCCAG. The audits support under Section 60 of the Health and Social Care Act to use patient identifiable information was approved after amendments to standard consent forms.

9.2.6 Data Confidentiality

The audit data is owned by the audit participants represented by the Steering Group which delegate the day to day working of the audit to the chairman, secretaries and audit

facilitators. There is no patient identifiable data released and each surgeon and unit are given a code known only to the surgeon, the relevant unit and the audit facilitators who have signed a declaration of confidentiality. Precedent for disclosure of unit identifiable data has been set by the National Lung Cancer Audit (LUCADA), the National Head and Neck Cancer Audit (DAHNO), the Society for Cardiothoracic Surgery and the Healthcare Commission, but previously the NORCCAG membership have voted against disclosure of what is currently incomplete, and non-risk adjusted outcomes data.

9.3 Chapter Conclusion

This Chapter shows the set-up of the Northern Colorectal Cancer Audit Group (NORCCAG) database. As with the BCSP database, the data items which will be used in this study are summarised.

Chapter 10 Aims of the Project

10.1 Introduction

The project is a large scale epidemiological study of all colorectal cancers within the Bowel Cancer Screening Programme in the Northern Region of England.

The purpose of this MD is to examine in detail patients diagnosed with colorectal cancer since the national bowel cancer screening programme was implemented.

There are three important research questions:

1. How effective is the current screening programme?

This section will look at the rates of detection of colorectal cancers in the population who were offered screening. Patient demographics, level of deprivation, tumour location and stage profile of the cancers detected, how they were managed and the outcomes for those patients will be compared between each of the four patient classification groups shown below. The null hypothesis for this section will be:

‘There is no difference in survival rate between subjects diagnosed with a colorectal cancer between those who were offered screening, and those who weren’t.’

2. What are the reasons behind the rates and outcomes of interval and non-uptake cancers?

By comparing the screen-detected group with the interval cancer group, an explanation will be sought for patient and tumour characteristics that may influence the positivity of the FOBt in diagnosing a colorectal cancer. For those diagnosed with a colorectal cancer who did not take up the FOBt, any relationship between uptake and level of deprivation will be analysed. The null hypothesis for this section will be:

‘There is no difference in the patient demographics, tumour characteristics, and survival rate between screen detected and interval/non-uptake colorectal cancers.’

3. How can we improve on the screening process?

This section will look at the implications of changing the classification of an abnormal result according to the window positivity of the faecal occult blood test. Other possible areas for improvement to the screening process will also be discussed.

Within the bowel cancer screening programme, the cases of colorectal cancers can be split into four groups as shown below (shaded):

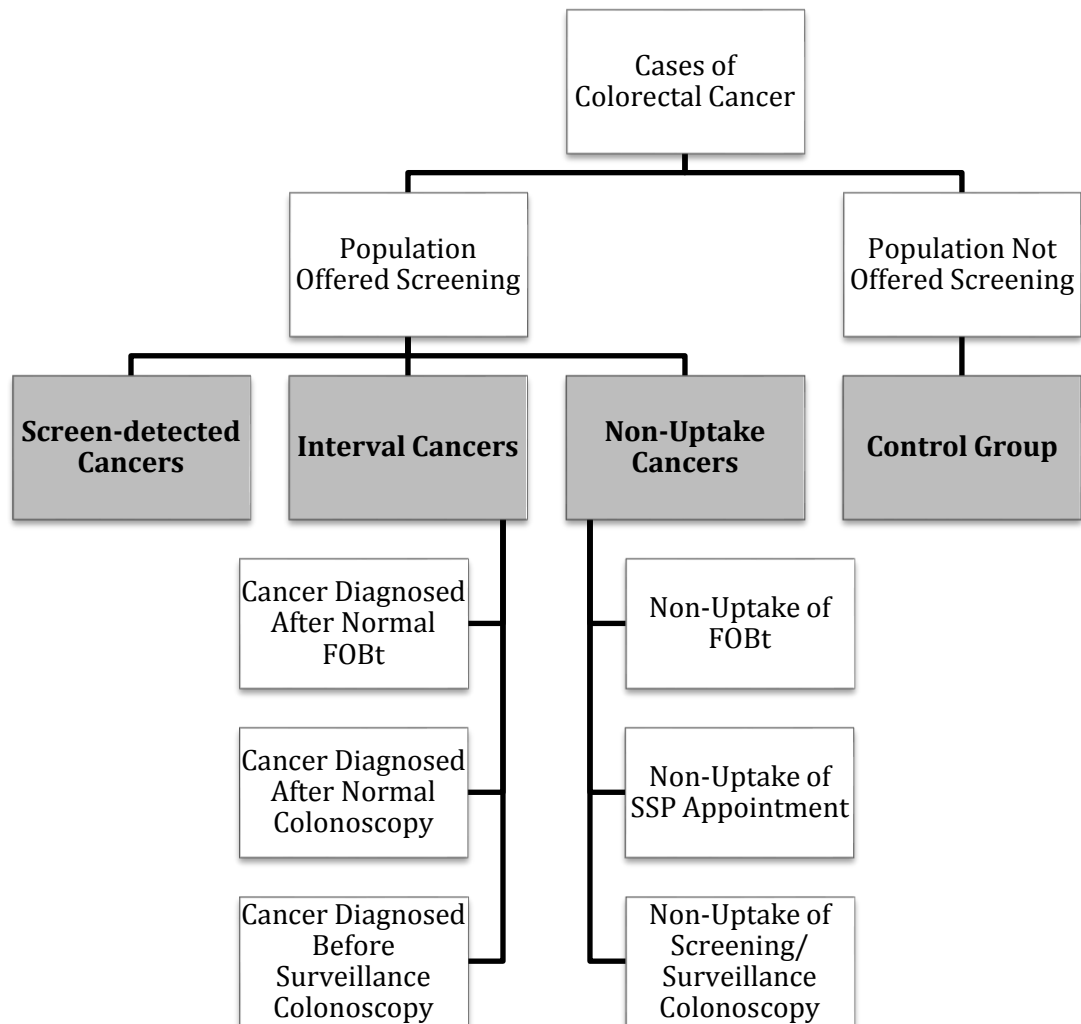


Figure 10.1 Classification of Study Groups

10.2 Colorectal Cancer Occurring in the Non-Uptake Group

This group of patients comprises those persons who decline to undergo part, or all, of the screening process. This might be refusal to submit a FOB result, approximately 40-50% of the population eligible for screening. As discussed from the pilot study, these patients tend to be in the younger age groups, of a lower socioeconomic group, and male.

Reasons that were given to the pilot study group for non-completion of the FOB test were that the test itself was “disgusting”, “unhygienic”, “difficult to use”, and “difficult to store” [136].

A smaller group of patients (approx. 13%) will be those who have a positive FOB test, and then decline the offered colonoscopy examination. This can be with or without seeing the screening nurse practitioner. The main reason for not undergoing a colonoscopy from the pilot study was simply unwillingness to have the procedure.

10.3 Interval Cancers

The possible reasons behind the diagnosis of an interval cancer have been discussed in Chapter 6. Given that the bowel cancer screening programme has three parts to it, there are therefore three situations where interval cancer might occur.

The first type occurs in patients who have a negative FOBt and are then diagnosed with a colorectal cancer within two years of the test, i.e. before they are due to have their next round of FOB testing. This group will account for the largest proportion of interval cancers and classified as a false negative screening test.

The second type occurs in patients who have a positive FOB test and subsequently have a negative colonoscopy, and are then diagnosed with a cancer within two years of the colonoscopy. This group is classed as a false negative colonoscopy.

The final group of patients occurs in those who have a non-cancerous adenomatous polyp found on colonoscopy and are then put in a surveillance programme, to be diagnosed with a cancer before they are due for their planned surveillance colonoscopy. This group will most likely have undergone a false negative colonoscopy, although a rapidly growing cancer is also a possibility.

10.4 Screen-Detected Cancers

This group of patients are those that who are diagnosed as a direct result of the screening investigations. They will have received a positive FOB test result, followed by a colonoscopy where their colorectal cancer was diagnosed. Screen-detected cancers can also include those diagnosed on the planned surveillance colonoscopy.

In the Nottingham study, within the screening arm of the trial: “of the 893 cancers... (CRC incidence of 1.49 per 1000 person-years), 236 (26.4%) were detected by FOB screening, 249 (27.9%) presented after a negative FOB test or investigation, and 400 (44.8%) presented in nonresponders” [100].

10.5 Control Group

Within this study there is a fourth control group. This is the population of patients who were diagnosed with their colorectal cancer within the time frame and age range of the above groups, but before they completed their first screening episode. Included in this category are all patients who were diagnosed with a CRC before they received the screening invite, or were diagnosed through symptomatic services before a planned screening colonoscopy (even if they submitted a positive FOBt).

This control group was available for analysis due to the long lag time in the roll-out of the programme through the North East of England in inviting the whole population who were eligible to be screened. Completion of the initial invitation to be screened lasted nearly two years. Although this may seem like a prolonged time period, it was necessary as otherwise the programme would have been inundated with subjects requiring a colonoscopy. Given the limited resources within the region, this would have potentially led to those with a positive FOBt result waiting prolonged periods for their endoscopy.

10.6 Chapter Conclusion

This study aims to establish the performance of the NHS BCSP since its national implementation. This involves comparing the intervention (population offered screening) group against the control group, and then reviewing the outcomes of the patients detected through the screening programme against those not detected by the screening programme (either due to a false negative test result, or by non-uptake of the test). An explanation of the possible reasons behind the false negative test results, and methods to minimise these will be put forward.

Chapter 11 Methods

11.1 Study Location

The study took place in the North East of England. The geographical area that NORCCAG covers has been described in the Chapter 9. From the description of the two databases, it is evident that they cover slightly different populations. NORCCAG also encompasses the population that the Cumberland Infirmary in Carlisle and the West Cumberland Hospital in Whitehaven serve.

As the bowel cancer screening regional hub for Cumbria is based in Rugby and therefore includes patients that will not be registered on the NORCCAG database, all patients who sent their screening tests to the North West England regional hub were excluded. By doing this, it allows the total numbers of screening invites/responses, the total number of screening nurse practitioner appointments and colonoscopies to be obtained. This gives the denominator for many of the planned analyses.

The exclusion was performed by reviewing the cancer unit that each patient was registered with on the NORCCAG database, and excluding those with a Cumbria hospital identifier. A secondary method was reviewing the postcode of each patient, and excluding any beginning with "CA".

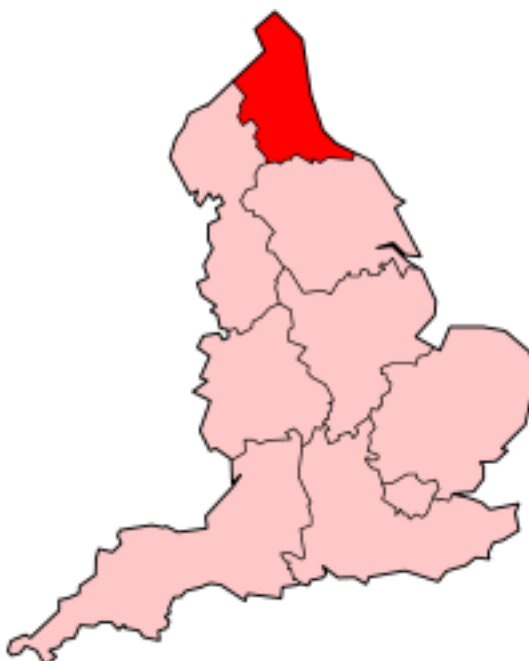


Figure 11.1 The North East of England. [142]

11.2 Regional Population Demographics

The population of the North East is approximately 2.6million (5.0% of England's population), making it the smallest region in England. It is also one of the slowest growing populations in England (from 2001 to 2010 it grew by 2.6% vs. 5.6% for England). In mid-2010, 17.2% of the North East population was aged 65 or older (447,200 people). This proportion compared to other English regions is shown in the figure below. [143]

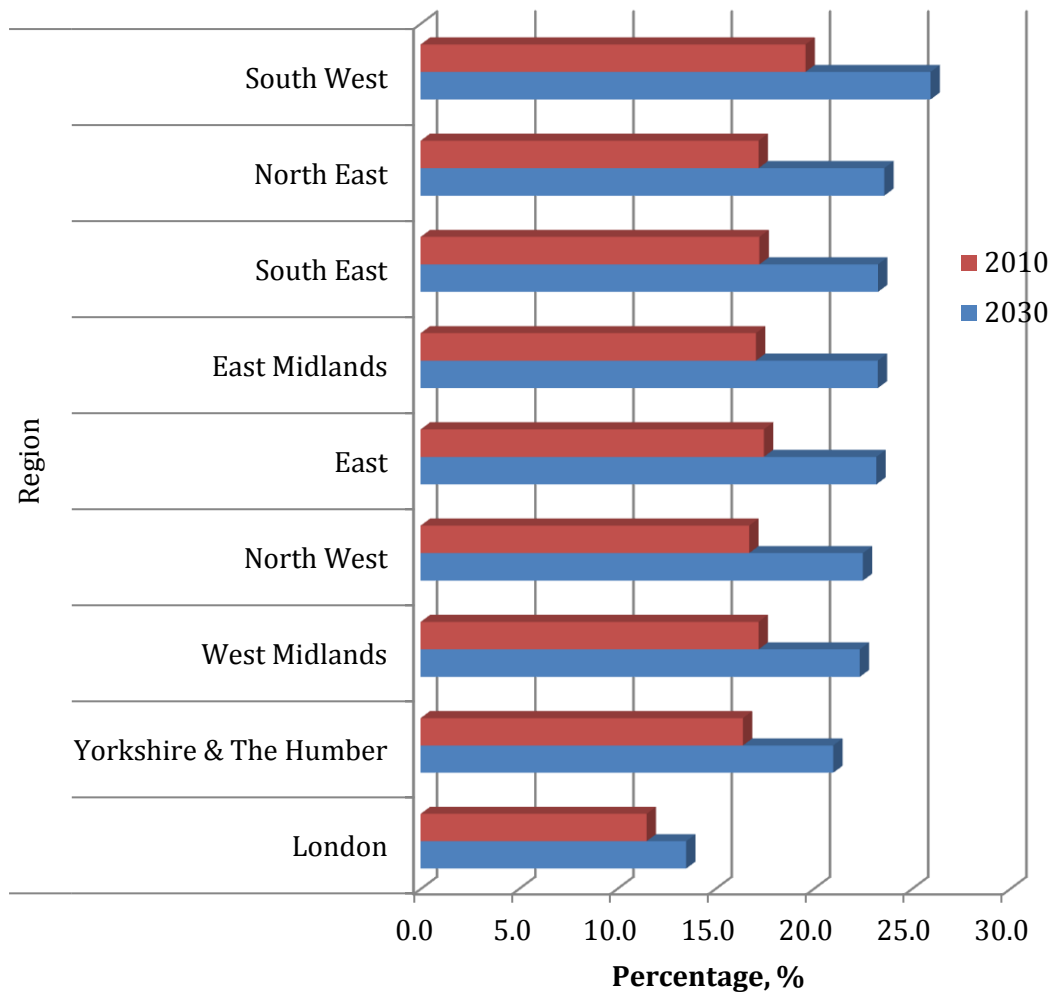


Figure 11.2 Percentage of population aged 65 and over, 2010 and 2030.

The total number of the North East population who are eligible for screening (aged 60-74 years) is expected to grow over the next 25 years as shown in Figure 11.3 [144].

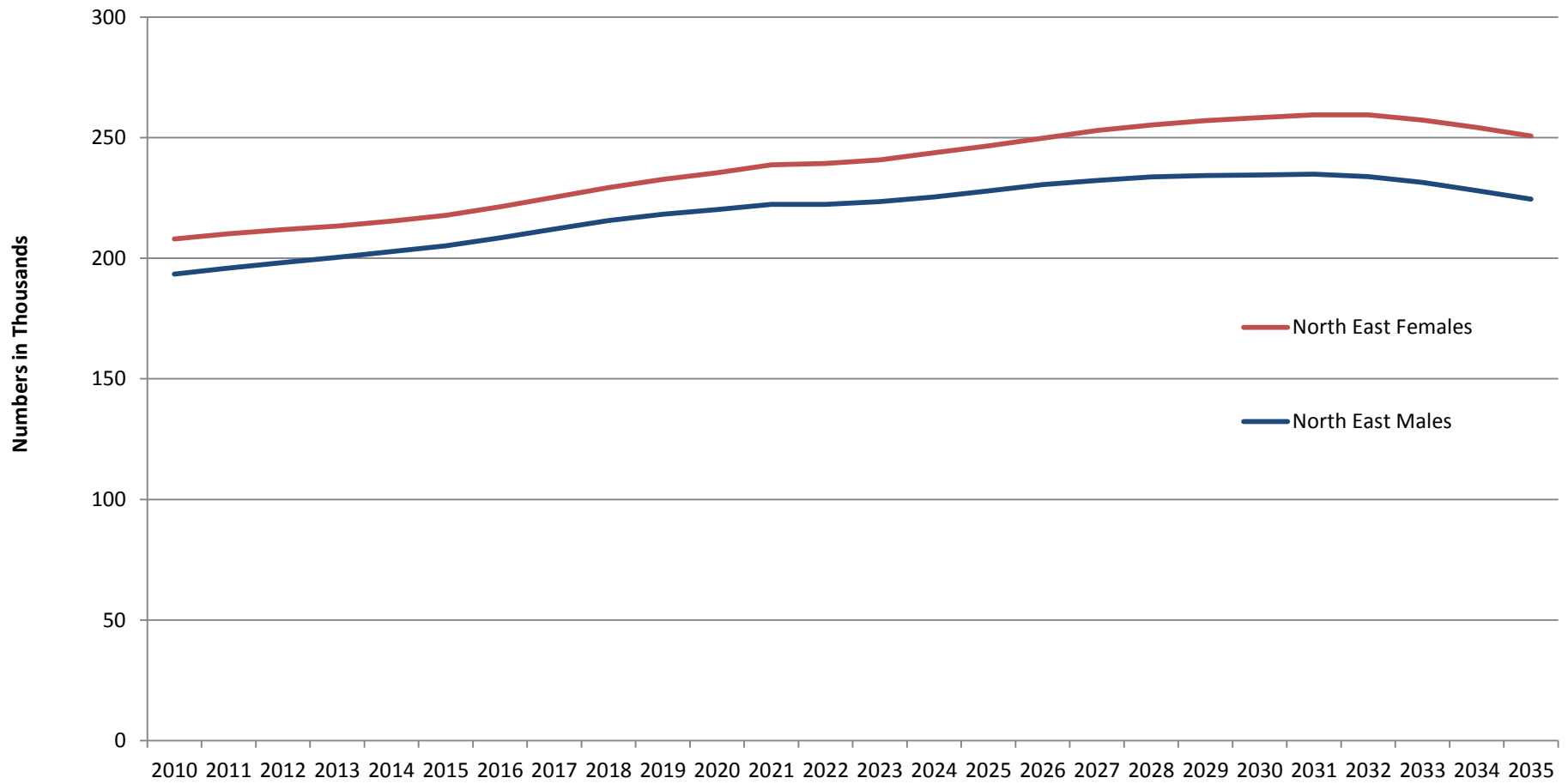


Figure 11.3 Predicted total numbers of North East England population aged 60 to 74. [144]

The North East is also one of the most deprived regions in England. By using data from the English Indices of Deprivation Report of 2007, it is possible to show this against other English regions, as demonstrated in the chart below.

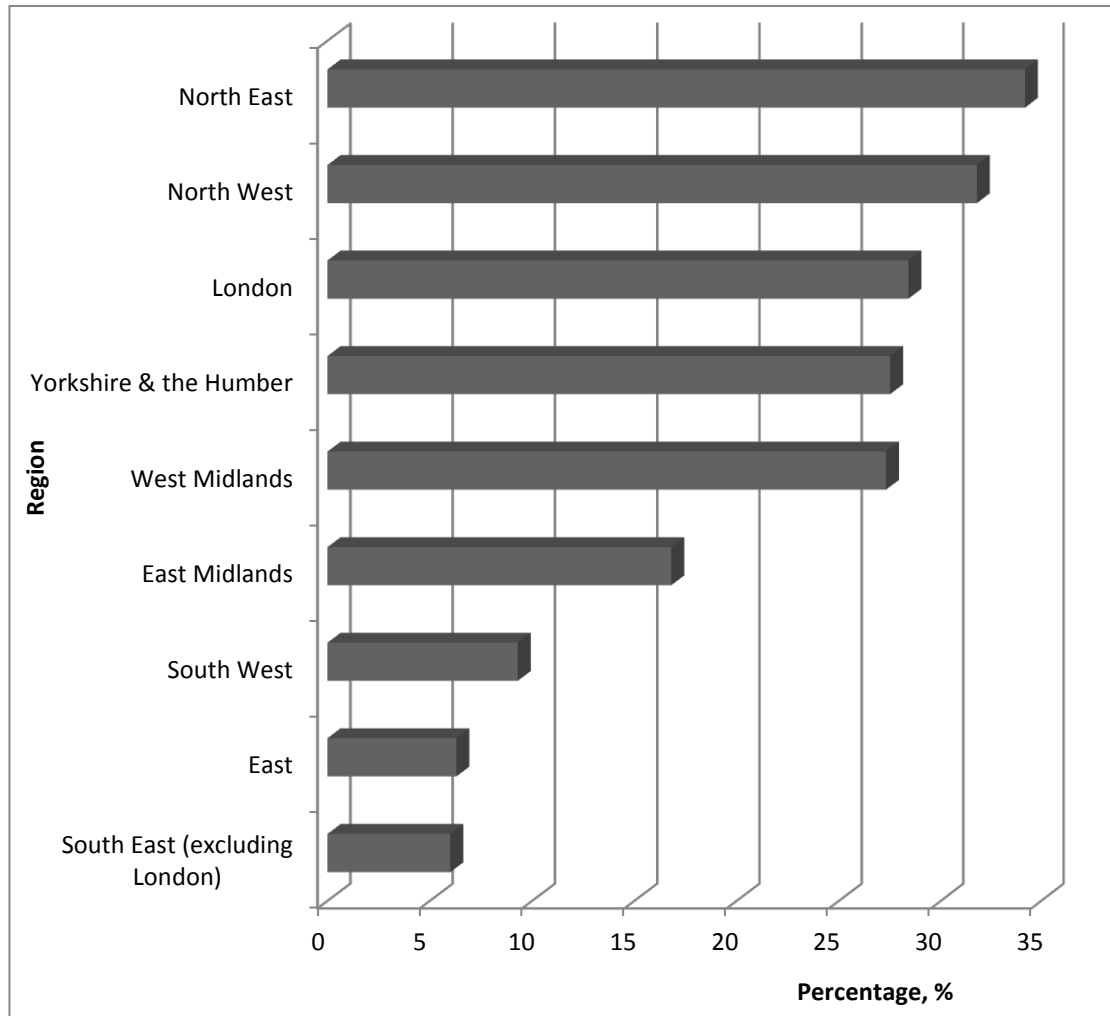


Figure 11.4 Percentage of Lower Super Output Areas (LSOAs) In Each Region Falling In 'Most Deprived 20% Of LSOAs In England'. [145]

The below table shows how the North East of England ranks with the rest of England when social indicators are compared, during the study time period [146].

Social Indicator	Average Rate/Percentage	North East in Relation To Other English Regions
Disposable Household Income	£327 per week	Lowest
Crime	650 per 10,000 adults against the person	Lowest
Income	24 % (6.2 million) in households below the poverty threshold	
Adults with Disabilities	15%	Highest
One Person Households	30%	Amongst the Highest
Lone Parent Households	7.7%	Amongst the Highest
Median House Price	£120,000	Lowest
Rented Accommodation	23%	2 nd Highest
Unemployment	9.3%	Amongst the Highest
Life Expectancy at birth	77.2 for males, 81.2 for females	Amongst the Lowest
Smoking >20 cigarettes/day	10% of men and women	Amongst the Highest
Alcohol consumption on five or more days/week	18% men, 9% women	Lowest

Table 11.1 Comparison of North East Social Indications against other English regions [146]

North East industry traditionally had a high proportion in coal mining. In 2007, 17% of the region's gross value added (GVA, a measure of economic output of a region) was from manufacturing (UK average 13%). 19% of the GVA was from real estate, renting and business activities (UK average 24%) [147].

11.3 Study Population

Subjects selected for the analysis were the population eligible for screening as part of the national programme. Inclusion criteria were defined as:

- Date of diagnosis of cancer between 1st April 2007 and 31st March 2010.
- Aged 60 to 69 years on date of diagnosis.

As mentioned, the North East region bowel cancer screening hub began screening in February 2007. To allow time for the initial invites to be sent out and kits returned, the study period began on the 1st April 2007. At the time of data extraction, the NORCCAG database was complete up until 31st July 2010 therefore a three year time period was selected. Dates of diagnosis of each patient's cancer were used as an inclusion criterion, with the final dates extending to the 31st March 2010.

In February 2010, the age range for screening was increased to 74. Given the relatively slow distribution of invites and the lag time between invite and possible diagnosis, it was felt that there would be a minimal number of patients diagnosed in the two month period of age extension, in the older age bracket. Therefore, the age at diagnosis criteria was kept between 60 and 69. This also minimises on the potential differences in outcomes that may be associated with an older age group, as they may be more likely to have a greater level of comorbidities, compared to the younger age group. There may also be differing views on management choice for a 75 year old compared to a 60 year old, i.e. endoscopic resection and follow up vs. segmental bowel resection.

11.4 Permissions

As part of my role as a clinical research fellow, I was granted automatic access to the NORCCAG database. The clinical supervisor for my post is the chairperson of NORCCAG, Miss Sarah Mills.

The study design and methodology was endorsed by members of the Northern Region Endoscopy Group (NREG), a collaborative research network representing over 300 endoscopists [148]. The vice chairman of NREG is Dr Matt Rutter who is also the chairman of the bowel cancer screening programme evaluation committee. This committee grants access to the national BCSP database. Dr Rutter reviewed the project plan and agreed to release of the appropriate screening data, but felt that this could be satisfactorily obtained from the regional hub database, instead of the national hub.

All bowel cancer screening research should be reviewed by the National Information Governance Board (NIGB) [149]. Their ethics and confidentiality committee review

applications related to the processing of health and social care information under section 251 of the NHS Act 2006. An application was made and reviewed by their committee who responded explaining that formal approval was not required as long as there was pseudo-anonymization of the two databases.

Pseudo-anonymization includes removing all identifiable data items from the database and replacing them with non-identifiable items. The only data item that remained on the NORCCAG dataset was NHS number. This was therefore replaced with a study number (A1000 to A2556). A list of NHS numbers with their corresponding study numbers (and no other data items) was sent to the hub analyst at the regional BCSP hub, Mr Colin Taylor. Mr Taylor then returned the appropriate BCSP data using this study number, and removing the NHS number. This meant that there was no patient identifiable data on any of the files that contained analysis data.

As discussed, there are eight NHS trusts which comprise 13 hospitals that are part of the North East screening hub. These are:

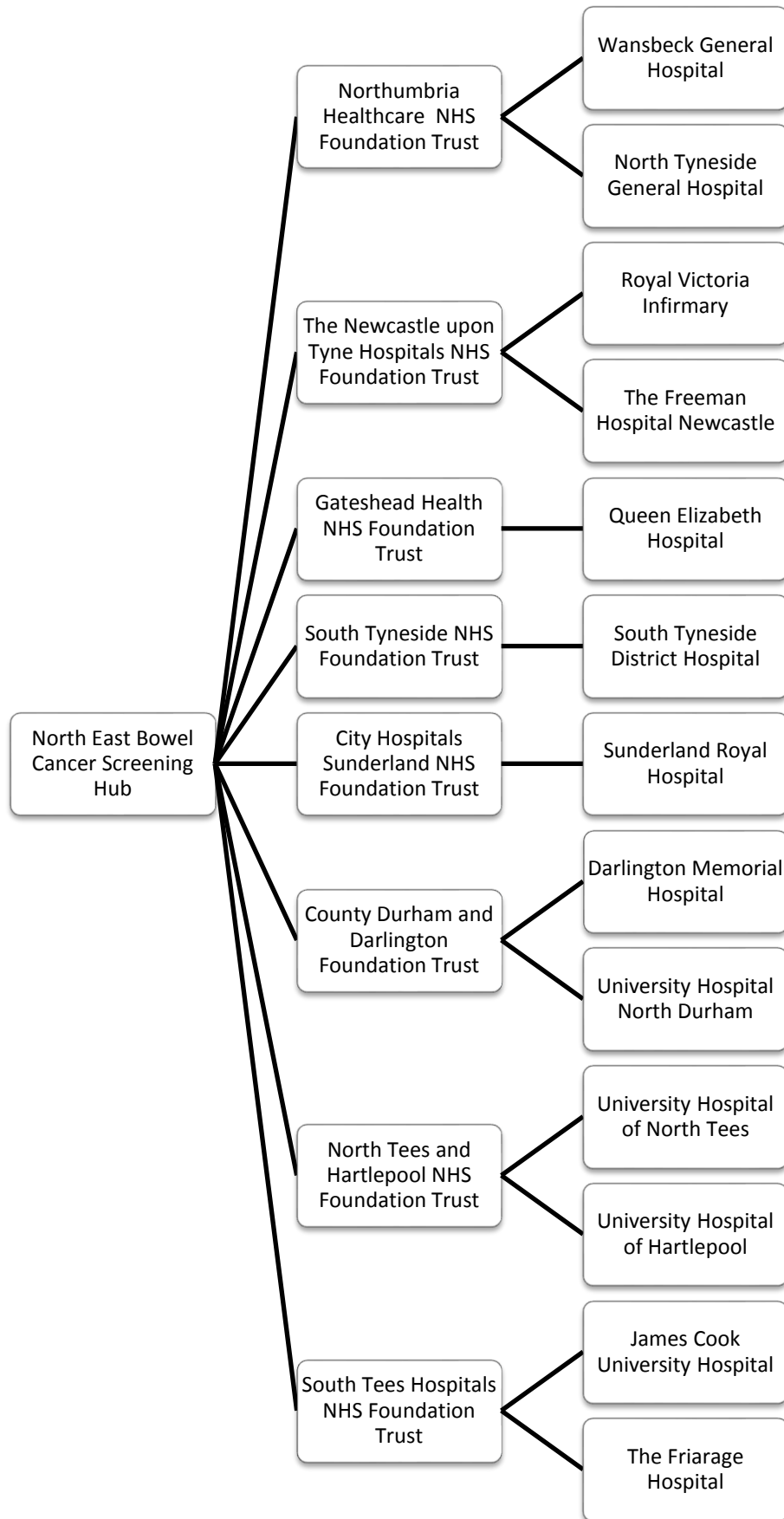


Figure 11.5 Hospitals and Trusts within the North East Bowel Screening Hub.

Through the research and development team at Northumbria Health Care Trust, I obtained a list of all R&D managers in each of the above trusts. Each one of these was individually contacted to obtain access to medical records and their IT systems to allow data validation. The response from each of the trusts was variable. As the project was deemed a service evaluation (see below), certain research and development departments felt that it was not part of their role to aid me in gaining access to their data. This meant a great deal of time wasted in emailing the trusts to get their advice on whom to contact to gain access to their computer systems.

Although the initial email explaining the nature of the project was sent out in December 2010, it took until July 2011 to gain full access to each of the trust's data. Each trust varied in the proof they required to grant this access. For example, South Tees NHS Foundation Trust was happy with the details provided in the project plan and was able to grant access within one month. However, other trusts required Caldicott approval, copies of criminal records bureau (CRB) clearance, ethics approval clearance, and copies of my passport before granting access. Many of the R&D facilitators informed me that they do not often deal with service evaluations and so weren't familiar themselves as to what was required. The above process proved to be one of the biggest hurdles faced in carrying out this study.

11.5 Ethics and Consent

A service evaluation is "designed and conducted solely to define or judge current care" and is developed to answer "what standard does this service achieve?" [150]. A service evaluation has no current reference standard, with the intervention being currently in use. There should be no randomisation or allocation instilled.

The project was reviewed by the University of Durham School of Medicine and Health Research and Ethics Committee and approved.

To confirm that this study fell within the service evaluation category, the local NHS Research and Ethics Committee was contacted. They reviewed the project plan and agreed that formal ethical approval was not required.

However, as this study progressed, it became apparent that although this project started out as a service evaluation of the screening programme, it began to generate research hypotheses. Some of these hypotheses could be answered by examining the data available in further detail. However, with regards to the use of medication around the time of FOBt (Chapter 11.13), extra data was actively sought out that was not included in the original

study protocol. These hypotheses were then addressed individually with the aims of the project altered to answer more specific research questions.

11.6 Study Materials

Patient identification from the NORCCAG database took place via two methods. First, all patients with a date of diagnosis and age within the inclusion criteria were extracted. One of the compulsory data items for entry onto the National Bowel Cancer Audit Project database is date of diagnosis. Along with tumour site and NHS number, it forms a unique patient identifier for this database. However, it was noted that there were a proportion of patients who were missing their date of diagnosis, with only minimal data items entered for each patients.

A search was therefore performed based on the patient's date of birth in an attempt to identify additional patients who may have been eligible for screening. The records of each of these were reviewed against each Trust's IT system to obtain the date of diagnosis. The vast majority of these additional patients were patients who were currently being investigated for a colorectal cancer and so had incomplete records.

11.7 Database Validation

After validation work of the NORCCAG database (Chapter 9), patient records were reviewed for errors and missing data.

By reviewing all incomplete pathology records, it was possible to complete all T, N and M stages as well as lymph node status and Dukes stage. From the pathology reports, the type of operation was extracted. There were a number of patients with duplicate procedures, an initial endoscopic excision (i.e. a polypectomy) who went on to have a segmental bowel resection. In these instances, the bowel resection was treated as the operative procedure (even if no residual tumour was found post polypectomy).

All cases of Dukes D cancer were reviewed as it was found that if there was a degree of uncertainty on the staging investigations, they were sometimes incorrectly recorded as having metastatic spread of the cancer.

Missing patient postcodes, GP codes, and ASA grades (where available) were supplemented from hospital computer records.

11.8 Postcode Deprivation Data

Using the patient's postcode, it was possible to obtain deprivation indices for each patient. This was performed by using the GeoConvert data from the Economic & Social Research Council (ESRC) Census Programme website [151]. A text file of all patient postcodes was uploaded which provided the Lower Super Output Area (LSOA) for each area. Through this, it was possible to derive what the score and rank of each LSOA was according to the English Indices of Deprivation from 2007. There are 32,482 LSOAs in England. The LSOA ranked 1 by the Indices of Multiple Deprivation (IMD) 2007 is the most deprived and that ranked 32,482 is the least deprived. The IMD 2007 was constructed by combining the seven transformed domain scores, using the following weights: Income (22.5%), Employment (22.5%), Health Deprivation and Disability (13.5%), Education, Skills and Training (13.5%), Barriers to Housing and Services (9.3%), Crime (9.3%), Living Environment (9.3%). The above data was obtained from the Communities and Local Government website [152].

11.9 Combining Databases

As described in Chapter 8, the data from the bowel cancer screening programme was provided in several parts: Invitation data, FOB results, SSP appointment data and, Colonoscopy results.

Using the study number and episode ID as identifiers, the invites and FOB results data was combined using Microsoft Access® 2010. This was then exported into a Microsoft Excel® 2010 file for initial analysis.

As each patient potentially had submitted several tests over different screening episodes, their FOB results could be spread over numerous rows. Therefore, each patient was reviewed in turn against their date of diagnosis to identify which screening episode was the correct one prior to their diagnosis. The results of their FOB kits were then put onto a single line in excel under the column headings: FOB kits 1-3, Earlier kits 1-3, and Later kits 1-3.

For each kit, the overall result and total number of positive windows was recorded, as well as the date returned to the regional hub.

By streamlining the data to a single row, reviewing it against the FOB test results and the patient's date of diagnosis, it was possible to classify patients into their respective cancer groups on a preliminary basis.

A similar process of condensing the SSP appointment data and colonoscopy results onto a single row in Excel was performed.

Once complete, it was possible to combine the NORCCAG database with the BCSP database and postcode deprivation data. This was performed using study numbers as identifiers and combining the three datasets into one. Once completed, the data was transferred into SPSS version 19-0® (SPSS Inc., Chicago, Illinois, USA).

11.10 Classification of Data Items in SPSS

To aid analysis, each data type was given numerical codes and grouped where appropriate.

The full list of steps can be seen in Appendix 1. To summarise, these included using:

- American Society of Anaesthesiologists (ASA) physical status grade as a surrogate for severity of patient comorbidities, being dichotomised into two groups of 1-2, and 3-5.
- Tumour location was dichotomised on being distal to the splenic flexure or proximal (up to and including the splenic flexure).
- Deprivation level was then dichotomised into two groups; whether or not the patient lived in one of the 10% most deprived areas within England.
- Coding of medication use to within 2 months of carrying out a FOBt.
- All resective surgery grouped into one category.
- All palliative procedures (stents, bypass operation, etc.) grouped together.
- Local excisions included all endoscopic polypectomies and trans-anal resection of tumours.
- The modified Dukes' staging classification (Stages A to D) was used to stage each tumour.
- Dukes C1 and Dukes C2 cancers were combined to form Dukes' C cancers.
- Lymph node harvests grouped into greater than or less than 12 lymph nodes for resective surgery.
- Creation of 30-day mortality variable.

11.11 Classification of Study Group

The two databases were combined to allow classification of patients into their respective groups of control, interval, non-uptake and screen-detected cancers. Figure 11.6 is a flow chart that summarises the process of allocation for each subject, into their appropriate classification groups.

