Detection of advanced colonic neoplasia in the NHS bowel cancer screening programme and surveillance outcomes in the first six years: are current guidelines overcautious and is it time to change clinical practice?

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Detection of advanced colonic neoplasia in the NHS bowel cancer screening programme and surveillance outcomes in the first six years: are current guidelines overcautious and is it time to change clinical practice?

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Thesis submitted for the degree of Doctor of Medicine

2016

Abstract

Colorectal cancer (CRC) screening aims to reduce mortality by detecting cancer at an earlier stage. The National Health Service Bowel Cancer Screening Programme (BCSP) offers faecal occult blood screening followed, in positive cases, by colonoscopy to screen for CRC. Participants diagnosed with colorectal adenomas then undergo surveillance according to the British Society of Gastroenterology guidelines.

Data obtained from the BCSP database from June 2006 to June 2012 were studied to evaluate the magnitude of the detection of advanced neoplasia, and identify the predictive factors that influence the presence of carcinoma in adenomas and the proportions of advanced neoplasia detected in different segments of the colon. The outcome of first surveillance procedures was evaluated to assess the validity of the current risk stratification guidelines for BCSP participants. The appropriateness and safety of the time interval used in surveillance for high- (HR) and intermediate-risk (IR) groups were analysed.

The majority of adenomas (59.75%) detected in the BCSP were non-advanced adenomas (NAAs). Advanced neoplastic features were more prevalent in larger adenomas. Increasing size and distal location were significantly associated with the presence of carcinoma in adenomas. The current surveillance strategy is effective in risk-stratifying BCSP participants as the HR group had a significantly higher proportion of adenomas (60.24 *vs*. 40.14%; $P<0.001$) at first surveillance; the majority of the IR group did not have any colorectal neoplasia at first surveillance compared to the HR group (59.98 *vs*. 39.06%; $P<0.001$). The proportion of HR participants who had their surveillance after one and half years instead of one year, did not demonstrate any increased likelihood of advanced colorectal neoplasia.

Adenoma size and segmental location were the important factors associated with the presence of advanced neoplasia in adenomas. The current guidelines are effective in risk-stratifying BCSP participants; however, the surveillance interval can be safely prolonged for HR and IR patients.

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List of abbreviations

AA	advanced adenoma
AC	ascending colon
ACN	advanced colorectal neoplasia
AGA	American Gastroenterology Association
ADR	adenoma detection rate
BCSP	Bowel Cancer Screening Programme
BCSS	Bowel Cancer Screening System
BSG	British Society of Gastroenterology
CI	confidence interval
CRC	colorectal cancer
DC	descending colon
ESGE	European Society of Gastrointestinal Endoscopy
FOBT	faecal occult blood test
HF	hepatic flexure
HGD	high-grade dysplasia
HR	high-risk
IR	intermediate-risk
JAG	Joint Advisory Group on GI Endoscopy
LACN	left-sided advanced colorectal neoplasia
LR	low-risk
NAA	non-advanced adenoma
NHS	National Health System
NPS	National Polyp Study
OR	odds ratio
RACN	right-sided advanced colorectal neoplasia

RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
SF	splenic flexure
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TA	tubular adenoma
TC	transverse colon
VH	villous histology

Declaration of authorship and statement of copyright

I confirm that this is my own work and the use of all materials from other sources has been fully acknowledged. This thesis represents new material and has not previously been submitted for a degree at this or any other university.

Acknowledgements

First, I would like to thank my supervisors, Professor APS Hungin, Professor Mike Bramble and Professor Matt Rutter for their help, support and guidance during the last four years.

I would like to thank Professor Julietta Patnick for her support in obtaining the relevant data for this work from the national database. I would also like to thank Miss Claire Nickerson, who interrogated the national database with the queries to obtain the data, and Dr Tom Lee, who helped me to set out this project from the onset.

Thanks must go to Dr Douglas Wilson, who worked painstakingly with me to help with the data processing and the statistical analysis and was very enthusiastic and encouraging throughout the process.

I must thank Dr Basant Chaudhury, Dr Deepak Dwarakanth, Dr Christopher Wells and Dr John Hancock for their ongoing encouragement to continue with this work. I would also like to thank Miss Sonia Cutler for copy-editing this thesis and Susan Williams for finalising the revisions.

Thanks to my parents and other family and friends who were very supportive during this period to carry on with my work.

And finally thanks to my wife Mohar, who was a constant source of inspiration and support.

Chapter 1: Introduction

Colorectal cancer (CRC) is the fourth most common cancer and second most common cause of cancer-related mortality in men and women in the United Kingdom (UK) [1]. The disease causes significant impact and burden on society due to its high mortality and morbidity. The disability-adjusted life years (the number of years lost due to ill-health, disability or early death) related to CRC are significant. In England and Wales, 8 605 362 disability-adjusted life years were lost in the period from 2002 to 2006 due to all cancers, and CRC ranked as the third major cause among men and women in this league table [2], demonstrating the disease burden on the population .

If CRC is diagnosed early, mortality and morbidity can be prevented with curative surgical resection, when the tumour is still confined to the bowel [3–5]. Various population-based screening programmes have been developed to identify CRC at its earlier stages; they have shown a reduction in mortality from CRC because curative surgery is offered following early detection [5, 6].

The majority of CRCs develop from pre-cancerous adenomas. The progression from adenoma to early invasive cancer takes years and this time window provides an opportunity to detect pre-cancerous adenomas along with early CRC at screening [7, 8]. In fact, a colorectal adenoma is the most common neoplasm found during CRC screening [9]. Detection and removal of adenomas reduce future incidence and therefore CRC mortality [10]. Individuals with adenomas are at increased risk of developing metachronous colorectal neoplasia compared to individuals without adenomas; therefore, they require surveillance colonoscopy after initial detection and removal of adenomas.

A successful population-based screening programme for CRC should therefore have a strategy and framework to deliver a widespread, population-based surveillance programme for patients with colorectal adenomas detected at screening.

Delivering an effective adenoma surveillance programme needs an appropriate, safe and cost-effective use of colonoscopic examination, a resource-intensive and invasive procedure, to be performed in such a way that patients with the highest risk of developing advanced colorectal neoplasia (ACN) (>=1 cm or HGD) would benefit the most. Such surveillance programmes in turn require a skilled endoscopic workforce, a well-organized service framework and a valid and effective risk stratification strategy that could identify a cohort of patients with colorectal adenomas at the highest risk of developing future ACN.

These concepts led to the development of population-based screening programmes and guidelines for adenoma surveillance. Depending on the resources available, various invasive and non-invasive modalities were adopted as screening tools in different parts of the world [7], and national and international guidelines for adenoma surveillance were created.

In England and Wales, the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) was launched in 2006. The screening tool chosen for bowel cancer screening was the faecal occult blood test (FOBT), which had been validated in a prior randomized controlled trial (RCT) [11] and was also shown to be cost-effective [12] in the NHS setting. In the BCSP, patients who have a positive FOBT test and then agree undergo a screening colonoscopy. Those who are diagnosed with CRC are referred for treatment; patients with colorectal adenomas take part in a subsequent colonoscopy-based adenoma surveillance programme after adenoma removal at the screening colonoscopy.

The surveillance guidelines for colorectal adenomas after polypectomy were published by the British Society of Gastroenterology (BSG) in 2002 and then updated in 2010 [13, 14] (**Figure 1.1**); they provide the framework for surveillance in the BCSP. Patients are stratified into different risk groups according to their increasing likelihood of developing metachronous ACN depending on the number and size of the adenomas found during the screening colonoscopy and therefore undergo surveillance colonoscopy at different intervals. The three risk groups are low (LR), intermediate (IR) and high (HR); they undergo their first surveillance colonoscopy after one, three and five years after screening, respectively. In the BCSP, the LR group undergoes a biennial FOBT test rather than a surveillance colonoscopy every five years.

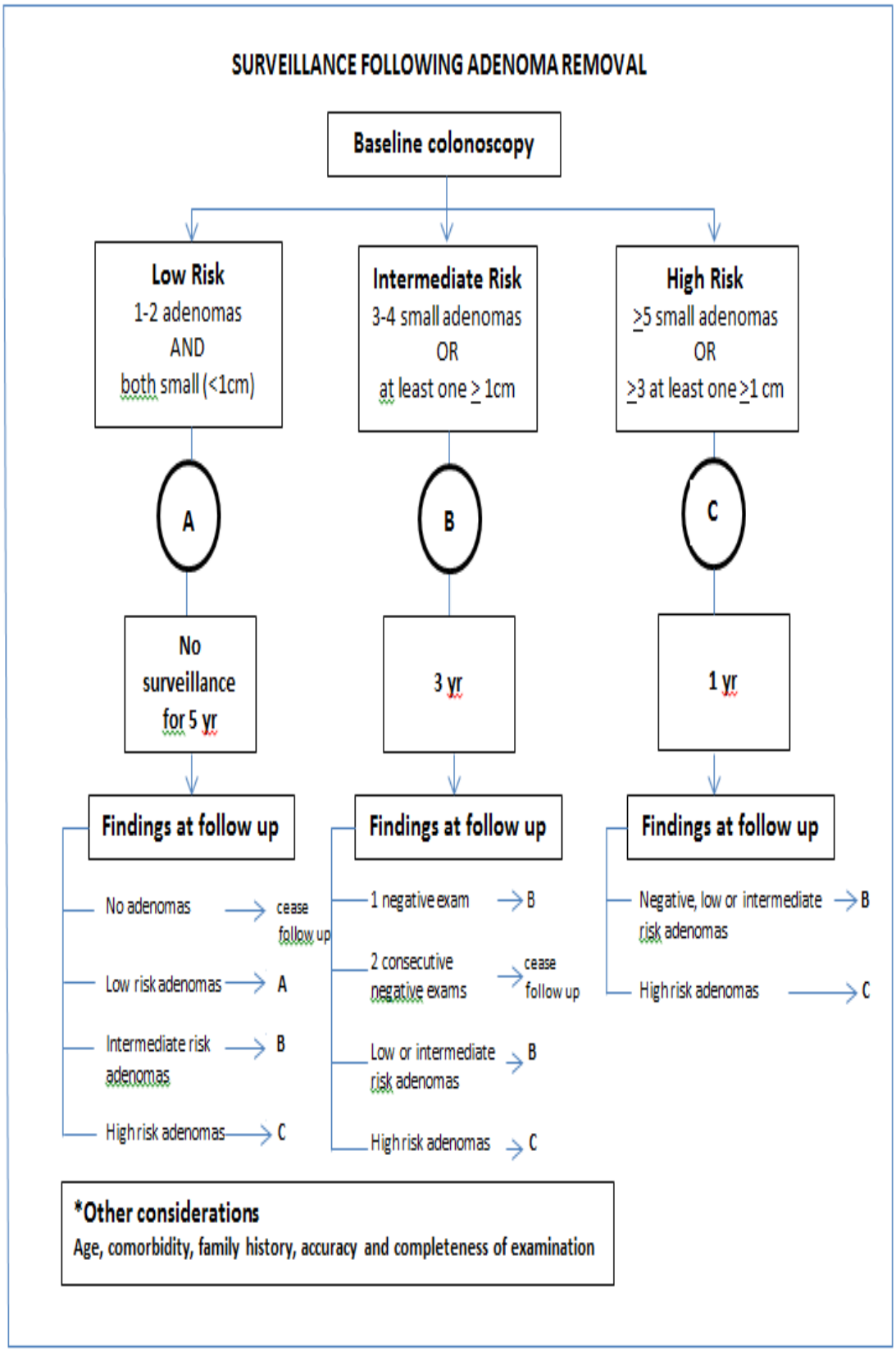

Figure 1.1 Adapted from the BSG adenoma surveillance guidelines.

The available evidence behind the current BSG surveillance guidelines was derived from RCTs and cohort studies. The study population in these studies consisted of individuals with an average risk of having colorectal neoplasia; the colonoscopies were performed by independent practitioners in a hospital-based setting, but were not performed within the setting of a screening service.

The overall picture of the adenoma surveillance guidelines loses its uniformity if we consider guidance followed in Europe and in the USA also derived from population-based studies; yet, UK guidelines differ from those adopted in Europe and the USA, and there is heterogeneity among risk stratifications strategies and surveillance intervals among English, European and American guidelines.

The American Gastroenterology Association (AGA) guidelines stratify patients to undergo surveillance colonoscopies at four different time intervals according to the number and size of adenomas; they also consider the presence of sessile serrated polyps, villous adenomas and high-grade dysplasia (HGD) as determinants of risk stratification. The surveillance interval varies from 1 to 10 years according to baseline risk at screening [9]. The AGA guidelines are summarized in **Table 1.1**.

Table 1.1 Outline of the AGA guidelines

Baseline colonoscopy: most advanced findings	**Surveillance interval (years)**
No polyps/small (<10-mm) hyperplastic polyps in rectum/sigmoid colon	10
1–2 (<10-mm) tubular adenomas (TAs)	5–10
3–10 TAs; one or more TAs ≥10 mm; one or more villous adenomas; adenomas with HGD; sessile serrated polyp(s) ≥10 mm/sessile serrated polyp(s) with dysplasia/traditional serrated adenoma	3
>10-mm adenomas	<3
Serrated polyposis syndrome	1

Note: AGA = American Gastroenterology Association; HGD = high-grade dysplasia.