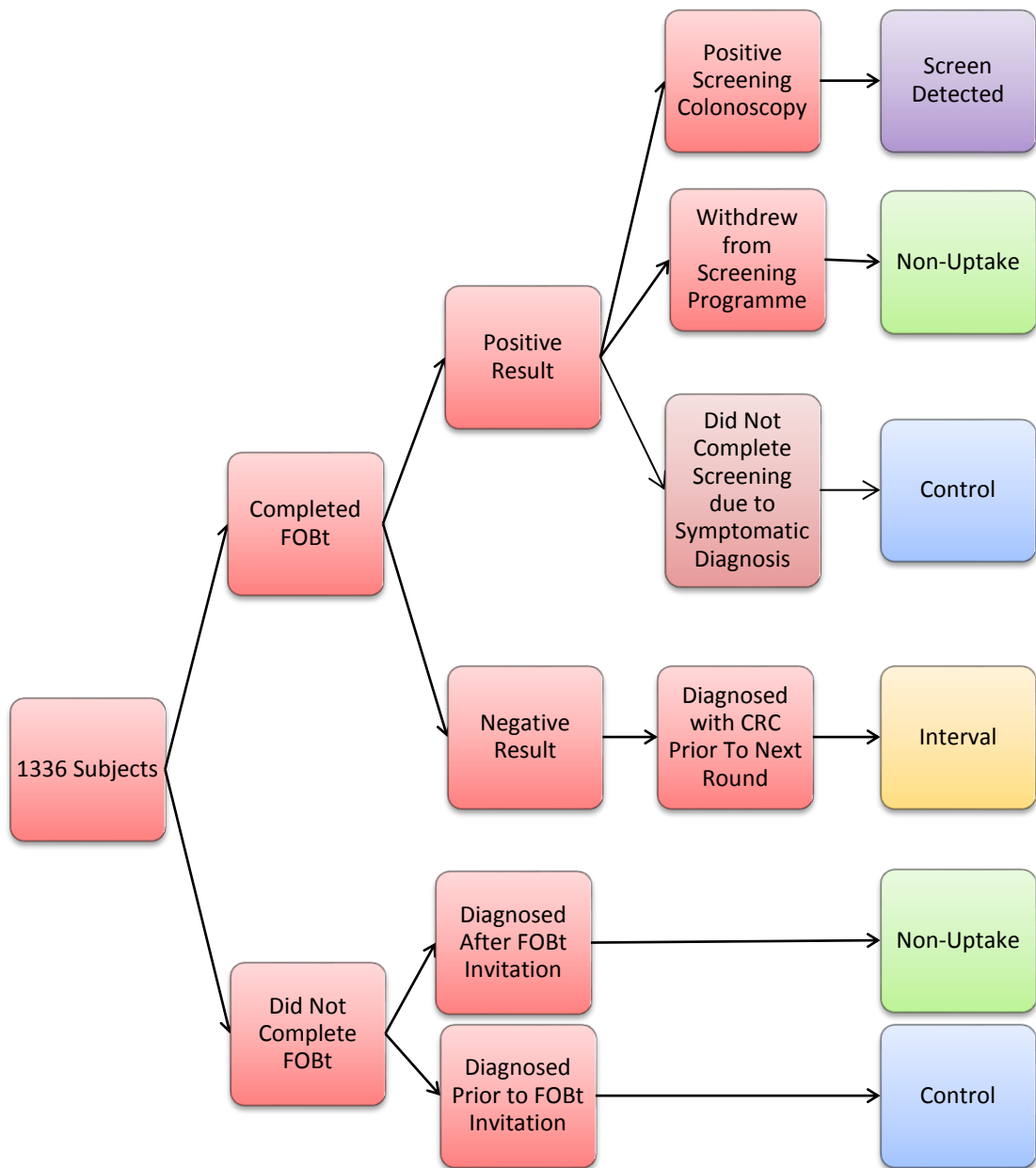


Figure 11.6 Flow chart representation of allocation to each study group.

All subjects who were found to have a positive FOBT result were identified from the combined database. This subject group were then reviewed to ensure they had attended a SSP appointment, and had undergone a screening colonoscopy. Screen-detected cancers had to submit a positive FOBT, attend a screening nurse practitioner appointment and undergo a screening colonoscopy to be included in this group. All patients who were referred to symptomatic services with a histological diagnosis of a cancer, or with a suspicion of a cancer that had not been confirmed histologically by endoscopic biopsy were included in this group. The hospital records for each patient who had submitted a positive FOBT, but did not undergo a screening colonoscopy were reviewed. If they dropped out

from the programme, they were classified as a non-uptake cancer. If they were diagnosed with a CRC before they were due to undergo the next part of their screening tests (either repeat FOBt or screening colonoscopy), and had not been part of a previous round of screening, then they were classified into the control group. An example of this is if a subject submitted a positive FOBt, but then was admitted to hospital as an emergency with a bowel obstruction, before they due to have their planned screening colonoscopy.

The above scenario for inclusion into the control group, ties with its definition: A subject who was diagnosed with their colorectal cancer through symptomatic bowel cancer services, prior to completion of their first screening round. Therefore, even if they submitted a positive FOBt result (n=19), they were still classed as a control if they did not complete the planned screening round.

Interval colorectal cancers were classed as a cancer diagnosed between screening rounds, after a negative screening episode (either FOBt or colonoscopy).

Non-uptake cancers were in patients who declined a part of the screening process: the FOBt, a SSP appointment or a screening colonoscopy.

11.12 Data Analysis

As described above, the control group was available for analysis due to the lag time in programme implementation across the study region. This is the only time in the history of the screening programme where such a group will be available for comparison, since it has been introduced nationally. It was assumed that this control group were uninfluenced by the screening programme, as none had completed a screening episode at the time of their diagnosis. To ensure that this is the case, analysis of the impact of different variables on survival of the control group will be performed. These variables are widely accepted as being independent factors in altering (or not altering) the outcome of cancer patients, and include gender, ASA grade, and deprivation level. The effect of these variables on the intervention group will also be reviewed, to ensure both groups are influenced by the above in the same way.

To achieve the above aims, the following classification groups were compared against each other:

- Control vs. Intervention
- Control vs. Screen detected
- Control vs. Non-uptake
- Control vs. Interval

- Screen detected vs. Interval

Between the above groups, Pearson Chi-squared tests were used to look for significant differences in proportions for variables of deprivation, gender, ASA grade, and tumour location. Kruskal-Wallis test was used for Dukes' stage analysis as an ordinal variable, with log rank Mantel-Cox test used for survival analysis. Ages were compared with Students t-test. Results will be displayed in tabular form, with Kaplan-Meier survival curves shown to demonstrate any differences in survival. Subgroup analyses were performed where appropriate. Data were analysed using SPSS version 19.0® (SPSS Inc., Chicago, Illinois, USA). Primarily, a comparison between the control group and intervention (those who were offered screening) group will be made. This will establish whether the patient demographics and tumour characteristics between the two groups are equivalent. If there are no significant differences between these groups, then it will mean that the control group is valid for use as a comparator.

To answer the research question: 'There is no difference in survival rate between subjects diagnosed with a colorectal cancer between those who were offered screening, and those who weren't', the survival rates will be compared between the control group and the intervention group.

The second research hypothesis: 'There is no difference in the patient demographics, tumour characteristics, and survival rate between screen detected and interval/non-uptake colorectal cancers' will be answered by comparing the screen detected group against the interval and non-uptake groups. The interval cancer group will be reviewed in detail to establish any areas that would potentially improve the detected rate of colorectal cancers, leading to a decrease in false negative FOB results.

11.13 Medication Use Dataset

All interval and screen-detected cancer patients were identified along with their GP code. From the list of GP codes supplied with the screening invite data, it was possible to obtain the GP addresses for all these patients.

A proforma was designed (see Appendix 2) and sent with an accompanying letter (Appendix 3) to each identified GP practice. The proforma asked the practice to complete whether their patient(s) had ever taken specific medications, the dates they were taken, and whether the patient had undergone a previous cholecystectomy.

The medications asked about were:

- Non-steroidal anti-inflammatories (NSAIDs), e.g. diclofenac, ibuprofen

- Hormone Replacement Therapy
- Hormone Antagonists, e.g. tamoxifen
- Anti-coagulants, e.g. aspirin, warfarin

A stamped, addressed return envelope was included within the initial letter. This was sent out on the 7th February 2012. A reminder letter was sent out on the 7th March 2012 (Appendix 4). A generic reminder letter was sent out to practices that had not responded by the 7th March, and individual letters were sent out for further clarification of missing details returned by a number of practices.

A 2nd reminder letter, with proforma and return envelope was sent out on the 18th May 2012 to all non-responders (Appendix 5).

The results were inputted onto the SPSS worksheet, highlighting patients that had been taking the relevant medications at, or up to 2 months prior, to returning their FOBt.

11.14 Chapter Conclusion

By using a combination of the regional BCSP database, along with the North East's regional cancer registry, it is possible to establish the screening history of all colorectal cancers diagnosed in the population eligible for screening.

Comprehensive data cleansing and consolidation was carried out to create a workable dataset, with the combination of all data sources. Methods of statistical analysis have been shown. The steps taken to obtain and analyse the medication use of screen-detected and interval cancer groups has been shown.

Chapter 12 How Effective is the Current Screening Programme in North East England?

12.1 Introduction

This is a comprehensive study of colorectal cancers in one English region, following the implementation of the National Bowel Cancer Screening Programme. By using the combination of the NORCCAG database and the BCSP database, an accurate comparison of all cancers and their short term outcomes can be demonstrated.

The North East of England was one of the first regions to achieve complete coverage of its entire geographical area. It is therefore an ideal area to analyse the impact of the screening programme since its national implementation, in a region that hasn't been involved with any preliminary studies. This allows the true effect of screening to be seen, without any influence from previous interventions or media campaigns.

As described in earlier chapters, clinical mass population studies from Nottingham, Funen, Minnesota, Burgundy, and Goteborg, [100, 104-107, 115] have shown that screening increases the detection of earlier colorectal cancers, accompanied by an overall improvement in survival for screen-detected cancers. Pilot studies performed by Hardcastle et al. in Nottingham between 1981 and 1991 showed that there was a 15% reduction in cumulative CRC mortality in the screening group, as well a larger proportion being diagnosed with earlier bowel cancers (Dukes A). Of the 893 cancers diagnosed in the group offered screening (CRC incidence of 1.49 per 1000 person-years), 236 (26.4%) were detected by faecal occult blood (FOB) screening, 249 (27.9%) presented after a negative FOB test or investigation, and 400 (44.8%) presented in nonresponders [100].

12.2 Uptake of Screening in North East England

The below figure shows the total number of invitations to complete the FOB test in the study period of 1st April 2007 to 31st March 2010. This is for the population aged 60-69 and does not include those who self-referred or any as part of the age extension (70-75). The 2,463 that were discharged were allocated to this group as they did not complete a full round of faecal occult blood tests.

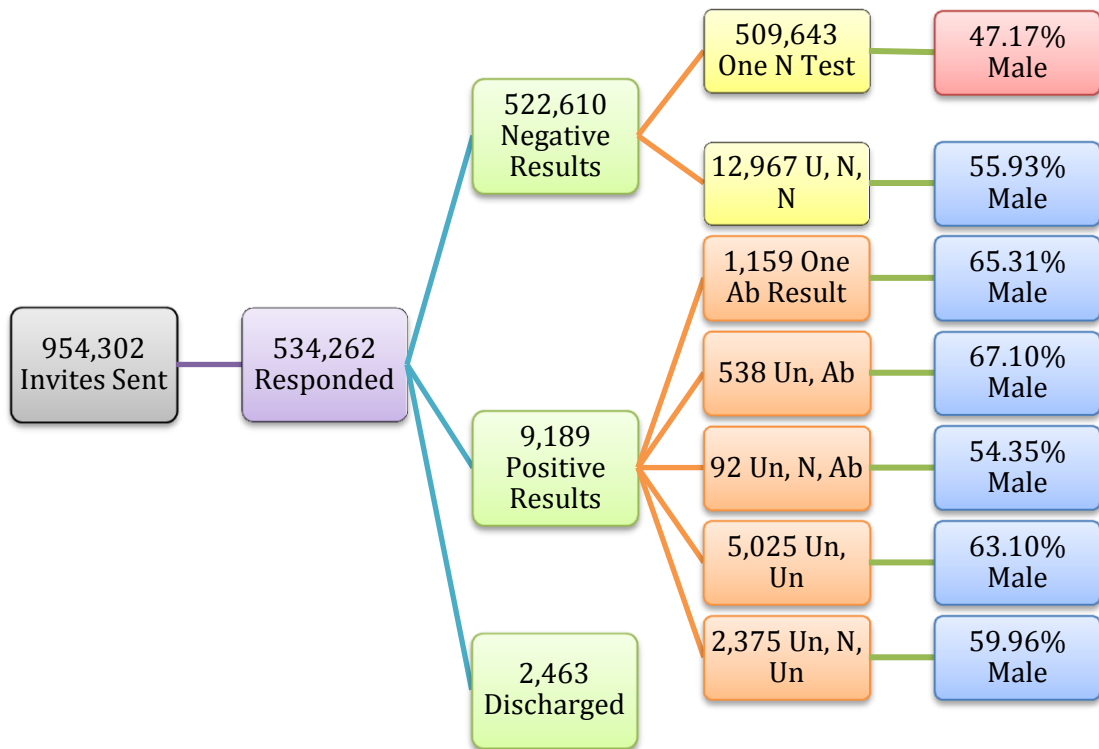
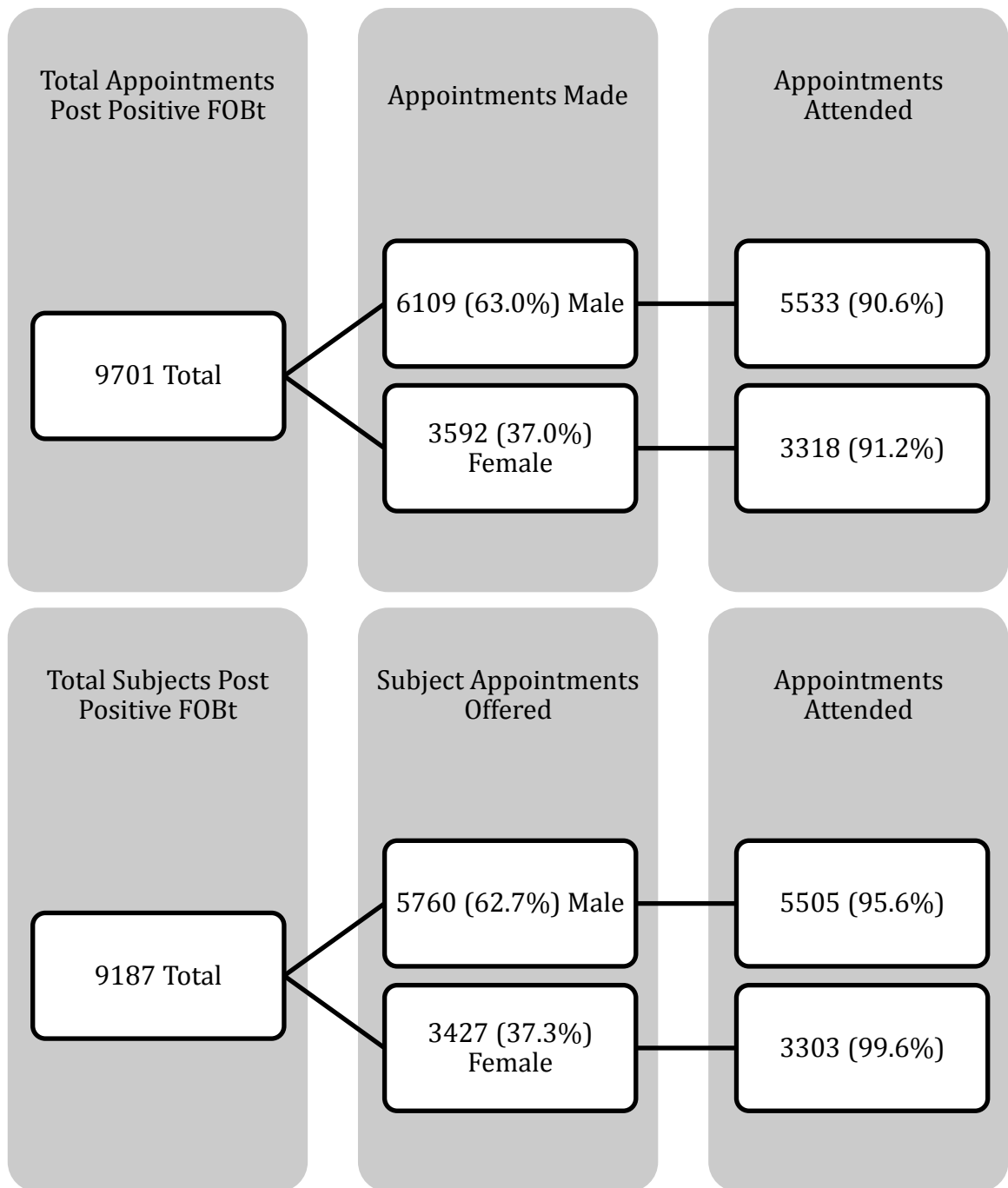


Figure 12.1 Overall number of FOB invites, their uptake and results. N=Normal, Ab=Abnormal, Un=Unclear.

An uptake of 56.0% (54.0% for men and 58.0% for women), is slightly higher than uptake rates from national figures (49.6% for men, 54.4% for women) [153]. When uptake was divided into deprivation level quintiles for the first one million population screened nationally, the North East of England was found to have a better uptake in each five divisions compared to other regions in England.

There were 9,701 screening nurse practitioner appointments made for 9,187 persons after a positive FOBt. The maximum number of appointments per person was three. The discrepancy of 2 persons between positive results and SSP appointments is unknown, but could be due to them being discharged due to not highlighting exclusion criteria prior to appointment being made. The attendance rates per appointment number and per person are shown in the below figures.



Figures 12.2 a and b. Numbers of SSP appointments post positive FOBT, total and per subject.

There were 9,428 investigations carried out in 8,828 persons which are summarised in the figure below. Figure 12.3 shows that colonoscopy is the gold standard for large bowel investigation with 90.3% of patients undergoing at least one procedure.

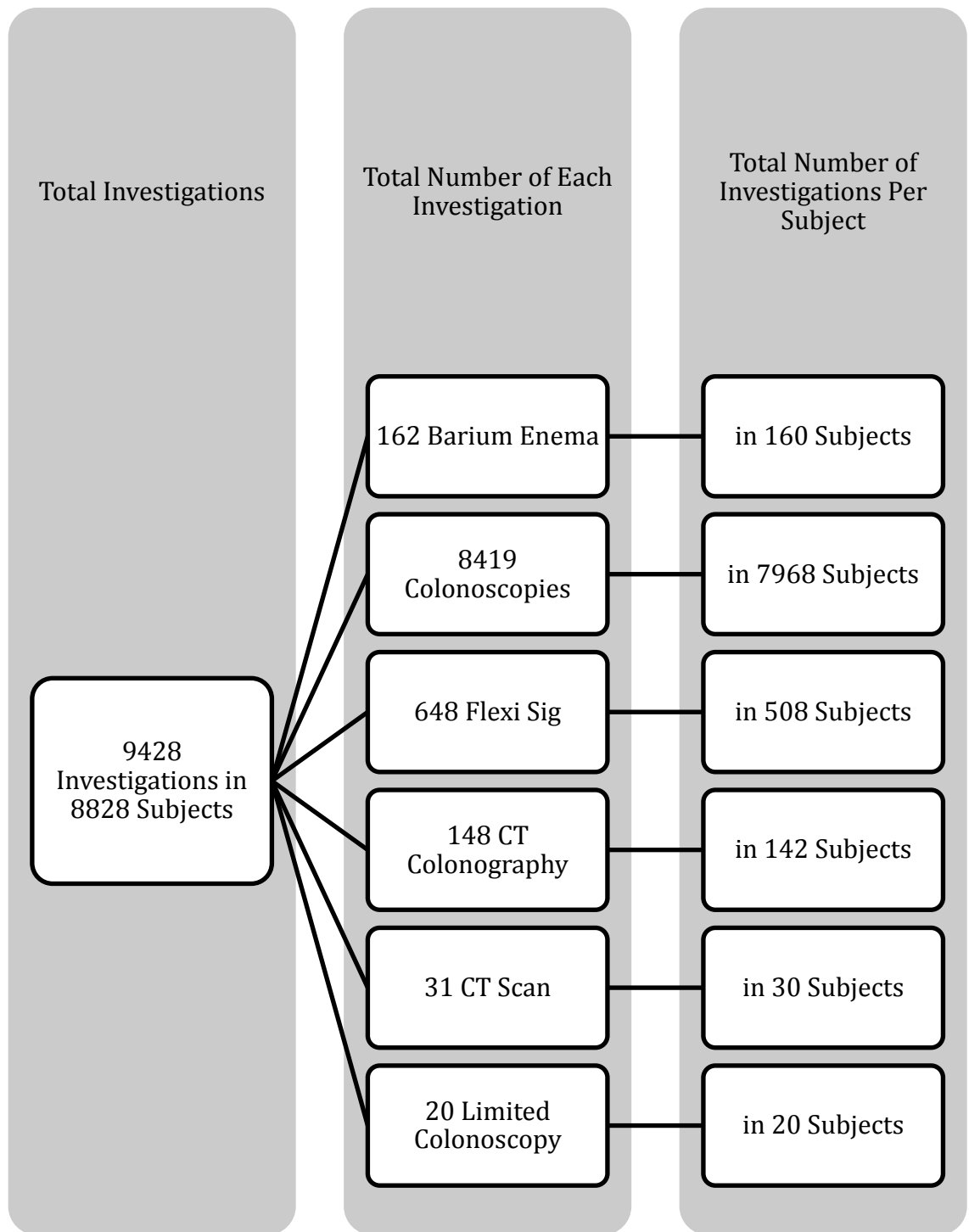
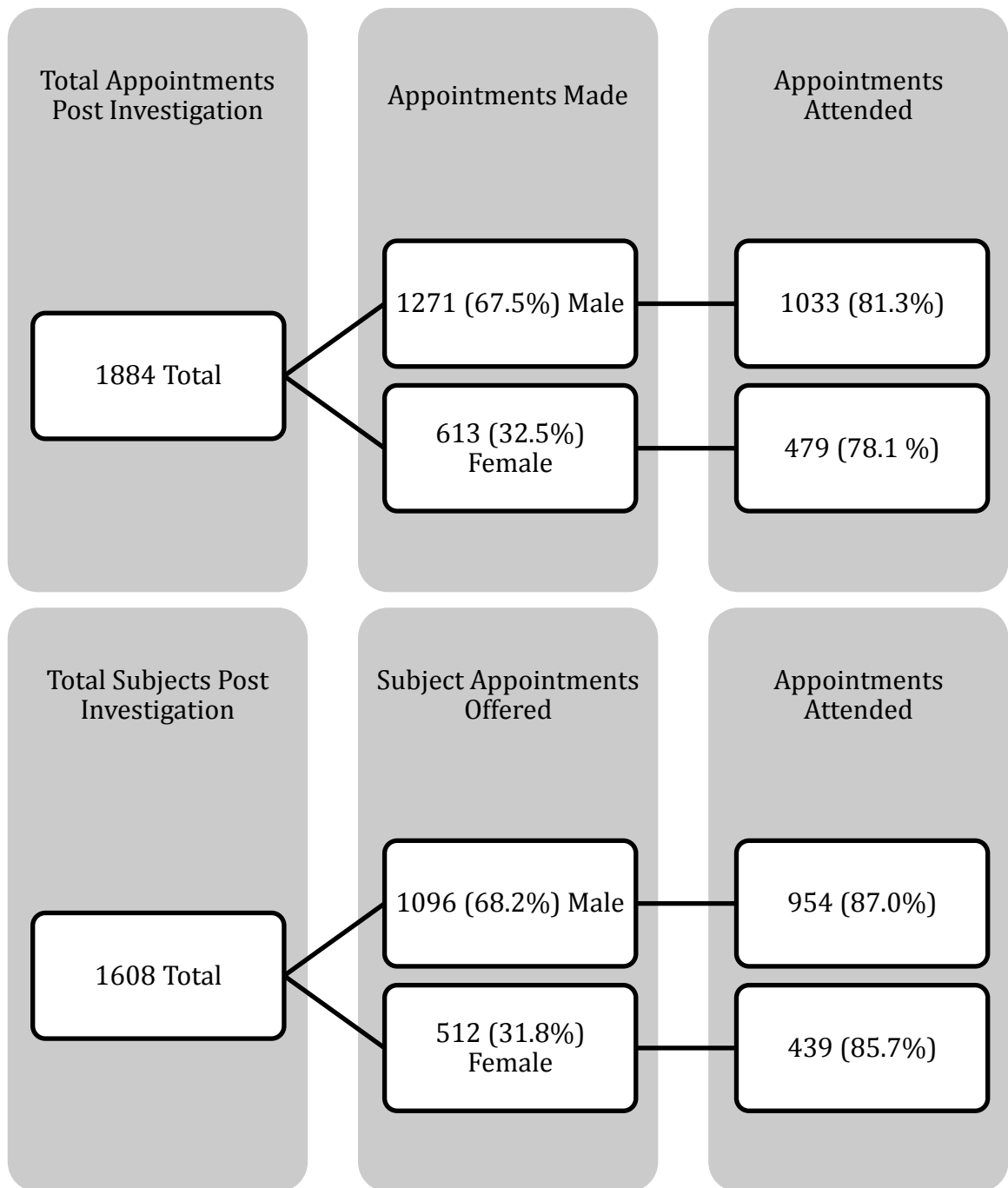


Figure 12.3 Numbers of investigations, total and per subject.

There were 1,884 screening nurse practitioner appointments made post investigation in 1,608 persons with uptake rates for both shown below.



Figures 12.4 a & b. Numbers of SSP appointments post investigation, total and per subject.

12.3 Study Group

Within the study period, 1336 patients diagnosed with a colorectal cancer were identified as being suitable for analysis. These included 825 (61.8%) in the population that were

offered screening (intervention group), and 511 (38.2%) in the control group. Of the cancers that were diagnosed in the group that were offered screening, 311 were in those who did not complete the screening tests (non-uptake group), 192 were interval cancers and 322 were screen detected. This is shown graphically in Figure 12.5 below.

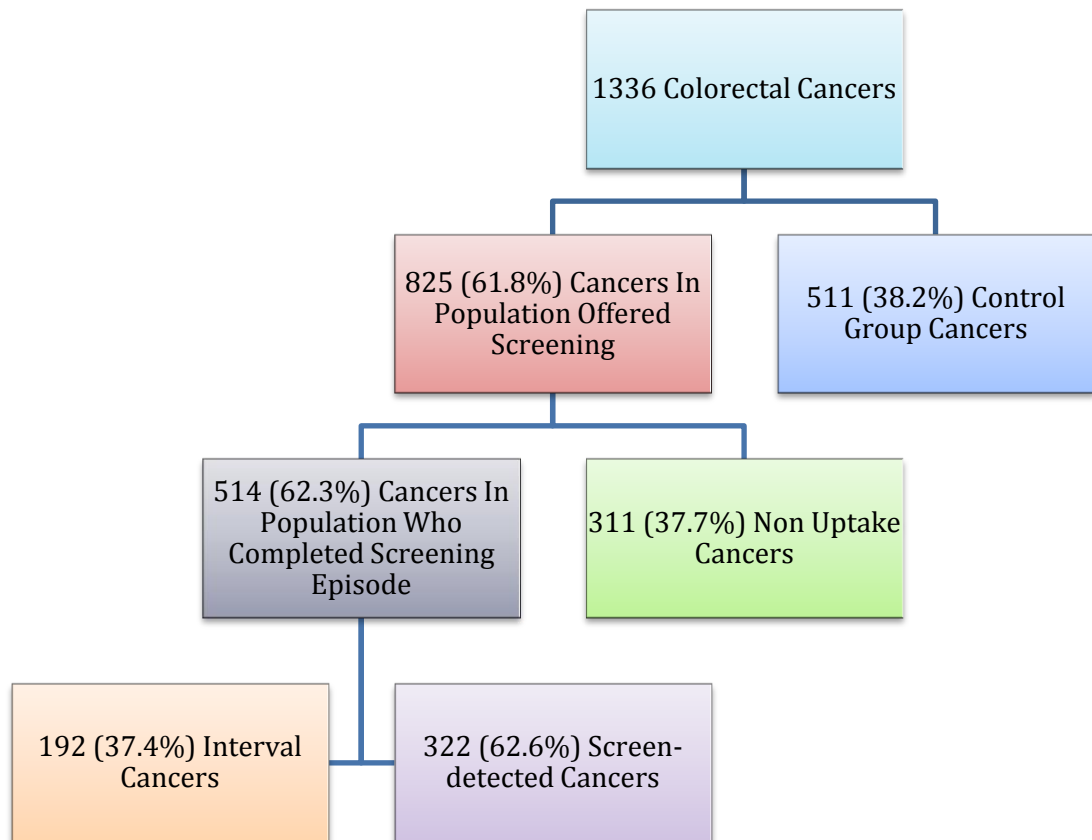


Figure 12.5. Proportion of cancers by classification group.

12.4 Control Group vs. Intervention Group

For an accurate comparison to be made between the three classification groups that were offered screening, a comparison must be made between the intervention group and the control group. Although the outcomes may differ in the intervention group, the patient demographics should be the same for an accurate comparison to be made.

		Control, n=511	Intervention, n=825	Total, n=1336
Mean Age At Diagnosis (years)		64.97	65.27	65.16
Gender	<i>Male</i>	319 (62.4%)	543 (65.8%)	862 (64.5%)
	<i>Female</i>	192 (37.6%)	282 (34.2%)	474 (35.5%)
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	60 (11.7%)	113 (13.7%)	173 (12.9%)
	<i>No</i>	451 (88.3%)	712 (86.3%)	1163 (87.1%)
ASA Grade Grouped	<i>1-2</i>	224 (77.8%)	436 (72.8%)	660 (74.4%)
	<i>3-5</i>	64 (22.2%)	163 (27.2%)	227 (25.6%)
Tumour Site	<i>Distal To Splenic Flexure</i>	358 (70.1%)	586 (71.0%)	944 (70.7%)
	<i>Splenic Flexure and Proximal</i>	153 (29.9%)	239 (29.0%)	392 (29.3%)

Table 12.1 Patient demographics and tumour details for control group and intervention group.

	Chi-square	Degrees of Freedom, df	Significance, p value
Gender	1.586	1	0.208
Lives in 10% Most Deprived Areas In England	1.070	1	0.301
ASA Grade	2.543	1	0.111
Tumour Site	0.144	1	0.705

Table 12.2 Pearson Chi-Square Tests comparing control group vs. intervention group.

The above tables show that gender proportions, ASA grade, deprivation level and tumour site were not significantly different between intervention and control groups.

The influence of the above variables on survival was reviewed for both intervention and control groups. The survival curves for each of these are shown below in Figures 12.6 to 12.8.

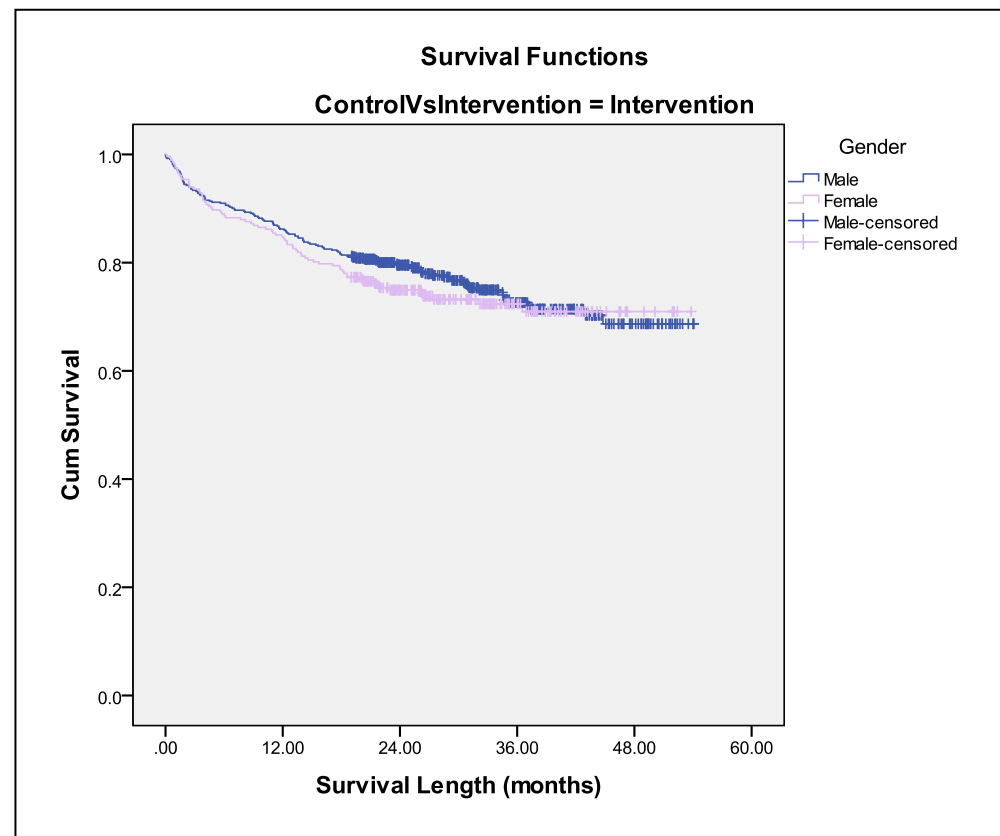
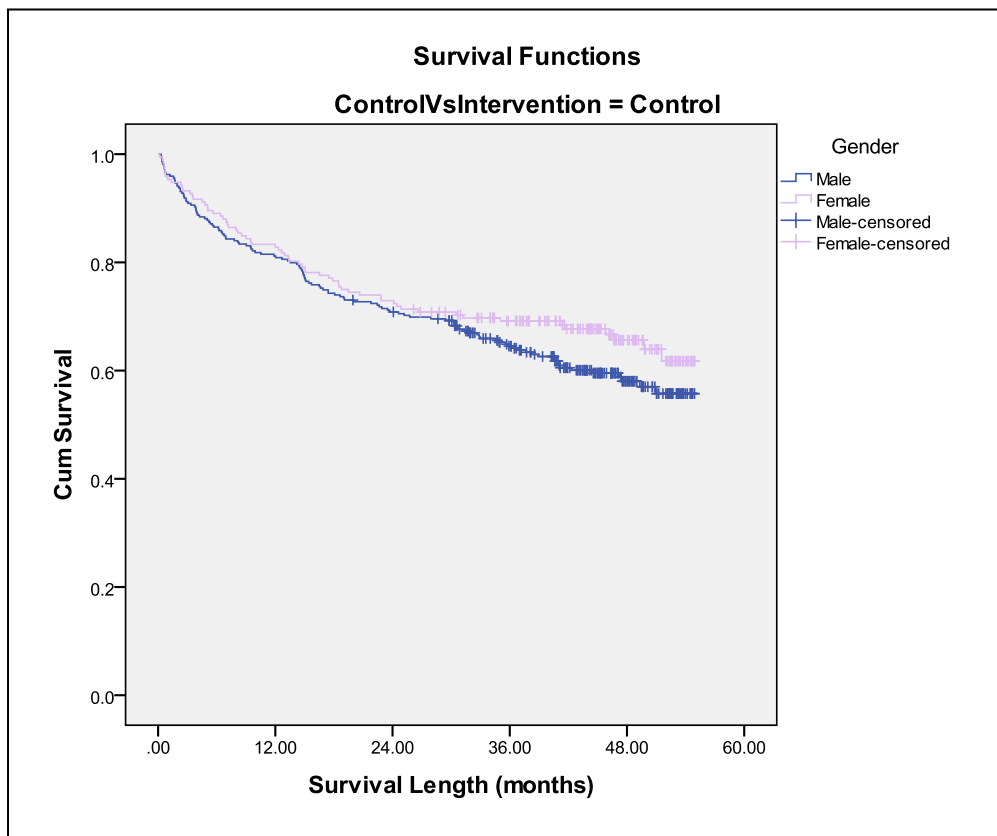


Figure 12.6 a & b. Survival curve comparing gender for control and intervention groups.

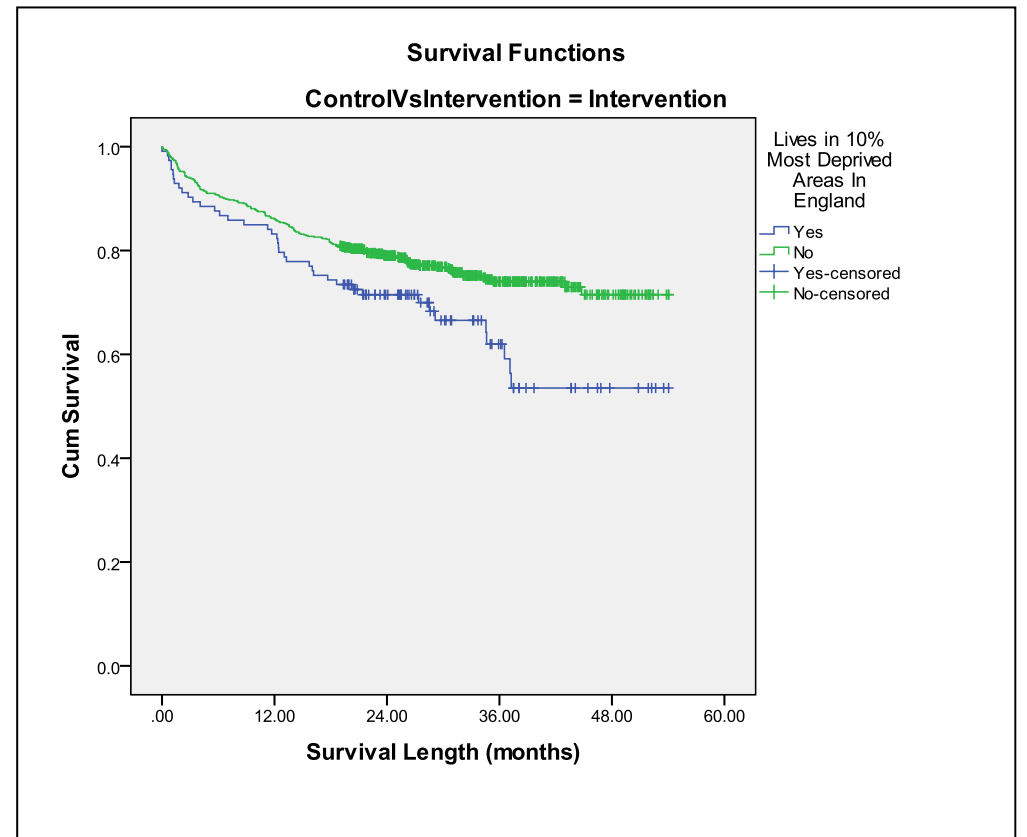
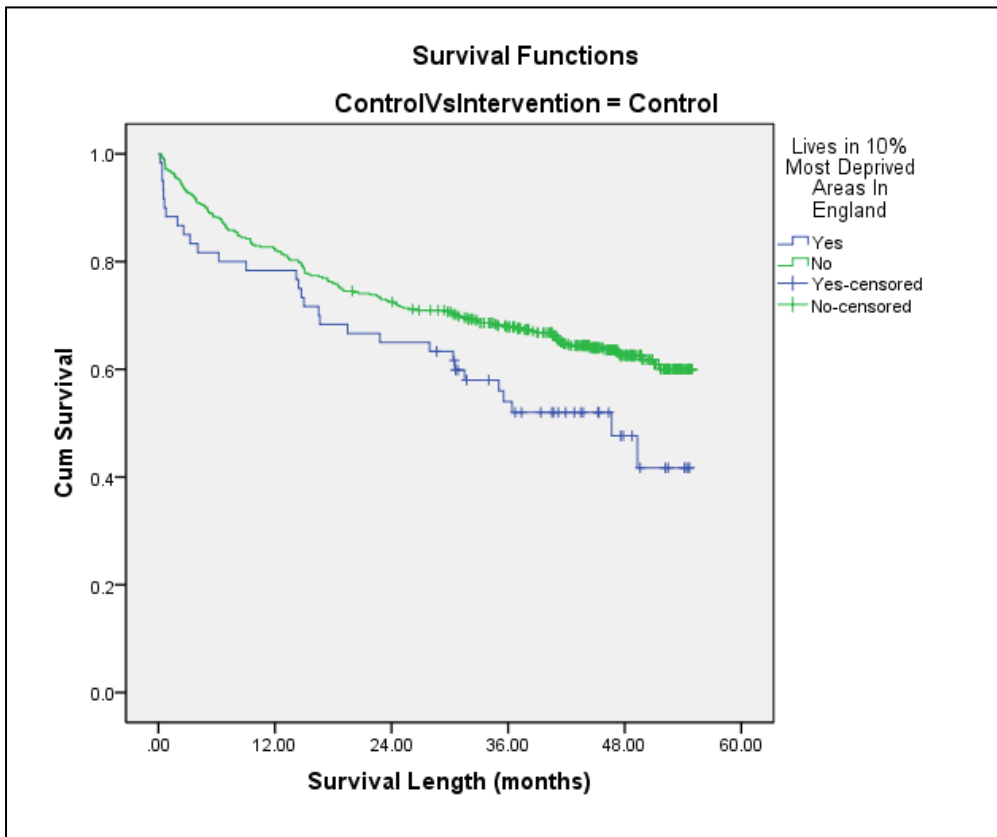


Figure 12.7 a & b. Survival curve comparing deprivation level for control group and intervention groups.