The European guidelines for CRC screening and adenoma surveillance were first published in 2010. They stratified patients into three different risk categories and considered villous adenomas and HGD along with the number and size of adenomas

as determinant factors for risk stratification [15]. The guidelines recommended surveillance colonoscopy to be performed at three different intervals for LR, IR and HR groups. The recommendations are outlined in **Figure 1.2**.

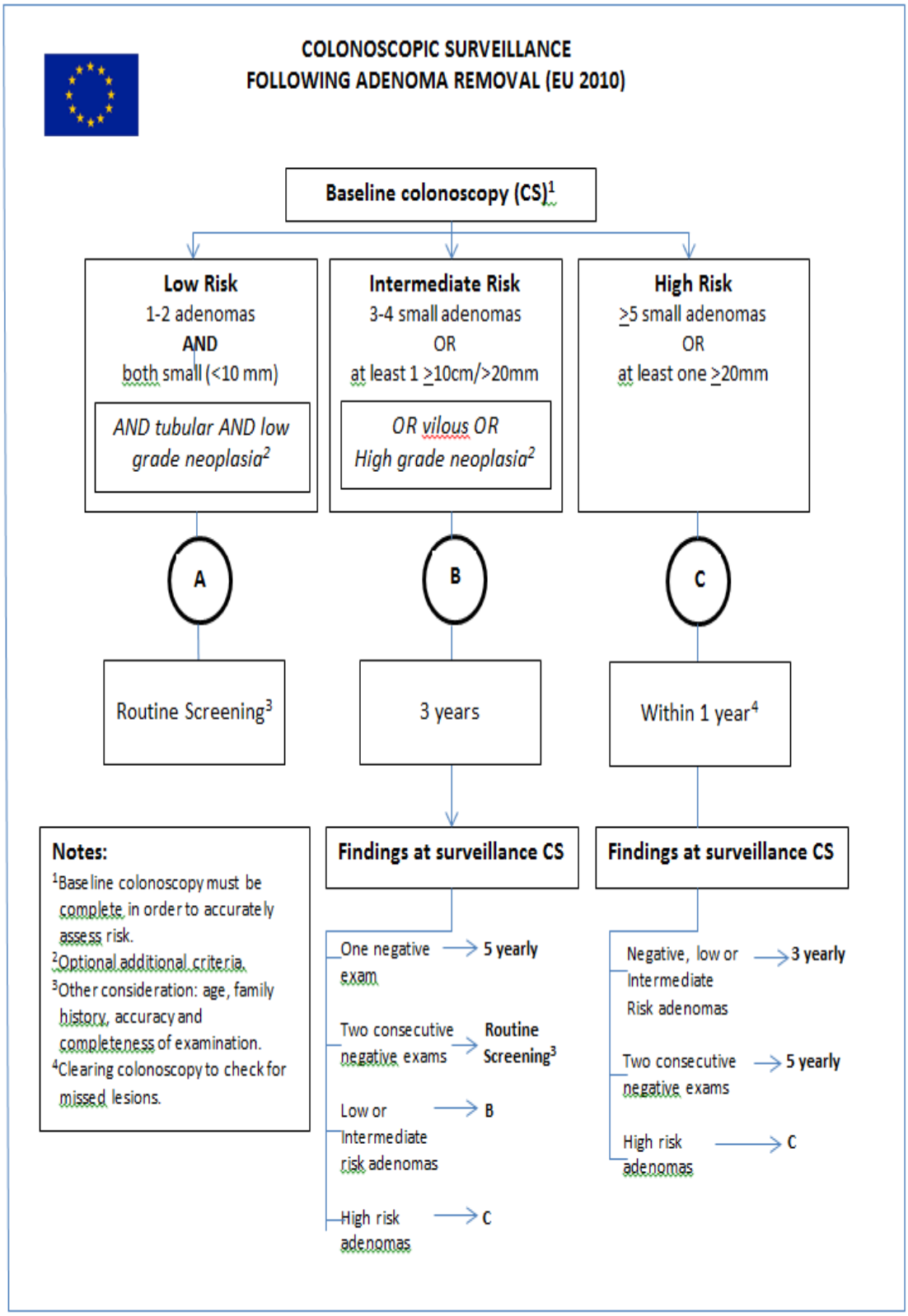

Figure 1.2 Adapted from the 2010 European guidelines for CRC screening and surveillance.

The European post-polypectomy surveillance guidelines published in 2013 (**Figure 1.3**) take into account the value of high-quality colonoscopy, stratify patients into HR and LR groups and recommend first surveillance at the third and 10th year, respectively. The guidelines also identify villous adenomas and HGD as high-risk features [16]. The high-quality colonoscopy outlined in the European guidelines was defined as 'complete colonoscopy with a meticulous inspection of adequately cleaned colorectal mucosa. Neoplastic lesions have also been completely removed and retrieved for histological examination' [16].

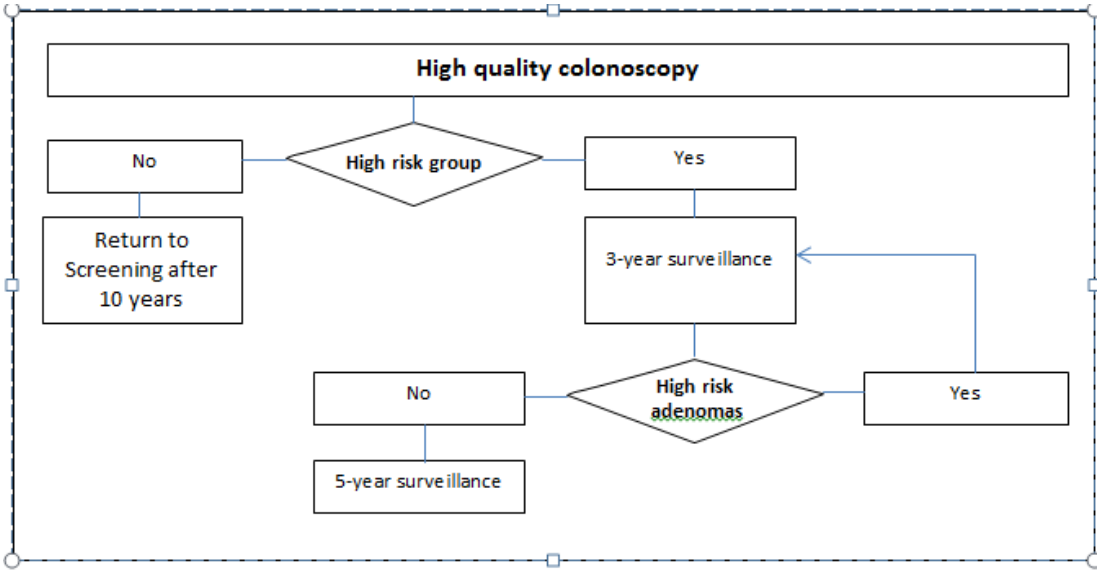

Figure 1.3 Adapted from the ESGE 2013 post-polypectomy surveillance guidelines.

Note: ESGE = European Society of Gastrointestinal Endoscopy.

In my personal journey as a trainee gastroenterologist, I came across the BSG guidelines while performing procedures in patients with colorectal adenomas. With the commencement of the BCSP, I was intrigued to find out that the BCSP adopted population-based adenoma surveillance; patients were different from the general population, and only colonoscopists accredited to perform a screening colonoscopy performed the procedures.

The screened population consists of men and women aged 60–74 years of age who have a positive FOBT test; they do not represent a population at an average risk of having

colorectal neoplasia. The prevalence of CRC and colorectal adenomas is much higher in this FOBT-positive cohort compared to the general population.

The colonoscopies performed in the BCSP are high-quality colonoscopies. The procedures are performed in screening centres accredited by the Joint Advisory Group on GI Endoscopy (JAG); the endoscopists involved are certified through an accreditation process and have to demonstrate achievement of a certain pre-defined practice standard (that is, completion rate and adenoma detection, which are performance indicators for a colonoscopist) in their own colonoscopy practice. Once accredited, they undergo an ongoing performance audit and quality assurance checks during their participation in the BCSP.

With the evolving European adenoma surveillance guidelines against the backdrop of high-quality colonoscopy, it seems clear that the adenoma surveillance interval could be safely prolonged and this could prove to be more cost-effective.

Since a population-based risk stratification strategy is currently being used in the BCSP for FOBT-positive patients of a defined age group, it is essential to examine the outcome of adenoma surveillance in the BCSP, evaluate the appropriateness and validity of the current screening strategy for the FOBT population and also assess whether the surveillance interval could be increased. Since various determinant factors were used in the different guidelines, the important factors that could predict clinical outcomes in a screened population need to be identified.

This thesis provided the opportunity to examine the outcomes of adenoma surveillance in the BCSP and also evaluate a valid design for risk stratification.

The current chapter provides the general background and explains the purpose of the study. Chapter 2 describes the current evidence from the literature relevant to this work

and Chapter 3 describes the methodology followed. The aims and objectives of the study are described in Chapter 4.

The results of the study are discussed in Chapters 5, 6 and 7 with the specific relevant discussions integrated in each chapter.

Chapter 5 examines all the colorectal adenoma data identified in the BCSP at screening and surveillance; it also evaluates and determines the distributions of advanced histological features in the different size categories, important predictor factors that determine the presence of carcinoma in adenomas, and the differences between proximal and distal adenomas. The distribution of ACN in different bowel segments is estimated and the importance of location in determining the presence of ACN in adenomas is determined.

Chapter 6 evaluates the outcome of continuous surveillance of IR and HR groups over the six-year study period and evaluates whether the current BSG guidelines are effective in stratifying the screened population depending on the surveillance outcomes. It also highlights that, within the setting of high-quality colonoscopy performed in the BCSP, one can safely prolong the surveillance interval for the IR group.

Chapter 7 examines the different relevant patient- and adenoma-specific characteristics seen during screening; these may, in turn, predict any adverse outcomes at first surveillance and hence throw light on the re-stratification risk.

Chapter 8 highlights the important conclusions and discussions derived from this work.

This thesis comprises a retrospective study, but provided the unique opportunity to examine data from the BCSP, which was collected contemporaneously; hence, it is a retrospective study of prospectively collected data that allows us to revisit the adenoma surveillance guidelines in the context of screening and provides stimulus for future RCTs

safely performed in the light of the outcomes of this study. Thus, it can change the way adenoma surveillance is currently performed.

Chapter 2: Literature review

2.0 Strategy for the literature review

This review is based on evidence contained in relevant articles published in the medical literature and is divided into nine sections.

The aim of the first part of the literature review is to provide an overview of the:

- magnitude of the burden of CRC and its demographics;
- natural history of CRC;
- concept of bowel cancer screening;
- the BCSP.

This is not an exhaustive overview of all aspects of CRC, but it focuses on those aspects pertaining to the basis for CRC screening and the evidence supporting population-based screening programmes.

In the second part, a detailed review of the following key areas was carried out:

- surveillance of patients with colorectal adenoma;
- risk stratification for surveillance: relationship between the number and size and advanced histological features of adenomas at index screening colonoscopy and the number, size and advanced histology at surveillance.

In this section of the literature review, a detailed review of the available evidence and a perspective of current opinions on this are provided. Areas in which ongoing research for this thesis is relevant are then identified.

Research was performed to evaluate the detection of advanced neoplasia in BCSP by T.J.W.Lee and the strategy and part of the knowledge in this literature review was adopted from that work.

PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was interrogated for relevant publications between 1990 and 2014. This time period was chosen because it reflects modern and current clinical practice. Articles from earlier than 1990 were included if they proved relevant to the patient and did not contain outdated information. The following MeSH subject headings were used: colonic polyps; colonoscopy; colorectal neoplasms; early detection of cancer. Logical operators were used where relevant. Terms from the U. S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed were selected. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts. These concepts were selected because they pertained to the aims of the literature review (17).

Abstracts were reviewed and articles were excluded if they were in a language other than English or if they were not of sufficient relevance to the stated aims of the literature review. Full-text articles were then obtained. The reference lists of selected articles were scrutinized for additional articles (not restricted by year of publication). Because of the wide range of topics covered by this literature review, a single quality assessment protocol or data extraction process could not be applied to all the papers (17).

Part 1

2.1 Colorectal cancer: the current magnitude

Cancer is among the leading causes of morbidity and mortality worldwide, with approximately 14.1 million new cases diagnosed and 8.2 million cancer-related deaths occurring in 2012 [18]. In 2012, globally 1.67 million new cases of CRC were diagnosed,

making CRC the third most common cancer and the fourth most common cause of cancer-related death worldwide, causing 694 000 deaths worldwide in 2012 [19].

Bowel cancer was the second most common cancer in Europe, with around 447 000 new cases diagnosed in 2012 (13% of all newly diagnosed cancers) [20].