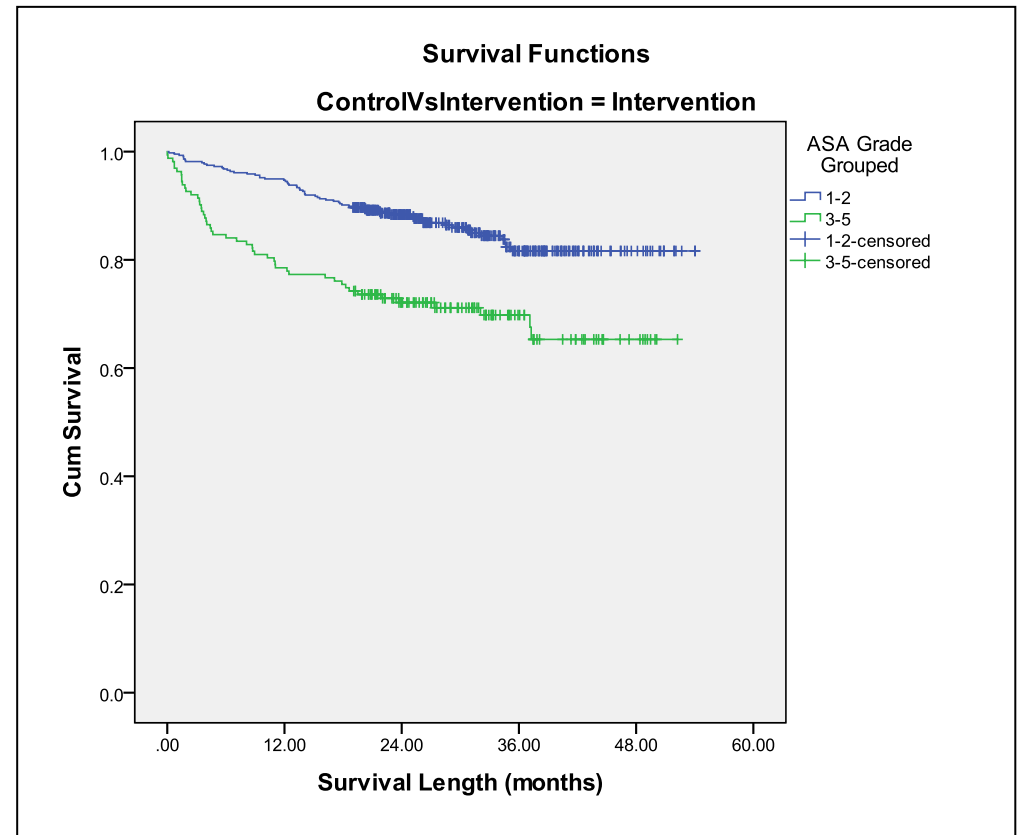
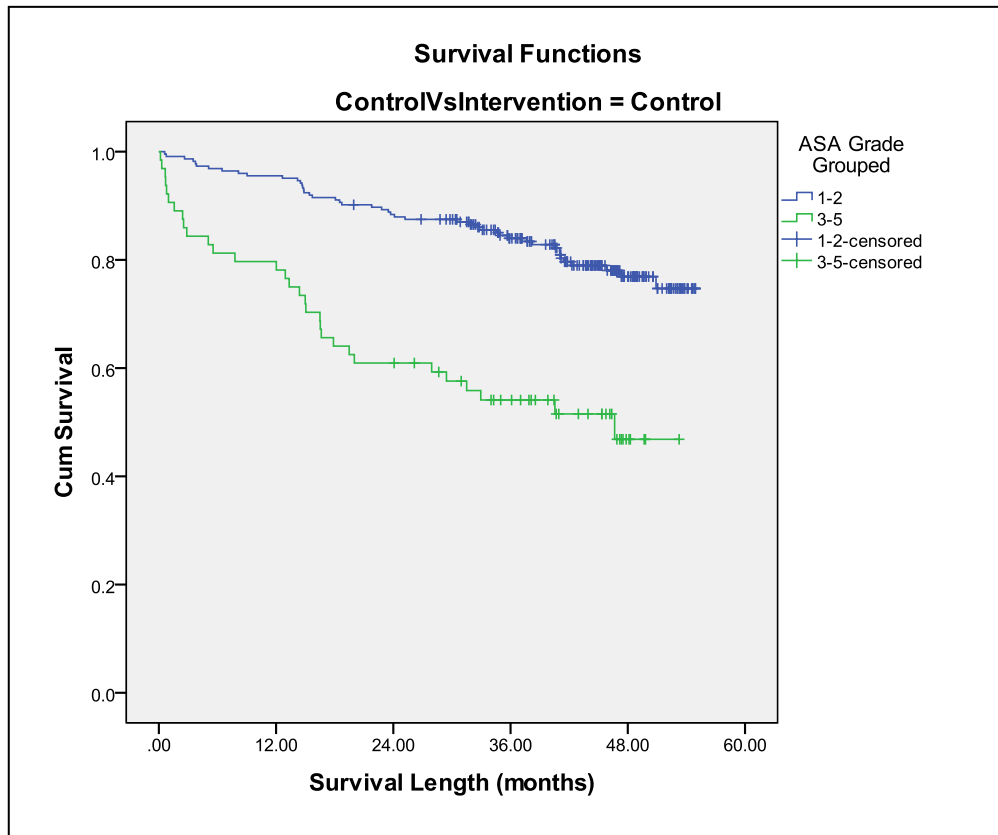


Figure 12.8 a & b. Survival curve comparing ASA grade for control group and intervention groups.

For each variable, a comparison was made between groups. The results of these are shown in Table 12.3 below.

	Control Group	Intervention Group	All Cases
	Significance, p value		
Gender M vs. F	0.180	0.425	0.706
Deprivation Level Most Deprived 10% vs. Rest	0.024	0.008	0.001
ASA Grade 1-2 vs. 3-5	<0.001	<0.001	<0.001

Table 12.3 Log Rank (Mantel-Cox) comparison of control group against intervention group for each variable, df=1 for all comparisons.

As would be expected, the influences of deprivation level and a patient's comorbidities have a significant effect on their outcome. This effect is seen in both the control group and intervention group showing that both groups behave in the same way, based on their pre-existing patient demographics.

12.5 Chapter Conclusion

This chapter shows the total uptake of FOBt screening within the North East of England. There was a 1.7% positivity rate of the faecal occult blood test, in those who completed all test kits. The total numbers of each kit result are shown.

The patient demographics and tumour details were found to be equivalent between the control group and the intervention group (all groups offered screening). Outcomes in both of these groups are influenced by the same risk factors. This means that the comparison between the control and intervention groups is a valid one, and allows the effect of screening to be established. This will be shown in the next chapter.

Chapter 13 The Impact of Screening Programme

13.1 The Impact of the Screening Programme

The mass population trials from around the globe have reported on the comparison between a control group and the intervention group, with the intervention being the offer of screening.

As shown in the previous chapter, the patient demographics and tumour locations are equivalent between groups. The impact of the screening programme can be viewed as any change in the stage of tumours detected, and the outcome of the population offered screening. These are shown in Table 13.1 below.

		Control, n=511	Intervention, n=825	Total, n=1336
Type of Surgery	<i>Resective</i>	405 (79.3%)	666 (80.7%)	1071 (80.2%)
	<i>Local Excision</i>	15 (2.9%)	50 (6.1%)	65 (4.9%)
	<i>Palliative</i>	33 (6.5%)	39 (4.7%)	72 (5.4%)
	<i>No Procedure</i>	58 (11.4%)	70 (8.5%)	128 (9.6%)
Dukes Stage	<i>A</i>	89 (17.9%)	204 (25.5%)	293 (22.6%)
	<i>B</i>	132 (26.6%)	219 (27.4%)	351 (27.1%)
	<i>C</i>	154 (31.0%)	240 (30.0%)	394 (30.4%)
	<i>D</i>	121 (24.4%)	137 (17.1%)	258 (19.9%)
30 Day Mortality	<i>Yes</i>	21 (4.1%)	20 (2.4%)	41 (3.1%)
	<i>No</i>	490 (95.9%)	805 (97.6%)	1295 (96.9%)

Table 13.1 Outcomes of the control and intervention groups.

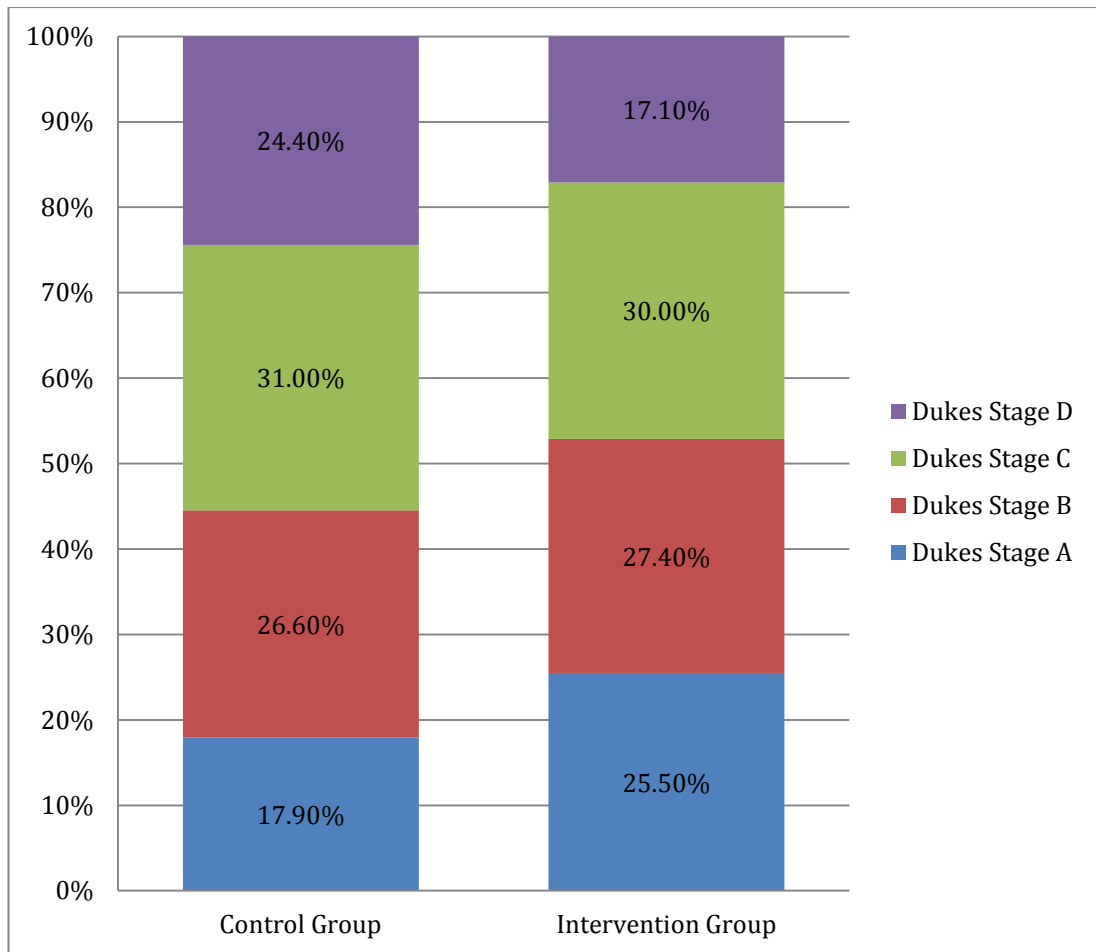


Figure 13.1 Tumour stage proportions between groups.

As shown in the above table and figure, there were significantly more Dukes' A cancers and significantly fewer Dukes' D cancers within the intervention group. The choice of management between these two groups varies in the use of a local excision (without a segmental bowel resection and regional lymphadenectomy). A significantly greater proportion of patients in the intervention group were managed this way.

There were no significant differences found in the 30-day mortality between groups. However, over the full follow-up period, the intervention group was found to have a superior survival rate (Log Rank Mantel-Cox $\chi^2 = 7.352$, $df=1$, $p=0.007$), as shown in Figure 13.2 below.

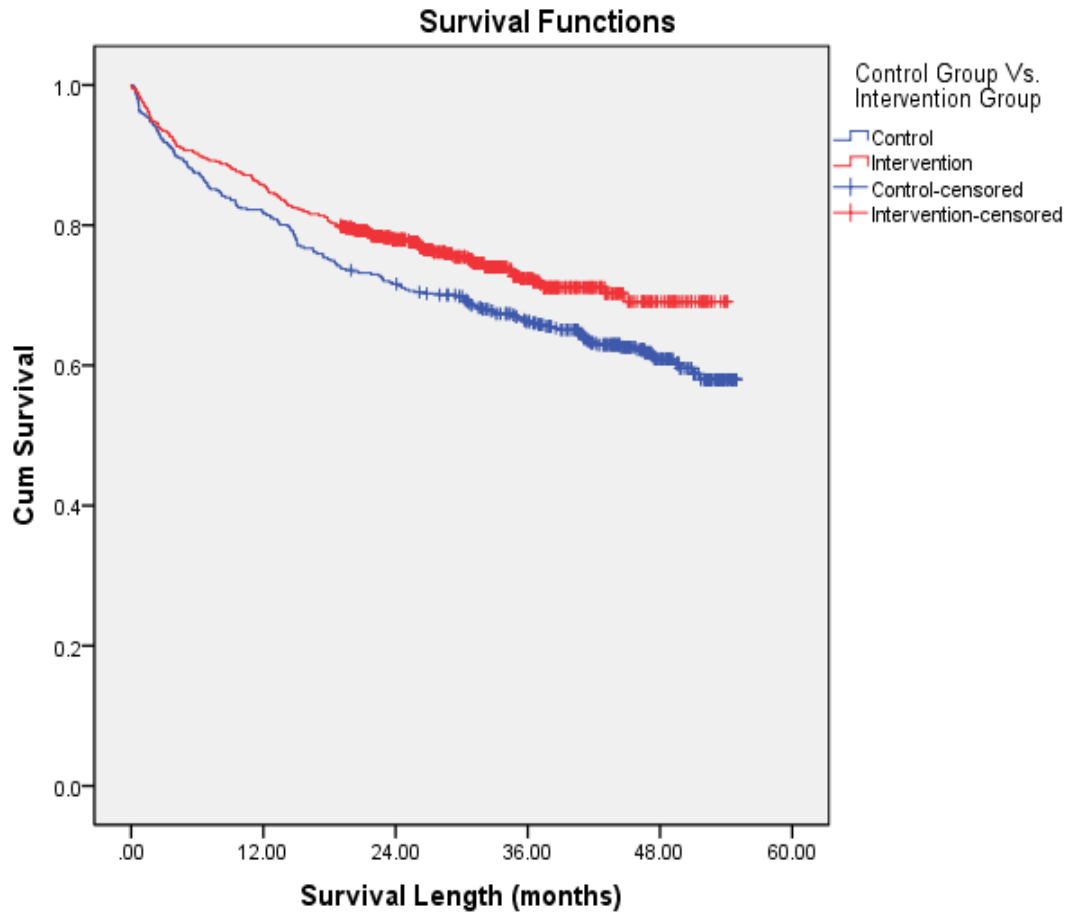


Figure 13.2 Kaplan-Meier survival curves for control group and intervention group.

To determine the reasons behind the improved survival rate due to carrying out screening, it is necessary to review each subgroup within the intervention group. As previously described, colorectal cancer patients who were offered screening can be categorised into three distinct groups. These are screen-detected cancers, interval cancers and non-uptake cancers.

13.2 Screen-Detected Cancers

There were 1,336 colorectal cancers diagnosed in the study population. The proportions in each group are shown in the figure below. This chapter will concentrate on the impact of a patient being diagnosed with a colorectal cancer through screening, highlighted in purple below.

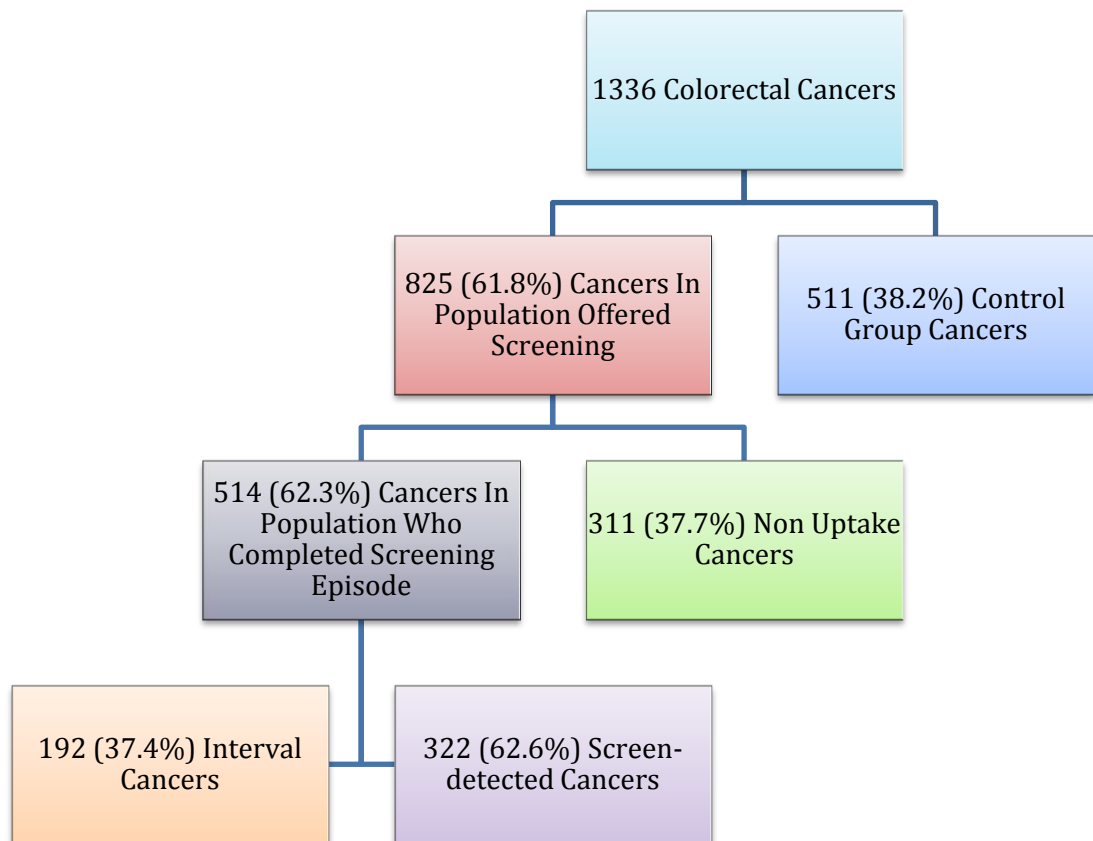


Figure 13.3 Proportion of cancers by classification group.

By comparing the screen-detected cancer group against the control group, it is possible to show the implications of detecting a cancer through screening. Table 13.2 below shows the demographics and cancer details of both the screen-detected group and the control group.

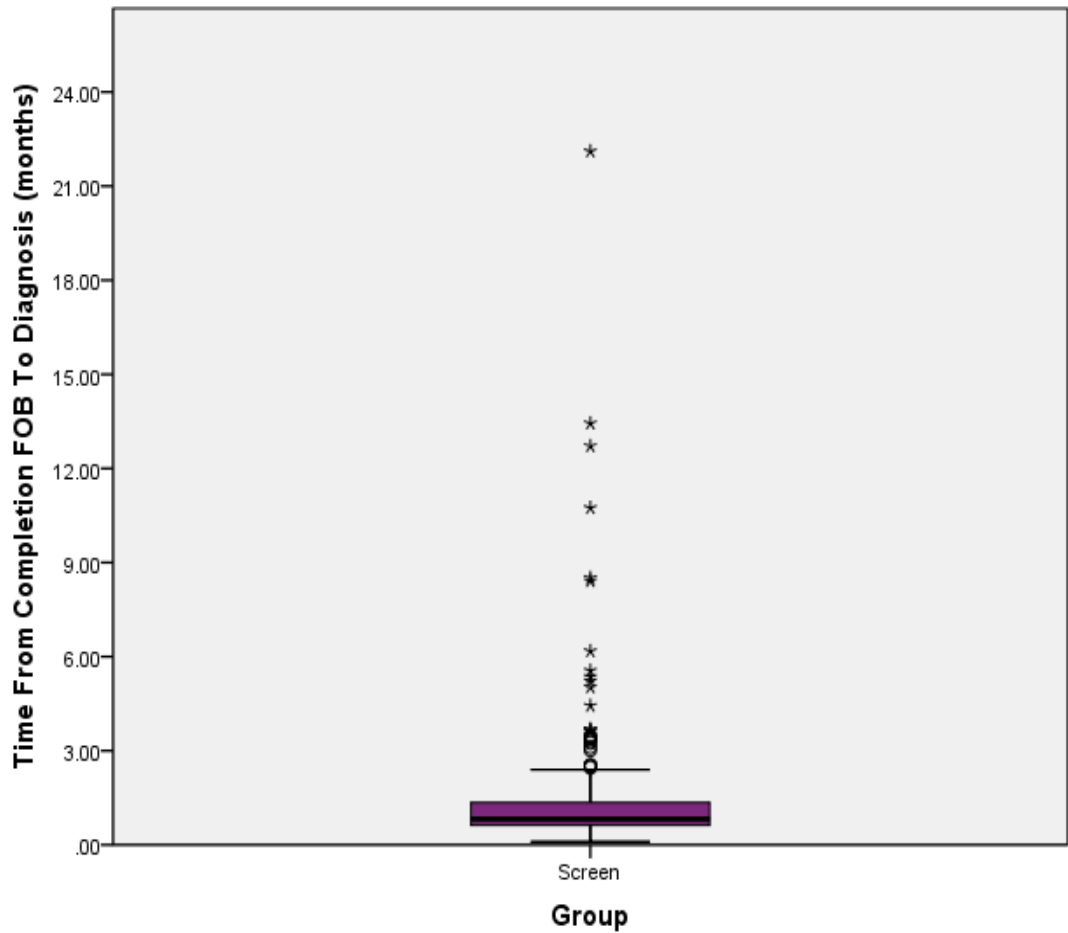


Figure 13.4 Box plot of time from completion of FOBt to diagnosis for the screen-detected cancer group.

The above figure (Figure 13.4) shows that the mean time from completion of the FOBt to diagnosis was 1.3 months (Standard Deviation 1.9 months), with 95% of cancers being diagnosed within 3.5 months.

		Control Group, n=511	Screen- detected Group, n=322	Comparison, p Value
Mean Age (Years)		64.97	64.96	NS
Gender	<i>Male</i>	319 (62.4%)	235 (73.0%)	0.002
	<i>Female</i>	192 (37.6%)	87 (27.0%)	
ASA Grade	<i>1-2</i>	224 (77.8%)	197 (79.8%)	NS
	<i>3-5</i>	64 (22.2%)	50 (20.2%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	60 (11.7%)	36 (11.2%)	NS
	<i>No</i>	451 (88.3%)	286 (88.8%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	358 (70.1%)	253 (78.6%)	0.007
	<i>Splenic Flexure and Proximal</i>	153 (29.9%)	69 (21.4%)	
Dukes Stage	<i>A</i>	89 (17.4%)	125 (38.8%)	<0.001
	<i>B</i>	132 (25.8%)	81 (25.2%)	
	<i>C</i>	154 (30.1%)	89 (27.6%)	
	<i>D</i>	121 (23.7%)	21 (6.5%)	
	<i>T0</i>	6 (1.2%)	5 (1.6%)	
	<i>Unknown</i>	9 (1.8%)	1 (0.3%)	
Type of Procedure	<i>Resective</i>	405 (79.3%)	274 (85.1%)	<0.001
	<i>Local Excision</i>	15 (2.9%)	38 (11.8%)	
	<i>Palliative</i>	33 (6.5%)	3 (0.9%)	
	<i>No Procedure</i>	58 (11.4%)	7 (2.2%)	

Table 13.2 Distribution of patient demographics, tumour characteristics and management of patients between control and screen-detected cancer groups. χ^2 test used in nominal variables, students t-test used to compare ages, Kruskal-Wallis test for Dukes stage as an ordinal variable. NS=Not significant.

Compared to the control group, screen-detected cancers were found more frequently in men ($p=0.002$), distal to the splenic flexure ($p=0.007$), had a better stage profile ($p<0.001$) with significantly more Dukes' A cancers and fewer Dukes' D cancers. A greater proportion were treated with local excision ($p<0.001$).

30-Day Mortality	Group			
	Control, n=511	Non-Uptake, n=311	Interval, n=192	Screen, n=322
Yes	21 (4.1%)	13 (4.2%)	6 (3.1%)	1 (0.3%)
No	490 (95.9%)	298 (95.8%)	186 (96.9%)	321 (99.7%)

Table 13.3 30-day mortality figures for each cancer group.

The above table shows the numbers and percentages of the 30-day mortality for each group. Screen-detected cancers have a significantly lower mortality rate compared to each other group ($\chi^2=11.4$, $df=3$, $p=0.01$). However, when this is broken down by type of procedure performed for each group (Table 13.4 below), there are no longer significant differences for each (Table 13.5). Therefore, it is likely that the overall numbers of local excision procedures performed in the screen-detected group, is the predominant factor in achieving an extremely low early mortality rate.

Type of Surgery	30 Day Mortality	Group			
		Control, n=511	Non-Uptake, n=311	Interval, n=192	Screen, n=322
Resective	Yes	5 (1.2%)	4 (1.7%)	1 (0.7%)	1 (0.4%)
	No	400 (98.8%)	236 (98.3%)	151 (99.3%)	273 (99.6%)
Local Excision	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	15 (100.0%)	8 (100.0%)	4 (100.0%)	38 (100.0%)
Palliative	Yes	4 (12.1%)	2 (7.7%)	3 (30.0%)	0 (0.0%)
	No	29 (87.9%)	24 (92.3%)	7 (70.0%)	3 (100.0%)
No Procedure	Yes	12 (20.7%)	7 (18.9%)	2 (7.7%)	0 (0.0%)
	No	46 (79.3%)	30 (81.1%)	24 (92.3%)	7 (100.0%)

Table 13.4 30 day mortality figures for each cancer group by level of operative intervention.

Type of Surgery	χ^2	Significance, p value
<i>Resective</i>	2.523	0.471
<i>Local Excision</i>	NA	NA
<i>Palliative</i>	3.782	0.286
<i>No Procedure</i>	3.760	0.289

Table 13.5 Chi-squared figures and significance for each level of operative intervention, df=3 for all.

As shown by the graph below, screen-detected cancer patients have a superior survival rate (Log Rank Mantel-Cox $\chi^2=53.62$, $df=1$, $p<0.001$), when compared against the control group. This is for all-cause mortality.

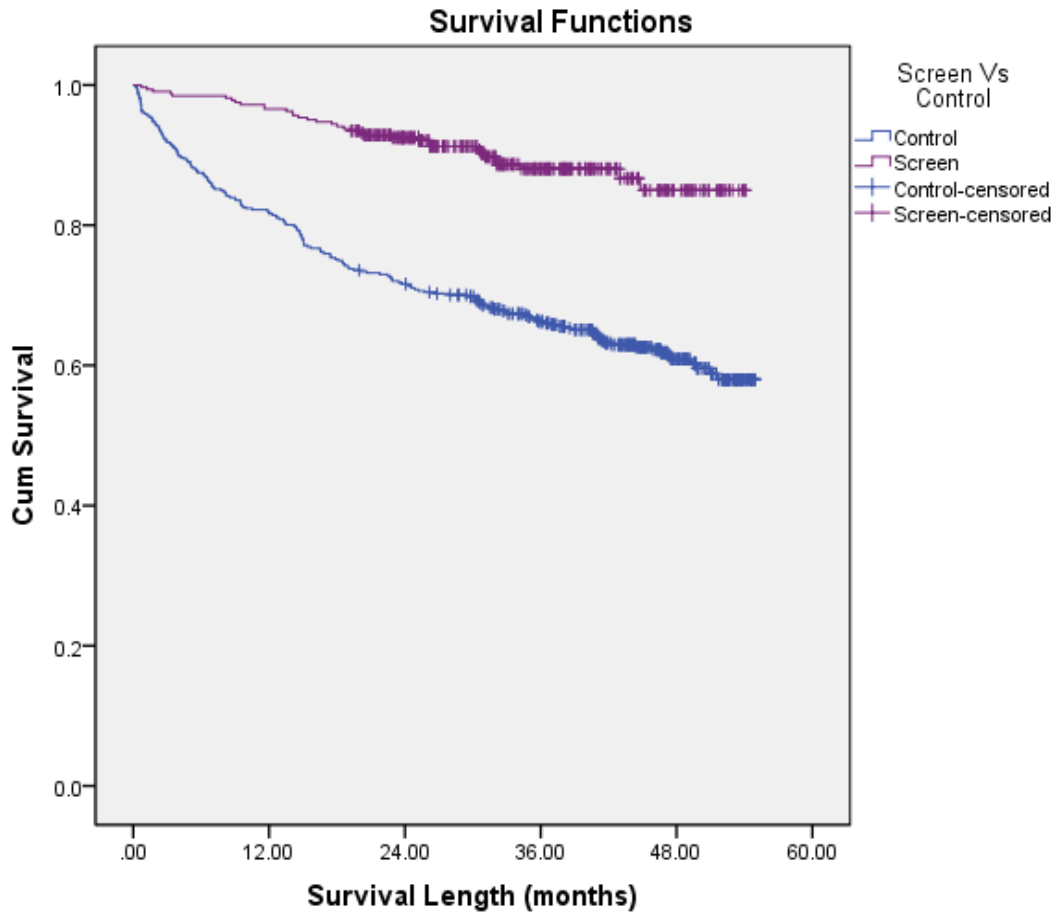


Figure 13.5 Kaplan-Meier survival curves for control and screen-detected cancers.

13.3 Chapter Conclusion

By comparing the outcomes of the intervention group and the control group, this study has shown that the screening programme has resulted in a more favourable stage profile, with significantly more Dukes' A cancers and significantly fewer Dukes' D cancers. The intervention group were found to have a superior survival curve.

When the intervention group was split into its three subgroups, the screen-detected cancer group were found to have a far superior outcome to the control group, with a marked shift in tumour stage. Cancers detected through the screening programme were also found to be managed with a greater proportion of endoscopic treatment alone.

Chapter 14 Cancers Not Detected through the Screening Programme

14.1 Introduction

Colorectal cancers that are diagnosed concurrently, but outside, the screening programme can be split into two groups. These are non-uptake cancers and interval cancers.

Non-uptake cancers occur in the population that do not complete part, or all, of the screening process. Within the bowel cancer screening programme, this can occur at several stages: the non-uptake of all, or part, of the faecal occult blood test; the non-attendance at a screening nurse practitioner appointment (either after an abnormal FOBt result, or abnormal investigation), or non-uptake of a screening investigation (likely a colonoscopy, which could be after an abnormal FOBt, or as part of surveillance). These cancers are highlighted in green in the below figure.

Interval colorectal cancers are defined as a cancer that is diagnosed between screening episodes, after a negative screening investigation. Again, these can be subdivided into post FOBt interval cancers (occurring after a normal FOBt), post colonoscopy (or other 2nd line investigation) interval cancers or, a cancer that is diagnosed prior to a planned surveillance colonoscopy. These cancers are highlighted in orange in the below figure.

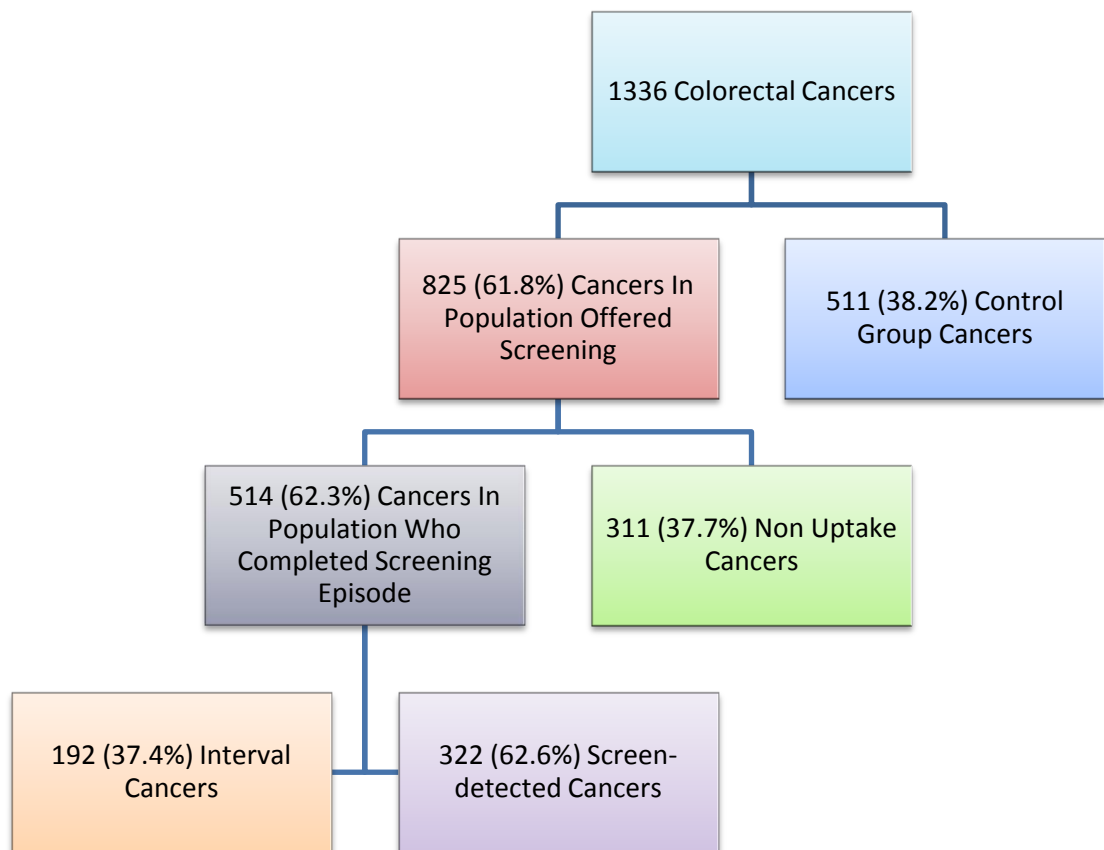


Figure 14.1 Proportion of cancers by classification group.

14.2 Non-Uptake Cancers

The comparison of the non-uptake group and the control group aims to identify whether the process of inviting patients to undergo a screening test, will improve their outcomes, even if they do not take up the test itself. Each FOBt kit that is sent to subjects contains a patient information leaflet that contains information about the screening test and the symptoms of a colorectal cancer.

By inviting a population to take part in a screening programme, it could be expected that awareness of colorectal cancer is increased. Therefore, patients may be more likely to see their GP's if they are currently experiencing bowel related symptoms.

As previously discussed, the aims of this study were not to look into reasons behind non-uptake of the screening program. Although the demographics of the non-uptake cancer group are likely to reflect the demographics of those who do not take up the test and do not have a colorectal cancer, we do not have the evidence to support this.

The types of non-uptake cancers are shown in the figure below. The population that returned an incomplete number of FOBt kits are included in the non-uptake of FOBt group.

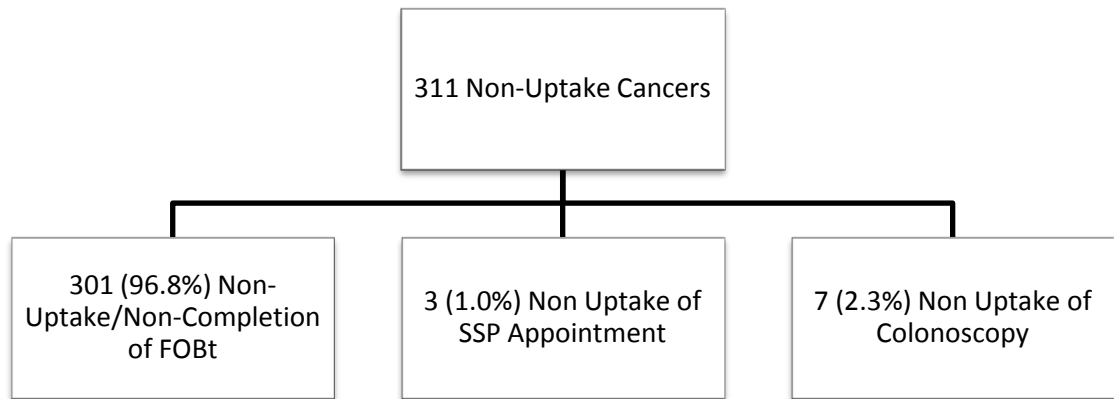


Figure 14.2 Types of Non-Uptake Cancers.

		Control, n=511	Non-Uptake, n=311	Comparison, p Value
Mean Age (Years)		64.97	65.32	NS
Gender	<i>Male</i>	319 (62.4%)	192 (61.7%)	NS
	<i>Female</i>	192 (37.6%)	119 (38.3%)	
ASA Grade	1-2	224 (77.8%)	138 (64.2%)	<0.001
	3-5	64 (22.2%)	77 (35.8%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	60 (11.7%)	60 (19.3%)	0.003
	<i>No</i>	451 (88.3%)	251 (80.7%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	358 (70.1%)	205 (65.9%)	NS
	<i>Splenic Flexure and Proximal</i>	153 (29.9%)	106 (34.1%)	
Dukes Stage	<i>A</i>	89 (17.4%)	43 (13.8%)	NS
	<i>B</i>	132 (25.8%)	87 (28.0%)	
	<i>C</i>	154 (30.1%)	95 (30.5%)	
	<i>D</i>	121 (23.7%)	72 (23.2%)	
	<i>T0</i>	6 (1.2%)	2 (0.6%)	
	<i>Unknown</i>	9 (1.8%)	12 (3.9%)	
Type of Procedure	<i>Resective</i>	405 (79.3%)	240 (77.2%)	NS
	<i>Local Excision</i>	15 (2.9%)	8 (2.6%)	
	<i>Palliative</i>	33 (6.5%)	26 (8.4%)	
	<i>No Procedure</i>	58 (11.4%)	37 (11.9%)	

Table 14.1 Distribution of patient demographics, tumour characteristics and management of patients between control and non-uptake groups. χ^2 test used in nominal variables, students t-test used to compare ages, Kruskal-Wallis test for Dukes stage as an ordinal variable. NS=Not significant.

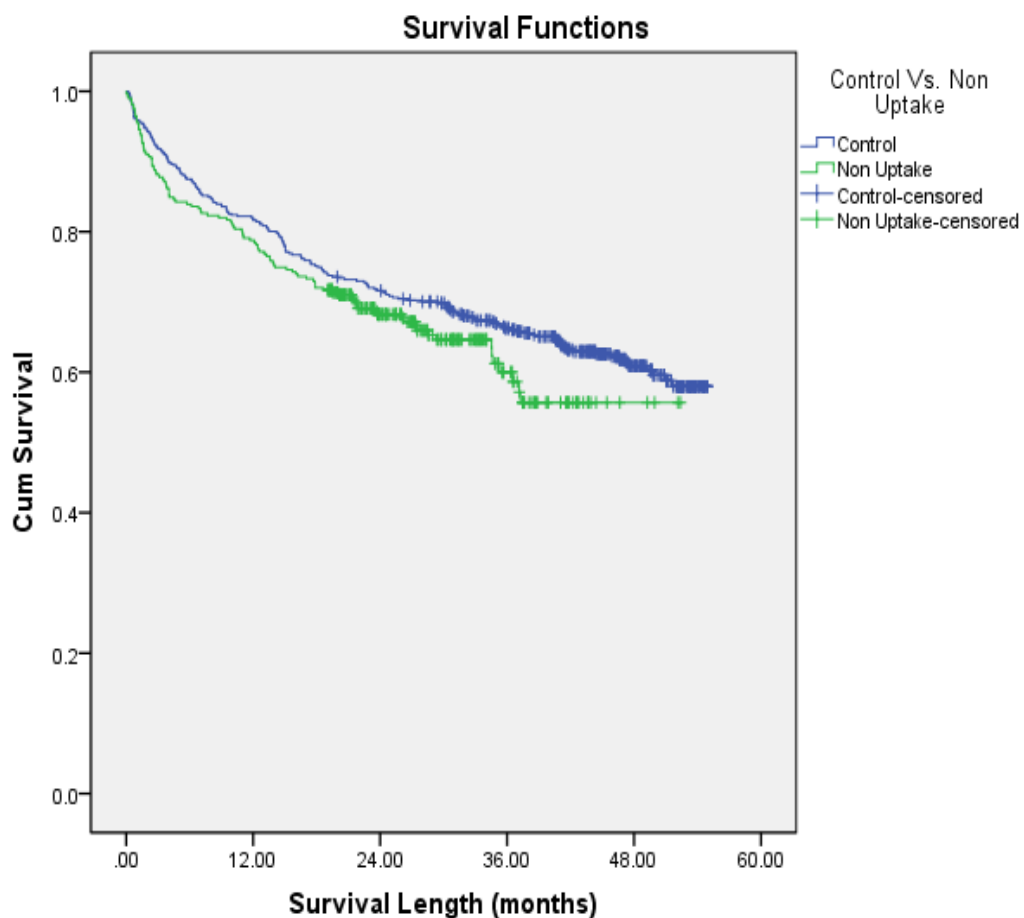


Figure 14.3 Kaplan-Meier survival curve comparing control against non-uptake groups.

Compared to the control group, the non-uptake cancer group had a significantly greater proportion of patients from a more deprived area, and with a greater level of co-morbidities.

However, these factors did not cause an overall change in survival rate, as may have been expected. We have shown in the previous chapter that both a higher ASA grade and a more deprived geographical residence have a negative impact on survival. When the control group was compared against the non-uptake group, there was no significant difference in survival rate found (Log Rank Mantel-Cox $\chi^2=2.16$, $df=1$, $p=0.142$).

14.3 Interval Cancers

Interval colorectal cancers are either due to the cancer being missed by the screening test, i.e. a false negative or, due to the cancer being fast growing in pathology and hence

developing in between screening episodes. If the cancer is of the latter group, we might expect patients to be diagnosed with a greater proportion of more advanced tumours, which may have already disseminated to regional lymph nodes compared to a control population. We might also expect their survival outcomes to be worse. To answer this question, a comparison between the interval cancer and control group should be made. A confounding factor may be the degree of false reassurance that a negative test brings. This is not only for the patient, but also for the patient's health professional. The possible implications of a negative test result brings may be that the patient ignores symptoms caused by their bowel cancer, allowing time for the cancer to disseminate prior to diagnosis. This may also lead to a worse survival outcome for the patient.

		Control, n=511	Interval, n=192	Comparison, p Value
Mean Age (Years)		64.97	65.71	0.002
Gender	<i>Male</i>	319 (62.4%)	116 (60.4%)	NS
	<i>Female</i>	192 (37.6%)	76 (39.6%)	
ASA Grade	<i>1-2</i>	224 (77.8%)	101 (73.7%)	NS
	<i>3-5</i>	64 (22.2%)	36 (26.3%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	60 (11.7%)	17 (8.9%)	NS
	<i>No</i>	451 (88.3%)	175 (91.1%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	358 (70.1%)	128 (66.7%)	NS
	<i>Splenic Flexure and Proximal</i>	153 (29.9%)	64 (33.3%)	
Dukes Stage	<i>A</i>	89 (17.4%)	36 (18.8%)	NS
	<i>B</i>	132 (25.8%)	51 (26.6%)	
	<i>C</i>	154 (30.1%)	56 (29.2%)	
	<i>D</i>	121 (23.7%)	44 (22.9%)	
	<i>T0</i>	6 (1.2%)	1 (0.5%)	
	<i>Unknown</i>	9 (1.8%)	4 (2.1%)	
Type of Procedure	<i>Resective</i>	405 (79.3%)	152 (79.2%)	NS
	<i>Local Excision</i>	15 (2.9%)	4 (2.1%)	
	<i>Palliative</i>	33 (6.5%)	10 (5.2%)	
	<i>No Procedure</i>	58 (11.4%)	26 (13.5%)	

Table 14.2 Distribution of patient demographics, tumour characteristics and management of patients between control and interval cancer groups. χ^2 test used in nominal variables, students t-test used to compare ages, Kruskal-Wallis test for Dukes stage as an ordinal variable. NS=Not significant.

When the interval cancer group is compared against the control group, no significant differences are found in gender, ASA grade, deprivation level, tumour location, Dukes stage, management or survival rate. Survival rates between control and interval cancer groups were found to be equivalent (Log Rank Mantel-Cox $\chi^2=0.48$, $df=1$, $p=0.489$).

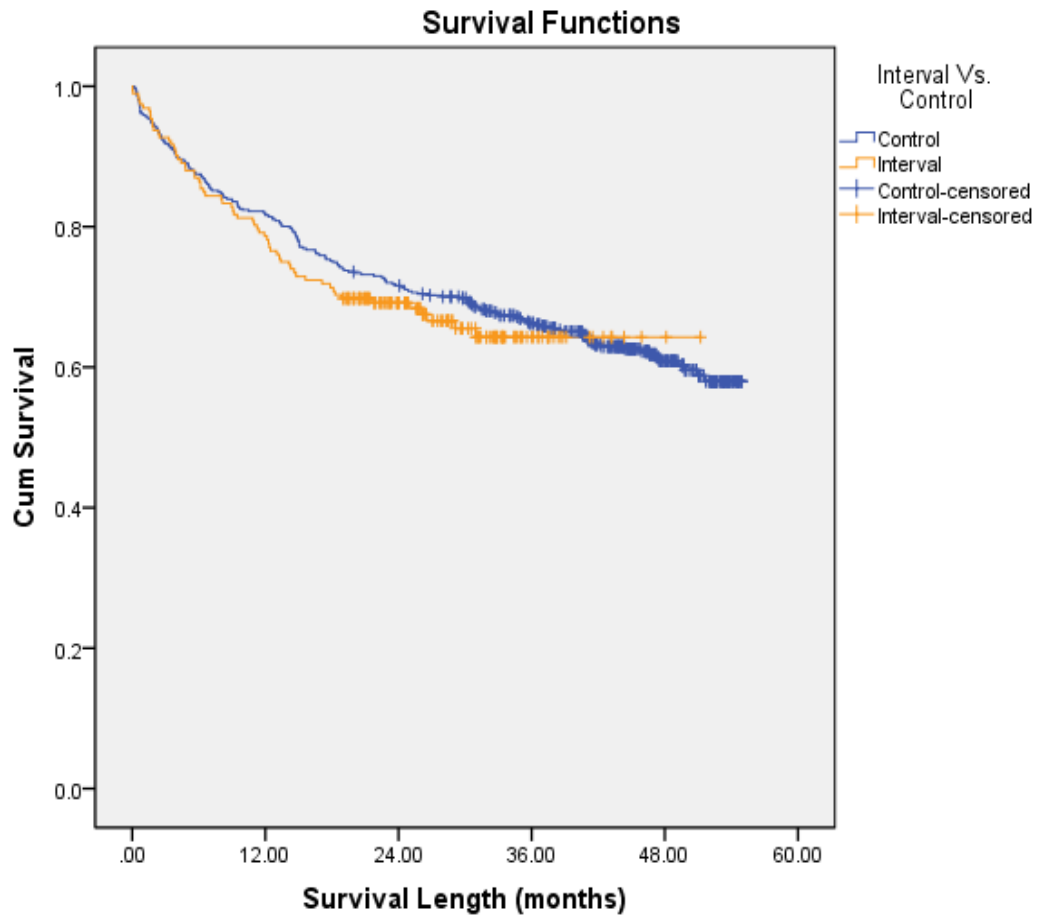


Figure 14.4 Kaplan-Meier survival curves for control and interval cancers.

14.3.1 Interval Cancers with an Unclear First Test Result

There are several combinations of an individual FOBt result that leads to an overall positive or negative result. These are dependent on the number of positive windows for each test, out of a maximum of six. A normal test has no positive windows, an unclear test has between one and four positive, with an abnormal test having five or six positive windows. The results for screen-detected cancers and interval cancers are shown in the table below.

FOB Result	Interval Cancer, n=192	Screen-detected Cancer, n=322
Normal	177 (92.2%)	
Unclear, Normal, Normal	15 (7.8%)	
Abnormal		83 (25.8%)
Unclear, Unclear		158 (49.1%)
Unclear, Abnormal		40 (12.4%)
Unclear, Normal, Unclear		38 (11.8%)
Unclear, Normal, Abnormal		3 (0.9%)

Table 14.3 FOB results for interval and screen-detected cancers

As shown above, 37.4% of cases who completed a screening episode were missed by the faecal occult blood test. Of the 192 interval cancers, 15 (7.8%) had a FOBT that had between one and four windows positive in the first round of tests. These patients then repeated two further tests, both of which had zero of the six windows positive, giving them an overall normal result.

The above table shows the number and percentage of cancers by the total number of each test result for interval and screen-detected cancers. A group of patients within the control group (n=19) and non-uptake group (n=17) sent a minimum of one test kit back, but did not complete the screening process, hence not being allocated to the screen-detected or interval cancer group.

When interval cancers were compared against the population who were offered but did not take up screening (non-uptake group), there was no difference found between Dukes stage ($\chi^2=0.646$, $df=3$, $p=0.422$) or survival ($\chi^2=0.156$, $df=1$, $p=0.692$). It can be concluded that completing a negative screening in itself offers no additional benefit in terms of stage shift or survival. Kaplan-Meier curves for interval cancers, non-uptake cancers and the control group are shown in Figure 14.5.

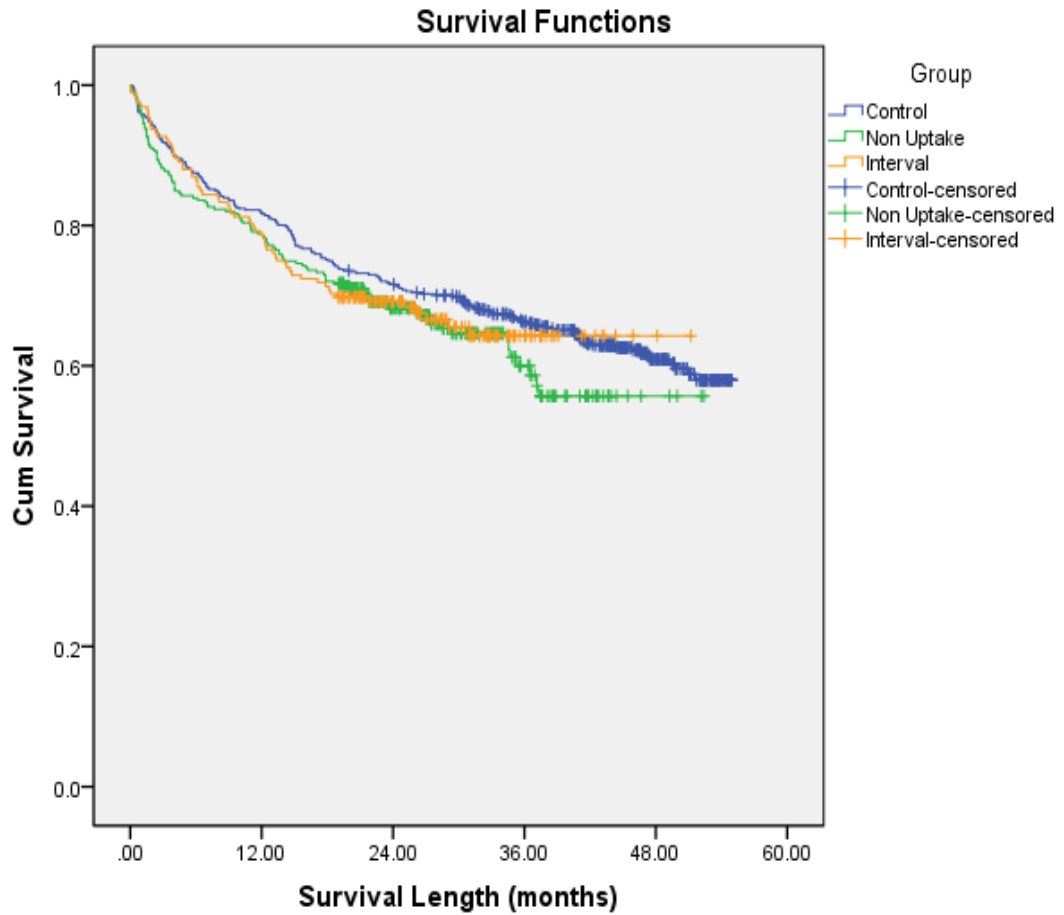


Figure 14.5 Kaplan-Meier survival curve comparing control against non-uptake and interval cancer groups.

14.4 Incident Screening Round Cancers

5.6% (46 of 825) of colorectal cancer patients were diagnosed in the incident round of screening (diagnosed during the second round of tests), having been offered a FOBt in the prevalent round (the first round of tests). 32 of the 46 returned a negative FOBt result, with 30 returning one normal test kit (0/6 positive windows). The stage profile of each result is shown in Table 14.4 below.

		Screen-detected Cancer		Interval Cancer
		Earlier Normal Test Result, n=24	Earlier Unclear, Normal, Normal Test Result, n=2	Earlier Normal Test Result, n=6
Dukes Stage	<i>A</i>	10 (41.7%)	1 (50.0%)	1 (16.7%)
	<i>B</i>	4 (16.7%)	1 (50.0%)	1 (16.7%)
	<i>C</i>	7 (29.2%)	0 (0.0%)	3 (50.0%)
	<i>D</i>	3 (12.5%)	0 (0.0%)	1 (16.7%)
Tumour Site	<i>Distal to Splenic Flexure</i>	16 (66.7%)	2 (100.0%)	4 (66.7%)
	<i>Splenic Flexure and Proximal</i>	8 (33.3%)	0 (0.0%)	2 (33.3%)

Table 14.4 Stage and site of tumours by earlier test result

Given the length of development of a colorectal cancer, and the range of stages of the cancers when they were eventually diagnosed, these cases could be classed as interval cancers. There were no cases where a subject had a normal test and then declined further screening, to be diagnosed with their cancer through symptomatic services. This would have implied a sense of false reassurance that may come with a normal result. However, given the small numbers of patients who were diagnosed in their second round of screening, it is possible that this group of patient may increase in number in future rounds.

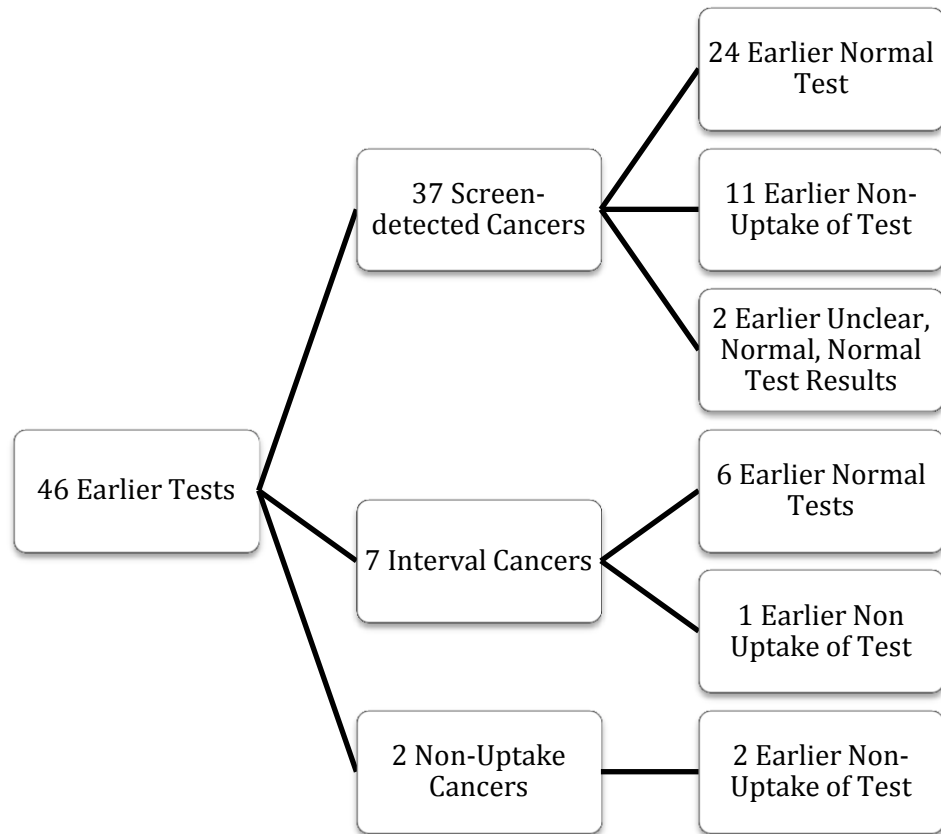


Figure 14.6 Horizontal organisation chart of the results of earlier FOB tests by group.

There were no statistically significant differences found in the stage or location of tumour between the two types of earlier FOBt results in the patients diagnosed with a cancer through screening.

14.5 Chapter Conclusion

Within this chapter, the rates and outcomes of cancers not detected through the screening programme have been presented. The vast majority of non-uptake cancers were after non completion of the FOBt. This cancer group were associated with a greater proportion of patients from deprived areas, with a higher level of co-morbidities. Their stage profile and survival rate found to be equivalent to that of the control group.

In the population who took up screening and were diagnosed with a cancer, 37.4% were after a negative FOBt result. Of these 7.8% were after an unclear result in their first kit, followed by two normal results. The interval cancer group had an equivalent stage profile and survival rate as the non-uptake group, as well as the control group.

There were also a proportion of patients that had a cancer detected in the second round of screening, who had a normal result in the first round, two years earlier. They were found to have a range of tumour stages.

Chapter 15 The Effectiveness of the Faecal Occult Blood Test

15.1 The Effectiveness of the Faecal Occult Blood Test

All patients within the screen-detected and interval cancer groups returned a FOBt, with screen-detected cancers having a positive result and interval cancers a negative result. No interval cancers were diagnosed after a false negative colonoscopy. This means that 37.4% of the population who completed a screening episode, had a cancer that was missed due to the low sensitivity of the FOBt. This figure does not include cancers that were picked up at the next screening round, after a negative screening episode.

A comparison between screen-detected and interval cancer groups can be viewed as a surrogate analysis of the FOB test in detecting a colorectal cancer. The aim of the comparison is to identify patient and tumour demographics that might lead to a positive or negative FOBt result, in the detection of a colorectal cancer.

The patient demographics, tumour stage and location, and management of these two groups are shown below in Table 15.1.

		Screen, n=322	Interval, n=192	Comparison, p Value
Mean Age (Years)		64.96	65.71	0.005
Gender	<i>Male</i>	235 (73.0%)	116 (60.4%)	0.003
	<i>Female</i>	87 (27.0%)	76 (39.6%)	
ASA Grade	1-2	197 (79.8%)	101 (73.7%)	NS
	3-5	50 (20.2%)	36 (26.3%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	36 (11.2%)	17 (8.9%)	NS
	<i>No</i>	286 (88.8%)	175 (91.1%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	253 (78.6%)	128 (66.7%)	0.003
	<i>Splenic Flexure and Proximal</i>	69 (21.4%)	64 (33.3%)	
Dukes Stage	<i>A</i>	125 (38.8%)	36 (18.8%)	<0.001
	<i>B</i>	81 (25.2%)	51 (26.6%)	
	<i>C</i>	89 (27.6%)	56 (29.2%)	
	<i>D</i>	21(6.5%)	44 (22.9%)	
	<i>T0</i>	5 (1.6%)	1 (0.5%)	
	<i>Unknown</i>	1 (0.3%)	4 (2.1%)	
Type of Procedure	<i>Resective</i>	274 (85.1%)	152 (79.2%)	<0.001
	<i>Local Excision</i>	38 (11.8%)	4 (2.1%)	
	<i>Palliative</i>	3 (0.9%)	10 (5.2%)	
	<i>No Procedure</i>	7 (2.2%)	26 (13.5%)	

Table 15.1 Distribution of patient demographics, tumour characteristics and management of patients between screen-detected and interval cancer groups. χ^2 test used in nominal variables, students t-test used to compare ages, Kruskal-Wallis test for Dukes stage as an ordinal variable. NS=Not significant.

Gender	Tumour Location	Group		Comparison, p value
		Screen	Interval	
Male	<i>Distal To Splenic Flexure</i>	191 (81.3%)	79 (68.1%)	0.006
	<i>Splenic Flexure and Proximal</i>	44 (18.7%)	37 (31.9%)	
Female	<i>Distal To Splenic Flexure</i>	62 (71.3%)	49 (64.5%)	NS
	<i>Splenic Flexure and Proximal</i>	25 (28.7%)	27 (35.5%)	

Table 15.2 Proportions of screen and interval cancers by tumour site for men and women.

Tumour Location	Gender	Group		Comparison, p value
		Screen	Interval	
Distal To Splenic Flexure	<i>Male</i>	191 (75.5%)	79 (61.7%)	0.005
	<i>Female</i>	62 (24.5%)	49 (38.3%)	
Splenic Flexure and Proximal	<i>Male</i>	44 (63.8%)	37 (57.8%)	NS
	<i>Female</i>	25 (36.2%)	27 (42.2%)	

Table 15.3 Proportions of screen and interval cancers by gender for left and right-sided tumours.

The above tables show that, for male patients, there is a significantly greater proportion of cancers detected through screening that are distal to the splenic flexure (81.3% vs. 68.1%). This effect is not significant for female patients, although still present (71.3% vs. 64.5%). Similarly, for cancers that are distal to the splenic flexure, there are a significantly greater proportion of men that are diagnosed through screening (75.5% vs. 61.7%). This effect is not significant for right sided cancers, although the male proportion is still greater (63.8% vs. 57.8%). As the numbers become relatively small in each of the subgroups, this is a

possible reason why some results are not found to be significant on statistical analysis. A larger sample size may (or may not) confirm these findings.

Screen-detected cancers have a significantly improved survival, compared against the interval cancer group (Log Rank Mantel-Cox $\chi^2=50.36$, $df=1$, $p<0.001$).

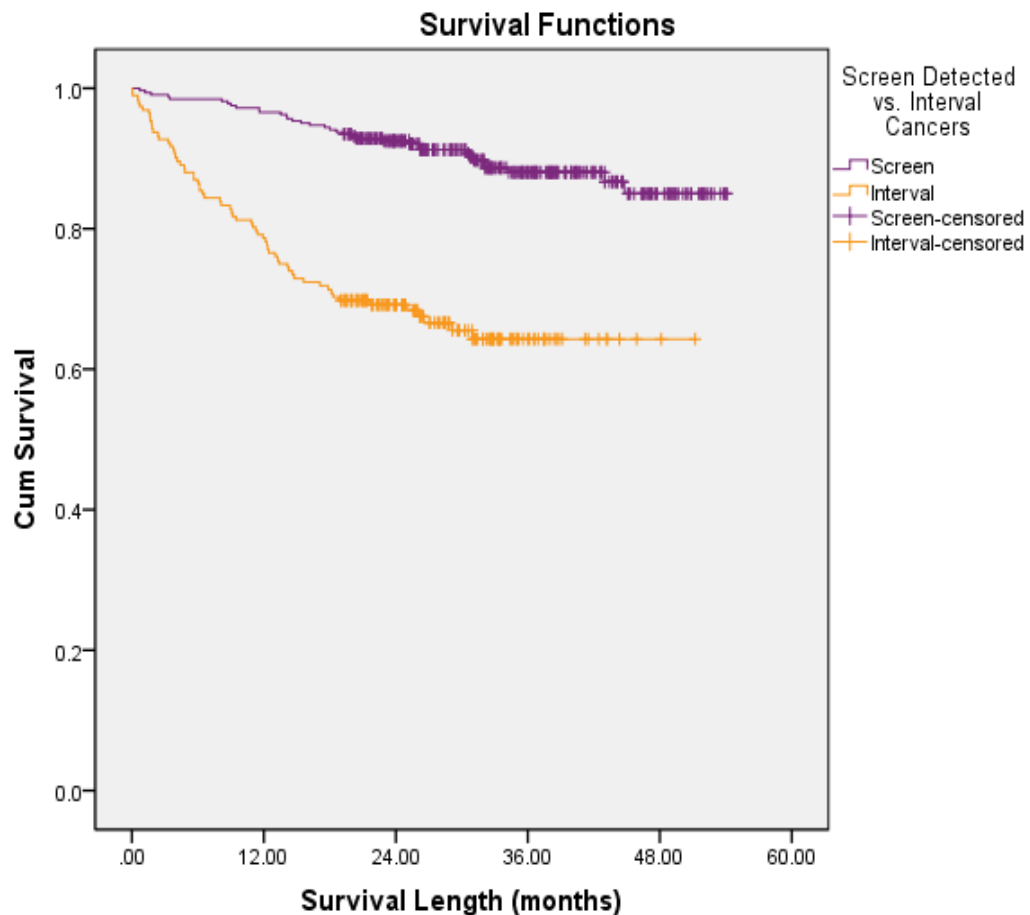


Figure 15.1 Kaplan-Meier survival curves for screen and interval cancer groups.

15.2 Outcomes for Screen-Detected and Interval Cancer Groups by Dukes Stage

With significant differences in outcomes between screen-detected and interval cancer groups, it is important to determine the reasons behind this. If these differences are solely due to a more favourable tumour stage profile, then it should be expected that the outcomes for each stage of tumour should be the same between groups.

15.2.1 Outcomes for Dukes' A Cancers

Initially, a comparison of patient and tumour demographics must be made to ensure that there are no pre-existing variables that will have an influence on patient outcome. As shown in Chapter 12, a high ASA grade and more deprived residential area have a negative impact on survival. These variables for Dukes' A cancers are shown in the table below.

		Screen, n=125	Interval, n=36	Comparison, p Value
Mean Age (Years)		64.75	65.80	NS
Gender	<i>Male</i>	87 (69.6%)	20 (55.6%)	NS
	<i>Female</i>	38 (30.4%)	16 (44.4%)	
ASA Grade	<i>1-2</i>	70 (77.8%)	19 (73.1%)	NS
	<i>3-5</i>	20 (22.2%)	7 (26.9%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	11 (8.8%)	2 (5.6%)	NS
	<i>No</i>	114 (91.2%)	34 (94.4%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	108 (86.4%)	30 (83.3%)	NS
	<i>Splenic Flexure and Proximal</i>	17 (13.6%)	6 (16.7%)	
T Stage	<i>pT1</i>	86 (68.8%)	22 (61.1%)	NS
	<i>pT2</i>	39 (31.2%)	14 (38.9%)	
Type of Procedure	<i>Resective</i>	87 (69.6%)	32 (88.9%)	0.02
	<i>Local Excision</i>	38 (30.4%)	4 (11.1%)	
	<i>Palliative</i>	0 (0.0%)	0 (0.0%)	
	<i>No Procedure</i>	0 (0.0%)	0 (0.0%)	
30 Day Mortality	<i>Yes</i>	0 (0.0%)	0 (0.0%)	NS
	<i>No</i>	125 (100.0%)	36 (100.0%)	

Table 15.4 Demographics, tumour stage and location, and management for screen and interval Dukes' A cancers.

As shown in the above table, there were no significant differences found in tumour site, location, T stage, patient co-morbidity level, or deprivation level between interval and screen-detected Dukes' A cancers. The only difference found was that significantly more screen-detected Dukes' A cancers were managed with local excision. This is despite having comparable proportions of pT1 tumours (which could be used as a surrogate for polyp cancers). This outcome does not appear to be related to patients undergoing a major resection itself, as the 30 day mortality rate is the same for both groups.

In the Kaplan-Meier curve below, patients who are diagnosed with a Dukes A cancer through screening have a superior survival rate compared to interval Dukes' A cancers (Log Rank Mantel-Cox $\chi^2=6.168$, $df=1$, $p=0.013$).

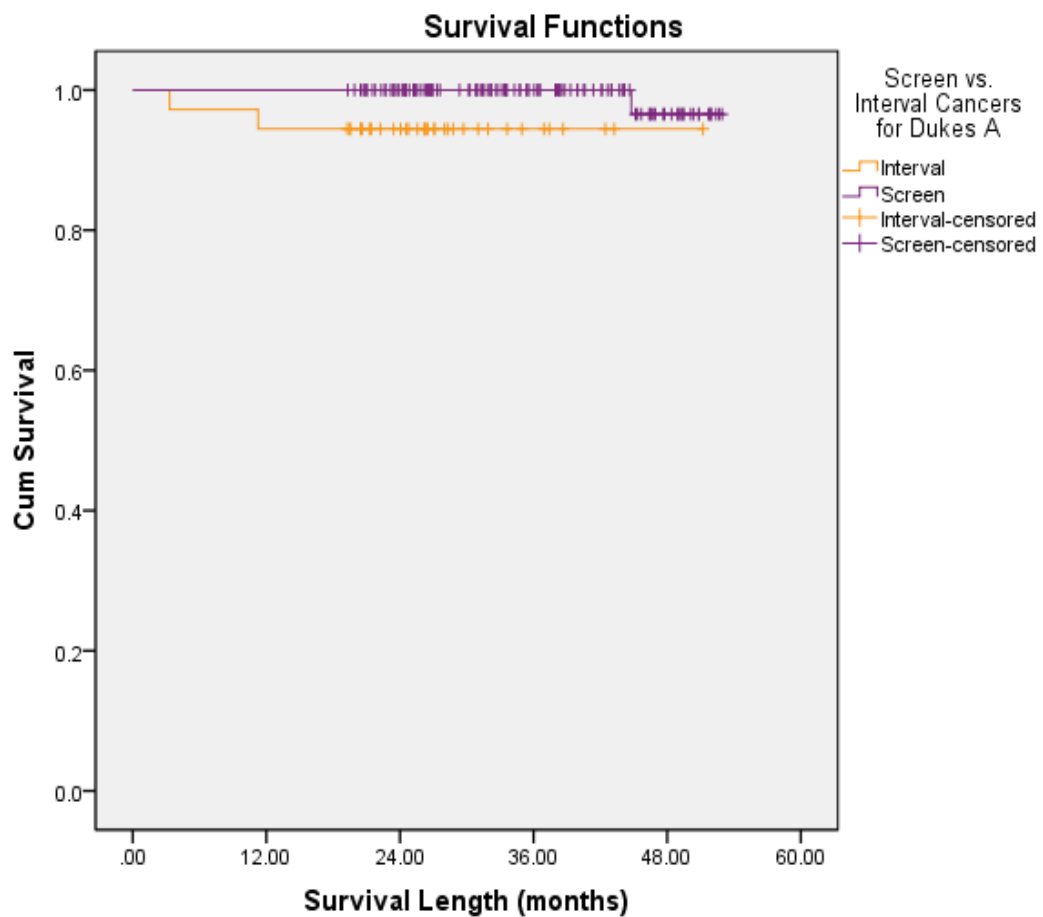


Figure 15.2 Survival Curve for Screen and Interval Cancers of Dukes' A stage.

15.2.2 Outcomes for Dukes' B Cancers

When the demographics and tumour details of the above groups for Dukes' B cancers are reviewed, the only significant differences are found in mean age at diagnosis (screen-detected = 64.9 years, interval = 66.0 years, $t=2.29$, $p=0.023$) and T stage (screen-detected

= 86.3% T3, interval = 70.6% T3, $\chi^2=4.959$, $df=1$, $p=0.026$). This difference in age is unlikely to be clinically significant. The greater proportion of T3 tumours (tumours invading through all bowel wall layers but not into adjacent structures) in the screen-detected group does not appear to have translated into a better survival, as may have been expected. Gender, ASA grade, deprivation level, tumour site, management (all resections), and 30 day mortality rate (nil for both groups) were not significantly different between screen and interval cancer groups.

If we perform the same analysis as above for Dukes' B cancers, then the survival rates between the two groups is equivalent (Log Rank Mantel-Cox $\chi^2=0.117$, $df=1$, $p=0.732$).

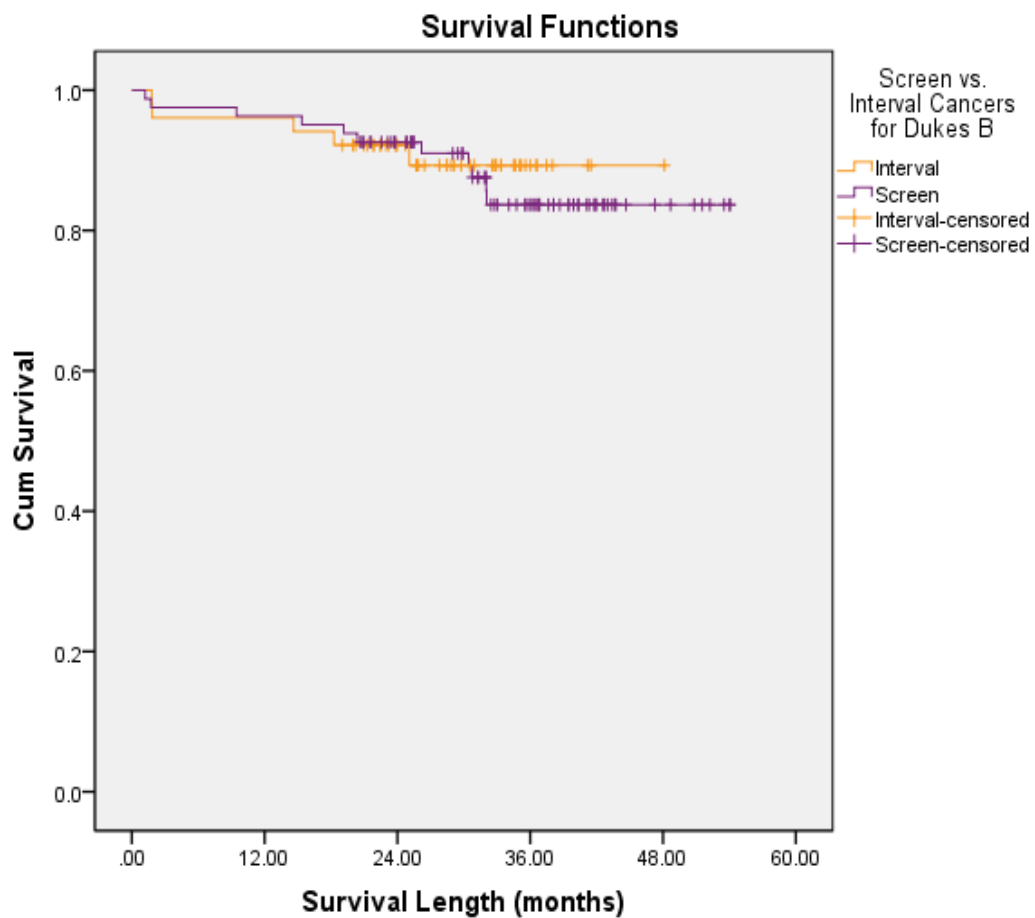


Figure 15.3 Kaplan-Meier curve for interval and screen-detected Dukes' B cancers.

15.2.3 Outcomes for Dukes' C Cancers

Dukes' C cancers are cancers of any T stage that have metastasised to regional lymph nodes. The patient demographics and tumour details for these cancers are shown in the table below.

		Screen, n=89	Interval, n=56	Comparison, p Value
Mean Age (Years)		65.49	65.77	NS
Gender	<i>Male</i>	66 (74.2%)	31 (55.4%)	0.019
	<i>Female</i>	23 (25.8%)	25 (44.6%)	
ASA Grade	<i>1-2</i>	65 (85.5%)	35 (77.8%)	NS
	<i>3-5</i>	11 (14.5%)	10 (22.2%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	8 (9.0%)	6 (10.7%)	NS
	<i>No</i>	81 (91.0%)	50 (89.3%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	69 (77.5%)	34 (60.7%)	0.03
	<i>Splenic Flexure and Proximal</i>	20 (22.5%)	22 (39.3%)	
T Stage	<i>pT0</i>	0 (0.0%)	0 (0.0%)	NS
	<i>pT1</i>	6 (6.7%)	3 (5.4%)	
	<i>pT2</i>	11 (12.4%)	4 (7.1%)	
	<i>pT3</i>	51 (57.3%)	28 (50.0%)	
	<i>pT4</i>	20 (22.5%)	21 (37.5%)	
	<i>pTx</i>	1 (1.1%)	0 (0.0%)	
Type of Procedure	<i>Resective</i>	89 100.0%)	56 100.0%)	NS
	<i>Local Excision</i>	0 (0.0%)	0 (0.0%)	
	<i>Palliative</i>	0 (0.0%)	0 (0.0%)	
	<i>No Procedure</i>	0 (0.0%)	0 (0.0%)	
30 Day Mortality	<i>Yes</i>	1 (1.1%)	1 (1.8%)	NS
	<i>No</i>	88 (98.9%)	55 (98.2%)	

Table 15.5 Demographics, tumour details and outcome for interval and screen-detected Dukes' C cancers.