In 2011, in the UK, 41 581 new cases of bowel cancer were diagnosed and it became the third most common cancer among men and women [21]. Prostate and lung cancer were more common among men and the incidence of breast and lung cancer preceded that of bowel cancer in women. Bowel cancer became the fourth most commonly detected cancer in the combined population including both sexes (incidence 13%), preceded by breast, lung and prostate cancer [1]. **Figures 2.1** and **2.2** show cancer incidence in men and women in 2011 (England).

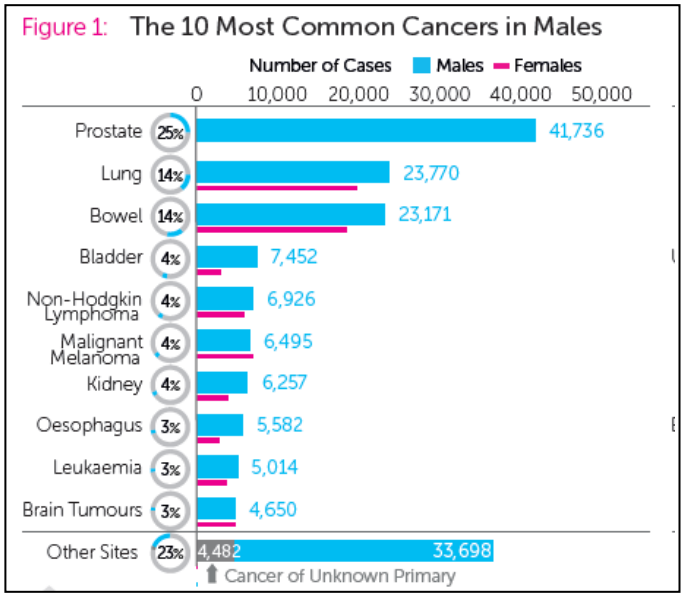

Figure 2.1 Cancer incidence in men in 2011 (England).

Source: Cancer Research UK, Office for National Statistics. Cancer Statistics Registrations, England (Series MB1).

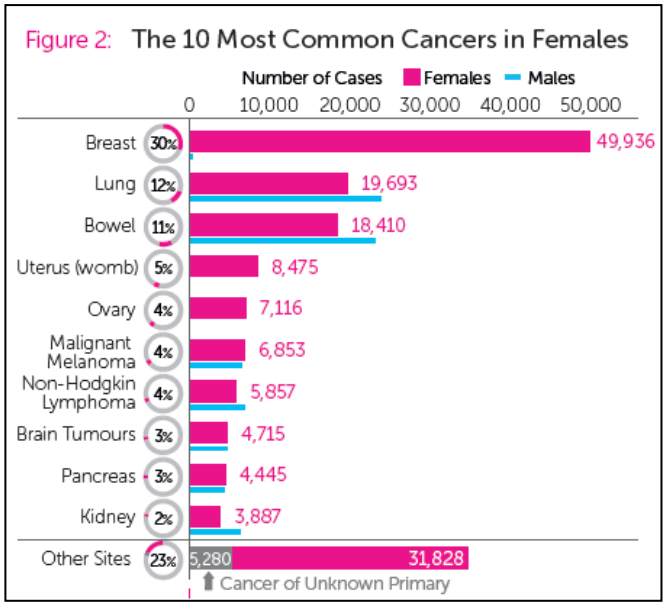

Figure 2.2 Cancer incidence in women in 2011 (England).

Source: Cancer Research UK, Office for National Statistics. Cancer Statistics Registrations, England (Series MB1).

In 2012, bowel cancer contributed to 16 187 deaths in the UK, making it the third most common cause of cancer-related death in men and women, and the second most common cause of cancer-related mortality (10%) in the combined male and female population [1]. It was preceded only by lung cancer in the mortality league table (**Figure 2.3**).

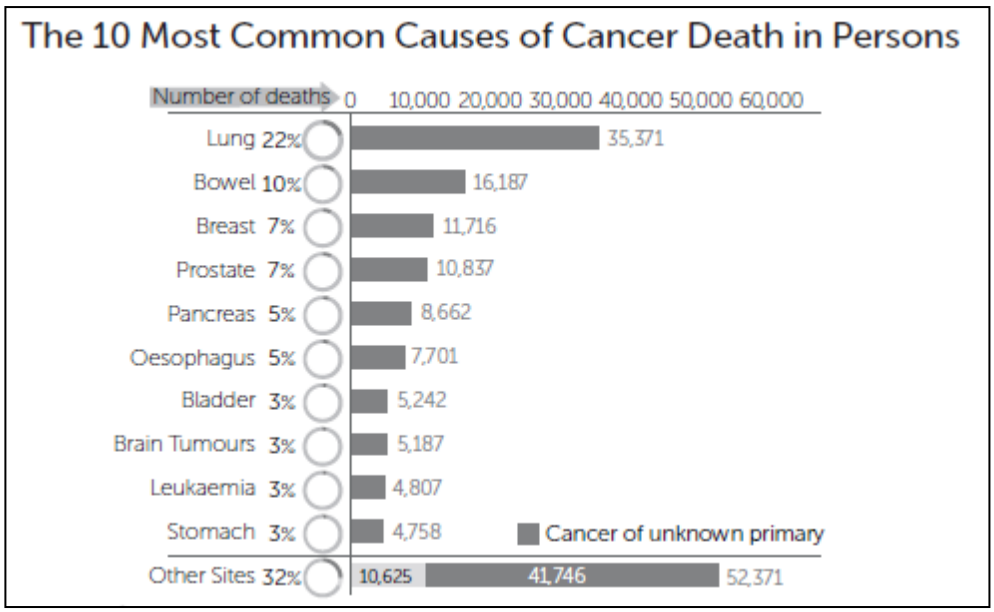

Figure 2.3 Cancer-related mortality in 2012 (UK).

Source: Cancer Research UK. Cancer Statistics Report: Cancer Incidence and Mortality in the UK, January 2014.

In an average year as per the data available in 2007, 35 000 people are diagnosed with cancer in the UK and more than 15 000 people die every year, making bowel cancer the second most common cause of death from cancer [22].

The national cancer survival data for December 2014 showed that the 10-year survival rate from bowel cancer among men and women was 56 and 57%, respectively. There has been a 35% overall improvement in the 10-year survival rate over the last 40 years [23]. However, the survival rate can be improved further by detecting more bowel cancer cases at an earlier stage, when a curative treatment can be offered.

2.2 The demographics of colorectal cancer

Over 100 cases of CRC are diagnosed in the UK each day. The lifetime risk of CRC is 1 in 16 for men and 1 in 20 for women [24]. The incidence of CRC increases with age and 83% of CRC cases are diagnosed in individuals aged ≥60. CRC is more common in men, with an

overall age-standardized male to female ratio of 1.6:1 [24]. This preponderance in men is most marked between the ages of 60 and 80 years; however, over the age of 80, CRC is numerically more prevalent in women than men. This is a result of women living longer than men and thus forming the numerical majority in that age group.

Across the UK and Ireland, small geographic variations in the incidence of bowel cancer have been recorded, with higher rates noted in Scotland, Northern Ireland and Ireland and lower rates found in South East England [25].

2.3 The natural history of colorectal cancer

The term CRC comprises cancer in two distinct locations of the large bowel. The large bowel is the portion of the digestive tract that connects the small bowel to the exterior of the body. The colon is the large bowel proximal to the rectum. The rectum can reach up to 15 cm proximal to the anal verge. The location of a cancer with regard to the colon and rectum has important implications from both diagnostic and therapeutic perspectives.

The majority of cancers of the large bowel arise in the left side of the bowel; this holds true for the cases diagnosed in the UK (**Figure 2.4**) [26].

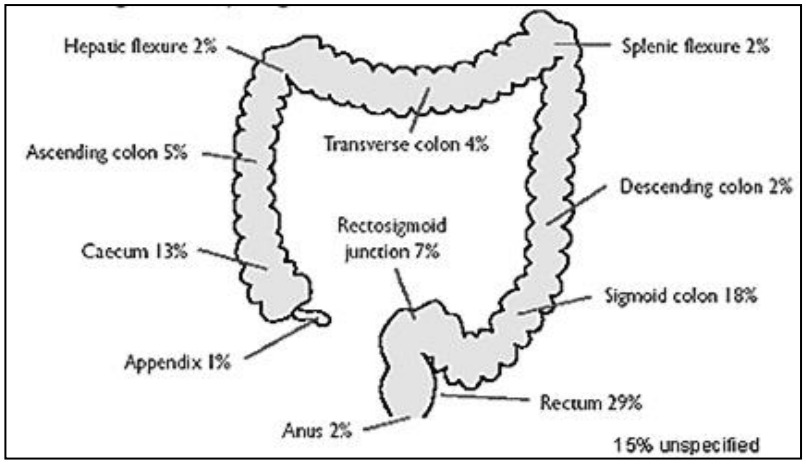

Figure 2.4 Percentage distribution of CRC cases by site, England 1997–2000.

Note: CRC = colorectal cancer.

One of the major breakthroughs in understanding the natural history of CRC was the establishment of the 'adenoma–carcinoma' model. Cancer development is a neoplastic process, with epithelial cells going through progressive phases of genetic alteration leading to the loss of the normal control mechanism of cellular growth and proliferation [27]. In the large bowel, these phases of aberrant proliferation lead to the development of adenomas; these represent the morphologically categorized precursor of the vast majority of CRCs [8]. Morson [28] was the first to describe this evolution of CRC from a precursor lesion. It is now recognized as the major pathway for the development of CRC in the general population and in HR patients with a family history of adenomatous polyposis or hereditary non-polyposis CRC [28–30]. Later on, Vogelstein and colleagues [31] studied and described the genetic alterations detected in these precursor lesions and the adenoma–carcinoma model became known as 'Vogelstein's hypothesis'.

Colorectal adenomas start as small, superficial, protruding lesions, morphologically known as polyps, although by definition they are neoplastic lesions. Polyps are any protruding superficial mucosal pathology and can be neoplastic or non-neoplastic. Examples of

non-neoplastic polyps are inflammatory and hyperplastic polyps. This distinction is made here because these terms will be used later in this thesis.

In the model of tumour progression proposed by Vogelstein et al. [31], epithelial cells undergo genetic alterations leading to the development of a neoplastic clone, which in turn leads to the emergence of adenomas with a progressively aggressive phenotype. Therefore, this mechanism illustrates the occurrence of adenomas varying in size and dysplasia extent.

The progression from adenoma to invasive cancer is a slow process and can vary from five to more than 20 years [30]. Research has shown that only few adenomas transform into invasive cancer (0.25% per year) [32]. Although every adenoma has a malignant potential, not all of them will progress to cancer; some stabilize while others may even regress [33–35]. Non-progression or regression of adenomas is supported by the fact that, although adenoma prevalence in the Western world varies from 15 to 40%, only 3% of people with adenomas go on to develop carcinomas [36–45].

A different pathway of serrated neoplasia has been identified, where dysplasia can affect the serrated epithelium of hyperplastic polyps, featuring mainly right-sided colonic neoplastic polyps, the serrated adenomas. This tumour genetic pathway parallels therefore the classical adenoma–carcinoma sequence of the large bowel, in which metaplastic epithelium undergoes progressive steps of architectural and nuclear dysplasia, to colorectal cancer. Such polyps, are noted to occur in large number in hyperplastic polyposis and in attenuated familial adenomatous polyposis (43).

Another alternative pathway of adenomatous transformation was noted where due to DNA microsatellite instability, hyperplastic polyps develop atypical or adenomatous feature and show progression to carcinoma (44)

Various factors determine the progression of benign adenomas to carcinomas; some of these factors have been identified. The development of CRC from an adenoma depends on size, growth pattern and dysplasia extent [8]. For individuals with adenomas, the annual conversion rate to malignant adenomas has been given as 3, 17 and 37% when large adenomas, villous (VH) or tubulovillous histology, and HGD are present, respectively [32]. Generally adenomatous growth is progressive and the increase in size parallels the extent of dysplasia [10]. Adenoma size is the major independent factor for the development of VH and HGD; this, in turn, is the most important factor determining malignant transformation of a benign adenoma [46].

This has led to the identification of advanced adenomas (AAs) that are at high risk of developing into malignant lesions [47]. These adenomas have one or more of the following characteristics, described in different studies as risk factors for an adenoma to be malignant:

- size ≥10 mm [48];
- VH in ≥25% of the mass [49];
- HGD [50].

These are neoplastic lesions that progress at a higher rate (up to 5% a year) towards cancer [50]. Adenomas missing these features are described as non-advanced adenomas (NAAs) in this thesis. Adenomas with the features of AAs and adenomas where cancer has developed are collectively described as ACNs in the subsequent sections of this work.

Once an adenoma develops into a cancer, it can then progress further into different stages depending on:

1. the depth of invasion of the bowel wall;
2. the presence or absence of lymph node invasion;
3. the presence or absence of distant metastases.

Dukes devised this staging classification in the 1930s, though it is still widely in use [3]. It was originally used for staging rectal cancer, but also proved useful in staging CRC. The original Dukes' staging system was based solely on pathological findings and did not take into account distant metastases. A modified Dukes' classification that also includes stage D (distant metastases (liver, lung, bones)) has therefore been widely adopted (**Table 2.1**).