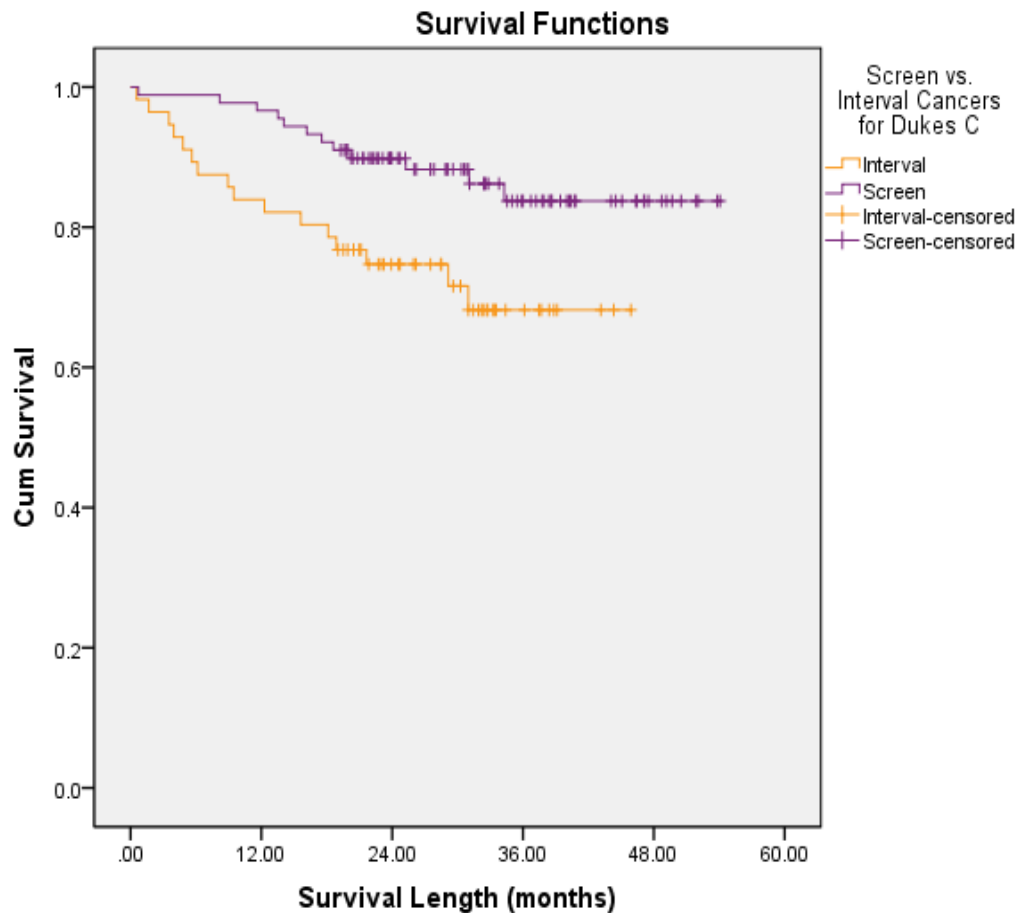


Figure 15.4 Kaplan-Meier curve for interval and screen-detected Dukes' C cancers.

As shown in the survival curve above, Dukes' C screen-detected cancers do significantly better than those of interval cancers (Log Rank Mantel-Cox $\chi^2= 6.051$, $df=1$, $p=0.014$). Within the screen-detected cancer group, there were significantly more men with left sided tumours. A greater proportion of pT4 tumours was seen in the interval cancer group (37.5% vs. 22.5%), although this and the overall T stage profile was not significantly different between groups. There was no difference found in the ASA grade, deprivation level, modality of surgery, or 30-day mortality between groups.

To determine the reasons behind this marked difference between these groups for Dukes' C cancers, the lymph node status for each case was reviewed. A Dukes' C cancer can be split into Dukes' C1 (positive lymph nodes but negative apical node), and Dukes' C2 (positive apical lymph node). Dukes' C2 cancers are associated with a worse prognosis compared with Dukes' C1. The proportions of each of these are shown in Table 15.6. No significant differences were found between the proportions of these groups ($\chi^2=0.2$, $df=1$, $p=0.66$).

Dukes Stage	Screen, n=89	Interval, n=56
C1	80 (89.9%)	49 (87.5%)
C2	9 (10.1%)	7 (12.5%)

Table 15.6 Proportions of Dukes C1 and C2 for screen and interval cancers.

Dukes Stage	Mean Lymph Nodes	Screen	Interval	t-test, p value
		n=80	n=49	
C1	<i>Positive Lymph Nodes</i>	2.90	3.61	NS
	<i>Total Lymph Nodes</i>	15.26	16.53	NS
		n=9	n=7	
C2	<i>Positive Lymph Nodes</i>	3.89	14.57	0.017
	<i>Total Lymph Nodes</i>	13.00	20.29	NS
		n=89	n=56	
C Combined	<i>Positive Lymph Nodes</i>	3.00	4.98	0.013
	<i>Total Lymph Nodes</i>	15.03	17.00	NS

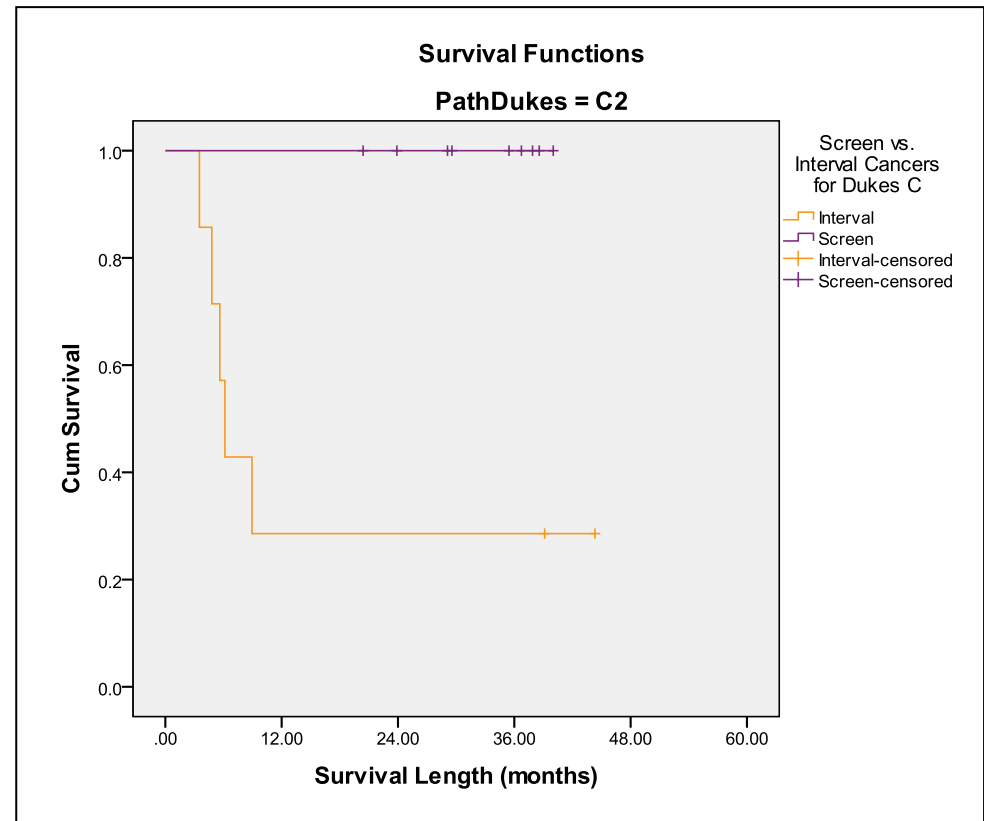
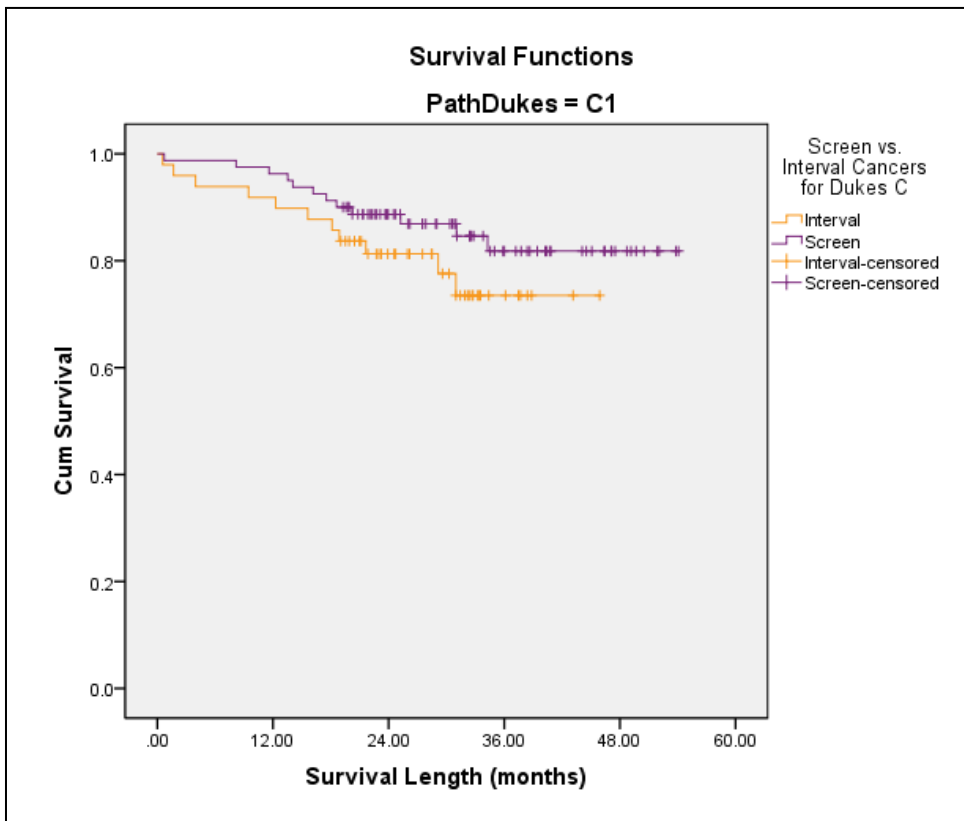
Table 15.7 Mean number of positive lymph nodes and total nodes harvested for each Dukes C stage.

Dukes Stage	Total Number of Lymph Nodes Harvested	Screen, n=89	Interval, n=56	χ^2 Comparison, p value
C1	<12	26 (32.5%)	12 (24.5%)	NS
	>12	54 (67.5%)	37 (42.9%)	
C2	<12	3 (33.3%)	3 (42.9%)	NS
	>12	6 (66.7%)	4 (57.1%)	
C Combined	<12	29 (32.6%)	15 (26.8%)	NS
	>12	60 (67.4%)	41 (73.2%)	

Table 15.8 Number and percentage of each Dukes C cancer with less than or greater than 12 lymph nodes harvested for screen and interval cancers.

A value of 12 lymph nodes harvested is widely accepted as an adequate amount of nodes to enable accurate staging of a patient's cancer [154]. Achieving this is related to both surgical and pathological skill. The implication of not harvesting 12 nodes or more is that a cancer may be under-staged, or positive lymph nodes may remain in situ post procedure. Table 15.8 above shows the proportion of cancers in which such an adequate clearance was achieved. As shown, Dukes' stage C1, C2 and combined Dukes' C cases had equivalent proportions where there were 12 or more lymph nodes harvested.

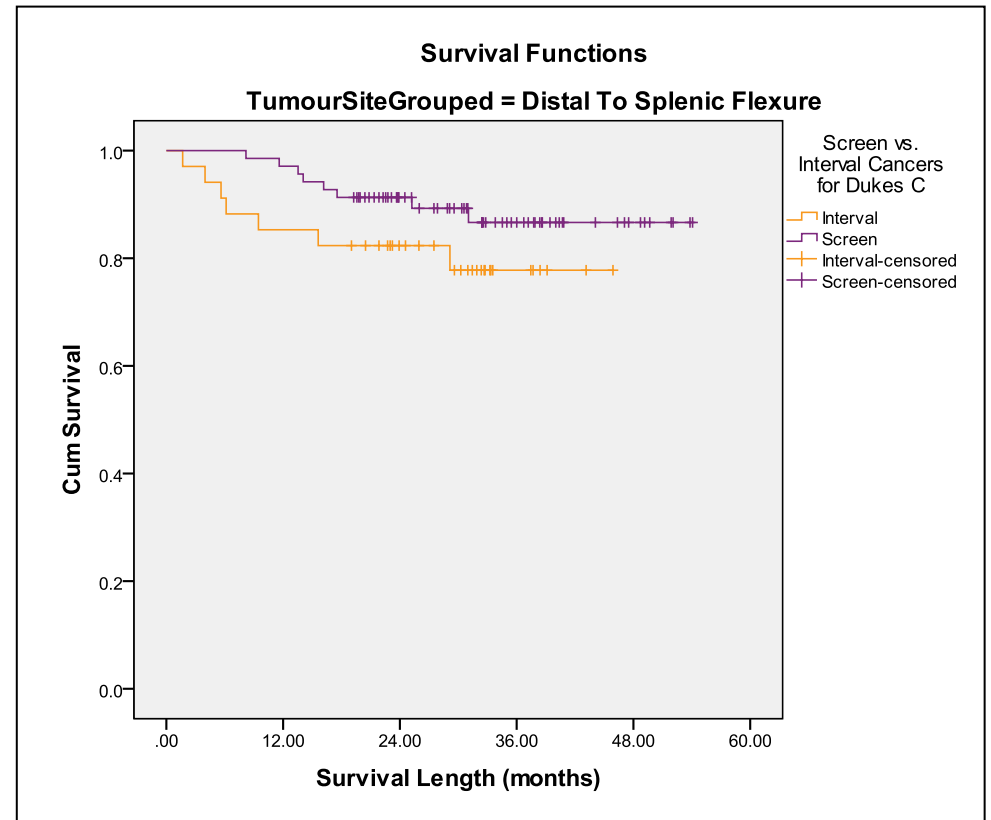
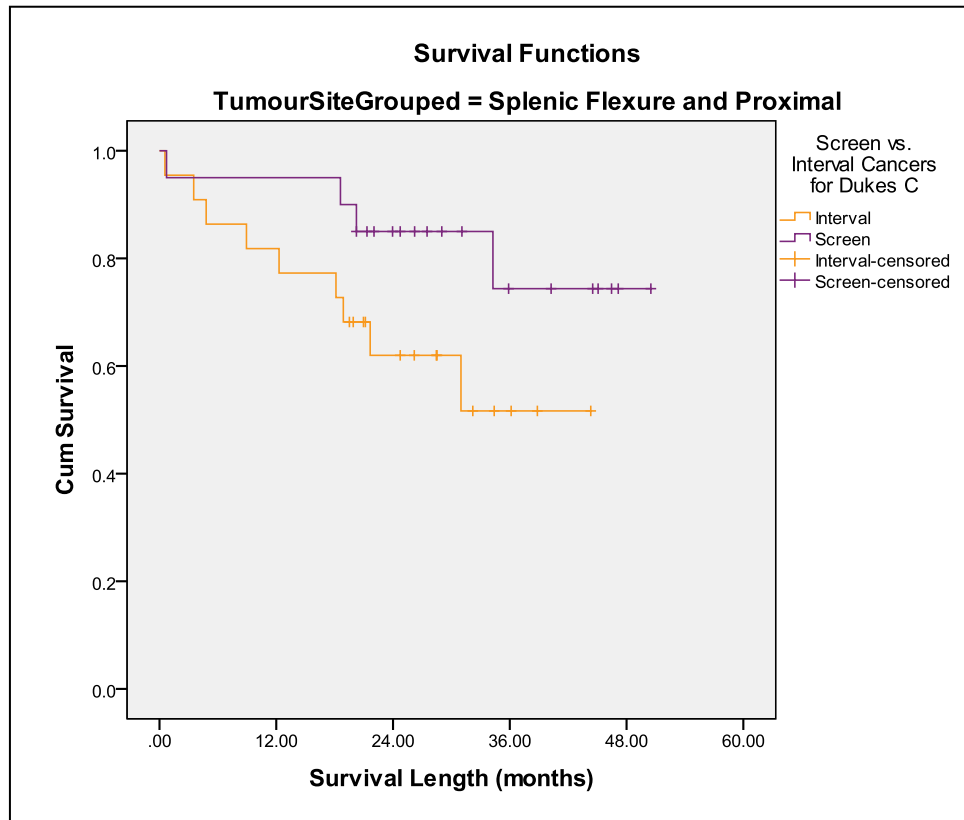
When the survival curves are broken down into Dukes' C1 and C2, tumour site, and gender, only screen-detected cancers of Dukes' C2 stage have a significantly superior survival curve compared with the equivalent interval cancer group. The Kaplan-Meier curves for each subgroup are shown below.



Figures 15.5 a & b Kaplan-Meier survival curves for Dukes' C1 and C2 cancers comparing interval vs. screen-detected groups

Screen vs. Interval Cancers	Chi-Square	df	Significance, p value
Dukes C1	1.525	1	0.217
Dukes C2	9.449	1	0.002

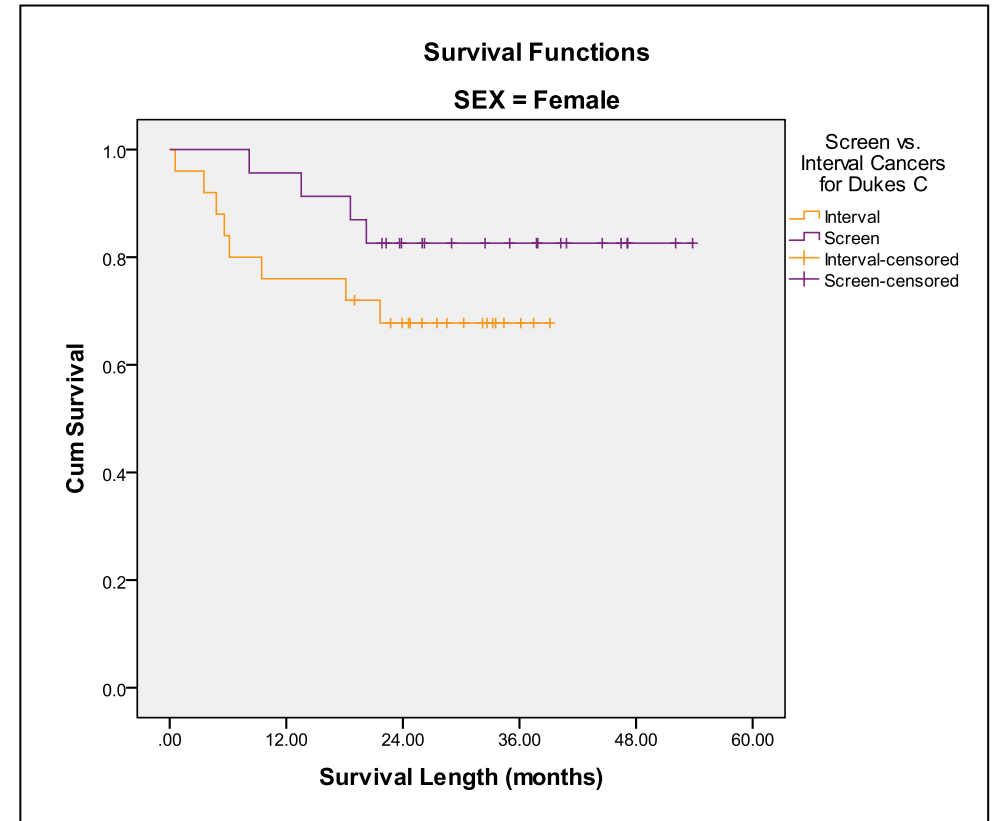
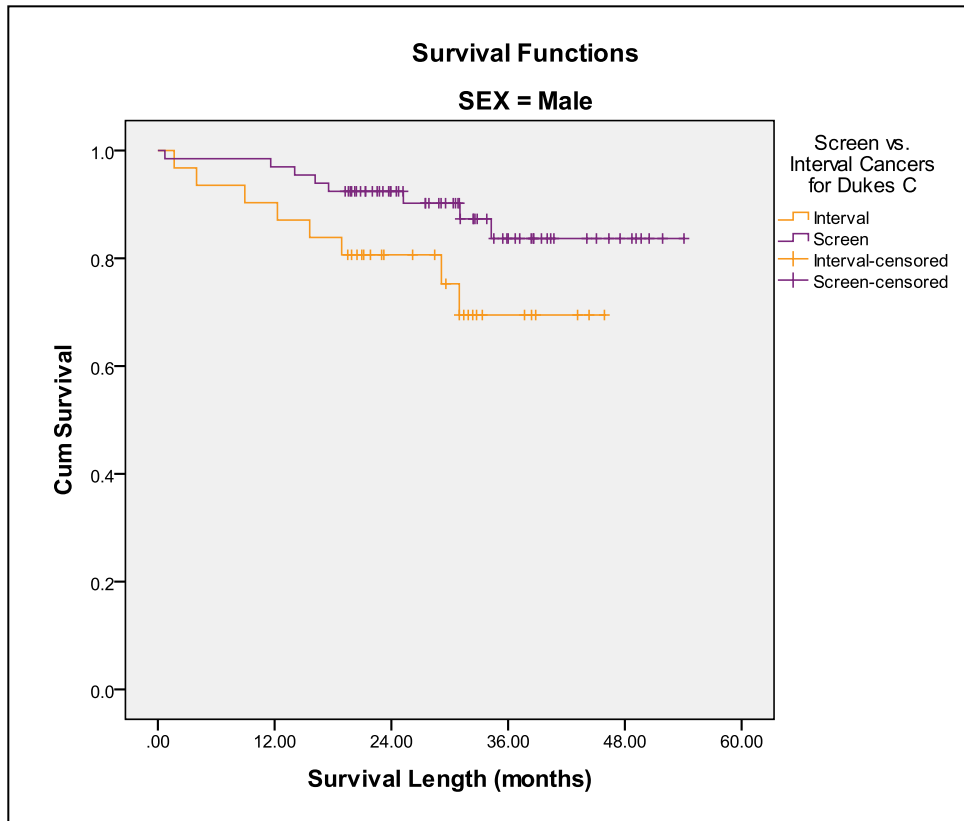
Table 15.9 Log Rank (Mantel-Cox) test for survival curve equality for Dukes' C1 and C2 cancers.



Figures 15.6 a & b. Kaplan-Meier survival curves for left and right sided cancers comparing interval vs. screen-detected groups.

Screen vs. Interval Cancers	Chi-Square	df	Significance, p value
Splenic Flexure and Proximal	2.750	1	0.097
Distal To Splenic Flexure	1.764	1	0.184

Table 15.10 Log Rank (Mantel-Cox) test for survival curve equality for left and right sided cancers.



Figures 15.7 a & b. Kaplan-Meier survival curves for male and female gender comparing interval vs. screen-detected groups.

Screen vs. Interval Cancers	Chi-Square	df	Significance, p value
Male	3.321	1	0.068
Female	1.662	1	0.197

Table 15.11 Log Rank (Mantel-Cox) test for survival curve equality for male and female gender.

15.2.4 Outcomes for Dukes' D Cancers

The table below shows the demographics and tumour details of patients with a Dukes D cancer in both the screen-detected and interval cancer groups.

		Screen, n=21	Interval, n=44	Comparison, p Value
Mean Age (Years)		64.05	65.24	NS
Gender	<i>Male</i>	15 (71.4%)	29 (65.9%)	NS
	<i>Female</i>	6 (28.6%)	15 (34.1%)	
ASA Grade	<i>1-2</i>	9 (75.0%)	9 (52.9%)	NS
	<i>3-5</i>	3 (25.0%)	8 (47.1%)	
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	1 (4.8%)	6 (13.6%)	NS
	<i>No</i>	20 (95.2%)	38 (86.4%)	
Tumour Location	<i>Distal To Splenic Flexure</i>	16 (76.2%)	30 (68.2%)	NS
	<i>Splenic Flexure and Proximal</i>	5 (23.8%)	14 (31.8%)	
T Stage	<i>pT1</i>	0 (0.0%)	0 (0.0%)	NS
	<i>pT2</i>	1 (8.3%)	0 (0.0%)	
	<i>pT3</i>	5 (41.7%)	4 (40.0%)	
	<i>pT4</i>	6 (50.0%)	6 (60.0%)	
Type of Procedure	<i>Resective</i>	12 (57.1%)	10 (22.7%)	0.02
	<i>Local Excision</i>	0 (0.0%)	0 (0.0%)	
	<i>Palliative</i>	3 (14.3%)	8 (18.2%)	
	<i>No Procedure</i>	6 (28.6%)	26 (59.1%)	
30 Day Mortality	<i>Yes</i>	0 (0.0%)	5 (11.4%)	NS
	<i>No</i>	21 (100.0%)	39 (88.6%)	

Table 15.12 Demographics, tumour details and outcome for interval and screen-detected Dukes' D cancers.

As shown, there is no difference in gender, ASA grade, deprivation level, tumour location or T stage. Although 11.4% of interval cancers died within the first 30 days post diagnosis compared to 0% of screen-detected cancers, this was not statistically significant on analysis. The only significant difference between groups is the rates of resective surgery for these cancers. 57.1% of screen-detected cancers underwent a resection of their primary tumour, compared to 22.7% of interval cancers. Also, 28.6% of screen-detected cancers did not undergo any procedure, compared to 59.1% of interval cancers.

Survival for these groups was found to be significantly different, with screen-detected cancers having a more favourable survival rate (Log Rank Mantel-Cox $\chi^2 = 11.479$, $df=1$, $p=0.001$), as shown in Figure 15.8 below.

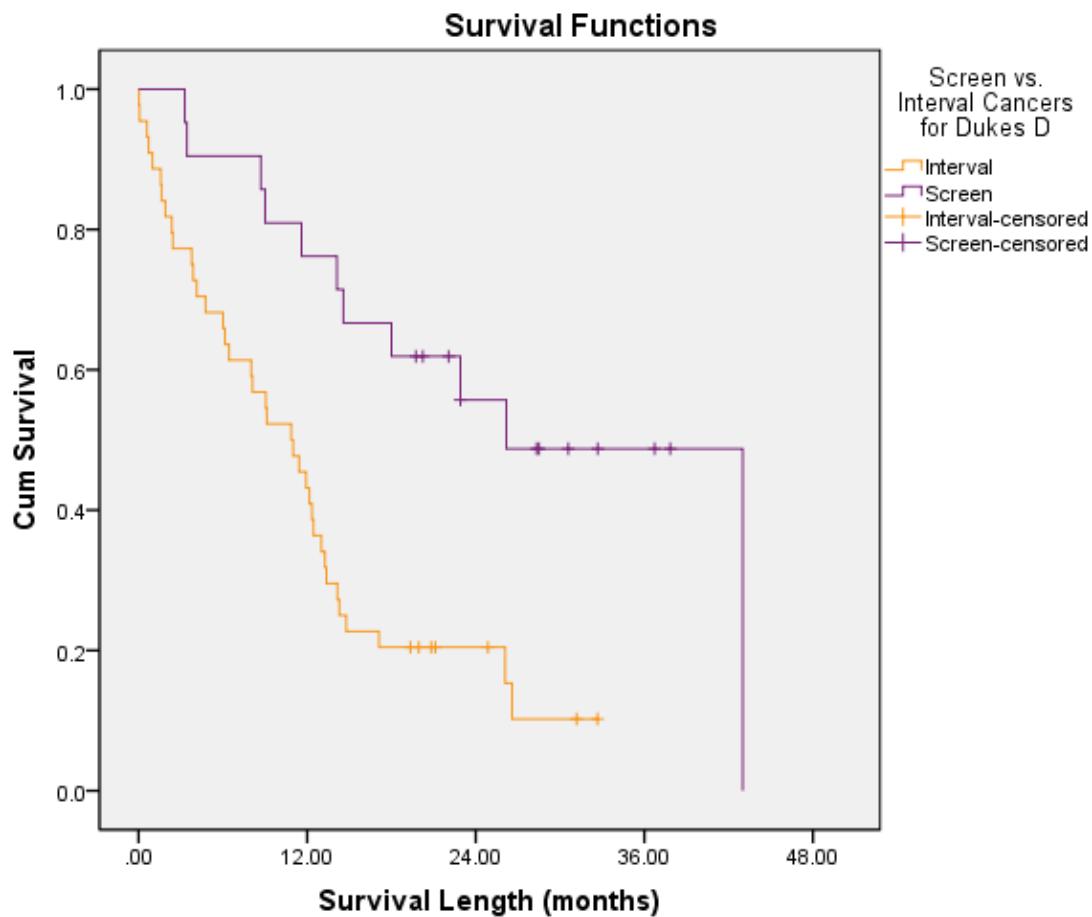


Figure 15.8 Kaplan-Meier curve for interval and screen-detected Dukes' D cancers.

15.3 Interval Cancer Group vs. Control Group by Dukes Stage

When the interval cancer group is compared against the control group for each Dukes stage, we might expect to see if the cancers at each stage behave differently to that of the general population.

This might explain why the interval cancer group does significantly worse for most Dukes' stages compared to the screen-detected group.

In comparing interval cancers against control group cancers for each Dukes stage, there were no significant differences found in any patient demographic, tumour characteristics and location, management choice and 30 day mortality rate. No significant differences were found between groups in the mean positive lymph nodes, mean total lymph nodes, and proportion of cases with 12 or more nodes harvested for Dukes' C1, C2 and Dukes' C cancers.

The survival curves for each of these Dukes' stages are shown below in Figures 15.9 to 15.11. There were no significant differences found between the curves of these groups on analysis as shown in Table 15.13.

Dukes Stage	Log Rank (Mantel-Cox)		
	Chi-Square	df	Significance, p value
A	0.682	1	0.506
B	0.128	1	0.958
C	0.485	1	0.684
D	2.547	1	0.156

Table 15.13 Tests of equality of survival distributions for interval vs. control cancer groups for each Dukes stage.

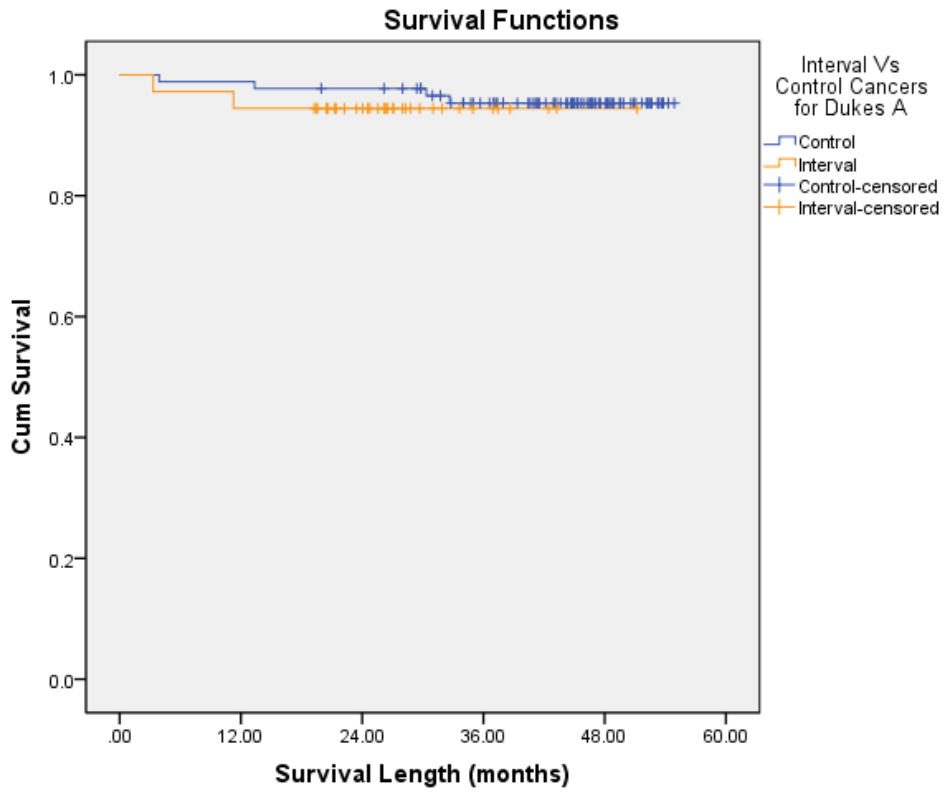


Figure 15.9 Survival curve for interval and control cancers of Dukes Stage A.

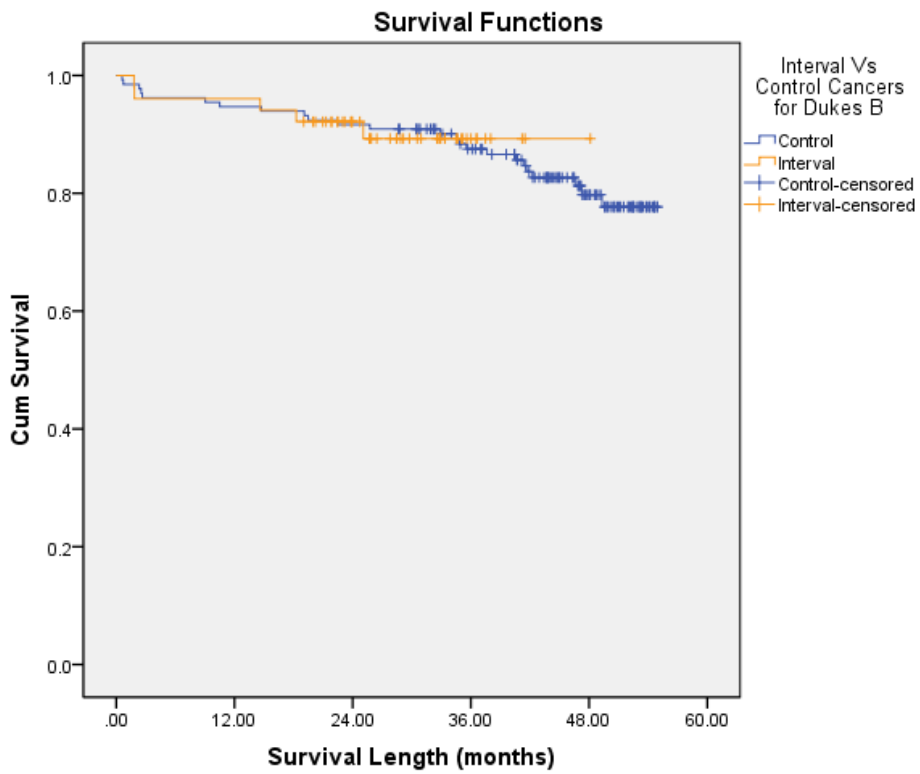


Figure 15.10 Survival curve for interval and control cancers of Dukes Stage B.

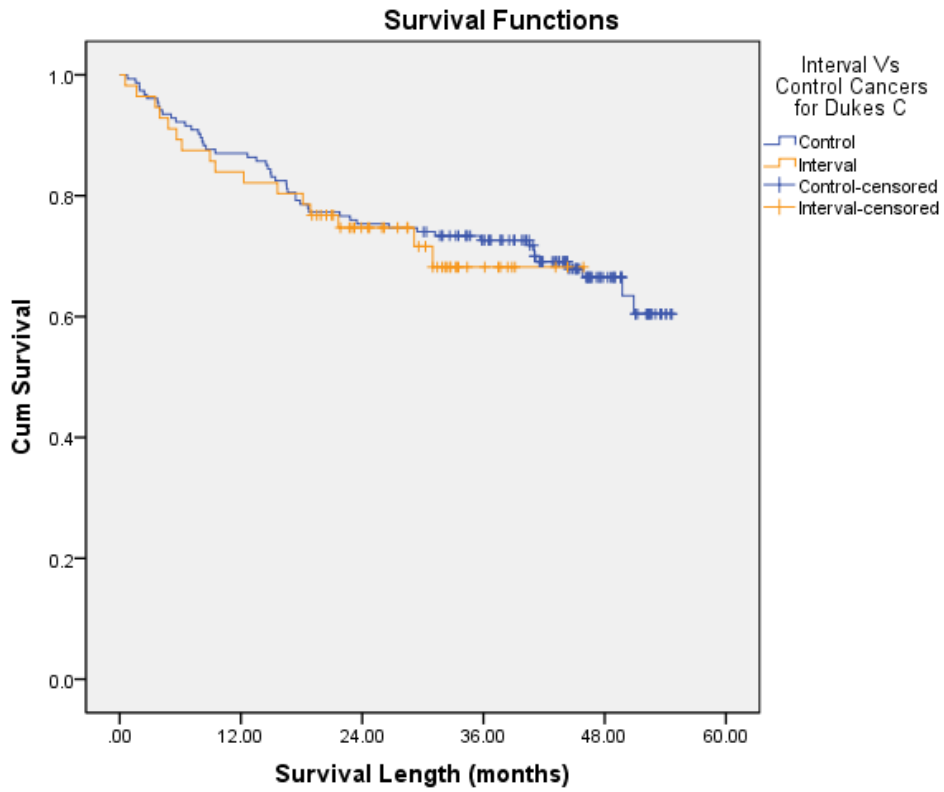


Figure15.11 Survival curve for interval and control cancers of Dukes Stage C.

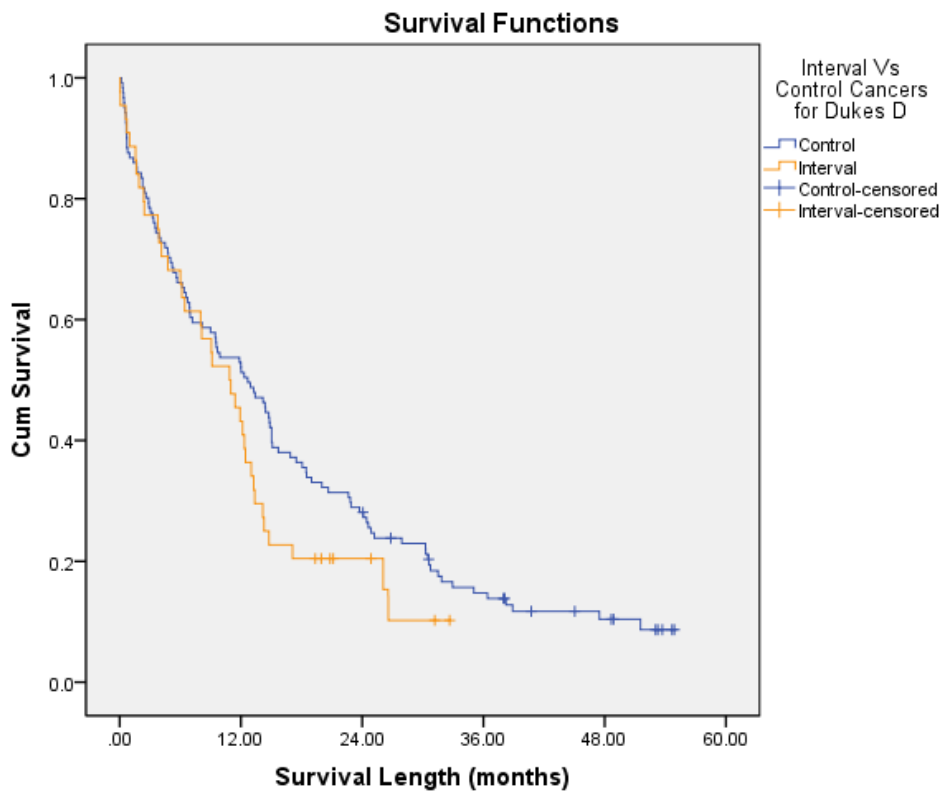


Figure15.11 Survival curve for interval and control cancers of Dukes Stage D.

15.4 Role of Medication Use on FOBt Positivity

To further understand the possible reasons behind the disproportionate positivity of the FOBt by gender and tumour site, an analysis of the role of medications was performed.

Out of 514 patients with a screen or interval colorectal cancer, we received 346 proformas suitable for analysis (67.3%). This included 100% response rates for all the medication information, and a 98.6% response rate for data regarding pre-FOBt cholecystectomy. 120 patients analysed were in the interval cancer group, with 226 in the screen-detected cancer group.

32/346 (9.2%) patients had previously taken hormone replacement therapy. No patients were taking this at the time of completing the FOBt. This included 10.8% of patients (n=13) in the interval cancer group, and 8.4% of patients (n=19) in the screen-detected group. The difference in proportions between groups was not significantly significant ($\chi^2=0.55$, $df=1$, $p=0.46$).