Table 2.1 Modified Dukes' staging of colorectal tumours: pathological criteria, five-year survival and case distribution

Stage	Pathological criteria	Five-year survival (%) [48]	Cases (%) [48]
A	Tumour is confined to the bowel wall with no lymph node metastases	93.2	8.7
B	Tumour has penetrated the bowel wall to the serosa or perirectal fat with no lymph node metastases	77.0	24.2
C	Lymph node metastases present	47.7	23.6
D	Distant metastases (for example, in the liver, lungs or bones) present	6.6	43.5

The reason for the five-year survival rate being reported as an outcome measure of CRC is because at least 90% of disease-related events (cancer recurrence or death) will occur within five years of diagnosis. If diagnosed at an earlier stage, patients can be offered a curative resection.

Slow progression of adenomas into cancer and the increased survival of early-stage CRC provide a window of opportunity to detect pre-malignant adenomas and early cancers. Removal with endoscopic and surgical resection respectively can thereby decrease both CRC

incidence and mortality. The endoscopic procedure used to resect adenomas is generally called a polypectomy.

It is clear that early CRC diagnosis and treatment provide considerable survival advantages to the patient. If a patient is diagnosed with Dukes' A cancer, they have approximately a 90% chance of surviving for five years. If, however, they are diagnosed at Dukes' stage C, their five-year survival drops to approximately 50% [24]. The main aim of a screening programme for CRC is therefore to diagnose cancers earlier to confer these survival benefits.

The evidence for the protective benefit of adenoma removal is largely based on historical studies and observational data. Prospective RCTs of polypectomy for adenomas with watchful waiting as the control are not feasible for ethical reasons. However, data regarding different surveillance strategies following polypectomy are available from RCTs. The available evidence is discussed later on in this literature review.

2.4 Bowel cancer screening

The UK National Screening Committee defined 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.' For a disease to be amenable to screening it should fulfil the criteria laid out by Wilson and Jungner for the World Health Organization (WHO) in 1968 [52]. These criteria are shown in **Table 2.2** [52]; details relevant to CRC are shown in the right-hand column.

Table 2.2 Criteria for a disease to be suitable for screening

Criteria	**Relevance to CRC**
Wilson and Jungner [52]	Evidence supporting CRC screening
The condition is an important health problem	CRC is the fourth most common cancer in the UK [1]
Its natural history is well understood	Adenoma–carcinoma sequence [31]
Recognition at an early stage is possible	Pre-malignant lesion is an adenoma
An acceptable treatment exists	Polypectomy or surgery is the acceptable treatment
A suitable test exists	FOBT shows a 50–70% sensitivity for CRC (the proportion of people with the target condition who have a positive test result) [53]
An acceptable test exists	FOBT is accepted by approximately 50% of those invited for the test
Adequate facilities exist to cope with any abnormalities detected	Colonoscopy and surgical services are adequately equipped to cope with demand [54]
Screening is carried out at repeated intervals when onset is insidious	FOBT trials have used a biennial FOBT strategy
Risk–benefit ratio is favourable	FOBT is safe
Cost is balanced against benefit	Similar cost-effectiveness to breast cancer screening in the short term. Possibly superior in the long term [12]

Note: CRC = colorectal cancer; FOBT = faecal occult blood test.

In light of these criteria suggesting that CRC should be amenable to screening, numerous studies have examined various approaches to screening. Colonoscopy is the current 'gold standard' for adenoma and CRC detection because it provides opportunities for optical diagnosis and histological sampling. Mass population screening in the UK using colonoscopy is not economically or logistically viable because manpower and financial resources could not currently allow every adult of a specific age to undergo colonoscopy. In addition, the potential risks of colonoscopy would need to be taken into account. The use of colonoscopy for mass population screening, however, is used in the USA where guidelines recommend that average-risk adults should undergo colonoscopy at 50 years of age and subsequently every 10 years [55].

In the UK an alternative, cost-effective approach for mass population screening is required, and one that is also safe and acceptable to patients. The most widely studied test that fulfils these criteria is the FOBT; it is based on the peroxidase-like activity of haematin in faeces on guaiac (a phenolic compound derived from a wood resin extracted from trees of the genus *Guaiacum*). When hydrogen peroxide is mixed with guaiac and faecal material that contains blood, the peroxidase activity of haemoglobin and haematin oxidizes guaiac, turning it from a neutral to a blue colour. The reaction is very slow and takes minutes, but the pseudoperoxidase activity of haematin (if present in blood in stool) catalyses the reaction so that it takes place in seconds.

FOBT relies on the fact that adenomas, particularly AAs and CRC, tend to bleed. This bleeding is intermittent and occurs at a slow rate; it occurs because of the hypervascular structure of adenomas/CRC and trauma from passing faeces. The peroxidase-like activity of haematin diminishes as it passes through the gastrointestinal tract, reducing the chance that upper gastrointestinal bleeding will cause false-positive results. Ingestion of animal

haemoglobin or peroxidase-containing vegetables (for example, cabbage, leeks, potatoes, onions and green beans), however, may also cause false-positives; therefore, dietary restrictions should be recommended, particularly if the FOBT result is equivocal [56].

2.5 The faecal occult blood test

In 1967, Greecor [38] first described the usefulness of the FOBT in the detection of asymptomatic colon cancer. Over a three-and-a-half-year period, 900 adult patients were administered the FOBT; 5% of them had a positive test results and then underwent barium enema examination, while 1% of the entire cases had CRC and 1% had a non-malignant polyp; this illustrated the effectiveness of the FOBT in identifying asymptomatic CRC.

Three large prospective RCTs of FOBT have been conducted in Minnesota (USA) [57], 56Denmark [58] and Nottingham (UK) [11], respectively. In the Minnesota study, 46 551 participants were randomized into control, annual FOBT and biennial FOBT groups and followed up for a period of 13 years. The 13-year cumulative mortality (per 1000 participants) from CRC was 5.88 (95% confidence interval (CI) = 4.61–7.15),

8.33 (95% CI = 6.82–9.84) and 8.83 (95% CI = 7.26–10.4) in the annual, biennial and control groups, respectively. The difference between the control and the group screened annually was statistically significant.

Mandel et al. [59] followed up the same Minnesota group for a period of 18 years and showed that the biennial group had a 21% reduction in CRC mortality rate compared to the control group, thus establishing the effectiveness of biennial screening. In this 18-year follow-up period, they demonstrated that the cumulative incidence ratios for CRC in the screened groups compared with the control group were 0.80 (95% CI = 0.70–0.90) for the annual group and 0.83 (95% CI = 0.73–0.94) for the biennial group [60]. Their findings illustrated that the use of annual or biennial FOBT significantly reduced CRC incidence.

In the landmark study carried out by Kronborg et al. [58] in Denmark, 61 933 participants were followed up for a 10-year period after randomization into biennial FOBT and control groups. The study revealed that CRC mortality, including deaths attributable to complications from CRC treatment, was significantly lower in the screened group compared to the control group (mortality ratio 0.82, 95% CI = 0.68–0.99; *P* = 0.03). They also demonstrated that Dukes' A CRCs were less common and Dukes' stage C CRCs were more common in the control group compared to the screened group; the cumulative survival of patients was higher in the screen-detected CRC than in the control group.

In the UK, the Nottingham study consisted of a RCT of FOBT; the authors recruited 152 850 participants after performing a pilot study. Their results were similar to those of Kronborg et al. [58]. There were more Dukes' A and fewer Dukes' C CRCs in the screening-detected group compared to the control group and there was a significant survival advantage in the screening-detected group. The study also showed that the detection rates for adenoma and CRC after a positive FOBT were higher in individuals aged ≥65 years at the entry point [11]. The results from these studies laid the foundations for the BCSP.

2.6 The NHS Bowel Cancer Screening Programme

The screening programme in England consists of five national programme hubs across the country, operating a national call and recall system that sends out FOBT kits to eligible individuals (**Figure 2.5**). Adults aged between 60 and 69 years were screened initially.

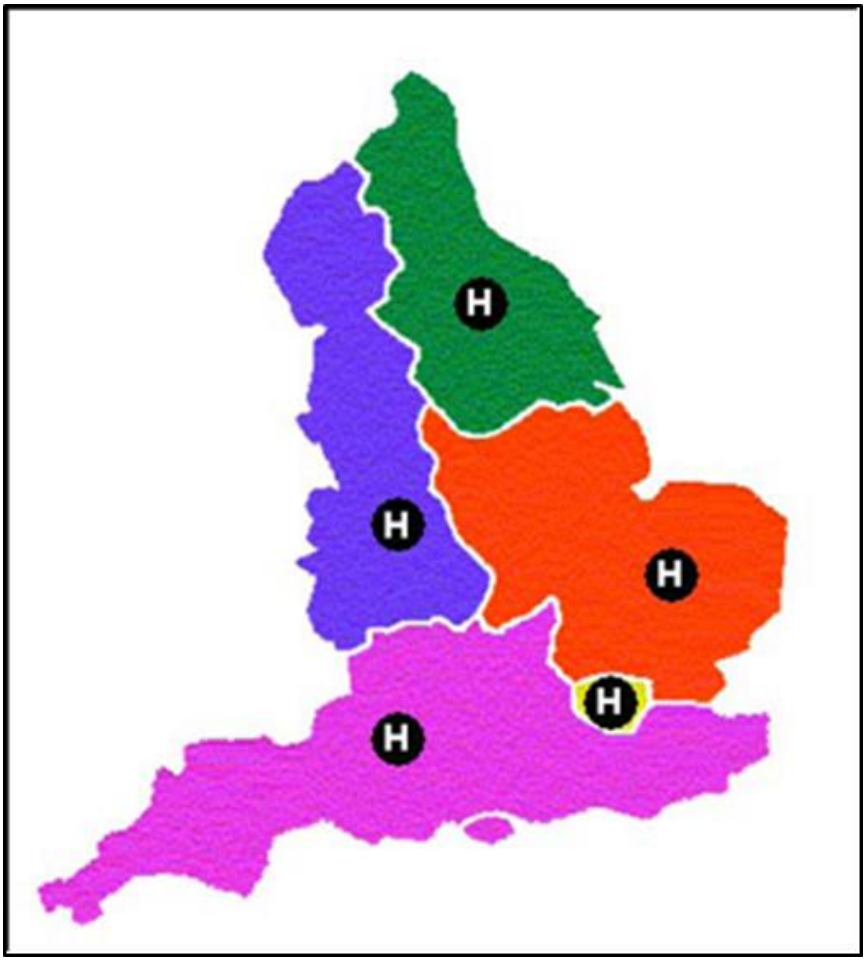

Figure 2.5 The five BCSP hubs.

Note: BCSP = Bowel Cancer Screening Programme.

Later on, the screening programme was extended to include 70–74-year-old adults and was rolled out across England (**Figure 2.6**).

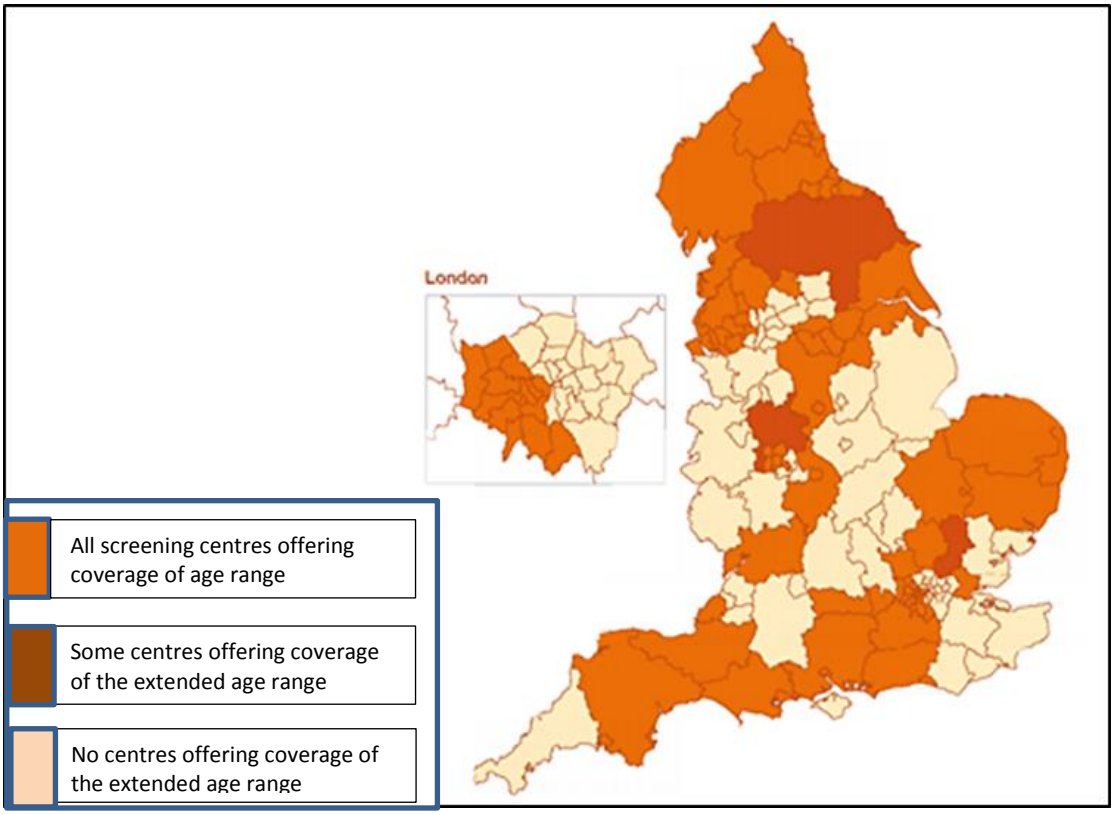

Figure 2.6 National coverage of the BCSP in June 2011 including roll out of the age extension.

Note: BCSP = Bowel Cancer Screening Programme.

The FOBT was performed according to a protocol designed to optimize the sensitivity and specificity of the test. (Specificity is the proportion of people without the target condition who have a negative test result.) No dietary restrictions are recommended before test completion. Individuals receive the kit by post and, after completion, return it by post to the screening hub within 14 days. Participants are provided with a WHO-approved, postage-paid envelope. When repeat testing is required, this is performed within 13 weeks of the previous test. Trained individuals based at the hub assess all FOBT kits on the day they are received. Quality assurance consists of continuous internal and external assessment of both FOBT kits and kit readers to ensure that standards remain high. A survey to assess the uptake of FOBT

screening in March 2015 revealed that the FOBT screening programme has been rolled out covering the entire population in the country (61).

Table 2.3 shows how FOBTs are interpreted and when repeat testing is necessary.

Table 2.3 Classification of FOBT results

Test result	Criteria	Action
Normal	No positive windows	Discharge to next screening round in two years
Unclear	1–4 positive windows	Patient given up to two further FOBT kits. If either subsequent FOBT is unclear or abnormal, patient is referred for colonoscopy. These are classified as a '**weak positive**' result. If both subsequent FOBT kits are normal, discharge to next screening round
Abnormal	5 or 6 positive windows	Patient referred for colonoscopy
Technical failure or spoilt kit	Lab processing problem or unreasonable kit due to incorrect use	Further FOBT kit sent

Source: Adapted from [62].

Note: FOBT = faecal occult blood test.

Screening centres (up to 20 per hub; see **Figure 2.7**) then provide endoscopy services and specialist screening nurse clinics to individuals as necessary. For instance, if a patient had a positive FOBT at the hub, they would then be invited to attend a screening centre closer to their home for assessment and colonoscopy. Patients found to have cancer are managed and followed up through the colorectal multi-disciplinary meeting at the patient's local hospital. The screening programme, in line with the current BSG guidelines, coordinates adenoma management and surveillance [13, 14].

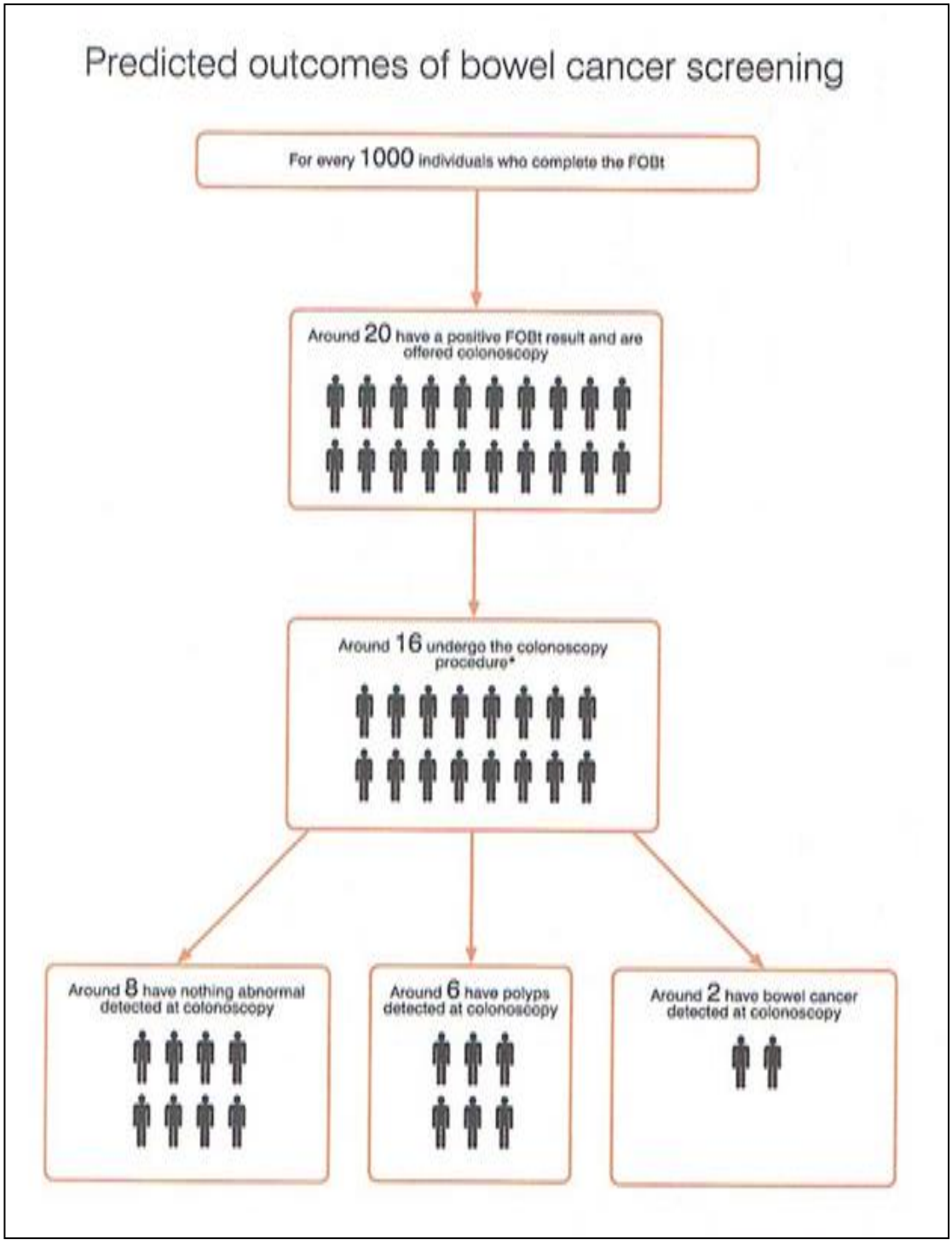

Figure 2.7 Predicted outcomes of Bowel Cancer Screening.

Source: Population screening programmes: NHS bowel cancer screening (BCSP) programme. Available from: http://www.cancerscreening.nhs.uk/bowel/#screening-work (accessed 21 September 2016).

Note: FOBT = faecal occult blood test.

Based on data from the pilot studies, around 98 in 100 people will receive a normal FOBT result and will be returned to routine screening. They will be invited for bowel cancer screening every two years if still within the eligible age range.

Around two in 100 people will receive an abnormal result. They will be referred for further investigation and usually offered a colonoscopy. Around 40–50% of patients who go on to have a colonoscopy will be found to have one or more adenomas; approximately 10% will be found to have bowel cancer. This is illustrated in **Figure 2.8**.

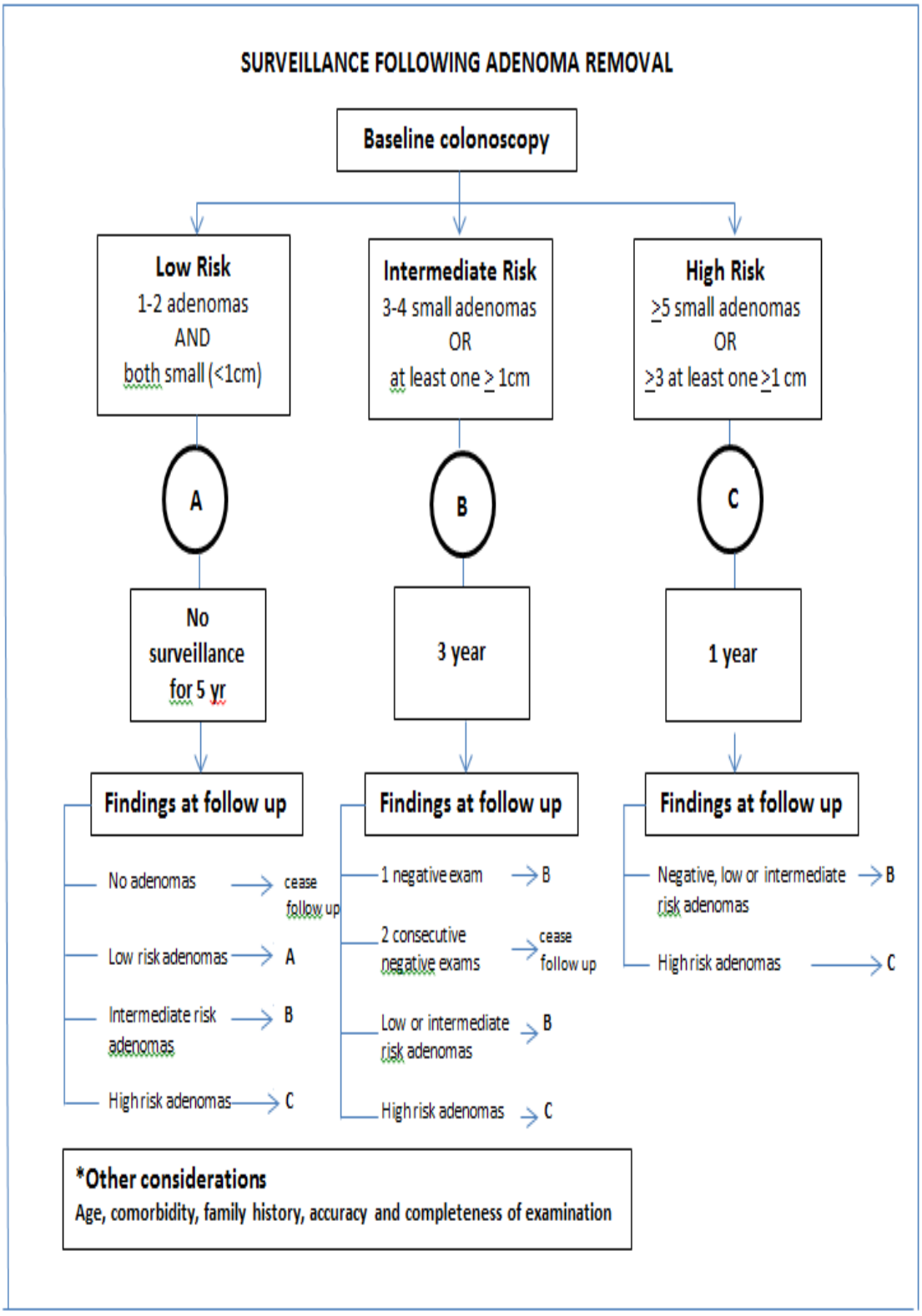

Figure 2.8 Adapted from the BSG guidelines for adenoma surveillance.

Note: BSG = British Society of Gastroenterology.

Part 2

2.7 Surveillance of patients with colorectal adenoma

2.7.1 The need for adenoma surveillance

Colorectal adenomas are common findings in repeat examinations after index colonoscopy and polypectomy. Findings of metachronous or recurrent adenomas during follow-up colonoscopy, after initial colonoscopy and polypectomy, are a widely reported and well-known phenomenon.

In one study, 227 patients had all their adenomas removed during the initial colonoscopy; when they were re-examined after one year, 56% were detected to have further adenomas and 9% had adenomas larger than 10 mm [63].

In the National Polyp Study (NPS) (UK), a total of 27.5 and 32.0% of patients were found to have adenomas after one and three years, respectively, following their index colonoscopy (87). In another prospective case-control study with 36 months of follow-up, the cumulative incidence rate and cumulative recurrence rate of colorectal adenomas detected were 16 and 42% respectively [50].

In the study by Kronborg et al. [58], the cumulative risk of a patient developing new adenomas was 35.0% (28.7–41.4%) after 24 months and 35.5% (28.4–42.7%) after 48 months of surveillance [51] after removal of all colorectal adenomas at the index colonoscopy.

In a further prospective study, 785 patients were followed up for 10 years. Individuals were categorized following their index colonoscopy into LR and HR groups according to the number and size of the adenomas detected. Patients were then randomized into annual, three-yearly or five-yearly surveillance colonoscopy. During follow-up, 48% of the HR and 36% of the LR patients had at least one adenoma detected [64].

In a pooled analysis, Martínez et al. [65] 64analysed data from eight prospective studies involving 9167 patients and showed that during a median follow-up of 47.2 months ACN was detected in 1082 (11.8%) of which 58 (0.62%) had invasive cancer.

Thus, it is evident that patients with colorectal adenomas are at greater risk of developing adenomas with ACN (adenomas ≥10 mm, unfavourable histology) in the future. Similar findings have been replicated in more recent studies [66–69].