		Group		Total	p value
		Interval	Screen		
Ever Used Hormone Antagonists	<i>No</i>	117 (97.5%)	218 (96.5%)	335 (96.8%)	0.60
	<i>Yes</i>	3 (2.5%)	8 (3.5%)	11 (3.2%)	
Hormone Antagonist Use at Time of FOBt	<i>No</i>	120 (100.0%)	221 (97.8%)	341 (98.6%)	0.10
	<i>Yes</i>	0 (0.0%)	5 (2.2%)	5 (1.4%)	

Table 15.14 Use of hormone antagonists at time and prior to carrying out FOBt.

Table 15.14 summaries the use of hormone antagonists both pre-FOBt and at the time of test. No association with the use of hormonal medication and FOBt positivity was found.

		Group		Total	p value
		Interval	Screen		
NA-NSAID Use Within 2 Months of FOBt	<i>No</i>	115 (95.8%)	202 (88.9%)	317 (91.6%)	0.039
	<i>Yes</i>	5 (4.2%)	25 (10.6%)	29 (8.4%)	
Anticoagulant Use Within 2 Months of FOBt					
	<i>No</i>	103 (85.8%)	201 (88.9%)	304 (87.9%)	0.40
	<i>Yes</i>	17 (14.2%)	25 (11.1%)	42 (12.1%)	
Aspirin Use Within 2 Months of FOBt					
	<i>No</i>	105 (87.5%)	203 (89.8%)	308 (89.0%)	0.51
	<i>Yes</i>	15 (12.5%)	23 (10.2%)	38 (11.0%)	

Table 15.15 Use of Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs (NA-NSAID), Anti-Coagulants and Aspirin within two months of carrying out a FOBt.

11 of 341 patients (3.2%) had undergone a cholecystectomy prior to carrying out their FOBt. 3/115 (2.5%) of patients belonged to the interval cancer group, with 8/215 (3.6%) having a screen-detected cancer. The difference in proportions was not found to be significant ($\chi^2=0.27$, $df=1$, $p=0.60$). Although, all 11 cholecystectomy patients had a tumour that was distal to the splenic flexure, this was not found to be significant ($\chi^2=3.10$, $df=1$, $p=0.08$). Significantly more women were found to have undergone a cholecystectomy than men (6.4% vs. 1.7%, $\chi^2=5.24$, $df=1$, $p=0.02$).

The use of NA-NSAIDs appears to be associated with a positive FOBt. This effect does not appear to be the case for anti-coagulants (either aspirin or warfarin), or for aspirin alone. For the population who used NA-NSAID within two months of carrying out their FOBt, within both interval and screen-detected cancer groups, there was no significant differences in gender ($p=0.97$ & $p=0.92$ respectively), tumour location ($p=0.65$ & $p=0.67$), or stage of tumour ($p=0.22$ & $p=0.36$).

On univariate logistic regression analysis of factors that predict a positive result of the FOBt, male gender ($p=0.003$), NA-NSAID use within 2 months of test ($p=0.047$), and a location distal to the splenic flexure ($p=0.003$).

The combination of tumour site & gender, NA-NSAID use & gender, and tumour site & NA-NSAID use, do not appear to be predictors of a positive result ($p=0.26$, $p=0.29$, $p=0.21$ respectively).

On multivariate logistic regression analysis, NA-NSAID use and tumour site remained significant predictors of a positive FOBt result ($p=0.047$ & $p=0.025$).

15.5 Chapter Conclusion

This chapter has shown that the guaiac based faecal occult blood test is more effective at detecting cancers in the left colon and in men. Screen-detected cancers had a superior survival rate compared to the interval cancer group.

On comparing these two groups for each individual Dukes stage, the screen-detected group was found to have a significantly better survival rate for Dukes' A, C and D cancers. This is despite equivalent patient demographic proportions between groups.

The interval cancer group and control group were found to have equivalent survival rates when analysed by Dukes stage.

Non-aspirin non-steroidal anti-inflammatory medications (NA-NSAIDs) were found to be associated with a positive FOBt result, whereas anti-coagulant use and hormonal therapy was not.

Chapter 16 How Can the Screening Programme Be Improved?

16.1 Analysis of Window Positivity of First Returned FOBt Kit

7.8% of interval cancers had a FOBt that was had between one and four windows positive in their first test. They then repeated two further tests, both of which had none of the six windows positive, giving them an overall normal (negative) result.

When this group is compared against the interval cancer group with one normal test, there was no difference found in gender ($\chi^2=1.286$, $df=1$, $p=0.257$), ASA grade ($\chi^2=0.007$, $df=1$, $p=0.933$), deprivation level, ($\chi^2=2.505$, $df=1$, $p=0.114$), tumour location ($\chi^2=1.302$, $df=1$, $p=0.254$), Dukes stage ($\chi^2=0.055$, $df=1$, $p=0.815$) or survival (Log Rank Mantel-Cox, $\chi^2=1.638$, $p=0.201$). However, those with one unclear test were diagnosed with their cancer significantly sooner (7.5 vs. 12.8 months from completion of the FOB test, $t=2.987$, $p=0.003$).

If consideration is taken to changing the criteria for an abnormal test to a lower number of positive windows, then the first test returned in all those who were diagnosed with a colorectal cancer must be reviewed. This must be ideally of one screening round, so as to get an accurate number of interval cancers after one round. Table 16.1 below shows the overall number of individuals who were invited for screening, divided into those who had a first round test and those who had taken part in a second round of screening. 9,861 subjects (1.0%) had a screening test prior to the study period commencement. As we do not have data regarding cancer detection for this time period, these patients were not included in the analysis of the first round numbers.

		1 st Screening Round	2 nd Screening Round	Total For Study Period (Apr 07-Mar 10)
Invitations Sent	<i>Male</i>	433,495	38,726	472,221
	<i>Female</i>	441,158	40,923	482,081
	<i>Total</i>	874,653	79,649	954,302
Returned Test Kits	<i>Male</i>	232,904	21,914	254,818
	<i>Female</i>	255,425	24,019	279,444
	<i>Total</i>	488,329	45,933	534,262
Kit Result:				
Normal	<i>Male</i>	219,751	20,661	240,412
	<i>Female</i>	246,105	23,126	269,231
Unclear, Normal x2	<i>Male</i>	6,525	727	7,252
	<i>Female</i>	5,165	550	5,715
Abnormal	<i>Male</i>	703	54	757
	<i>Female</i>	362	40	402
Unclear x2	<i>Male</i>	2,938	233	3,171
	<i>Female</i>	1,710	144	1,854
Unclear, Abnormal	<i>Male</i>	335	26	361
	<i>Female</i>	169	8	177
Unclear, Normal, Abnormal	<i>Male</i>	44	6	50
	<i>Female</i>	38	4	42
Unclear, Normal, Unclear	<i>Male</i>	1,273	151	1,424
	<i>Female</i>	849	102	951
Discharged	<i>Male</i>	1,335	56	1,391
	<i>Female</i>	1,027	45	1,072
Window Results:				
Only Returned 1 Test Kit – Discharged	<i>+ve Spot x1</i>	375	21	396
	<i>+ve Spot x2</i>	271	7	278
	<i>+ve Spot x3</i>	67	4	71
	<i>+ve Spot x4</i>	51	5	56
Didn't Complete All Offered Screening Tests - Discharged	<i>+ve Spot x1</i>	318	11	329
	<i>+ve Spot x2</i>	188	14	202
	<i>+ve Spot x3</i>	38	1	39
	<i>+ve Spot x4</i>	41	1	42
Completed Screening Tests (Number of First Kits Only)	<i>+ve Spot x1</i>	10,251	1,091	11,342
	<i>+ve Spot x2</i>	6,189	616	6,805
	<i>+ve Spot x3</i>	1,466	143	1,609
	<i>+ve Spot x4</i>	1,129	112	1,241
Abnormal Kits	<i>+ve Spot x5</i>	721	48	769
	<i>+ve Spot x6</i>	932	90	1,022

Table 16.1a Total number of individuals offered and taking up the FOB test and their results.

		1 st Screening Round	2 nd Screening Round	Total For Study Period (Apr 07-Mar 10)
Outcomes After WP Result:				
Outcome After 1+ve Test Kit Result	<i>Abnormal Result</i>	129	11	140
	<i>2nd Unclear</i>	2,938	301	3239
	<i>2x Normal Results</i>	7,184	779	7963
	Total	10,251	1,091	11,342
Outcome After 2+ve Test Kit Result	<i>Abnormal Result</i>	166	16	182
	<i>2nd Unclear</i>	2,457	218	2,675
	<i>2x Normal Results</i>	3,566	382	3948
	Total	6,189	616	6,805
Outcome After 3+ve Test Kit Result	<i>Abnormal Result</i>	138	6	144
	<i>2nd Unclear</i>	782	73	855
	<i>2x Normal Results</i>	546	64	610
	Total	1,466	143	1,609
Outcome After 4+ve Test Kit Result	<i>Abnormal Result</i>	153	10	163
	<i>2nd Unclear</i>	588	48	636
	<i>2x Normal Results</i>	388	54	442
	Total	1,129	112	1,241

Table 16.1b Outcomes after an unclear first test result by number of positive windows.

The table below (Table 16.2) shows which cancer group patients were classified in according the result of their first FOBt, in those who had not been offered screening in an earlier round (i.e. cancers in relation to the prevalent screening round). As previously discussed, if patients did not complete the required number of FOBt kits before they were diagnosed with their cancer, then they fell into the control group. If they did not complete the required number of tests due to their own choice, and were later diagnosed with a cancer, then they belonged to the non-uptake group.

		Control, n=19	Non-Uptake, n=15	Interval, n=185	Screen, n=285
First FOB Kit, Number of Windows Positive	<i>0</i>	11 (57.9%)	0 (0.0%)	170 (91.9%)	0 (0.0%)
	<i>1</i>	1 (5.3%)	5 (33.3%)	6 (3.2%)	62 (21.7%)
	<i>2</i>	1 (5.3%)	2 (13.3%)	5 (2.7%)	61 (21.4%)
	<i>3</i>	3 (15.8%)	5 (33.3%)	3 (1.6%)	50 (17.4%)
	<i>4</i>	1 (5.3%)	3 (20.0%)	1 (0.5%)	41 (14.4%)
	<i>5</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (7.4%)
	<i>6</i>	2 (10.5%)	0 (0.0%)	0 (0.0%)	52 (18.2%)

Table 16.2 Number of cancers per number of positive windows for each cancer classification group.

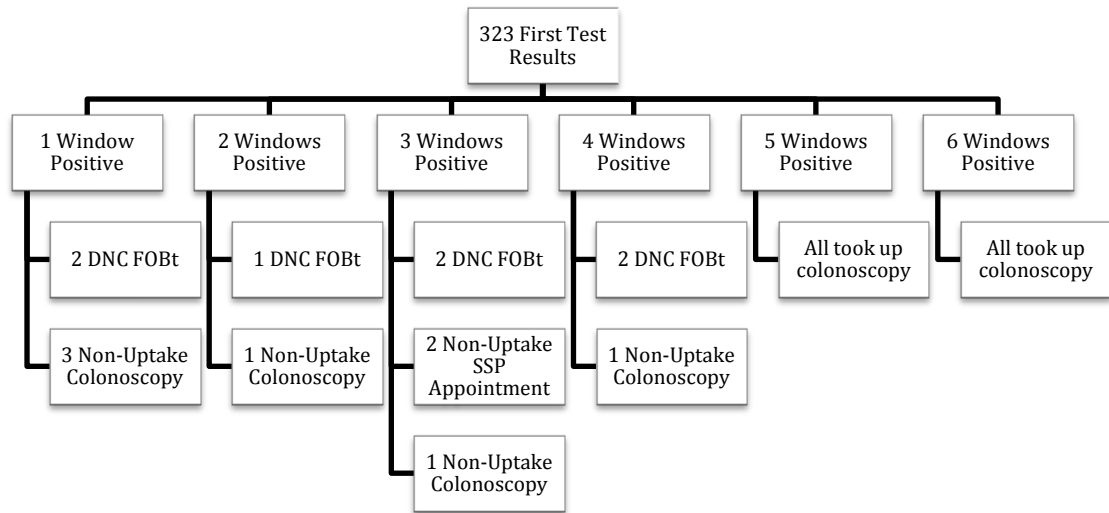


Figure 16.1 Types of Non-Uptake by Positive Windows.

Figure 16.1 shows the number of patients who did not complete a screening episode, after they had returned one FOB kit. It should be noted that, in the patients who had an initial abnormal test (five or six windows positive), all took up a screening colonoscopy.

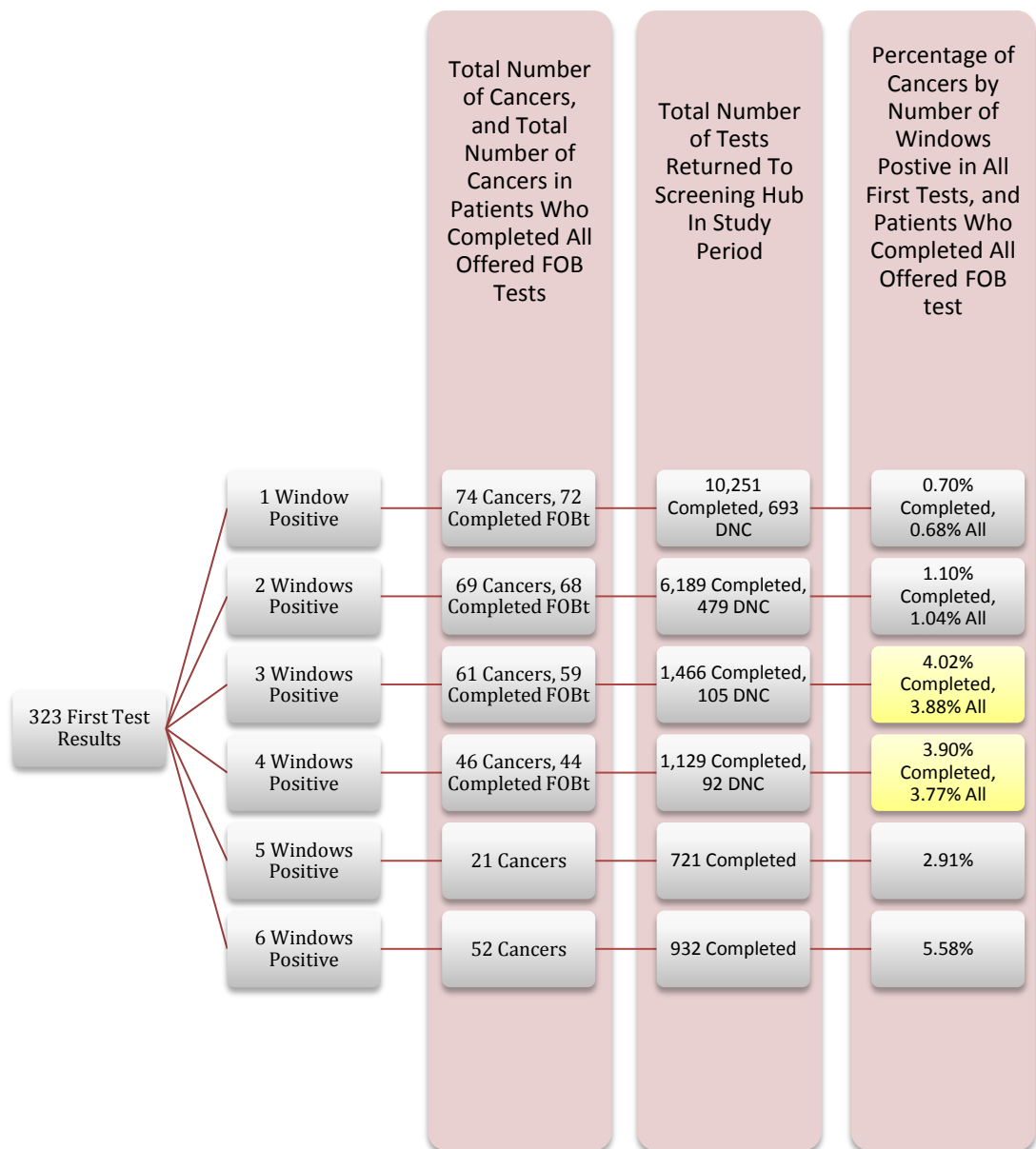


Figure 16.2 Number of cancers in each group of positive first FOB test result.

The above figure shows the percentage of colorectal cancers that are found in each degree of window positivity on a patient's first test result. This shows the total number of cancers and the total number in those who completed the FOB screening test by each positive first kit result. The percentages shown are the predictive values for colorectal cancer by each degree of positive first test. This is for those who completed all the offered FOB tests, as well as those who just completed one test. The boxes highlighted in yellow correspond to three and four positive windows. Given the relatively high predictive level in the diagnosis of a colorectal cancer, a cut-off level of a minimum of three positive windows seems the most likely area for change. Figure 16.3 is a diagrammatic representation of the total number of invites, and the individual results based on the result of the first FOBt. A traffic

light colour scheme is used to show each cancer that was diagnosed according to their potential to be diagnosed through the screening programme. The green colour represents cancers that were diagnosed through screening, amber roughly corresponds to non-uptake and control group cancers, and red cancers are interval cancers. The rationale behind each allocation is explained in the discussion. The figures are for prevalent round cancers over the study period.

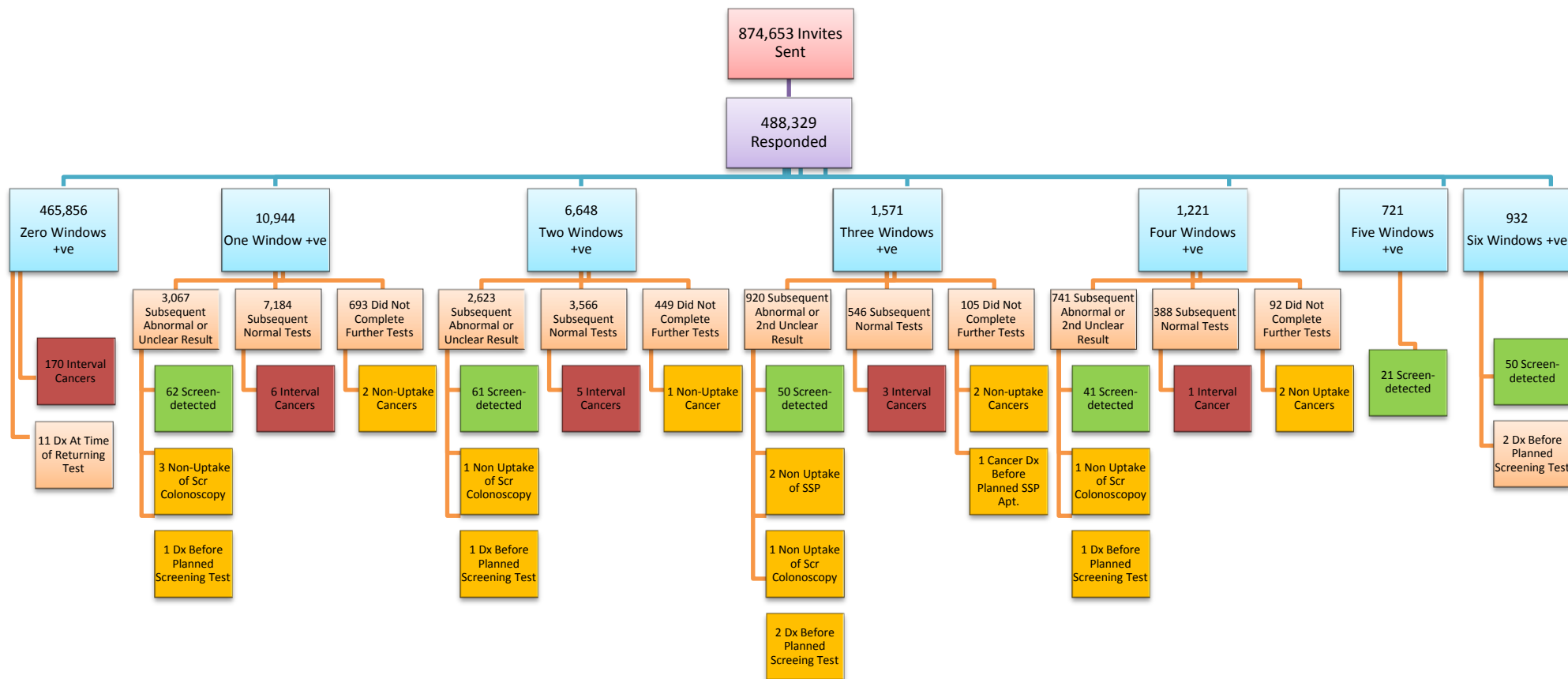


Figure 16.3 Outcomes of the first round of screening.

From the above figures, we have shown that the positive predictive values of patients with three and four positive windows on their first FOB test are high, compared to those with one or two positive windows.

When outcomes are compared between these groups of window positivity on a screened individual's first test, those with an unclear result have a significantly better survival rate compared with those with an abnormal test (both with screen-detected cancers), and the interval cancer group.

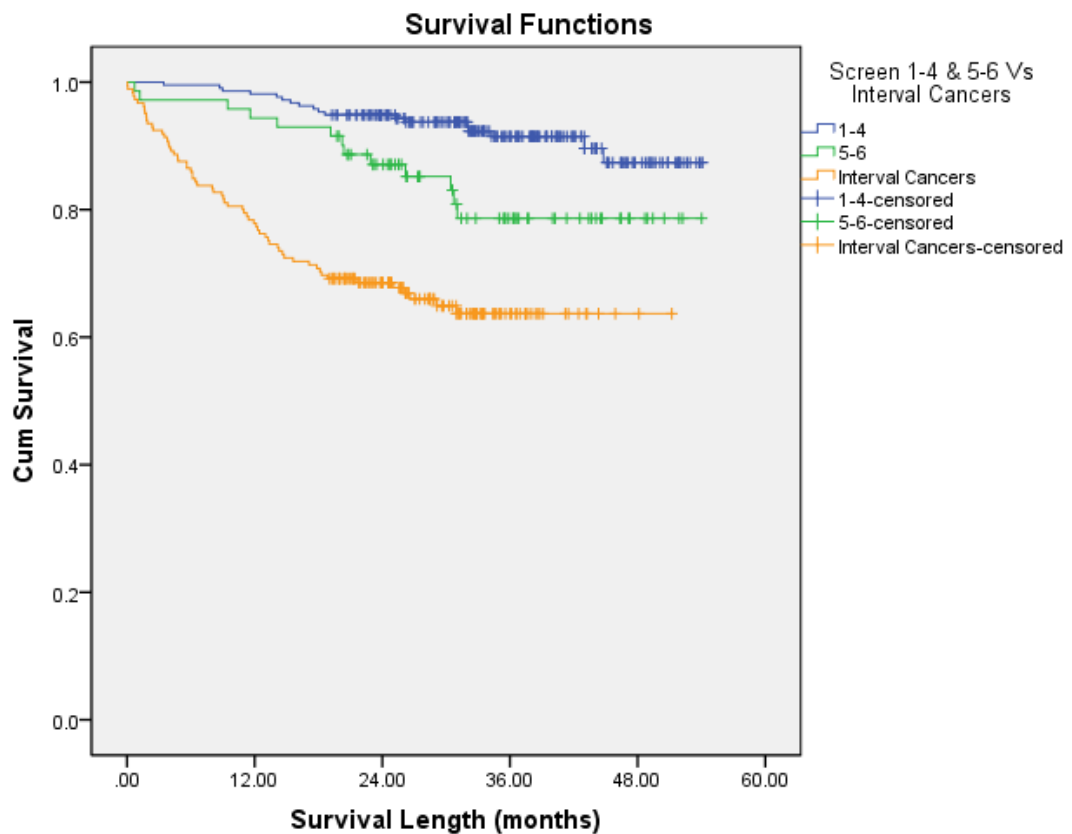


Figure 16.4 Kaplan-Meier survival curves of screen-detected cancers with 1-4 & 5-6 windows positive on first FOBt against interval cancer group.

Comparison, p value	1-4	5-6	Interval Cancers
1-4		0.014	<0.001
5-6	0.014		0.006
Interval Cancers	<0.001	0.006	

Table 16.3 Log rank (Mantel-Cox) test comparing groups of screen-detected cancers and interval cancers.

When the unclear initial test group (1-4 positive windows) is split into 1-2 and 3-4, they were found to have equivalent survival rates as each other.

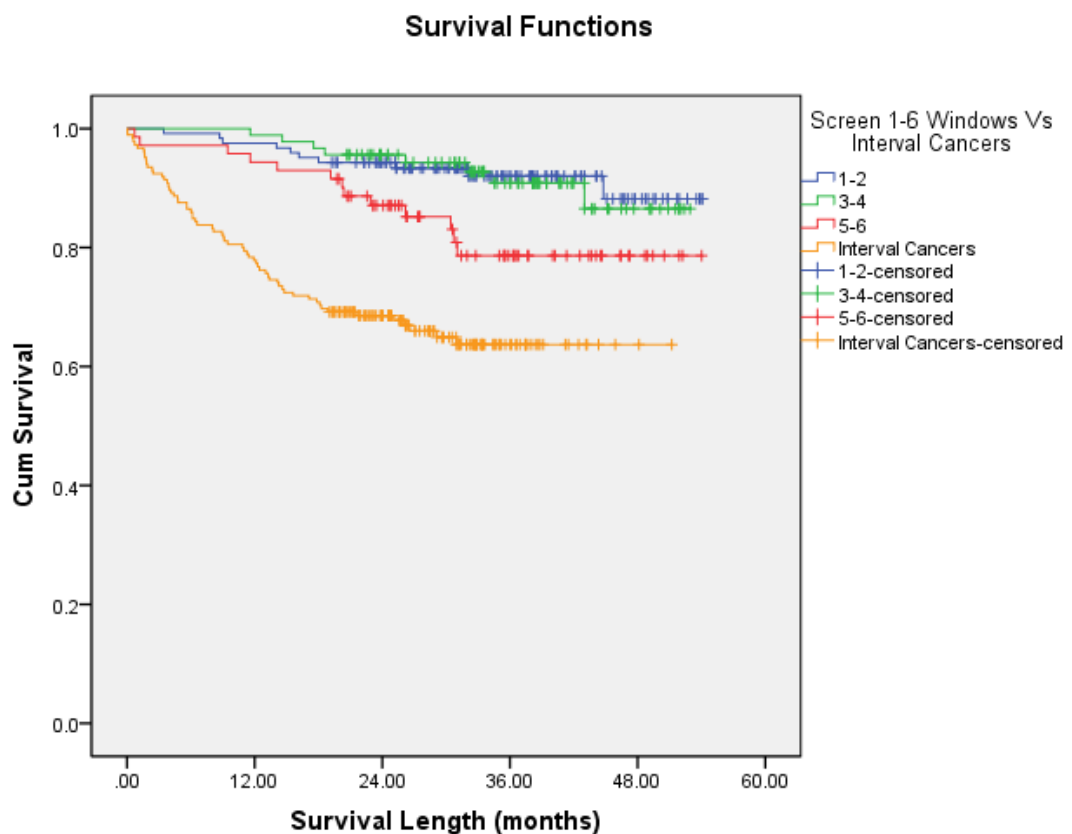


Figure 16.5 Kaplan-Meier survival curves of screen-detected cancers with 1-2, 3-4 & 5-6 windows positive on first FOBt against interval cancer group.

The p-values in the comparison of each group are shown in Table 16.4 below.

Comparison, p value	1-2	3-4	5-6	Interval Cancers
1-2		0.922	0.029	<0.001
3-4	0.922		0.050	<0.001
5-6	0.029	0.050		0.006
Interval Cancers	<0.001	<0.001	0.006	

Table 16.4 Log rank (Mantel-Cox) test comparing groups of screen-detected cancers and interval cancers.

Table 16.5 below shows the patient, tumour and operative management variables for each subgroup of window positivity in the screen-detected group, when compared against each other, and the interval cancer group.

The cancers detected after an abnormal test result have an equivalent overall stage profile to the interval cancer group (however with fewer Dukes' D cancers), with similar patient demographics.

The group with a 3-4 positive window first test, when compared against the interval cancer group, were found in a significantly greater proportion of men, distal to the splenic flexure, and had a more favourable stage profile (including 43.3% Dukes' A cancers).

	Screen-detected Number of Positive Windows On 1 st Test			Interval Cancers	Comparison, p value				
	1-2	3-4	5-6		1-2 Vs. 3-4	1-4 Vs. 5-6	3-4 Vs. Interval	5-6 Vs. Interval	
Mean Age At Diagnosis (SEM)	64.83 (±0.28)	65.10(±0.35)	64.91(±0.40)	65.71(±0.21)	NS	NS	NS	NS	
Gender	<i>Male</i>	85 (69.1%)	71 (78.0%)	52 (73.2%)	112 (60.5%)	NS	NS	0.004	NS
	<i>Female</i>	38 (30.9%)	20 (22.0%)	19 (26.8%)	73 (39.5%)				
Lives in 10% Most Deprived Areas In England	<i>Yes</i>	16 (13.0%)	3 (3.3%)	9 (12.7%)	16 (8.6%)	0.014	NS	NS	NS
	<i>No</i>	107 (87.0%)	88 (96.7%)	62 (87.3%)	169 (91.4%)				
ASA Grade Grouped	<i>1-2</i>	70 (76.9%)	51 (82.3%)	46 (78.0%)	96 (73.3%)	NS	NS	NS	NS
	<i>3-5</i>	21 (23.1%)	11 (17.7%)	13 (22.0%)	35 (26.7%)				
Grouped Tumour Site	<i>Distal To Splenic Flexure</i>	102 (82.9%)	75 (82.4%)	50 (70.4%)	123 (66.5%)	NS	0.026	0.006	NS
	<i>Splenic Flexure and Proximal</i>	21 (17.1%)	16 (17.6%)	21 (29.6%)	62 (33.5%)				
Type of Surgery	<i>Resective</i>	105 (85.4%)	70 (76.9%)	65 (91.5%)	146 (78.9%)	NS	NS	<0.001	0.001
	<i>Local Excision</i>	15 (12.2%)	15 (16.5%)	5 (7.0%)	4 (2.2%)				
	<i>Palliative</i>	2 (1.6%)	1 (1.1%)	0 (.0%)	9 (4.9%)				
	<i>No Procedure</i>	1 (0.8%)	5 (5.5%)	1 (1.4%)	26 (14.1%)				
Dukes Stage	<i>A</i>	57 (47.1%)	39 (43.3%)	14 (20.6%)	35 (19.4%)	NS	0.003	<0.001	NS
	<i>B</i>	28 (23.1%)	19 (21.1%)	25 (36.8%)	50 (27.8%)				
	<i>C</i>	31 (25.6%)	25 (27.8%)	23 (33.8%)	53 (29.4%)				
	<i>D</i>	5 (4.1%)	7 (7.8%)	6 (8.8%)	42 (23.3%)				
30 Day Mortality	<i>Yes</i>	0 (0.0%)	0 (0.0%)	1 (1.4%)	6 (3.2%)	NS	NS	NS	NS
	<i>No</i>	123 (100.0%)	91 (100.0%)	70 (98.6%)	179 (96.8%)				

Table 16.5 Patient, tumour and management variables for each positive window on first FOBt and interval cancers, and Chi-squared comparisons.

16.2 Implications of Changing the Minimum Criteria for an Abnormal Test to 3/6 Positive Windows

As shown above, the aim of changing the criteria for an abnormal test to a lower number of positive windows on the first test would be to decrease the number of interval cancers. The benefits of this would be to detect cancers at an earlier stage, thereby improving survival rates for these patients. A change such as this would inevitably result in an increase in the number of nurse appointments, as well as screening colonoscopies. It would also save on the number of repeat test kits that would need to be issued, therefore decreasing the time from positive test result to screening colonoscopy.

A secondary aim would be to decrease the number of patients who only complete one FOBt kit, before dropping out of the program. If the criteria for an abnormal test was to be lowered, then a subgroup of patients would only require one test to be completed, which would also decrease the time from test result to screening colonoscopy.

Table 16.6 below shows the outcomes of each patient after they submitted one FOBt kit with each degree of positive windows (between one and four positive). It shows the number of patients that were discharged having not completed the screening episode, the number with a subsequent unclear or abnormal test, and the number who submitted two further tests which both had zero of six windows positive giving them an overall normal result. The numbers are for the prevalent round only.

Outcomes After WP Result:		Discharged	Normal Result	Abnormal Result
Outcome After 1+ve Test Kit Result	<i>Returned only 1 Kit</i>	375 (3.4%)	7,184 (65.6%)	129 (1.2%) 2,938 (26.8%)
	<i>Did not complete all Kits</i>	318 (2.9%)		
	<i>Abnormal Result</i>			
	<i>2nd Unclear</i>			
	<i>2x Normal Results</i>			
	Total	10,944 (100.0%)		
Outcome After 2+ve Test Kit Result	<i>Returned only 1 Kit</i>	271 (4.1%)	3,566 (53.6%)	166 (2.5%) 2,457 (37.0%)
	<i>Did not complete all Kits</i>	188 (2.8%)		
	<i>Abnormal Result</i>			
	<i>2nd Unclear</i>			
	<i>2x Normal Results</i>			
	Total	6,648 (100.0%)		
Outcome After 3+ve Test Kit Result	<i>Returned only 1 Kit</i>	67 (4.3%)	546 (34.8%)	138 (8.8%) 782 (49.8%)
	<i>Did not complete all Kits</i>	38 (2.4%)		
	<i>Abnormal Result</i>			
	<i>2nd Unclear</i>			
	<i>2x Normal Results</i>			
	Total	1,571 (100.0%)		
Outcome After 4+ve Test Kit Result	<i>Returned only 1 Kit</i>	51 (4.2%)	388 (31.8%)	153 (12.5%) 588 (48.2%)
	<i>Did not complete all Kits</i>	41 (3.4%)		
	<i>Abnormal Result</i>			
	<i>2nd Unclear</i>			
	<i>2x Normal Results</i>			
	Total	1,221 (100.0%)		

Table 16.6 Outcomes after 1-4 positive windows on first FOBt in prevalent screening round.

If the criteria for an abnormal test were set at a lower threshold, there are a maximum and minimum number of additional colorectal cancers that would have been detected.

The minimum number corresponds to the interval cancer group that had one to four positive windows on their first FOBt, who went on to submit two further normal tests (both zero windows positive). The total numbers by degree of positive windows is shown in Table 16.7 below. If the non-uptake group is included in the additional number of potential cancers to be detected, then the percentage prevalence improves to the maximum number of cancers able to be detected.

Number of Positive Windows on 1st Test		Number of Cancers	Number Affected By Test Result	Prevalence (95% Confidence Interval)
1	<i>Minimum</i>	6	7184	0.084% (0.0167 to 0.1503)
	<i>Maximum</i>	12	7887	0.152% (0.0661 to 0.2382)
2	<i>Minimum</i>	5	3566	0.140% (0.0179 to 0.2630)
	<i>Maximum</i>	8	4015	0.199% (0.0613 to 0.3337)
3	<i>Minimum</i>	3	546	0.550% (-0.0706 to 1.1695)
	<i>Maximum</i>	11	651	1.690% (0.6996 to 2.6798)
4	<i>Minimum</i>	1	388	0.258% (-0.2468 to 0.7622)
	<i>Maximum</i>	5	480	1.042% (0.1333 to 1.9500)
3 & 4	<i>Minimum</i>	4	934	0.428% (0.0095 to 0.8471)
	<i>Maximum</i>	16	1131	1.415% (0.7264 to 2.1030)

Table 16.7 Minimum and maximum numbers of additional cancers detected by number of positive windows on first FOBt kit.

As shown in the tables above, an alteration to the minimum criterion for an abnormal test to three positive windows would give the greatest return in additional cancers detected,

whilst also being the most realistic to be achievable with the finite resources of the screening programme. Alteration to three positive windows would result in a reduction of total numbers of retest FOBt kits sent out (549-615 per year), with an increase in the number of SSP appointments and screening colonoscopies performed (311-377 per year). By using the figures published as part of the SCHARR report on FOBt (and FIT) cost-effectiveness, it is possible to determine what the cost implications would be if the suggested alteration were carried out [155]. This is shown below in Table 16.8. An assumption of 100% uptake of a SSP appointment and screening colonoscopy was made.

Minimum Number of Positive Windows on 1 st Test		Number of Cancers	Number of Persons Affected	Net Cost of Sending Out Retest Kits (£)	Net Cost of Additional SSP Appointments	Net Cost of Additional Colonoscopies	Total Cost	Cost Per Cancer Detected (95% CI)
1	<i>Minimum</i>	15	11,684	-70,729	175,260	2,862,580	2,967,111	£197,807 (131,368 to 400,231)
	<i>Maximum</i>	36	13,033	-75,032	195,495	3,193,085	3,313,548	£92,043 (69,403 to 136,609)
2	<i>Minimum</i>	9	4,500	-34,548	67,500	1,102,500	1,135,452	£126,161 (76,337 to 363,242)
	<i>Maximum</i>	24	5,146	-36,640	77,190	1,260,770	1,301,320	£54,221 (38,743 to 90,242)
3	<i>Minimum</i>	4	934	-12,256	14,010	228,830	230,584	£57,646 (29,144 to 2,598,715)
	<i>Maximum</i>	16	1,131	-12,884	16,965	277,095	281,176	£17,574 (11,822 to 34,225)
4	<i>Minimum</i>	1	388	-5,257	5,820	95,060	106,137	£106,137 (35,889 to -107,705)
	<i>Maximum</i>	5	480	-5,551	7,200	117,600	119,249	£23,850 (12,740 to 186,373)

Table 16.8 Net costs of alteration to different minimum numbers of positive windows on first FOBt. Cost for sending one retest kit=£3.19, cost of one SSP appointment=£15, cost for one screening colonoscopy with pathological analysis of specimen=£245.

Table 16.8 above shows that altering the criteria for an abnormal test to a minimum of three positive windows gives the most cost-effective improvement per cancer detected, with a range of £17,574 to £57,646 for the minimum to maximum number of cancers potentially detectable with this change.

It must be assumed that any additional cancers detected due to a change in classification of a test result would have an equivalent survival rate as that of those that are currently detected through screening, for each group of window positivity (e.g. 3-4 positive windows). When this takes place, lowering the minimum number of positive windows would equate to an approximately 20% improvement in survival rate over five years. The cost per life year gained is therefore £17,574 (95% CI £11,822 to £34,225) if all potentially detectable cancers are detected as part of the change in screening protocol.

16.3 Chapter Conclusion

Analysing the first round only, the total numbers of patients who returned a FOBt kit with an unclear (one to four positive windows) as their first test result are shown above. The outcomes after this result are presented, with the number of cancers that are detected with the current screening protocol, and the maximum possible number that could be detected, for each degree of positive window.

The cost implications of changing the criteria for an abnormal test to a minimum of three windows (which gives the maximum yield of cancers potentially detectable) is shown.

Chapter 17 Discussion

17.1 Introduction

Although this work began as a service evaluation, it became apparent that, as the project progressed, there were key research questions that needed to be answered. These research hypotheses have been described in Chapter 10 and relate to new knowledge that was generated from this work.

This chapter discusses the impact of the screening programme: the effect that it has had as a whole on the stage profile and survival of patients against a control group who were not offered screening. This control group was analysed in detail to ensure that there was minimal bias secondary to the concurrent commencement of the programme.