These studies highlight the fact that patients with colorectal adenomas can develop new metachronous lesions after the initial colonoscopy and removal of all existing adenomas. A proportion of those metachronous adenomas will contain advanced neoplasia. Therefore, patients with adenomas require surveillance procedures to detect and remove new adenomas to reduce the chance of developing future CRC.

2.7.2 Missed synchronous lesions are common in colonoscopy

Colonoscopy provides the opportunity to detect and resect all colorectal adenomas. By removing all potential pre-malignant lesions, it also reduces the subsequent incidence and mortality from CRC.

The correlation between missed adenomas and future development of advanced neoplasia is well established. In a population-based study, 126 851 patients underwent colonoscopies and 159 of them developed interval cancer within 6–60 months of their initial colonoscopy. A significantly higher proportion of patients with interval cancer had adenomas during their index colonoscopy (57.2 *vs.* 26%; $P<0.001$) compared to patients without interval cancer [70]. In this particular series, the cohort with interval cancer had a higher proportion of patients with adenomas ≥10 mm in size and underwent polypectomies. This signifies that the cohort with interval cancer developed new adenomas, had incomplete resection or had missed synchronous adenomas.

In another study, 163 patients with multiple adenomas were followed up by colonoscopy within nine months after their initial procedure and polypectomy. Additional adenomas were detected in almost one quarter of all patients resulting in 'missed rates' for adenomas <5 mm, ≥5 mm and AAs of 17.7, 3.2 and 0.9%, respectively [67].70

Several risk factors that increase the chance of an adenoma being missed during colonoscopy were identified. Several studies identified poor bowel preparation, morphology, size and right sided location of the adenomas, proficiency of the colonoscopist, withdrawal time and patient age as factors affecting adenoma detection and hence determining missed adenoma rates [72–74]. Smaller size and flat nature and inadequate bowel preparations have been identified as contributing factors for missed right sided adenomas. These factors can lead to increased detection of interval cancer in the right side of the colon which is reported in literature. In a population based study Interval CRCs were associated with the proximal colon, earlier-stage cancer, lower risk of death, higher rate of adenoma, and family history of CRC (75). In another population based study among the subjects who underwent surgical resection for right-sided colon cancer, the miss rate of colonoscopy for detecting cancer was noted to be 4.0% (76). These facts illustrate the evidence of interval cancer and right sided location of the pathology, which could result from missed right sided colonic lesions.

High-quality colonoscopy overcomes some of the risk factors for missed lesions and reduces the chance of undetected synchronous adenomas during the initial colonoscopy. This in turn reduces the risk of developing advanced metachronous neoplasia during follow-up. These key findings were noted in studies performed with demonstrable high-quality colonoscopy [10, 46, 77]. However, no test is 100% accurate and even with meticulous colonoscopy lesions can go undetected [72, 78].

In 1997, in a landmark study of back-to-back colonoscopies, Rex et al. [78] showed that the overall miss rate for adenomas was 24%. With regard to size, the miss rate was 27% for adenomas <6 mm, 13% for adenomas 6–9 mm in size and 6% for adenomas >9 mm. Experienced physician endoscopists performed all the colonoscopies in this particular study; all of them had performed at least 500 colonoscopies previously (range of experience: from 500 to >10 000 colonoscopies).

In another study colonoscopy was performed in 1233 patients by a single experienced endoscopist following virtual colonoscopy. The incidence of undetected adenomas ≥10 mm in size was 12% during colonoscopy [72].

Therefore, colonoscopies, even when performed in quality-controlled settings, cannot overcome all the factors that affect adenoma detection. Evidence of missed adenomas and high-risk lesions were also reported in patients with inadequate bowel preparation on initial colonoscopy, when performed in the setting of a BCSP. In one study, patients who attended for a screening colonoscopy and had poor bowel preparation underwent a repeat colonoscopy. Of these, 33.8% had at least one adenoma detected and 18% had HR lesions (three adenomas, one adenoma of 1 cm, or any adenoma with villous features or HGD) [73].

Similar findings were noted in another study where the missed rate of colorectal adenomas was measured after adjustment of the colonoscopy quality indicators [79]. The overall miss rate of polyps, adenomas and AAs measured was 16.8, 17 and 5.4%, respectively.

In a systematic review of studies that included tandem colonoscopies, the pooled miss rate for the adenomas ≥10 mm was 2.1% (95% CI = 0.35–7.3). The pooled miss rate for adenomas between 5 and 10 mm and below 5 mm was 13% (95% CI = 8.0–18) and 26% (95% CI = 27–35), respectively [80].

These studies show that a small but significant proportion of patients with colorectal adenomas will have a missed adenoma during their initial colonoscopy; this justifies the need to have a follow-up procedure to detect and resect synchronous AAs and NAAs and to prevent the development of future CRC.

2.7.3 Colonoscopy and polypectomy reduce the risk of colorectal cancer

Colorectal adenomas are well established as precursor lesions for CRC and have been described as a 'good epidemiologic indicator of colon cancer risk' [81]. Removal of these precursor lesions has been shown to reduce the incidence and mortality associated with CRC.

In the NPS, a cohort of 1418 patients who underwent colonoscopic polypectomy was followed up for an average period of 5.9 years to determine the true and expected incidence of CRC on the basis of the findings of three well-defined reference groups. Two of the reference groups contained patients where polyps were not removed (Mayo Clinic cohort from the USA and St Mark's cohort from the UK), and one was a group from the population-based Surveillance, Epidemiology, and End Result Program of the National Cancer Institute (USA). The study population was examined with one (examination in the third year) or two colonoscopies (examination in the first and third year) for each individual during follow-up; all patients were also offered an examination at the end of a six-year follow-up period. Only five asymptomatic early-stage CRCs were detected in the study group, whereas the number of expected cases on the basis of the reference groups were 48.3, 43.4 and 20.7, suggesting a 90, 88 and 76% reduction in the incidence of CRC [46].

Zauber et al. [10] followed up the NPS cohort for a further period and showed a reduction in CRC-related mortality in the polypectomy group. In this particular study, 2602 patients who had their adenomas removed by polypectomy were followed up for a median period of

15.8 years. The standardized incidence-based mortality ratio from CRC was 0.47 (95% CI = 0.26–0.80) in the group with polypectomy suggesting a 53% reduction in mortality from CRC (25.4 expected deaths from CRC in the non-adenoma group *vs.* 12 deaths from CRC in the polypectomy group).

In a population-based case-control study in Germany, colonoscopy with polypectomy was found to be associated with significant risk reduction from developing CRC in both men and women [82]. In this particular study, colonoscopy and polypectomy in the preceding 10 years was associated with a 77% lower risk for CRC. The strong risk reduction was noted for CRC in all stages and in all ages, except for right-sided cancer in persons aged 50–59 years.

Another recent large population-based study from Norway used data from the Cancer Registry and the Cause of Death Registry, revealing that CRC mortality was lower during the follow-up period among patients who had LR adenomas removed at their first colonoscopy [83]. In this study, the investigators followed up 40 826 patients diagnosed with colorectal adenomas over a median follow-up period of 7.7 years. This study showed that the standardized mortality ratio (SMR) from CRC was low in patients who had LR adenoma at the onset (expected deaths = 189; observed deaths = 141; SMR = 0.75; 95% CI = 0.63–0.88) but higher in patients who initially had HR adenomas (expected deaths = 209; observed deaths = 242; SMR = 1.16; 95% CI = 1.02–1.31). The higher SMR in patients with HR adenomas could be explained by the fact that the Norwegian guidelines recommended colonoscopy after 10 years for patients with HR adenomas (adenomas with HGD, a villous component or ≥10 mm) and after five years for patients with three or more adenomas.

All of these studies show that colonoscopy and polypectomy performed during initial and subsequent colonoscopy reduce the incidence and mortality from CRC during the follow-up

period. The fact that a missed colorectal adenoma (synchronous lesion) during the index colonoscopy and newly developed metachronous adenomas in patients with multiple adenomas could develop into advanced neoplasia, makes a strong argument for surveillance.

2.8 Risk stratification strategy and surveillance interval

Although surveillance colonoscopy is a rational way to follow up patients with colorectal adenomas, a skilled workforce and a structured framework are required to organize and deliver such a service nationally within the quality-controlled setting of bowel cancer screening practice. It is also not a risk-free procedure.

Diagnostic colonoscopy carries a small chance of significant adverse events and that probability increases with therapeutic procedures undertaken to remove adenomas. The overall complications reported in the UK National Colonoscopy Audit showed that bleeding, bowel perforation and cardiorespiratory adverse event rates (with a 95% CI) were 0.26 (0.2–0.36), 0.04 (0.02–0.08) and 0.02% (0.01–0.05), respectively [84].

The majority of complication data from colonoscopy were derived from practices in the secondary or tertiary care sector. Studies from community-based practices also showed complications from diagnostic and therapeutic colonoscopy. In one study looking into community-based practices in the USA, data were collected from an extensive electronic database of the integrated healthcare delivery system (Kaiser Permanente, Northern California). This study included 16 318 patients who had their colonoscopies between January 1994 and July 2002 [85]. Serious complications occurred in 0.8 per 1000 diagnostic colonoscopies and in 7.0 per 1000 colonoscopies with biopsy or polypectomy. Perforations occurred in 0.9 per 1000 colonoscopies (95% CI = 0.5–1.5 per 1000 colonoscopies), 0.6 per 1000 diagnostic procedures and 1.1 per 1000 colonoscopies with biopsy or polypectomy.

Adverse events from colonoscopies carried out in the BCSP have also been studied. The overall bleeding rate was 0.65% and the rate of bleeding requiring transfusion was 0.04%. The overall perforation rate was 0.06%. Polypectomy increased the risk of bleeding 11.14-fold and the perforation risk 2.97-fold [86].

A population-based adenoma surveillance programme needs a skilled endoscopy workforce and appropriate support services, incurring significant costs to the health service.

Consequently, surveillance colonoscopy should be targeted at the population who will benefit most from it, accepting that adverse events will be balanced in terms of the risk–benefit ratio towards the positive side and will be cost-effective. An effective and continuing surveillance programme in turn needs the establishment of an effective and skilful workforce with an appropriate support service and a valid strategy to identify people with colorectal adenomas who have a higher probability of developing advanced metachronous colorectal neoplasia, including AA and CRC. Targeted surveillance will identify this cohort and, by removing pre-malignant adenomas in this HR group, it will reduce the future incidence and mortality from CRC.

The NPS addressed these issues when it was launched in 1980 and sponsored by the AGA. This study was a multicentre, prospective, randomized trial designed to evaluate follow-up surveillance strategies in patients with colorectal adenoma with the aim of preventing future occurrence of CRC [87]. The study recruited 9112 patients who had their colonoscopy examinations in seven participating centres. A total of 1418 patients with adenomas were randomized into two arms, one arm having colonoscopy one year after the index procedure and the other arm having colonoscopy at the first and third year after their index procedure. A six-year colonoscopy was offered to patients in both arms of the study. The randomization of patients into different arms was performed by stratifying them using three variables to

ensure a balance of these variables between the follow-up treatment arms (that is, groups with different surveillance intervals): geographic location (each of the seven centres); number of adenomas (single *vs*. multiple); and adenoma histology (tubular *vs.* villous). Patients for this study were mainly referred for colonoscopy because of positive findings on barium enema examination (27%), sigmoidoscopy (15%), FOBT (11%) or other tests (10%), or because of symptoms (32%) or a family history (5%) of CRC [87]. The mean age of patients participating in this study in all seven centres varied from 56 ± 13 (mean and standard deviation) years to 64 ± 13 years. Interestingly, only 11% of patients were referred after a positive FOBT.

There was a significant difference in the proportion of patients having an adenoma detected during surveillance colonoscopy. The group with two examinations had a higher proportion (41.7 *vs.* 32.0%; $P = 0.006$) of adenomas, but the proportion of patients with adenomas exhibiting advanced pathological features was the same (3.3%) in both groups. The researchers concluded that the first surveillance colonoscopy could be performed at year 3 in the majority of patients diagnosed with colorectal adenoma on initial examination. They also showed that age, number of adenomas and size of the largest adenoma at enrolment were independent risk factors for predicting any adenoma detected during the first surveillance colonoscopy, but the only factor predicting the detection of adenomas with advanced pathological features was the number of adenomas at onset (≥3 adenomas; odds ratio (OR) = 6.9; 95% CI = 2.6–18.3; $P<0.001$) [48].

Noshirwani et al. [88] performed a retrospective study using the data from the Cleveland Clinic Foundation Adenoma Registry. They identified 697 patients eligible for the study who were seen in the period between 1979 and 1989, had one or more adenomas removed at colonoscopy and completed a surveillance examination within 10–42 months (mean =

18 months). Overall, 9% of their patients had an adenoma with advanced pathological features (advanced adenoma or adenoma containing a focus of cancer). Their findings showed that the number and size of baseline adenomas were significantly associated with clinical outcome (having four or more adenomas or any adenoma with advanced pathological features; $P<0.001$). Age, sex, pathology of baseline adenomas and time interval between colonoscopies were not significantly associated with clinical outcome. This study showed that patients with one or two sub-centimetre adenomas had a very low probability of having significant pathology at first surveillance colonoscopy and that their first surveillance examination could be delayed beyond three years.

Martínez et al. [65] performed a pooled study of 9167 patients (aged 22–80 years) from eight different prospective trials and a median follow-up period of 47.2 months. They showed that the risk of a metachronous AA was higher among patients with ≥5 adenomas (24.1%; standard error (SE) = 2.2) and those with an adenoma ≥20 mm (19.3%; SE = 1.5). Their multivariate analysis identified male sex, increasing age, number and size of adenomas, proximal location and villous architecture at baseline as independent risk factors for metachronous advanced neoplasia.

Saini, Kim and Schoenfeld [89] performed a meta-analysis to address the issue of AA incidence in LR and HR patients at the three-year surveillance colonoscopy to support the risk categorization strategy. They included 15 prospective studies; of these only five stratified their patients according to the findings at the index colonoscopy. The final result of this meta-analysis showed that the presence of ≥3 adenomas was associated with an increased risk of having AAs compared to patients with one or two adenomas (relative risk (RR) = 2.52; 95% CI = 1.07–5.97). Presence of HGD at the index colonoscopy was also

significantly associated with an increased risk of having AAs at follow-up (RR = 1.84; 95% CI = 1.06–3.19).

A recent study from Japan analysed the relationship between the number of surveillance colonoscopies and CRC prevention, using the detection of AAs at surveillance as the end point. They divided 2391 patients into LR (having one or two sub-centimetre adenomas) and HR (having ≥ 3 adenomas) groups and analysed data regarding their surveillance colonoscopy after their index colonoscopy over a period of five years. The results showed that comparing patients who had infrequent colonoscopies (once or not at all within the previous five years) with those who had two or three colonoscopies within five years resulted in a 67 and a 52% reduced risk for AAs in the LR and HR groups, respectively. However, for cases undergoing colonoscopy very frequently (≥ four times within five years), the additional risk reduction for AAs was relatively small [90].

In a polyp prevention trial, van Stolk et al. [91] evaluated the predictive effects of the number of adenomas, and their size, type and degree of atypia in 479 patients, using the same characteristics at follow-up (ORs with 95% CIs). Their study concluded that patients with one or two tubular adenomas constitute the LR group for whom follow-up might be safely extended beyond three years. Similar findings were reported in other studies [88, 92].

Lieberman et al. [77] conducted a study to measure the incidence of advanced neoplasia after five and a half years of an initial screening colonoscopy. In this study, 3121 asymptomatic patients underwent a screening colonoscopy and, according to their baseline adenoma characteristics, underwent a surveillance colonoscopy once after five years or twice at the second and fifth year. Compared to patients with no neoplasia, patients with only one or two tubular adenomas <10 mm did not show a statistically significant incidence of advanced neoplasia during surveillance (4.6 *vs*. 2.4%; *P* = 0.13); hence they were

described as the LR group. Patients with three or more tubular adenomas <10 mm had a higher rate of AAs compared to patients without any neoplasia at screening (11.9 *vs*. 2.4%; *P*<0.001) or having just one or two small sub-centimetre adenomas (11.9 *vs*. 4.6%; *P*<0.001).

Patients with one or two sub-centimetre adenomas have been described consistently as the LR group and the available evidence suggests that their surveillance colonoscopy could be safely performed after five years [64, 66, 88, 91, 92]. One study showed a higher incidence of advanced neoplasia in this group compared to controls (hazard ratio = 2.6; 95% CI = 1.6–4.2) [66]. Several other studies compared the incidence of advanced metachronous adenomas in control and LR groups; they did not find any significant difference during surveillance if this was performed [93, 94] or 10 years after screening [95].

The long-term risk of developing CRC in patients with adenoma has been well demonstrated in several studies. In one retrospective study, 1618 patients whose adenomas were resected during the rigid sigmoidoscopy were followed up [49]. Patients who were stratified as the LR group showed a similar risk of developing CRC as the general population (standardized incidence ratio (SIR) = 0.5; 95% CI = 0.1 – 1.3). Similar findings were reported in a registry-based study involving 5579 post-polypectomy patients and the SIR of CRC in the LR group was 0.68 (95% CI = 0.44–0.99), even when surveillance colonoscopy was not performed [68]. Case-control studies also showed a low risk of CRC during five years of follow-up in this group [96, 97].

The available evidence suggests that the risk of developing advanced metachronous neoplasia is smaller in patients who have one or two small (<10 mm) adenomas and they are referred to as the LR group in the literature. The risk was greater in patients who had ≥3 adenomas or had a larger (≥10 mm) adenoma at the initial colonoscopy; they have been described consistently in different studies as the HR group.

The risk of developing CRC has been extensively studied in HR groups. In the epidemiological study performed by Atkin, Morson and Cuzick [49], the HR patients were followed up for up to 14 years without endoscopic surveillance and they showed a 3.6–6.6-fold increased risk of developing CRC compared to the general population. The registry-based study mentioned previously showed a 4.26-fold (95% CI = 2.89–6.04) increased risk of developing CRC compared to the general population during the follow-up period [68]. Epidemiological case-control studies have shown that the HR group has a higher long-term risk of developing CRC compared to the general population after five years of surveillance following initial colonoscopy and polypectomy [96–98].

The incidence of advanced metachronous neoplasia in HR populations was detected and was significantly higher compared to populations without adenomas and LR groups. In prospective cohort studies, the incidence of advanced metachronous neoplasia was 5–7 times higher in HR groups compared to individuals without any adenomas [66, 77, 93]. In the pooled analysis study, the risk of advanced neoplasia in the HR group during surveillance was 15.5% compared to 6.9% in the LR group [65]. The study from the Cleveland Clinic Foundation Adenoma Registry also showed that the risk of incidence of AAs at surveillance increased fivefold in patients who had ≥4 smaller (<10 mm) adenomas removed compared to the LR group, and the risk increased 10-fold if patients with multiple adenomas had one adenoma >10 mm at the onset [89]. In a pooled analysis, Martínez et al. [99] analysed the data from four prevention trials which performed surveillance colonoscopies after one year. Patients with five small (<10 mm) adenomas or with three adenomas, one of which was >10 mm, had an 18.7% absolute risk of having advanced neoplasia at year 1, showing the benefit of having surveillance at year 1 in that group.

Along with adenoma-specific factors (number and size), colonoscopy quality indicators at surveillance were also identified as important factors that influence the incidence of advanced neoplasia. In a community-based study, van Heijningen et al. [100] showed that large size, number, VH and proximal location of adenomas, as well as insufficient bowel preparation and poor 'colonoscopy reach' at the first colonoscopy were associated with AA detection at surveillance. This study showed that along with the number and size of adenomas detected, colonoscopy quality indicators also had a vital role in adenoma detection. The limitation of including the villousness in the histology is that it is a subjective assessment and widespread inter-observant variation is a possibility.

Thus, the available evidence supports the idea of stratifying patients with colorectal adenomas into different risk groups depending on the number and size of adenomas at the onset and then continuing follow-up with colonoscopy at different time intervals depending on the projected risk of developing advanced metachronous colonic neoplasia.

In the UK, the adenoma surveillance guidelines were based on the available evidence in 2002 [13] and further updated in 2010 without any major changes [14]. The guidelines divide patients into three different risk categories depending on the number and the size of the adenomas detected at the initial colonoscopy; they suggest performing surveillance at different time intervals according to the risk of developing future advanced colonic neoplasia. Because of the paucity of evidence for future advanced neoplasia in the LR group, the guidelines suggest that patients could either be discharged or followed up after five years for surveillance purposes. The surveillance pathway is shown in **Figure 2.8**.

The chosen cut-off age for surveillance is 75 years because the remaining life expectancy is less than the average time required for new adenomas to develop into advanced pathology or CRC.

These guidelines are widely used in the UK and form the basis of adenoma surveillance in the BCSP. The only variation is that the LR patients in the BCSP are returned to the biennial FOBT screening pool [101] (**Figure 2.9**).

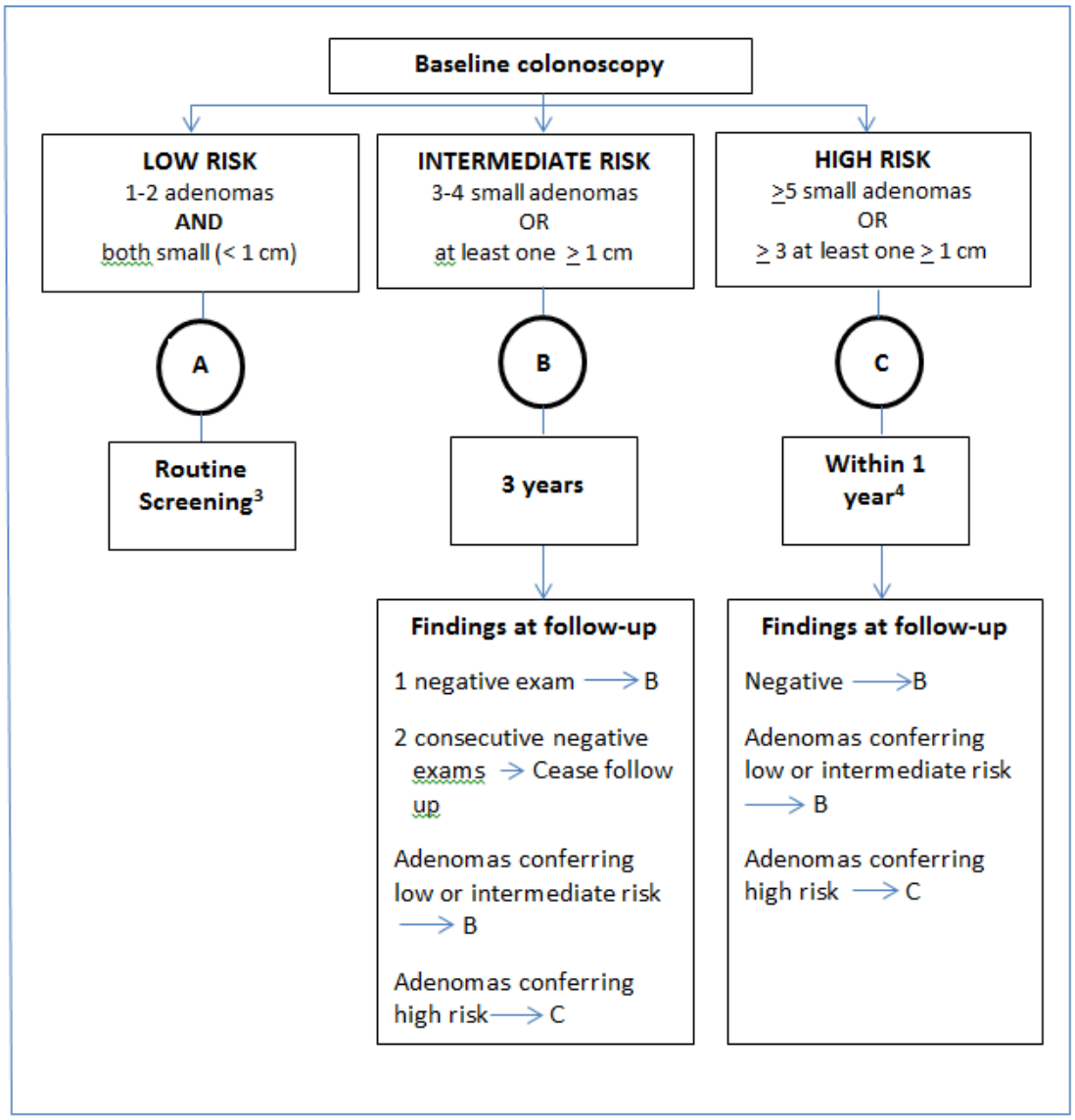

Figure 2.9 Adapted from the Adenoma surveillance NHS BCSP guidelines.

2.9 High-quality colonoscopy on surveillance

High-quality colonoscopy has been defined as 'complete colonoscopy with a meticulous inspection of adequately cleaned colorectal mucosa. Neoplastic lesions have also been completely removed and retrieved for histological examination [16].' Detection and removal

of all neoplastic lesions in the colon is important for screening efficacy; this can be achieved through a high-quality colonoscopy [96–98]. 101-103 If complete detection and removal of all

pre-malignant adenomas can be achieved during the index colonoscopy, then the proportion of advanced metachronous lesions that develop as a consequence of missed and incompletely removed pathology can be minimized; hence, the surveillance interval can be prolonged to detect future colorectal neoplasia that would develop *de novo* from a normal mucosa because of accelerated carcinogenesis in susceptible individuals who initially had multiple and larger adenomas. The degree of success with which colonoscopy detects adenomas depends on various factors.

Atkin et al. [99] 104proposed several performance indicators that need to be monitored to assure a high-quality screening colonoscopy service. Key performance indicators included: withdrawal time; adenoma detection; incomplete polyp excision; complications; and missed cancers. The study also focused on various other key areas of quality improvement for a screening service.