Although there is a vastly superior outcome for patients who have their cancer detected through screening, the programme does have significant limitations. The guaiac based faecal occult blood test has a miss rate of nearly 40% in the detection of a colorectal cancer, as determined by the interval cancer rate. If we include the advanced stage cancers that were detected in the second round of screening, after a negative first round test, this figure will increase. An explanation of reasons behind this significant miss rate, including the effect of medication use, is made below. Methods to minimise the proportion of missed cancers by altering the criteria for an abnormal FOBt kit result will be discussed.

17.2 The Impact of the Screening Programme

The availability of the control group was a serendipitous one. Having over 500 subjects suitable for comparison against those who were offered screening, of the same age group, and in the same study period, will not happen again within the life of the Bowel Cancer Screening Programme. A detailed review of the effect of demographic variables on the survival of patients within the control group was performed, which showed that the group behaved as would have been expected. I.e. No effect of gender on survival, but those with a greater level of comorbidities, and those from a more deprived background, having a significantly worse survival rate. As discussed, there were a small number of patients (n=19) who completed a FOBt (or part of), but were diagnosed out with the screening programme. These 3.7% may have a small amount of influence by their improved awareness of colorectal cancer, but this does not appear to have affected the results as a whole.

As shown in Chapters 12 and 13, the screening programme as a whole has produced a superior survival rate to that of the control group. The intervention group that was

diagnosed with a cancer was found to have equivalent levels of patient co-morbidities, gender proportions, and deprivation level. The effect of each of these on survival was equivalent for both groups.

There were significantly more Dukes' A cancers diagnosed in the intervention group (26% vs. 18%), that were managed via local excision. The intervention group was found to have a superior all-cause survival curve compared to the control group.

When the intervention group is analysed by its three subgroups, the reasons behind the more favourable stage profile and survival rate is due to the outcomes of screen-detected cancers alone. The interval cancer group and non-uptake cancer group were found to have equivalent outcomes as the control group (and each other).

Compared with the results from the Nottingham study, the proportion of cancers detected through screening has improved with implementation of the national programme, with a decrease in the proportion in non-responders [100]. This could be due to improved awareness of the screening programme through national media campaigns. This study also shows that nearly 40% of all screen-detected cancers are Dukes Stage A with an improved survival rate compared to the non-screen-detected cancer population. On initial review, the improved survival is likely to reflect the larger proportion of earlier stage tumours. This earlier stage profile in screen-detected cancers may represent the true prevalence of colorectal cancers within a population. The natural history of colorectal cancers (i.e. the long lag time associated with the adeno-carcinoma sequence) and the asymptomatic nature of early cancers mean that more advanced tumours are more likely to present through symptomatic services, as well as being present for a shorter duration before progressing to a more advanced stage (i.e. metastasising to nodes/distant organs).

It is encouraging that after a screening colonoscopy there were no missed colorectal cancers detected. All cancers detected through a screening colonoscopy were either at the initial invite, or diagnosed at the planned surveillance colonoscopy. Recent post colonoscopy interval rates have been published as 1.8% within three years of initial negative procedure, and 4% within ten years [156]. Therefore, this study follow up may be too short to confirm this excellence in colonoscopy standard. As mentioned, the rates of local excisions for Dukes A cancers are significantly higher for those who had a screening colonoscopy. Assuming there is no systematic difference in size or morphology of Dukes' A tumours between groups, this may be a reflection on the high level of ability in performing polypectomies for those accredited colonoscopists.

17.3 Cancers in the Population who do not take up Screening

At its outset, this research did not intend to look at the reasons for non-uptake of the offered screening tests. The proportion of colorectal cancers in the non-uptake group, out of the whole population who did not take up the screening test is minute (311 of 420,040 invitations, 0.08%). However, the patient demographics of this cancer group are likely to represent the patient demographics of the non-uptake group as a whole, and not specifically the demographics of this cancer group.

The higher proportion of unfit patients (ASA grades 3-5) in the non-uptake group may reflect the health beliefs of the non-uptake group in general. Patients from a higher level of social deprivation are less likely to engage with health promotion initiatives and have higher rates of smoking and alcohol consumption that may be a causative factor in their greater level of comorbidities. Smoking and alcohol consumption are also risk factors in the development of a colorectal cancer itself. These groups were also found to have a worse uptake of screening colonoscopy when analysed on a national basis [157]. Uptake of a screening colonoscopy varies from 89.5% in the least deprived areas to 86.4% in the most deprived areas. Other factors that influenced uptake were poor self-assessed health, non-white ethnicity, population density and certain geographical regions.

Despite the higher proportions of risk factors that are associated with a worse outcome in the non-uptake group, this has not resulted in an overall worse survival rate. This could be because of a potential counter-acting effect of the screening programme in raising awareness of colorectal cancer. Although this group of patients are less likely to complete the offered screening tool, they may have opted to seek advice from their general practitioner at an earlier stage. This may lead to an earlier referral to symptomatic services, and so increase the likelihood of the patient undergoing a curative resection. However, to confirm this, a qualitative study of patients diagnosed with a colorectal cancer, who did not take up the screening test, would need to take place. This would help to establish the effect of the offer of screening, in a patient's willingness to seek medical advice for bowel related symptoms.

If the uptake of screening as a whole improves with time, with a proportional decrease in non-uptake cancers and increase in screen-detected cancers, the poor prognostic effect of a more deprived, unhealthier population which then has their cancer detected through screening, may lead to a corresponding decrease in survival rate in this group. However, it is likely that the uptake rate would have to increase significantly for this to happen. Conversely, the cancer population from more deprived areas may continue to decline the

offer of screening, whereas the uptake rate in the more affluent areas may increase. This would potentially lead to a decrease in survival rate for the non-uptake group, as the deprivation level (and hence the proportion of ASA 3-5 patients) shifts towards the more deprived groups, and a further increase in the screen-detected survival rate as fitter patients (who will do better after treatment) are diagnosed with their cancer.

17.4 The Effectiveness of the Faecal Occult Blood Test

Of the 514 patients diagnosed with a colorectal cancer after completing a screening episode, 192 (37.4%) were missed by the guaiac based faecal occult blood test, a significant amount. There were also a group of patients who were diagnosed with a colorectal cancer in the incident (2nd) round of screening, having completed a normal FOBt in the prevalent round. 14 patients were diagnosed with either a Dukes C or Dukes D cancer in the 2nd round (all after submitting a normal FOBt in the 1st round). Given the time taken for a cancer to progress through each Dukes stage, it is likely that these cancers were present at the time of submitting their first test. They could therefore also be classed as interval cancers, bringing the total to 204 cancers (40.1%).

This study found that the guaiac based faecal occult blood test appears to be more effective at detecting cancers in the left colon and in men. Reasons for the difference due to gender are unclear. One possible explanation may be differing levels of oestrogen in women, and its effect on the stage of tumours at presentation (less advanced tumours associated with hormonal therapy) [158]. Combined hormonal therapy has also been used in treatment of angiodysplasia with its effects of improved endothelial integrity and shortened bleeding time. However, trial results using this therapy have been mixed [159]. With the median age of natural menopause being 49 years (interquartile range 45.0-51.0), the vast majority of women in the screening population will be post-menopausal [160]. Another possibility is the effect of non-steroidal anti-inflammatory drugs and anti-coagulants by increasing the amount of bleeding from these tumours, whose effect will be discussed below.

Brenner et al. compared incidence and mortality from colorectal cancer using several national databases from around the world [161]. Globally, women had an equivalent incidence rate and mortality rate as men, but between four and eight years later. Both Steele and Morris (whose papers are discussed below) noted that, as with this study, the proportion of men in the screen-detected group is significantly higher than all other cancer

groups, indicating that difference in incidence and prevalence between genders is not the sole reason behind this finding.

Right sided tumours (cancers proximal to the splenic flexure) are more likely to be sessile and undergo fewer traumas from bowel motion as it moves through the colon (as it will be of a more liquid consistency) [162]. For these reasons, right colon cancers may bleed less than cancers in the distal colon, and therefore will be less likely to cause a positive result. The guaiac based faecal occult blood test detects the haem portion of haemoglobin. As this moves round the large bowel, haem will degrade and hence will be less likely to cause a positive result for proximal lesions.

There have been two recent papers that have performed a similar analysis of the screening programme. The first is based on the pilot of the Scottish Bowel Cancer Screening Programme by Steele et al., which analysed the population screened between 2000 and 2007 [163]. The second analyses results from the English Bowel Cancer Screening Programme between July 2006 and December 2008, on a national scale [164].

Steele's paper looked at screen-detected, interval and non-uptake cancers as part of the Scottish demonstration pilot. They report on results of those screened aged between 50 to 69, with biennial guaiac-based faecal occult blood tests. They analysed results by screening round (3 rounds performed in total) and compared these against cancers diagnosed in the population not offered screening in the same time frame.

Throughout the three screening rounds, screen-detected cancers have a consistently favourable stage profile, with 49.9% of cancers being of Dukes stage A in the first round, 40.9% in the second round, and 38.8% in the third round. These results were reflected in this study. Similarly, the proportion of Dukes' D cancers was consistently low (7.6%, 3.6%, and 2.3%).

Interval cancers within Steele's study had variable stage proportions for each screening round. After the first round, there was no significant difference between this group and the control group ($\chi^2=6.783$, $df=3$, $p=0.079$). After the second round, interval cancers had a significantly less favourable stage distribution secondary to 41.5% of interval cancers being of Dukes' stage C compared to 29.1% in the non-screened group ($\chi^2=14.422$, $df=3$, $p=0.002$). Conversely, after the third round this effect is reversed, with interval cancers having a better stage distribution ($\chi^2=19.682$, $df=3$, $p<0.001$). Our current study encompasses a mix of the prevalent and incident screening rounds, although it primarily covers that of the first round. It is possible therefore, that if our current study was to continue, a change in the stage profile of the interval cancers may occur. Despite these

variations in stage profile of interval cancers, in each of the three rounds, the Scottish interval cancer patients were found to have a significantly superior survival rate to the non-screened population ($p < 0.001$ for all rounds). In our research, we did not find this. We found no difference in overall survival when the interval cancer group was compared against the control group and non-uptake group. As interval cancers will have presented through symptomatic services, it stands to reason that they will have a similar stage profile to the non-screened population (non-uptake and control), and hence have a similar outcome to these. It also does not support the suggestion that aggressive, fast-growing tumours may disproportionately present as interval cancers after a negative FOB test result.

Steele suggested that the interval cancer group are, by definition, more likely to engage with health professionals and hence have an overall better level of health. This would lead to a better outcome post cancer diagnosis. However, the ASA grade and deprivation level of the interval cancer group were not significantly different from the screen-detected group or the control group, and so this possible effect was not seen to be evident in our study.

As seen in our study, Steele found significantly more screen-detected cancers found in men ($\chi^2 = 29.046$, $p < 0.001$), and in the left colon ($\chi^2 = 41.353$, $p < 0.001$) when compared against interval cancers. This effect was also seen by Morris et al. [164]. Morris used the National Cancer Data Repository linked with the national Bowel Cancer Screening Programme database to review the screening history of those offered screening, with those out with the screening programme. Screen-detected cancers were found more frequently in men (69.2%) compared with the interval cancer group (56.2%), non-participants (62.5%), and their control group of those never invited (61.0%). As seen in our study, the proportion of cancers in patients from the most deprived areas (by income) is greater in the non-participant group, compared to those who underwent screening (23.9% vs. 13.8% for screen-detected cancers & 16.5% for interval cancers), and those who were never invited (15.2% in screening age range).

The stage profile in Morris' paper is again favourable for screen-detected cancers, with 28.9% of cancers being of Dukes stage A. However, the paper suffers from a large amount of missing stage data (17.6%) for screen-detected cancers. Clearly it is not feasible to backfill this missing data item as was done in our study on a national level. It is likely that the unknown Dukes' stages are a mix of polyp cancers that have not undergone a major surgical resection (and hence should be classed as Dukes stage A), along with patients who

were not fit for any procedure due to their co-morbidities or widespread disease dissemination (corresponding predominantly to Dukes stage D). Having a surgical resection means several points in the patient's cancer timeline that their information could be fed into local, and therefore national, cancer registries. Therefore the number of patients with an unknown Dukes stage are unlikely to be of Stage B or C. This will likely have an impact on the true proportions of tumour stage within each group, and so their published results of a 28.9% stage A cancers in the screen-detected group may well be an underestimate.

Morris also found that interval cancers had a similar 1 year survival compared to the control group (78.4% vs. 79.6%, $p=0.548$). This is more in keeping with our research and is likely to reflect the similar stage profiles between these two groups.

Overall 7.8% of interval cancers were found in patients who had returned one unclear kit (one to four windows positive) followed by two normal tests, giving an overall negative result. Whilst this subgroup of cancers showed no significant difference in patient demographics, tumour stage or survival, this may be due to the small sample size. They were, however, diagnosed with their colorectal cancer significantly sooner post completion of the FOBt. This raises the question regarding re-testing at an earlier interval, or for testing with an alternate kit such as an immunohistochemical FOBt (iFOBt) which allows for a differential cut-off level for a positive result.

The National Bowel Cancer Screening Programme in Scotland has adapted its test regime to incorporate the iFOBt. For the population who have an initial unclear test using the guaiac based FOB test, they are asked to repeat a faecal occult blood test using an iFOBt kit. Those with an abnormal iFOBt are invited for a colonoscopy as with the English programme. The results of this technique are yet unpublished. However, use of this test will only increase the sensitivity of a faecal occult blood test, it will not solve the issue of intermittent bleeding from a tumour.

17.5 Outcomes of Screen and Interval Cancers by Dukes Stage

The variable outcome between screen-detected and interval cancer groups for each Dukes stage is an interesting new finding.

At the beginning of the analysis comparing these two groups, the improved survival curve for screen-detected cancers over interval cancers was expected to be secondary to a more favourable stage profile. In particular, as nearly 40% of screen-detected cancers were of Dukes Stage A seemed to be the logical explanation for the survival difference.

The significant difference in survival curves for cancers of Stage A, C and even D, between interval and screen-detected groups, requires an explanation. As is well documented in the literature, survival in intervention group as a whole was found to be influenced by the same variables as that of the control group; patient co-morbidity (using ASA grade as a surrogate), and deprivation level. Even though the proportions of these variables was found to be similar between groups, screen-detected cancers still had an improved survival curve.

It has previously been postulated that interval cancers may develop between screening rounds, and hence be of an aggressive, fast-growing nature. They should therefore have a worse survival rate compared to a control group. However, for each stage of tumour, the survival curves for interval cancers and cancers within the control group were no different. An alternative explanation for the differences in outcomes for each stage of tumour, between interval and screen-detected groups is that, instead of interval cancer group being more aggressive, it is the screen-detected cancers that are more indolent.

The improved survival for virtually all stages of tumours in the screen-detected group could be secondary to these tumours having a low potential for metastasis, and so reducing the risk of a patient having micro-metastases remaining in situ after initial cancer treatment.

The significant difference in survival between screen-detected and interval cancers of Dukes A stage may be a Type II error secondary to the limited follow-up of cases. Dukes' A cancers as a whole have an excellent survival rate, with published figures of a five-year relative survival rate of 93.2% in those diagnosed in England between 1996-2002 [2]. At the end of the follow up period in this study, 99.2% of screen-detected and 94.4% of interval cancers were still alive. As both groups have survival rates equivalent to national data, and as the survival curves appear to converge towards the end of the follow up period, it could be concluded that the differing rates of survival are not clinically significant. A longer term follow up (10 years or more) with larger patient numbers would help to elucidate any true differences in survival.

There are several possible factors that could potentially explain the marked difference in survival for Dukes' C cancers. A difference in proportion of Dukes C1 to Dukes C2 (i.e. involvement of the apical lymph node) between groups does not appear to be one of them. Both groups had a very similar mix of C1 and C2 stages. When survival of each of these groups was analysed, although both curves were more favourable for screen-detected cancers, there was only a significant difference found for C2 tumours ($p=0.002$). However,

given the small numbers within these groups (n=9 and 7), it is difficult to draw any firm conclusions from this.

Another possibility for the difference between groups could lie in the surgical and pathological skill in harvesting an adequate number of lymph nodes for analysis. As mentioned, inadequate lymph node retrieval or identification could lead to under-staging of the tumour or leaving positive lymph nodes in situ. Again, the proportions of cases in which 12 or more nodes were harvested were equivalent between groups, meaning this is an unlikely cause for the survival difference. However, in the interval cancer group, for Dukes' C2 cancers, there was a significantly greater mean number of positive lymph nodes found (15 vs. 4). An explanation for this may be because this subgroup of interval cancers was more aggressive in its regional lymph node spread, and hence outcomes were worse for this group. Although, as discussed above, the small numbers in this subgroup preclude definitive conclusions.

The difference in survival for Dukes' C cancers could, in part, be explained by the significant differences in tumour location. There have been three recent papers that have suggested that for Stage III cancer (American Joint Commission on Cancer (AJCC) Stage, nodal spread), survival is better for left-sided colon lesions (and worse for Stage II) [165-167]. The reasons for this are unclear, but it is thought to be secondary to differences in embryological origin of the colon (i.e. differences in blood supply), genetic, and environmental factors [166]. As there was a significantly greater proportion of distal cancers within the screen-detected cancer group (78% vs. 61%, $p=0.03$), this may explain the superior survival curve for this group. Further evidence to support this is the survival curves broken down by tumour site (for Dukes' C cancers) are not significantly different (right-sided $p=0.097$, left-sided $p=0.184$).

As with other stages of tumour, ASA grade and deprivation level for Dukes' C cancers were found to be equivalent between groups. There was a difference between male and female proportions, with a greater proportion of men having a screen-detected cancer. The improved survival curve of screen-detected cancers is therefore contrary to the improved survival of women at all stages of cancer [2]. When outcomes between groups were broken down by gender, the screen-detected group continued to have a superior survival curve, although this difference was not found to be statistically significant. The lack of significant differences in survival curves between screen and interval cancer groups for Dukes' C cancers when split into Dukes C1 and C2, tumour location and gender may be a Type I error

due to a small sample size. Further analysis is needed on this specific cancer group, with larger numbers.

With regards to Dukes' D tumours, the NORCCAG database does not hold details as to the management of each case of cancer metastasis. It is possible that those screen-detected patients with a Dukes D cancer, may have had a metastasis that was amenable to a surgical resection. A small proportion of liver or lung metastases from a colorectal cancer primary may be amenable for surgical resection, offering the patient a potential cure from their cancer. The significantly higher rate of resective surgery for the primary tumour suggests that this may be the case. If there was widespread dissemination of the cancer, the patient would have likely undergone a palliative procedure, or no procedure at all.

The counter argument to the above discussion is that the differences in survival seen are all secondary to lead-time bias. To attempt to allow for this, an analysis of survival from invitation to screen (i.e. an intention to treat analysis) was performed. This showed that the differences in survival by stage were less marked and so ceased being significant in some stages. However, given the relatively small numbers in each group, an analysis with longer term follow up and larger numbers may prove or disprove the survival differences seen.

17.6 Medication Use in Screen-Detected and Interval cancer Groups

The effect of medication use and its effect on the positivity of the faecal occult blood test have not been previously published.

For a postal survey to healthcare professionals, an average response rate of 57.5% has been previously published for surveys published between 1996-2005 [168]. The response rate of 67.3% in this thesis therefore appears to be acceptable.

Although all patients who were using hormone antagonists at the time of test had a positive FOBt, the actual numbers are too small to draw any firm conclusions as to the significance of this result. This is likely further confounded by the mix of hormones that are being inhibited (testosterone and oestrogen, either directly or via precursors (aromatase inhibition and gonadotrophin releasing hormone, GnRH, agonists)).

Use of non-steroidal anti-inflammatory drugs (NSAIDs) will cause an increase in colonic bleeding due to their action of non-selective inhibition of the enzyme cyclooxygenase (specifically COX-1), and therefore an inhibition of the mucosal-protective prostaglandins [169]. It is unsurprising that use of non-aspirin NSAIDs (NA-NSAIDs) at, or just before, completing the FOBt, was associated with a significantly higher rate of test positivity, compared to the population with a false negative test result (interval cancer group). No

other factors that were associated with a positive test result, as described above, differed between the screen-detected group and interval cancer group, in those who were taking NA-NSAIDs at the time of test. This suggests that it is the medication that has influenced the test result.

Aspirin use has been shown to be associated with a lower neoplasia detection rate in patients with a positive FOBt, but its effect on the positivity of the FOBt in those with a CRC has not been established [170]. In this study, we did not find that aspirin, or other anti-coagulants, influenced the FOBt result. This is despite similar proportions of use. This difference could be secondary to the differing mechanisms of action of aspirin and NA-NSAIDs. Aspirin acts with non-selective inhibition of both COX-1 and COX-2, whereas NA-NSAIDs (such as diclofenac) act by preferentially blocking COX-2, although it still has some COX-1 inhibition.

The population who undergo a cholecystectomy, have an increased risk of colon cancer (119 vs. 86 per 100,000 person-years), with lithogenic bile having been postulated as the underlying mechanism [171]. We did not find a difference in tumour location related to a past history of cholecystectomy, although the total numbers of previous such operations is likely too small to detect such differences. The finding of a greater proportion of women having undergone a cholecystectomy is likely reflective of the higher prevalence of gallstones among women in a Western population [172].

This part of the study adds to our understanding as to why there is a significant rate of interval cancers as part of the screening programme. The bowel cancer screening programme evaluation committee is considering altering its database to include medication use as a key data item. With recent publications regarding the potential positive effects of aspirin in improving outcomes for patients at risk of developing a colorectal cancer, as well as those diagnosed with a cancer, a larger dataset with a longer follow-up period following users of these medications will help to establish their potential benefits. At present, the instructions provided with each test kit ask the screenee to avoid taking NSAIDs at the time of carrying out the test. This study has demonstrated the difficulties in detecting a cancer due to the low sensitivity of the FOBt, and the intermittent bleeding of colorectal cancers. To improve sensitivity (but potentially worsen specificity), removing this instruction from the patient leaflet may be beneficial. The risks associated if all screened individuals were asked to take a course of NSAID at the time of test, would likely outweigh the increase in cancer detection rate, but may be appropriate for those who are already using this group of medications.

17.7 Altering the parameters of an abnormal FOBt Result

The main aim of altering the classification of what is an abnormal faecal occult blood test is to minimise on the number of missed cancers. These occur when a screened individual has an initial unclear first test, followed by two normal tests, giving an overall negative result.

By lowering the minimum criteria for an abnormal an abnormal test, it will mean a greater number that will be invited for a colonoscopy without the need to repeat any test kits. Due to the additional accreditation that screening endoscopists are required to achieve, a screening colonoscopy is a very effective and safe investigation.

By reducing the number of repeat FOBt kits that the screening population need to carry out, it will also minimise the number of patients that drop out from the screening process after one test. Of the 22,410 screening episodes from the whole study group that returned an unclear (1-4 windows positive) first test result, 1,413 (6.3%) did not complete all required FOBt kits. The impact on a patient's health perception in being advised to undergo a colonoscopy after one test kit should not be underestimated. The survival of those who have three or four positive windows on their first FOBt is significantly better than those who have five or six positive windows. Patients with an abnormal first test are more reflective of symptomatic interval and non-uptake cancers in their stage profile, whereas those with three or four positive windows have a more favourable stage profile, and so should be targeted specifically to improve outcomes of those cancers potentially detectable by FOB screening.

The cost effectiveness analysis has shown that a change to the minimum number of positive windows to three, gives the best return for additional cancer detection, whilst being cost-effective in its implementation.

It could be argued that the control cancers and the non-uptake cancers should not be included in the overall figures as they were not diagnosed through screening. However, the speed of diagnosis from FOBt result to screening colonoscopy is likely to improve with patients only having to submit one test. Therefore the control group may be able to complete the screening process. For non-uptake cancers, the impact of a patient hearing the test is abnormal and that they will be offered a clinic appointment for consideration of a colonoscopy, is likely to improve uptake. It is of note that no patients who had an abnormal test declined a screening colonoscopy. One of the main barriers to completing a FOBt screening episode is the process itself. By increasing the proportion of the population who only need to complete one FOBt kit, compliance with further aspects of the screening process are also likely to improve.

The number of additional cancers detected is unlikely to reach the maximum numbers presented in Chapter 16, however, even if the value lies between this and the minimum number, it is possible that the increased costs in such a change to the screening protocol will lie close to NICE's willingness to pay threshold of £20,000 per quality adjusted life year (QALY).

17.8 Limitations of Study

17.8.1 Database Accuracy and Completeness

The largest problem with a database study is always going to relate to the accuracy of the inputted data, as well as missing data.

In this study, once the study group was identified and the relevant data extracted from the NORCCAG database, a large amount of time was spent validating the dataset. As described, this included reviewing the source hospital data for the majority of patients, filling in missing data as appropriate.

NORCCAG is known not to be a complete dataset. The 2010 NBOCAP annual report described case ascertainment of approximately 81% for the North of England cancer network [173]. Its aims are to record all colorectal cancer patients known to the colorectal multi-disciplinary team meetings (MDT's) in each region. Inherently, this may mean that patients who are not discussed in an MDT are missed from the database. This is likely to be less of a problem compared to the older age groups, as most patients will be suitable to undergo a form of treatment, be it surgical resection or palliative chemo/radiotherapy. At the least, possible treatment options will be discussed, which should trigger their information being recorded on the hospital cancer registry. With new advances into different chemotherapy regimes, the need for a tissue diagnosis so that the correct combination of therapeutic agents can be used, is increasing. This means that there are more cases of colonoscopies or liver biopsies being performed to obtain adequate samples to guide treatment. These interventions will increase the number of cases discussed at MDTs and therefore should improve completeness of the database.

Due to the large amount of missing data that was prevalent throughout the NORCCAG database, virtually all records were reviewed. This will have helped to minimise on the inaccuracies of the dataset. However, initial data entry to NBOCAP is performed by audit clerks who have no medical training or background, and therefore do not have the clinical knowledge to identify implausible data entries. NBOCAP has a small amount of inbuilt data

validation queries, such as no cancer may be classed as being located in the rectum if it's height from the dentate line is greater than 15cm. However, these validation steps are not exhaustive, hence the need for more extensive validation queries to be written after importing the data into the NORCCAG database.

The importing of data from multiple data sources and the combination of these is another possible source of data corruption. Although each record was reviewed for face validity, it is possible that one section of data from, for example, the BCSP database, may have been incorrectly linked with the corresponding data of the NORCCAG database. Without direct access to the screening database to validate all data entries, it is impossible to be sure of complete data accuracy.

The most important method of improving the completeness of the dataset, to ensure all eligible patients are captured, is by triangulating data sources. There are several different methods that this could take place. The first is using a national cancer registry. The National Cancer Intelligence Network "provides a national repository for cancer datasets" [174]. This database was used by Morris et al. [175], but has the specific problem with missing data. As described, 17.6% of screen detected cancers had a missing Dukes' stage. If this dataset were available for use, then I would expect that its role would be that of validation of the NORCCAG database, with the records that were complete. A similar database that could have been used would be that of "Hospital Episode Statistics (HES)", provided by the Health and Social Care Information Centre [176]. Its role is that of a "data warehouse containing details of all admissions, outpatient appointments and A&E attendances at NHS hospitals in England". Use of this dataset may minimise on any missing subjects, who will have received a form of treatment for their CRC. The third would be to use local hospital databases. Examples might be pathology databases for all with proven adenocarcinomas of a colorectal origin, or waiting-times data.

The problem with using multiple sources is that it increases the complexity of permissions to obtain each of them. Appropriate consolidation of data must take place to avoid duplicate records. Adequate data security is also needed.

For patients who had no surgical intervention, or for those who declined one part of the screening process, it was necessary to review patient letters. This allowed the actual route to diagnosis to be analysed, and for specific reasons as to why a patient did not undergo an operation. Missing from a database study are the qualitative aspects of the project. Access to databases was granted on the basis that there would be no direct patient contact,

therefore further permissions would have been required before any such study could take place.

Given the effort put into ensuring that the extracted NORCCAG dataset was as complete as possible, use of additional databases would have been unlikely to significantly alter the dataset that was used for analysis. The only exception to this may have been that there were a small number of subjects that could have been included in the study group. However, I would anticipate that this would not have significantly changed the results found.

17.8.2 Missing Cause of Deaths

Within this thesis, an improved all-cause mortality rate has been shown for screen-detected cancers over other cancer groups. Whilst NORCCAG collects dates of death via the Office of National Statistics, the database does not contain information regarding the cause of death. With the most recent update based on the Nottingham study showing no difference in all-cause mortality rates between intervention and control groups, but an improvement in colorectal cancer specific mortality, having an accurate validated cause of death would be extremely advantageous. As discussed, the risk factors and patient demographics that are associated with the development of a colorectal cancer (e.g. smoking, deprivation status, etc.), are also strongly associated other conditions and hence causes of death. Causes of death would have been of particular interest in the non-uptake group which was found to have higher proportions of these risk factors. If an analysis of cancer-specific mortality was performed, this may have potentially had a large impact on the survival curves seen. It may be that the non-uptake group has a better survival compared to the interval cancer group, which did not have these higher levels of risk factors.

Having cancer-specific causes of death would help in the comparison between screen and interval cancers, when corrected for Dukes' stage. If it is a cancer recurrence that is a primary cause of death in the interval cancer group, this would add to evidence of an aggressive interval cancer. This may also have implications as to how these cancers should be managed, either with a lower threshold for post-operative chemotherapy, or more aggressive management of early tumours with segmental bowel resection over local excisions.

17.8.3 Variable Patient Management between Hospital Trusts

Within the study location of the North East of England, there is a mix of district general hospitals and tertiary referral centres. Within each of these trusts, there is not always a screening colonoscopist. This may mean that for patients presenting through symptomatic services, they may have their cancer managed differently to that in other trusts. In particular, for T1 cancers, if the patient has a colonoscopy by a screening colonoscopist or by a consultant who performs TEMS procedures, they may be more likely undergo a local excision, without the need for a formal segmental bowel resection. Similarly, as we do not have the data regarding cause of death, there is a possibility of a missed cancer at endoscopy (screening or non-screening) which reflects the variable ability of the regions endoscopists. However, the chances of this happening are remote.

With the increasing prevalence of polyp cancers being detected through the screening programme, the need for accurate histological assessment of these is crucial to their further management. Differences in abilities of histopathologists in being able to confidently report on completeness of excision of these cancers between trusts, may impact on whether the patient undergoes a resective procedure. The management of these polyp cancers has been shown to vary between hospital trusts [177].

17.8.4 Mix of Screening Rounds

To date, the majority of screening research that has been published has concentrated on dividing the cancers detected by screening rounds. By doing this, the researcher can assess the impact that each screening round has on a population. The difficulty in doing this as part of the National Screening Programme, was the considerable time taken for the roll-out of the whole region. The extent of this delay was not expected initially, and hence the proportion of cancers that were included in the control group was higher than initially thought. The commencement of the study period in April 2007 was to allow two months of initial invites to circulate, expecting that this would be a significant number. In retrospect, the start of the study should have been at January or February 2007. This would have ensured that a complete screening round was captured.

As each colorectal cancer within the Northern Colorectal Cancer Database is stored predominately by diagnosis date, this was the easiest data item to identify the study population. A three year study period therefore meant that there was a mix of cancers that were diagnosed from the prevalent (1st) round and incident (2nd) round. Although the vast

majority of cases were diagnosed after an offer of a patient's first screening test, there were 5.6% (46 of 825) of cancers diagnosed in the incident round.

The difficulty that having a mix of two screening rounds leads to is that there may be pathological, and therefore outcome, differences between cancers from the two rounds. As seen by Steele in the results of the Scottish Pilot data, the stage proportions, particularly of interval cancers, vary between screening rounds. Although their interval cancers were found to have an improved survival rate compared to their control group in each screening round, we did not find this in our study population. Isolating the prevalent from the incident screening round is at present unfeasible, as the North East of England population should be commencing the third round of screening between March 2011 and March 2012. This means that the most recent colorectal cancer cases will not be available for analysis until January 2013, after entry to regional and national registries. Adequate follow up of these cases to review patient outcomes will delay analysis further.

Chapter 18 Conclusions and Areas for Future Research

18.1 Conclusion

This thesis demonstrates the impact of the bowel cancer screening programme within one region of England since it has been rolled out nationally. By using a combination of a regional colorectal cancer registry, as well as the regional bowel cancer screening database, it has been possible to identify the screening history for all patients diagnosed with a cancer, in the population eligible for screening.

We have shown that, of the virtually one million screening invitations sent, with an uptake of 56%, there were 825 colorectal cancers diagnosed. What was not expected at the outset of the study, was the availability of a control group of 511 patients, who were in the same age range and diagnosed in the same time frame as those invited for screening.

Of the 825 cancers diagnosed in those invited for screening, 311 (37.7%) were diagnosed in patients who did not take up or complete their screening episode. Of the 514 cancers diagnosed in those who completed a screening episode, 322 (67.6%) were detected through screening, and 192 (37.4%) were diagnosed between screening rounds after a negative episode (interval cancers).

With its national implementation, the NHS BCSP exceeds the outcomes of the preliminary studies. In particular, the proportion of screen-detected cancers has improved compared to the Nottingham based studies, with a decrease in the proportion of non-uptake cancers. Screen-detected cancers had a favourable stage profile, and a far superior survival rate compared to the control group.

However, there are still large numbers of cancers that are not detected through the guaiac-based faecal occult blood test. In particular, failure of the current methods to detect right sided cancers and cancers in women requires further research as this group comprise a significant number of patients falsely reassured by their results. For these interval cancers, in contrast to earlier research, they have an equivalent tumour stage profile, and survival rate, compared to those who do not take up screening, or the control group.

The earlier stage shift was not found to be the sole reason for the improved survival rates of screen-detected cancers over interval cancers. With an additional survival benefit for each Dukes stage of screen-detected cancers, it is possible that these cancers have a different biology to those previously seen. They bleed more, and appear to be more indolent in nature. Further research is needed to confirm this suggestion.

Non-aspirin non-steroidal anti-inflammatory use within two months of carrying out a FOBt has been shown to be associated with a positive test result. This effect has not previously

been demonstrated, and suggests that removing the instructions to avoid their use from the patient information may be beneficial in terms of cancer detection.

For the population who undergo screening, an argument has been made for altering the criteria for an abnormal faecal occult blood test from a minimum of five (out of six) positive windows, to a minimum of three. A cost-effectiveness analysis has shown that such an amendment to the screening pathway may be feasible. Suggestions for further research are described below.

18.2 Areas for Future Research

There are several areas that would benefit for future research on the basis of the results in this study. These are described below.

18.2.1 Cohort Study into Change to FOBt Result Classification

As discussed above, there may be a benefit in altering the criteria for an abnormal FOBt to a lower cut-off in the number of positive windows. Due to the small size numbers and the heterogeneity of the groups that had an initial unclear FOBt kit result, further research is needed to validate the findings described in Chapter 16.

An analysis of the national bowel cancer screening database along with national cancer registries would mean a larger sample size suitable for analysis. However, larger sample sizes would be inherently more challenging to match each patient to each FOB kit result.

An alternative would be a randomised controlled trial. The sample group of patients would be those who had three or four positive windows on their first FOBt, followed by two normal (0/6 windows positive) FOBt's, giving them an overall normal result under current guidelines. In one arm the subjects would be offered a colonoscopy, whereas no investigation would be offered to the other group. The second arm would be followed up to see if they were diagnosed through symptomatic services before the next screening round, and also the result of their subsequent screening episode. A comparison between these two groups would aim to identify all possible pathology that would have normally not have been detected under current screening practice. The cost-effectiveness of such a change in practice would be crucial to any potential alteration of the screening pathway.

18.2.2 Histological Analysis of Post-FOBT Interval Cancers and Screen-detected Cancers

As discussed in the interval cancer chapter, there are associations between a range of genetic abnormalities and the development of interval colorectal cancers. However, these studies have predominantly been based on post-colonoscopy interval cancers. As the sensitivity of a colonoscopy is extremely high at detecting a colorectal cancer, this will increase the likelihood that there will be histological differences in these cancers compared to one picked up through symptomatic or screening services. To date, there have been no studies that have performed this type of analysis on post-FOBT interval cancers. From the results of this study, we know that the FOBT appears to be more effective at detecting cancers in the left colon and in men. Do these interval cancers have the same overall macroscopic appearance? Do they have the same degree of microsatellite instability, or associated genetic abnormalities? Are there any differences in the vascularity of screen and interval cancers that lead one group to bleed more and hence improve detection rates using the faecal occult blood test? This analysis could take place on the cohort identified within this study and would add valuable information as to the relatively high rates of interval cancers within the bowel cancer screening programme.

This histological analysis should also include that of the screen-detected cancers. As suggested, patients with these cancers have a better survival rate with equivalent stage of tumour. Of particular interest would be the gross structure of these tumours, their histological subtypes and any associated genetic differences to that of a control group, and the interval cancers.

18.2.3 Qualitative Study with Interval Cancer Patients

There has been, and is, on-going research into the reasons behind why a large population do not take up the offer of FOBt screening. However, there have been no published articles on the health values of patients who are diagnosed with a colorectal cancer, after a normal FOBt. A qualitative study could be carried out on the impact of being diagnosed with a cancer after been given the 'all-clear' by the screening programme. The effects of a false negative in a screening programme can be split into the medical outcomes (morbidity and mortality, which have been covered in this study), the psychological outcomes, the economic outcomes and the legal outcomes. A systematic review was carried out in 2000 that looked at the above issues however colorectal cancer screening was not covered [178].

18.3 Personal Reflection on this Research

General surgical training has changed significantly over the past few years. Previously, doctors wishing to go into surgical practice would spend prolonged periods at a senior house officer (SHO) grade. During this time, they would gain valuable operative experience and improve their CV in preparation for gaining a registrar post and national training number. With the advent of modernising medical careers (MMC), this route into surgical training has gone. Current training is much more "stream-lined" with two years core surgical training after completion of the mandatory two foundation years. The application process for gaining a training number is now a national procedure, which means you are competing for places with a nationwide cohort. Therefore, to score highly on the relevant stations, an applicant must have an outstanding portfolio.

It was with this in mind that I decided to apply for and carry out this project. I feel I have gained a great deal from this MD research degree. It has helped me develop an analytical view point. I have changed the way in which I approach my surgical practice. I now frequently review the current literature and guidelines to develop my skills as an evidence-based practitioner. I have further developed my knowledge of statistical analysis of quantitative research, and would feel confident in applying its principles in future work.

The hardest challenge for me during the past two years has been gaining access to each hospital trust, in order to validate the dataset. This process took over 6 months from initial contact with the trusts to gaining access to all of them. I found it particularly frustrating when passed from department to department, with each contact denying any responsibility for helping with the project. There was a large discrepancy between trusts,

with some responding very quickly and allowing access almost immediately, and others taking 6 months of discussion, form filling, and meetings before approval. This difference made the process even more trying. If I were to repeat the process again, however, I feel I would be able to gain complete access quicker. Face to face meetings with research and development teams, as opposed to correspondence via email, would have been the most beneficial step in speeding up the process.

This project has highlighted areas for future research, based on this project. I plan to be involved with these, allowing me to further develop my skills as an academic surgeon.

References

1. Office for National Statistics. *Bowel Cancer: Little change in mortality*. 2010 [cited 2010; Available from: <http://www.statistics.gov.uk/CCI/nugget.asp?ID=2162&Pos=&ColRank=1&Rank=374>.
2. Cancer Research UK. *Bowel (colorectal) cancer - UK incidence statistics*. 2010; Available from: <http://info.cancerresearchuk.org/cancerstats/types/bowel/incidence/#source20>.
3. National Cancer Intelligence Network, *The Excess Burden of Cancer in Men in the UK*, 2010.
4. Regula, J., et al., *Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia*. *New England Journal of Medicine*, 2006. **355**(18): p. 1863-72.
5. Edna, T. and T. Bjerkeset, *Colorectal cancer in patients over 80 years of age*. *Hepatogastroenterology*, 1998 **45**(24): p. 2142-5.
6. Colorectal Cancer Collaborative Group, *Surgery for colorectal cancer in elderly patients: a systematic review*. *Lancet*, 2000. **356**(9234): p. 968-74.
7. European Commission, *European guidelines for quality assurance in colorectal cancer screening and diagnosis*, Segnan N, Patnick J, and v.K. L., Editors. 2011.
8. Ganapathi, S., et al., *Colorectal cancer in the young: trends, characteristics and outcome*. *International Journal of Colorectal Disease*, 2011. **26**(7): p. 927-934.
9. O'Connell, J.B., et al., *Colorectal cancer in the young*. *The American Journal of Surgery*, 2004. **187**(3): p. 343-348.
10. Faivre, J., A. Bouvier, and C. Bonithon Kopp, *Epidemiology and screening of colorectal cancer*. *Best Practice in Research and Clinical Gastroenterology*, 2002. **16**: p. 187-199.
11. National Cancer Intelligence Network, *Cancer Incidence by Deprivation England, 1995-2004*, 2008. p. 1-34.
12. Botteri, E., et al., *Smoking and Colorectal Cancer: A Meta-analysis*. *JAMA*, 2008. **300**(23): p. 2765-2778.
13. Matsumara, Y., *Nutrition trends in Japan*. *Asia Pacific Journal of Clinical Nutrition*, 2001. **10**(Suppl): p. S40-7.
14. Center, M.M., A. Jemal, and E. Ward, *International Trends in Colorectal Cancer Incidence Rates*. *Cancer Epidemiology Biomarkers & Prevention*, 2009. **18**(6): p. 1688-1694.
15. Thomas, E., et al., *Risk of malignancy among patients with rheumatic conditions*. *International Journal of Cancer*, 2000. **88**(3): p. 497-502.
16. Shadman, M., et al., *Non-steroidal anti-inflammatory drugs and statins in relation to colorectal cancer risk*. *World Journal of Gastroenterology*, 2009. **15**(19): p. 2336-9.
17. Chan, A.T., S. Ogino, and C.S. Fuchs, *Aspirin use and survival after diagnosis of colorectal cancer*. *JAMA*, 2009. **302**(6): p. 649-58.
18. Algra, A.M. and P.M. Rothwell, *Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials*. *The Lancet Oncology*, 2012. **13**(5): p. 518-527.
19. Rothwell, P.M., et al., *Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials*. *The Lancet*, 2012. **379**(9826): p. 1591-1601.

20. Burn, J., et al., *Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial*. The Lancet, 2011. **378**(9809): p. 2081-2087.
21. Dale, K.M., *Statins and Cancer Risk: A Meta-analysis*. JAMA: The Journal of the American Medical Association, 2006. **295**(1): p. 74-80.
22. Winawer, S.J., *Natural history of Colorectal Cancer*. The American Journal of Medicine, 1999. **106** (1A): p. 3S-6S.
23. Samowitz, W.S., et al., *The colon cancer burden of genetically defined hereditary nonpolyposis colon cancer*. Gastroenterology, 2001. **121**(4): p. 830-838.
24. Strate, L.L. and S. Syngal, *Hereditary colorectal cancer syndromes*. Cancer Causes & Control, 2005. **16**(3): p. 201-13.
25. Iino, H., *DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer*. Gut, 2000. **47**(1): p. 37-42.
26. Lynch, H., et al., *Natural History of Colorectal Cancer in Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndromes I and II)*. Diseases of the Colon & Rectum, 1988. **31**(6): p. 439-444.
27. Vasen, H.F.A., et al., *The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC)*. Diseases of the Colon & Rectum, 1991. **34**: p. 424-425.
28. Bellacosa, A., et al., *Hereditary nonpolyposis colorectal cancer: Review of clinical, molecular genetics, and counseling aspects*. American Journal of Medical Genetics, 1996. **62**(4): p. 353-364.
29. Umar, A., et al., *Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability*. Journal of the National Cancer Institute, 2004. **96**(4): p. 261-268.
30. Powell, S., et al., *APC mutations occur early during colorectal tumourigenesis*. Nature, 1992. **359**: p. 235-237.
31. Jass, J.R., *Do All Colorectal Carcinomas Arise in Preexisting Adenomas?* World Journal of Surgery, 1989. **13**(1): p. 45-51.
32. Koessler, T., et al., *Common variants in mismatch repair genes and risk of colorectal cancer*. Gut, 2008. **57**(8): p. 1097-101.
33. Kang, K.J., et al., *Adenoma incidence after resection of sporadic colorectal cancer with microsatellite instability*. Journal of Surgical Oncology, 2010. **101**(7): p. 577-81.
34. Popat, S., *Systematic Review of Microsatellite Instability and Colorectal Cancer Prognosis*. Journal of Clinical Oncology, 2004. **23**(3): p. 609-618.
35. Des Guetz, G., et al., *Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis*. European Journal of Cancer, 2009. **45**(10): p. 1890-6.
36. Des Guetz, G., et al., *Microsatellite instability: a predictive marker in metastatic colorectal cancer?* Targeted Oncology, 2009. **4**(1): p. 57-62.
37. Shaukat, A., et al., *Is BRAF mutation associated with interval colorectal cancers?* Digestive Diseases & Sciences, 2010. **55**(8): p. 2352-6.
38. Samowitz, W.S., et al., *Poor Survival Associated with the BRAF V600E Mutation in Microsatellite-Stable Colon Cancers*. Cancer Res, 2005. **65**(14): p. 6063-6070.
39. Sanchez, J.A., et al., *Genetic and epigenetic classifications define clinical phenotypes and determine patient outcomes in colorectal cancer*. British Journal of Surgery, 2009. **96**(10): p. 1196-204.
40. Ferracin, M., et al., *The methylator phenotype in microsatellite stable colorectal cancers is characterized by a distinct gene expression profile*. The Journal of Pathology, 2008. **214**(5): p. 594-602.
41. Toyota, M., et al., *CpG island methylator phenotype in colorectal cancer*. Proc. Natl. Acad. Sci. USA, 1999. **96**: p. 8681-8686.

42. UK National Screening Committee. *What is screening? Definition*. 2010; Available from: <http://www.screening.nhs.uk/screening>.
43. Wilson, J.M.G. and G. Jungner, *Principles and practice of screening for disease*. World Health Organization, 1968.
44. Morabia, A. and F.F. Zhang, *History of medical screening: from concepts to action*. Postgraduate Medical Journal, 2004. **80**: p. 463-469.
45. Quinn, M., et al., *Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics*. eBMJ, 1999. **318** p. 1-5.
46. Bretthauer, M. and G. Hoff, *Comparative effectiveness research in cancer screening programmes*. BMJ, 2012. **344**.
47. Mitchell, H., G. Medley, and G. Giles, *Cervical cancers diagnosed after negative results on cervical cytology: perspective in the 1980s*. BMJ, 1990 **300**(6740): p. 1622-1626.
48. Herbert, A., et al., *Invasive cervical cancer audit: a relative increase in interval cancers while coverage increased and incidence declined*. BJOG: An International Journal of Obstetrics & Gynaecology, 2009. **116**(6): p. 845-853.
49. McPherson, K., *Screening for breast cancer—balancing the debate*. BMJ, 2010. **340**.
50. Advisory Committee on Breast Cancer Screening, *Screening for Breast Cancer In England: Past and Future*, NHSBSP, Editor 2006. p. 1-60.
51. Gøtzsche, P. and M. Nielsen, *Cochrane review of breast cancer screening with mammography*. Cochrane Database of Systematic Reviews, 2009(4).
52. Kalager, M., et al., *Effect of Screening Mammography on Breast-Cancer Mortality in Norway*. New England Journal of Medicine, 2010. **363**(13): p. 1203-1210.
53. Welch, H.G., *Screening Mammography — A Long Run for a Short Slide?* New England Journal of Medicine, 2010. **363**(13): p. 1276-1278.
54. Baum, M., H. Thornton, and P.C. Gøtzsche, *Still awaiting screening facts*. BMJ, 2010. **341**.
55. Cancer Research UK. *Breast Screening Programme Activity*. 2012; Available from: <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/screening/Programme-Activity/>.
56. Jørgensen, K.J. and P.C. Gøtzsche, *Presentation on websites of possible benefits and harms from screening for breast cancer: cross sectional study*. BMJ, 2004. **328**: p. 148.
57. Pharoah, P.D.P., et al., *Cost effectiveness of the NHS breast screening programme: life table model*. BMJ, 2013. **346**.
58. Independent UK Panel on Breast Cancer Screening, *The benefits and harms of breast cancer screening: an independent review*. The Lancet, 2012. **380**(9855): p. 1778-1786.
59. Jellema, P., et al., *Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis*. BMJ, 2010. **340**(mar31 3): p. c1269-c1269.
60. Ahnen, D.J., et al. *Clinical manifestations, diagnosis, and staging of colorectal cancer*. 2010 September 20 2010; 18.3:[Available from: www.uptodate.com].
61. Steinberg, S.M., et al., *Prognostic indicators of colon tumors. The gastrointestinal tumor study group experience*. Cancer, 1986. **57**(9): p. 1866-1870.
62. Ford, A.C., et al., *Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis*. Gut, 2008. **57**(11): p. 1545-53.
63. Fijten, G.H., G.H. Blijham, and J.A. Knottnerus, *Occurrence & significance of overt blood loss per rectum in the general practice population and in medical practice*. British Journal of General Practice, 1994. **44**(384): p. 320-325.

64. Svendsen, R.P., et al., *Prevalence of cancer alarm symptoms: A population-based cross-sectional study*. Scandinavian Journal of Primary Health Care, 2010. **28**(3): p. 132-137.
65. Hamilton, W., et al., *The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study*. BMC Medicine, 2009. **7**(1): p. 17.
66. McCallion, K., et al., *Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening*. Gut, 2001. **48**(4): p. 522-525.
67. Thörn, M., et al., *Trends in colorectal cancer incidence in Sweden 1959-93 by gender, localization, time period, and birth cohort*. Cancer Causes and Control, 1998. **9**(2): p. 145-152.
68. Rabeneck, L., J.A. Davila, and H.B. El-Serag, *Is There a True "Shift" to the Right Colon in the Incidence of Colorectal Cancer?* American Journal of Gastroenterology, 2003. **98**(6): p. 1400-1409.
69. Majumdar, S.R., R.H. Fletcher, and A.T. Evans, *How does colorectal cancer present? Symptoms, duration, and clues to location*. American Journal of Gastroenterology, 1999. **94**(10): p. 3039-45.
70. Macrae, F.A. and D.J.S. John, *Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancers or adenomas*. Gastroenterology, 1982. **82**(5): p. 891-898.
71. Anand, P.P., *Unusual Infections Associated with Colorectal Cancer*. Reviews of Infectious Diseases, 1988. **10**(2): p. 347-364.
72. Thompson, M.R., et al., *Earlier diagnosis and treatment of symptomatic bowel cancer: can it be achieved and how much will it improve survival?* Colorectal Disease, 2011. **13**(1): p. 6-16.
73. Smith, D., et al., *Symptomatic presentation of early colorectal cancer*. Annals of the Royal College of Surgeons of England, 2006. **88**(2): p. 185-90.
74. Harmston, C., et al., *Are screen detected colorectal cancers asymptomatic?* Colorectal Disease, 2010. **12**(5): p. 416-9.
75. Ahmed, S., et al., *Lower gastrointestinal symptoms are not predictive of colorectal neoplasia in a faecal occult blood screen-positive population*. British Journal of Surgery, 2005. **92**(4): p. 478-481.
76. Conrad, M.E. *Iron Deficiency Anemia: Treatment & Medication*. 2009; Available from: <http://emedicine.medscape.com/article/202333-overview>.
77. NICE, *Improving Outcomes in Colorectal Cancers - Manual Update*, 2004. p. 1-136.
78. John, S.K.P., et al., *Symptoms and signs in patients with colorectal cancer*. Colorectal Disease, 2011. **13**(1): p. 17-25.
79. Thompson, M.R., et al., *Flexible sigmoidoscopy and whole colonic imaging in the diagnosis of cancer in patients with colorectal symptoms*. British Journal of Surgery, 2008. **95**(9): p. 1140-1146.
80. Atkin, W.S., et al., *Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial*. The Lancet, 2010. **375**(9726): p. 1624-1633.
81. Atkin, W.S., et al., *Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening*. Gut, 1998. **42**(4): p. 560-565.
82. Brotherstone, H., et al., *Uptake of population-based flexible sigmoidoscopy screening for colorectal cancer: a nurse-led feasibility study*. Journal of Medical Screening, 2007. **14**(2): p. 76-80.
83. Hoff, G., et al., *Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial*. BMJ, 2009. **338**.
84. Segnan, N., et al., *Once-Only Sigmoidoscopy in Colorectal Cancer Screening: Follow-up Findings of the Italian Randomized Controlled Trial—SCORE*. Journal of the National Cancer Institute, 2011. **103**(17): p. 1310-1322.

85. Piscatelli, N., N. Hyman, and T. Osler, *Localizing colorectal cancer by colonoscopy*. Archives of Surgery, 2005. **140**(10): p. 932-5.
86. Lansdorp-Vogelaar, I., et al., *Individualizing colonoscopy screening by sex and race*. Gastrointestinal Endoscopy, 2009. **70**(1): p. 96-108, 108.e1-24.
87. Imperiale, T.F., et al., *Five-year risk of colorectal neoplasia after negative screening colonoscopy*. New England Journal of Medicine, 2008. **359**(12): p. 1218-24.
88. Singh, H., et al., *Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies*. JAMA, 2006. **295**(20): p. 2366-73.
89. Burnand, B., et al., *Use, appropriateness, and diagnostic yield of screening colonoscopy: an international observational study (EPAGE)*. Gastrointestinal Endoscopy, 2006. **63**(7): p. 1018-26.
90. Tribonias, G., et al., *Comparison of standard vs high-definition, wide-angle colonoscopy for polyp detection: a randomized controlled trial*. Colorectal Disease, 2010. **12**(10Online): p. e260-e266.
91. Kahi, C.J., et al., *High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening*. American Journal of Gastroenterology, 2010. **105**(6): p. 1301-7.
92. van den Broek, F.J., P. Fockens, and E. Dekker, *Review article: New developments in colonic imaging*. Alimentary Pharmacology & Therapeutics, 2007. **26 Suppl 2**: p. 91-9.
93. Brown, S.R., W. Baraza, and P. Hurlstone, *Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum*. Cochrane Database of Systematic Reviews, 2007(4).
94. Kaltenbach, T., S. Friedland, and R. Soetikno, *A randomised tandem colonoscopy trial of narrow band imaging versus white light examination to compare neoplasia miss rates*. Gut, 2008. **57**(10): p. 1406-12.
95. Ignjatovic, A., et al., *Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study*. The Lancet Oncology, 2009. **10**(12): p. 1171-1178.
96. Moeller, D.D., *The Odyssey of Guaiac*. The American Journal of Gastroenterology, 1984. **79**(3): p. 236-237.
97. Beckman Coulter, Inc, *Hemoccult Physicians' #1 Choice in Fecal Occult Blood Testing*, in *Haemoccult Product Leaflet* 2003.
98. Hardcastle, J.D., et al., *Fecal occult blood screening for colorectal cancer in the general population. Results of a controlled trial*. Cancer, 1986. **58**(2): p. 397-403.
99. Hardcastle, J.D., et al., *Randomised, controlled trial of faecal occult blood screening for colorectal cancer. Results for first 107,349 subjects*. Lancet, 1989. **1**(8648): p. 1160-4.
100. Hardcastle, J., et al., *Randomised controlled trial of faecal-occult-blood screening for colorectal cancer*. The Lancet, 1996. **348**(9040): p. 1472-1477.
101. Scholefield, J.H., et al., *Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial*. Gut, 2002. **50**(6): p. 840-4.
102. Scholefield, J.H., et al., *Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up*. Gut, 2012. **61**: p. 1036-1040.
103. Thomas, W.M., et al., *Role of dietary restriction in Haemoccult screening for colorectal cancer*. British Journal of Surgery, 1989. **76**(9): p. 976-8.
104. Kronborg, O., et al., *Initial mass screening for colorectal cancer with fecal occult blood test. A prospective randomized study at Funen in Denmark*. Scandinavian Journal of Gastroenterology, 1987. **22**(6): p. 677-86.
105. Kronborg, O., et al., *Randomised study of screening for colorectal cancer with faecal-occult-blood test*. The Lancet, 1996. **348**(9040): p. 1467-1471.

106. Mandel, J.S., et al., *Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood*. Journal of the National Cancer Institute, 1999. **91**(5): p. 434-7.
107. Faivre, J., et al., *Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study*. Gastroenterology, 2004. **126**(7): p. 1674-80.
108. Faivre, J., et al., *Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study*. British Journal of Cancer, 1999. **79**(3-4): p. 680-3.
109. Selby, J.V., et al., *Effect of fecal occult blood testing on mortality from colorectal cancer. A case-control study*. Annals of Internal Medicine, 1993. **118**(1): p. 1-6.
110. Lindholm, E., H. Brevinge, and E. Haglund, *Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer*. British Journal of Surgery, 2008. **95**(8): p. 1029-36.
111. Heresbach, D., et al., *Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test*. European Journal of Gastroenterology & Hepatology, 2006. **18**(4): p. 427-433.
112. Towler, B., et al., *A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult*. BMJ, 1998. **317**(7158): p. 559-65.
113. Hewitson, P., et al., *Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update*. American Journal of Gastroenterology, 2008. **103**(6): p. 1541-9.
114. Kewenter, J., et al., *Screening and rescreening for colorectal cancer. A controlled trial of fecal occult blood testing in 27,700 subjects*. Cancer, 1988. **62**(3): p. 645-651.
115. Kewenter, J., et al., *Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects*. Scandinavian Journal of Gastroenterology, 1994. **29**(5): p. 468-73.
116. Autier, P., et al., *Is FOB screening really the answer for lowering mortality in colorectal cancer?* Recent Results in Cancer Research, 2003. **163**: p. 254-63; discussion 264-6.
117. Stone, C.A., et al., *Colorectal cancer screening in Australia: an economic evaluation of a potential biennial screening program using faecal occult blood tests*. Australian & New Zealand Journal of Public Health, 2004. **28**(3): p. 273-82.
118. Robinson, M.H., et al., *The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer*. Gut, 1999. **45**(4): p. 588-92.
119. Mandel, J.S., et al., *The effect of fecal occult-blood screening on the incidence of colorectal cancer*. New England Journal of Medicine, 2000. **343**(22): p. 1603-7.
120. Cooper, G.S., et al., *Prevalence and predictors of interval colorectal cancers in Medicare beneficiaries*. Cancer, 2012. **118**(12): p. 3044-3052.
121. Harvey, N.T. and A. Ruzkiewicz, *Serrated neoplasia of the colorectum*. World Journal of Gastroenterology, 2007 **13**(28): p. 3792-3798.
122. Hawkins, N.J. and R.L. Ward, *Sporadic Colorectal Cancers With Microsatellite Instability and Their Possible Origin in Hyperplastic Polyps and Serrated Adenomas*. Journal of the National Cancer Institute, 2001. **93**(17): p. 1307-1313.
123. Arain, M.A., et al., *CIMP Status of Interval Colon Cancers: Another Piece to the Puzzle*. American Journal of Gastroenterology, 2010. **105**(5): p. 1189-1195.
124. Lansdorp-Vogelaar, I., et al., *A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials*. Cancer, 2009. **115**(11): p. 2410-9.

125. Wu, D., D. Erwin, and G.L. Rosner, *Estimating key parameters in FOBT screening for colorectal cancer*. *Cancer Causes & Control*, 2009. **20**(1): p. 41-6.
126. Shah, H.A., et al., *Factors associated with incomplete colonoscopy: a population-based study*. *Gastroenterology*, 2007. **132**(7): p. 2297-303.
127. Schoen, R.E., et al., *Results of repeat sigmoidoscopy 3 years after a negative examination*. *JAMA*, 2003. **290**(1): p. 41-8.
128. Hixson, L.J., et al., *Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps*. *Gastrointestinal Endoscopy*, 1991. **37**(2): p. 125-127.
129. Rex, D.K., et al., *Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies*. *Gastroenterology*, 1997. **112**(1): p. 24-28.
130. Brenner, H., et al., *Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study*. *Journal of the National Cancer Institute*, 2010. **102**(2): p. 89-95.
131. Jacobs, E.T., et al., *Association between body mass index and colorectal neoplasia at follow-up colonoscopy: a pooling study*. *American Journal of Epidemiology*, 2009. **169**(6): p. 657-66.
132. Kaminski, M.F., et al., *Quality indicators for colonoscopy and the risk of interval cancer*. *New England Journal of Medicine*, 2010. **362**(19): p. 1795-803.
133. Leung, K., et al., *Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study*. *Gastrointestinal Endoscopy*, 2010. **71**(1): p. 111-7.
134. Brenner, H., et al., *Low risk of colorectal cancer and advanced adenomas more than 10 years after negative colonoscopy*. *Gastroenterology*, 2010. **138**(3): p. 870-6.
135. Brenner, H., et al., *Does a negative screening colonoscopy ever need to be repeated?* *Gut*, 2006. **55**(8): p. 1145-50.
136. The UK CRC Screening Pilot Evaluation Team, *Evaluation of the UK Colorectal Cancer Screening Pilot Final Report*, 2003. p. 1-229.
137. Ko, C.W., et al., *Serious complications within 30 days of screening and surveillance colonoscopy are uncommon*. *Clinical Gastroenterology & Hepatology*, 2010. **8**(2): p. 166-73.
138. NHS Cancer Screening Programmes, *Guide Book for Programme Hubs and Screening Centres: NHS Bowel Cancer Screening Programme*, 2006. p. 1-59.
139. Atkin, W.S. and B.P. Saunders, *Surveillance guidelines after removal of colorectal adenomatous polyps*. *Gut*, 2002. **51**(suppl 5): p. v6-v9.
140. NHS Connecting for Health, *Service Level Agreement (SLA) between NHS Cancer Screening Programme and NHS Connecting for Health Service Management for the support of Bowel Cancer Screening System*, P. Moores, Editor 2011.
141. Northern Colorectal Cancer Audit Group, NORCCAG,, *7th Annual Report*, 2006. p. 1-29.
142. Wikipedia. *North East England*. 2011.
143. Office for National Statistics. *Regional Profiles - Population and Migration - North East - October 2011*. 2011; Available from: <http://www.ons.gov.uk/ons/rel/regional-trends/region-and-country-profiles/population-and-migration/population-and-migration---north-east.html>.
144. Office for National Statistics, *2010-based subnational population projections by sex and five year age groups for England and the Regions*, 2012.
145. Government, D.f.C.a.L., *The English Indices of Deprivation 2007 Summary*, 2007.
146. Office for National Statistics. *Regional Profiles - Social Indicators - North East - February 2012*. 2012; Available from: <http://www.ons.gov.uk/ons/rel/regional-trends/region-and-country-profiles/social-indicators/social-indicators---north-east.html>.
147. Office for National Statistics, *Portrait of the North East*, 2010.

148. Rees, C. and M. Rutter, *NREG: old banger or new vehicle for research?* *Frontline Gastroenterology*, 2010. **1**(1): p. 59-62.
149. National Information Governance Board for Health and Social Care. *Section 251 of the NHS Act 2006*. 2011; Available from: <http://www.nigb.nhs.uk/>.
150. National Research Ethics Service, *Defining Research*, 2009, NHS National Patient Safety Agency.
151. Economic & Social Research Council (ESRC). *GeoConvert*. 2011; Available from: www.census.ac.uk.
152. Communities and Local Government. *Indices of Deprivation 2007*. 2007; Available from: <http://webarchive.nationalarchives.gov.uk/+http://www.communities.gov.uk/communities/neighbourhoodrenewal/deprivation/deprivation07/>.
153. Logan, R.F.A., et al., *Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests*. *Gut*, 2011.
154. Association of Coloproctology of Great Britain and Ireland, *Guidelines for the Management of Colorectal Cancer*, 2007.
155. University of Sheffield School of Health and Related Research, *Re-appraisal of the options for colorectal cancer screening*, S. Whyte, Editor 2011.
156. Brenner, H., et al., *Interval cancers after negative colonoscopy: population-based case-control study*. *Gut*, 2012. **61**(11): p. 1576-1582.
157. Morris, S., et al., *Socioeconomic variation in uptake of colonoscopy following a positive faecal occult blood test result: a retrospective analysis of the NHS Bowel Cancer Screening Programme*. *British Journal of Cancer*, 2012. **107**: p. 765-771.
158. Chlebowski, R.T., et al., *Estrogen plus Progestin and Colorectal Cancer in Postmenopausal Women*. *New England Journal of Medicine*, 2004. **350**(10): p. 991-1004.
159. Xavier Dray, et al., *Treatment of gastrointestinal angiodysplasia and unmet needs*. *Digestive and liver disease*, 2011. **43** (7): p. 515-522.
160. Pokoradi, A.J., L. Iversen, and P.C. Hannaford, *Factors associated with age of onset and type of menopause in a cohort of UK women*. *American Journal of Obstetrics and Gynecology*, 2011. **205**(1): p. 34.e1-34.e13.
161. Brenner, H., et al., *Gender differences in colorectal cancer: implications for age at initiation of screening*. *British Journal of Cancer*, 2007. **96**(5): p. 828-831.
162. Lorenzo-Zúñiga, V., V. Moreno de Vega, and J. Boix, *Changing trends in polypoid colorectal cancer diagnosed by colonoscopy*. *Colorectal Disease*, 2011. **13**(3): p. e37-e41.
163. Steele, R.J.C., et al., *Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site*. *Gut*, 2011.
164. Morris, E.J.A., et al., *A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme*. *British Journal of Cancer*, 2012.
165. Weiss, J.M., et al., *Mortality by Stage for Right- Versus Left-Sided Colon Cancer: Analysis of Surveillance, Epidemiology, and End Results–Medicare Data*. *Journal of Clinical Oncology*, 2011. **29**(33): p. 4401-4409.
166. Meguid, M.R.A., et al., *Is There a Difference in Survival Between Right- Versus Left-Sided Colon Cancers?* *Annals of Surgical Oncology*, 2008. **15**(9): p. 2388-2394.
167. Benedix, F., et al., *Comparison of 17,641 Patients With Right- and Left-Sided Colon Cancer: Differences in Epidemiology, Perioperative Course, Histology, and Survival*. *Diseases of the Colon & Rectum*, 2010. **53**(1): p. 57-64
10.1007/DCR.0b013e3181c703a4.

168. Cook, J., H. Dickinson, and M. Eccles, *Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study*. BMC Health Services Research, 2009. **9**(1): p. 160.
169. Ryan, A., et al., *COX-2 inhibitors: a potential target for drug therapy in the management of colorectal cancer*. Medical Journal of Malaysia, 1999. **54**(3): p. 293-5.
170. Lee, T.J., et al., *Aspirin users attending for NHS bowel cancer screening have less colorectal neoplasia: Chemoprevention or false-positive faecal occult blood testing?* Digestion, 2012. **85**(4): p. 278-281.
171. Shao, T. and Y. Yang, *Cholecystectomy and the risk of colorectal cancer*. American Journal of Gastroenterology, 2005 **100**(8): p. 1813-20.
172. Jørgensen, T., *Prevalence of gallstones in a Danish population*. American Journal of Epidemiology, 1987. **126**(5): p. 912-921.
173. National Bowel Cancer Audit Project, *National Bowel Cancer Audit Annual Report 2010*, 2011.
174. National Cancer Intelligence Network. *About the National Cancer Intelligence Network*. 2012; Available from: http://www.ncin.org.uk/about_ncin/default.aspx.
175. Morris, E.J.A., et al., *A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme*. British Journal of Cancer, 2012. **107**(5): p. 757-764.
176. Health & Social Care Information Centre. *Hospital Episode Statistics*. 2013; Available from: <http://www.hscic.gov.uk/hes>.
177. Gill, M.D., M.D. Rutter, and S.J. Holtham, *Management and short term outcome of malignant colorectal polyps in the North of England*. Colorectal Disease, 2012: p. Epub ahead of print.
178. Petticrew, M., et al., *False-negative results in screening programmes: systematic review of impact and implications*. Health Technology Assessment Reports, 2000. **4**(5).
179. Gill, M.D., et al., *Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme*. British Journal of Cancer, 2012. **107**(3): p. 417-421.
180. Gill, M.D., et al., *OC-115 Comparison of screen detected and interval colorectal cancers in the bowel cancer screening programme: experience from the North East of England*. Gut, 2012. **61**(Suppl 2): p. A50.
181. Gill, M., et al., *Comparison of Patient Demographics amongst Participants and Non-Participants of the National Bowel Cancer Screening Programme in those diagnosed with a Colorectal Cancer*. Colorectal Disease, 2012. **14**: p. 12-40.

Appendix 1 Database Variables Creation

Imported into Access the following data sheets:

- NORCCAG
- BCSP
 - Invites and FOB test
 - SSP Appointments
 - Colonoscopy Data
- Postcode and Deprivation Data

Using Study number as identifier from each – merged all records

- Duplicate entries removed

Data then extracted to Excel and put into SPSS.

SPSS Editing:

- Combination of study groups
 - Control vs. Intervention (screen, non-uptake & interval)
 - Uptake of FOBt (screen & interval vs. non-uptake)
 - Screen vs. non-uptake and interval groups
- Group in prevalent round of screening
- Deprivation quintile group created
- Type of non-uptake group
 - Non-uptake of FOBt
 - Non-uptake of screening nurse appointment
 - Non-uptake of screening colonoscopy
- Age at diagnosis created
- Age when first sent FOB test created
- Created binned variables for IMD and Health Rank
- Created variables identifying cases into both IMD and Health worst 10%/15%/20%/25% most deprived areas
- ASA grouped 1-2, 3-5
- Coded ASA grade, converting all “99” codes to missing values
- Coded variable of PCT name
- Coded gender

- Overall FOB Episode types numerically coded
 - Grouping of positive windows from 1st returned FOBt kit
- Created new variable – earlier FOB test?
- Created new variable – date of earlier FOB
- Time from completion of FOBt kits to diagnosis and from invitation
- Calculated mean number of positive windows over all FOB tests per episode
- Each medication coded for use at any time, and within two months of carrying out test kit
- Recoded reason as to why no operation into 5 categories
 - Advanced disease
 - Patient refused
 - Unfit for surgery
 - Died before treatment commenced
 - Unknown
- Coded cancer unit
- Created date of final screening colonoscopy
- Calculated time between final screening colonoscopy and diagnosis date
- Coded tumour site: distal or proximal to the splenic flexure
- Coded urgency of operation and streamlined into elective, emergency and unknown
- Coded surgical access
- Coded operation type
 - Streamlined incorporating all total/subtotal colectomies into one category
 - All local excisions together
 - All palliative procedures together
- New variable grouping operation types into resective surgery, local excision, palliative and no procedure
- Coded stoma type and intension (temp/perm)
- Coded grade of senior operating surgeon
- Coded Pathological Dukes Stage
- Created Updated Dukes stage, incorporating all Dukes' D cancers and combining C1 and C2 cancers together (to form Dukes' C)

- Created screen vs. interval variable for each Dukes stage
- Created interval vs. control variable for each Dukes stage
- Coded T and N Stage
- Cross-referenced TNM stage vs. recorded Dukes stage – one error found – corrected
- Calculated length of inpatient stay
- Compared positive number of lymph nodes vs. Dukes stage – 1 error found – corrected
- Coded peri-operative death
- Created 30-day mortality variable
- Created end date for follow up (31st Dec 2010) to calculate survival/follow up length

Appendix 2 Sample Proforma

GP Practice: THE DENSHAM SURGERY THE HEALTH CENTRE NHS Number: 012345678 Date of Death:

Medication Action Group:	Yes	No	Name of Drug(s):	Date Started:	Date Finished:
HRT	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
NSAIDs	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Hormone Antagonists	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Anti-Coagulants	<input type="checkbox"/>	<input type="checkbox"/>	_____	_____	_____
Past Medical History:	Yes	No	Date of Procedure:		
Cholecystectomy?	<input type="checkbox"/>	<input type="checkbox"/>	_____		

Appendix 3 1st Medication Request Letter

Wolfson Research Institute
Durham University Queen's Campus
University Boulevard Stockton on Tees
TS17 6BH

Dear Colleague,

We are seeking your help with a study of people diagnosed with colorectal cancer through the Bowel Cancer Screening Programme. As you know, the NHS Bowel Cancer Screening Programme involves biennial faecal occult blood tests (FOBT) followed by a colonoscopy for positive results. The main aim of the programme is to detect colorectal cancer. A secondary aim is to identify adenomas and remove them.

We are studying all of the colorectal cancers diagnosed within the North East of England between April 2007 and March 2010 which fall into 3 distinct groups:

- Screen-detected Cancers
- Interval Cancers
 - A cancer diagnosed between screening rounds, after a negative FOB
- Non-Uptake Cancers
 - A cancer in the population who decline screening

Patients diagnosed with an interval cancer are significantly more likely to be women and have tumours in the right colon (proximal to the splenic flexure). The reasons as to why the FOBT is worse at detecting right -sided tumours and in women are not fully understood. One possibility is that medication or surgery may have an effect on the positivity of a FOBT in someone with a cancer. Specifically: oestrogen therapy (e.g. HRT), NSAIDs/aspirin and cholecystectomy may have an effect. We need your help in obtaining the medication history for patients within your practice who have been diagnosed with a colorectal cancer within (or outwith) the screening programme.

We have enclosed a Proforma with edited details of the patients we are interested in who are registered at your practice. Only the NHS number has been used as a patient identifiable data item. We would be extremely grateful if you or your practice manager could fill in the appropriate details on medication history and previous cholecystectomy, and return it in the enclosed stamped addressed envelope. The average number of patients per practice is less than two (range 1-8) so we hope that this will not take up too much of your time to complete.

The project has been given ethical approval by the School of Medicine and Health at Durham University and forms part of the work of a postgraduate research degree. Ethical approval has been waived by the NHS Research and Ethics Committee as the project is classed as a service evaluation. If you have any further queries, please do not hesitate to contact us by letter or email.

Many thanks for your help in advance,

Yours sincerely,

Mr Mike Gill
SpR Surgery

Prof Greg Rubin
Professor of General Practice

Prof Mike Bramble
Consultant Gastroenterologist

Appendix 4 2nd Medication Request Letter

Wolfson Research Institute
Durham University Queen's Campus
University Boulevard Stockton on Tees

TS17 6BH

m.gill@nhs.net

5th March 2012

Dear Colleague,

We wrote to you on the 7th February 2012 regarding a study of people diagnosed with colorectal cancer through the Bowel Cancer Screening Programme. Specifically, we are looking at possible reasons why the biennial faecal occult blood test (FOBT) appears to be worse at detecting cancers in women and in the right colon (proximal to the splenic flexure).

One possibility is that medication or surgery may have an effect on the positivity of a FOBT in someone with a cancer. Specifically: oestrogen therapy (e.g. HRT), NSAIDs/aspirin and cholecystectomy may have an effect. We need your help in obtaining the medication history for patients within your practice who have been diagnosed with a colorectal cancer within (or outwith) the screening programme.

To date, we have not yet received the copy of the proforma that was enclosed with the initial letter sent to your practice. We would be extremely grateful if you could follow this up. If you find it easier, we are happy to receive a full print-out of the relevant patient's medication list.

Our records for patient dates of death are accurate to the 1st November 2011. Any patient who has died after this will not have their date of death recorded in the relevant box on the proforma. Therefore, please can you include all inactive patients on your IT system when searching for each patient.

If you no longer have a copy of the proforma, please contact Mr Mike Gill on the email address below and we will be happy to email you a new copy. Please accept our apologies if you have recently sent your response. If you have any further queries, please do not hesitate to contact us by letter or email: m.gill@nhs.net.

Many thanks for your help in advance,

Yours sincerely,

Mr Mike Gill
SpR Surgery

Prof Greg Rubin
Professor of General Practice

Prof Mike Bramble
Consultant Gastroenterologist

Appendix 5 3rd Medication Request Letter

Wolfson Research Institute
Durham University Queen's Campus
University Boulevard Stockton on Tees
TS17 6BH

m.gill@nhs.net

15th May 2012

Dear Colleague,

We wrote to you on the 7th February and the 5th March 2012 regarding a study of people diagnosed with colorectal cancer through the Bowel Cancer Screening Programme. Specifically, we are looking at possible reasons why the biennial faecal occult blood test (FOBT) appears to be worse at detecting cancers in women and in the right colon (proximal to the splenic flexure).

One possibility is that medication or surgery may have an effect on the positivity of a FOBT in someone with a cancer. Specifically: oestrogen therapy (e.g. HRT), NSAIDs/aspirin and cholecystectomy may have an effect. We need your help in obtaining the medication history for patients within your practice who have been diagnosed with a colorectal cancer within (or outwith) the screening programme.

To date, we have not yet received the copy of the proforma that was enclosed with the initial letter sent to your practice. We would be extremely grateful if you could follow this up. If you find it easier, we are happy to receive a full print-out of the relevant patient's medication list, in particular if the relevant patient has had multiple PRN prescriptions of non-steroidals, for example. This is now extremely important as even with a low response rate there are indications that the FOB test performs better in patients taking NSAIDs.

Our records for patient dates of death are accurate to the 1st November 2011. Any patient who has died after this will not have their date of death recorded in the relevant box on the proforma. Therefore, please can you include all inactive patients on your IT system when searching for each patient.

To date, we have only had a 53% response rate from all practices which has generated interesting but not definitive results due to the relatively small number of patients that were taking medications (specifically NSAIDs). We really need to increase the completeness of the data to see if the results are significant or not. A response rate of 70 -80% would be sufficient, and this is one of those projects where primary care involvement is crucial and can make a significant difference to the research findings. We need your support.

Many thanks for your help in advance,

Yours sincerely,

Mr Mike Gill
SpR Surgery

Prof Greg Rubin
Professor of General Practice

Prof Mike Bramble
Consultant Gastroenterologist

Publications and Presentations from this thesis

- Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. Gill MD, Bramble MG, Rees CJ, Lee TJ, Bradburn DM, Mills SJ. Br J Cancer. 2012 Jul 24;107(3):417-21. doi: 10.1038/bjc.2012.305. Epub 2012 Jul 10. [179]
- Comparison of Screen-detected and Interval Colorectal Cancers in the Bowel Cancer Screening Programme: Experience from the North East of England.
 - Oral Presentation, Presented at Digestive Disorders Federation (DDF) Joint Meeting, 17-20 June 2012.
 - Abstract published in Gut 2012;61:Suppl 2 A50 doi:10.1136/gutjnl-2012-302514a.115 [180]
- Comparison of Patient Demographics amongst Participants and Non-Participants of the National Bowel Cancer Screening Programme in those diagnosed with a Colorectal Cancer
 - Poster Presentation, Presented at Association of Coloproctologists of Great Britain and Ireland (ACPGBI) Annual Conference, 1-3 July 2012.
 - (2012), Poster Abstracts. Colorectal Disease, 14: 12–40. doi: 10.1111/j.1463-1318.2012.03072.x [181]