The importance of the adenoma detection rate (ADR) as a performance indicator has been studied in the context of bowel cancer screening. Kaminsky et al. [100]105 used Cox's proportional hazards model to evaluate the influence of colonoscopy quality indicators on the risk of interval cancer. The study involved 186 colonoscopists and data about quality indicators were collected. This was done within the setting of a colonoscopy-based CRC screening programme and involved 45 026 patients who participated in the screening during the study period. The study showed that an endoscopist's ADR was significantly associated with the risk of interval cancer. An ADR below 20% was associated with significant risk of interval cancer, compared to an ADR ≥20%.

The BCSP has aimed to develop and deliver a high-quality colonoscopy service from the onset. Performance quality control was well described by Logan et al. [107]. They suggested that all colonoscopies are undertaken at JAG-accredited screening centres (http://www.thejag.org.uk/) by screening-accredited colonoscopists, who have passed a formal assessment comprising a 12-month personal colonoscopy audit and multiple choice questionnaire, and have performed two directly observed colonoscopies assessed independently by two screening examiners. Ongoing quality assurance includes assessment of cecal intubation rate, ADR, polyp retrieval rate, colonoscopy withdrawal time, comfort score and complications. Screening colonoscopies are allocated 45-min time slots. A screening specialist practitioner accompanies the patient during the procedure and records a detailed data set onto the national Bowel Cancer Screening System (BCSS) database.

Before becoming accredited and starting to practise in the BCSP, all colonoscopists are required to have performed at least 1000 colonoscopies with a cecal intubation rate >90% and an ADR >20% in the preceding 12 months. In addition, sedation levels have to be in keeping with National Patient Safety Agency recommendations and the BSG guidelines; the complication rate has to be reported and deemed acceptable [108].

In the BCSP, to ensure the delivery of high-quality colonoscopy, quality indicators, standards and auditable outcomes were identified in the quality assurance guidelines [109]. These indicators, their definitions and level of accountability are shown in **Table 2.4**.

Table 2.4 Quality indicators in the BCSP

Quality indicator	Accountability	Definition
ADR	Colonoscopist	Number of colonoscopies at which one or more histologically confirmed adenomas were found divided by the total number of colonoscopies performed in the same time period
Polyp detection rate	Colonoscopist	Number of colonoscopies at which one or more polyps were found (regardless of histological type) divided by the total number of colonoscopies performed (in the same time period)
Colonoscopy withdrawal time	Colonoscopist	Average time taken to withdraw the colonoscope from the caecal pole to the anus in complete, negative procedures
Unadjusted cecal intubation rate	Colonoscopist	Proportion of all colonoscopic procedures in which the caecum, terminal ileum or anastomosis was reached (no adjustment made for poor bowel preparation or impassable strictures)
Rectal retroversion rate	Colonoscopist	Proportion of procedures in which the colonoscope was retroverted in the rectum
Polyp retrieval rate	Colonoscopist	Proportion of resected polyps that were retrieved and sent for histological analysis
Sedation practices	Colonoscopist	Mean doses of pethidine, fentanyl and midazolam, when used Patient comfort assessed during colonoscopy using the modified Gloucester discomfort score to grade patient discomfort as none, mild, moderate or severe [110]
Hyoscine butylbromide use	Colonoscopist	Proportion of procedures in which hyoscine butylbromide was administered
Bowel preparation scores	Screening centre	Quality of bowel preparation assessed by colonoscopist at the time of colonoscopy using a four-point modified Likert scale Descriptors for quality of bowel preparation are: incomplete examination due to inadequate preparation; complete examination despite inadequate preparation; adequate or excellent preparation [110]
Adverse events	Colonoscopist/ screening centre/unit	Data from BCSS, adverse event log and screening centres

Note: BCSS = Bowel Cancer Screening System; ADR = adenoma detection rate.

Similar quality indicators are accepted worldwide and also mentioned in recently published American guidelines for colonoscopy quality indicators [111].

The impact of high-quality colonoscopy on post-polypectomy surveillance is discussed in the European guidelines [16]; they recommend that surveillance procedures should be done at longer intervals, which will be more cost-effective.

In the light of these facts, the current adenoma surveillance guidelines need to be re-examined to evaluate whether their effectiveness and appropriateness in stratifying the FOBT-positive screened is adequate, as the population is of a specific age group (60 to 74 years) in which the incidence of colorectal adenoma is high. Since high quality colonoscopy is currently being used in the NHS BCSP it is relevant to determine whether current surveillance intervals in the BCSP can be prolonged.

The evidence presented in this literature review highlights that CRC is an important burden on society and health care, being one of the major causes of mortality in the UK and worldwide. If CRC could be detected at an earlier stage when localized to the bowel wall, then a curative treatment is feasible by providing curative resection, reducing both mortality and morbidity from the disease. The development of malignant bowel cancer from a benign, pre-malignant adenoma is slow, allowing time to make a diagnosis at this stage. Time is also needed for early-stage CRC to progress to an advanced stage. This time window, present during benign to malignant transformation of adenomas and progression from early-to advanced-stage CRC provides the opportunity to detect and remove adenomas with a consequent reduction in the future incidence of CRC.

The FOBT is a valid tool for population-based screening of CRC and is being currently used in the BCSP. The current surveillance guidelines are based on population-derived studies rather than on a FOBT-positive cohort. If a high-quality colonoscopy service could be routinely

provided within a quality-controlled framework, then the intensity of surveillance could be optimally prolonged. The BCSP is providing a quality-controlled screening colonoscopy service delivered by accredited and experienced endoscopists. It also provides the evidence to prolong surveillance intervals. Assessing the surveillance outcome in the BCSP will validate the current guidelines for a screening cohort but can also be used to assess whether the surveillance interval can be safely prolonged in routine clinical practice. This will allow more efficient use of the current workforce in an era of finite financial resources in the NHS.

2.10 Summary

CRC is a common disease that imposes a significant burden on society, being the second most common cause of cancer-related death in the UK.

Great advances in understanding the natural history of CRC have been made over the last 40 years. This has led to the acceptance of the adenoma–carcinoma model being the origin for most CRCs.

Fortunately, the transition from adenoma to cancer takes place over many years; this provides the ideal opportunity for a screening programme to detect and remove such lesions before they become malignant.

Larger adenomas and CRCs tend to bleed intermittently. This means that the detection of blood in faeces (using a FOBT) may allow their detection. However, the FOBT only detects around 50% of such lesions due to the intermittent nature of bleeding.

Early diagnosis of CRC confers significant survival advantages. Three large RCTs of biennial FOBT have shown a 13–21% reduction in CRC mortality. One of these studies showed a 17% reduction in CRC incidence after an 18-year follow-up.

On the basis of these large trials, the BCSP invites men and women aged 60–74 years to enter a biennial FOBT programme with colonoscopy recommended if the FOBT is positive. The BCSP aims to detect cancers at an earlier stage and detect and remove adenomas.

Advanced metachronous adenomas are a common finding among patients with colorectal adenomas during follow-up.

Colonoscopic polypectomy at the index colonoscopy and during continued surveillance reduced the incidence and mortality from CRC. Colonoscopic surveillance for patients with adenomas is best performed by targeting groups according to their risk of developing advanced metachronous adenomas.

The available evidence for risk stratification is derived from population-based studies, including symptomatic patients and FOBT-positive patients. The current BSG adenoma surveillance was developed on the basis of this evidence and is the basis of the adenoma surveillance programme in the BCSP.

Recent evidence suggests that with high-quality colonoscopy, surveillance intervals can be prolonged.

Colonoscopies performed in the BCSP are carried out by accredited clinicians and are done within quality-controlled settings, thereby delivering high-quality colonoscopy.

The appropriateness of the current adenoma surveillance guidelines needs to be validated for FOBT-positive patients in the BCSP population who have had a demonstrably high-quality colonoscopy.

Chapter 3: Methodology

3.0 Introduction

In this chapter, the general methodology followed in this thesis is discussed. The specific analytical methodologies used to obtain the results in different chapters are illustrated in each chapter:

- the study location;
- the study population;
- the BCSP database;
- ethical considerations and approval;
- data transfer and storage;
- aims and objective of the methodology;
- general methodology.

3.1 Study location and nature of the work

The study took place at the Wolfson Research Institute for Health and Wellbeing, Durham University, and University Hospital of North Tees, Stockton on Tees, UK. The project involved analysing the data obtained from the BCSP national database based in Sheffield. There was no direct involvement or interaction with any of the study patients. The data obtained were anonymized and then used for analysis.

3.2 Aims and objectives

The aims and objectives of this study included:

- identifying the size of adenomas detected in the BCSP that contained advanced neoplasia (adenomas containing HGD, VH, carcinoma, adenoma ≥10 mm);
- identifying the predictive factors that influence the presence or absence of advanced neoplasia in the adenomas of the FOBT-positive population and hence provide valuable information for endoscopists to enhance the ability to identify them;
- evaluating the outcomes of the continuing screening of HR and IR patients;
- determining the effects of continuous screening of HR and IR groups on the reduction of AAs at surveillance;
- determining the predictive factors (adenoma- and patient-specific) at screening that can effectively determine outcome at surveillance and can provide further information and knowledge to create a more effective risk re-stratification strategy at screening;
- determining an effective surveillance interval to better make use of the available workforce and resources needed to detect more AAs at surveillance without any significant increase in the detection of CRC at surveillance.

3.3 The study population

The individuals included in the study took part in the BCSP for the period from June 2006 to August 2012. The screening programme started in June 2006 and offered a guaiac-based FOBT to all men and women aged between 60 and 69 every two years. From February 2010, the age of participants was increased up to 75 years. The information relevant for use in this thesis included participants who had a positive FOBT test and who were subsequently examined with colonoscopy.

For the purpose of the objectives of this work, two separate data sets from the national databases were obtained, as described later in the chapter.

For the analysis of factors predicting the presence of advanced neoplasia, data for all polyps detected and removed was obtained, as documented in the BCSP, from June 2006 up to June 2012. Adenomas occur as superficial mucosal lesions on the inner surface of the bowel and are classified as polyps. All lesions identified as polyps during the study period have been included in this study. The data set is described later on in the chapter.

To analyse the surveillance outcomes of IR and HR participants, a separate data set containing the relevant participant-, procedure- and adenoma-specific information was obtained. All individuals identified as being in the IR and HR groups at their screening colonoscopy from June 2006 to September 2012 were included. The data set is described later in the chapter.

3.4 The BCSP database

The BCSP database contains the data for all patients entering the programme. Further data on patients undergoing colonoscopy were contemporaneously uploaded by specialist screening practitioners and administrative staff at screening centres around England, as patients followed the screening pathway. The data were entered with a graphical user interface (the BCSS) into an Oracle database. Data could be exported to a SQL server to allow specific queries to be written.

The database is comprehensive and data were prospectively gathered. A wide range of parameters were recorded including: demographics (age, sex, postcode of address at the time of entry into the screening programme, relevant medication history, weight and height); FOBT results; colonoscopy results; histology outcomes; and subsequent management.

Access to the national database is restricted. Professor Matt Rutter is chair of the National BCSP Service Evaluation Group and acted as sponsor for this research. The body of work contained within this thesis was formally sanctioned by the evaluation group. As the author's clinical supervisor, Professor Rutter facilitated access to the national database. Assistance in accessing the database was also provided by the BCSP National Office. Requests for specific data sets were made to the National Office who provided the data as a Microsoft Excel spreadsheet.

The process of extracting the data from the main database was undertaken by the author and by Claire Nickerson (data analyst, BCSP). This involved defining the specific data that were required and writing the 'query' used to search the database to ensure that the correct data were obtained. The author developed the list of variables for the 'query' after a series of meeting with his supervisors and after identifying important relevant factors from the literature review. The author planned to interrogate the BCSP database from June 2006 to September 2012 to capture five years of up-to-date information available in the database.

3.4.1 Data transfer and storage

All the required data were gathered after interrogating the BCSP database. The data were initially in Microsoft Excel format; they were then transferred electronically using NHS mail accounts. These are entirely encrypted and could only be accessed from a NHS computer. The data were stored in a dedicated account on the North Tees and Hartlepool NHS Foundation Trust server.

Initially, data were processed to eliminate the patient identifier variables (NHS number, patient ID), thereby allowing the data sets to be transformed into a pseudo-anonymized form and used for further analysis.

The anonymized data were stored in an encrypted external storage device, provided by the North Tees and Hartlepool NHS Foundation Trust and used for data transfer and analysis whenever required. For the purpose of analysis and data processing, the data sets were also stored in an encrypted and password-protected device, and kept at a safe location in the Wolfson Research Institute for Health and Wellbeing. Following completion of this work, the data would be stored only in the North Tees and Hartlepool NHS Foundation Trust server under the auspices of Professor Rutter. Caldecott approval was obtained from the Trust Information and Governance team to obtain and store NHS BCSP data and use it for analysis. Approval was obtained from the University to store pseudo-anonymized data and use that for analysis, which was followed throughout this work.

3.5 The data sets

3.5.1 Data set for the analysis of advanced neoplasia in adenomas

Information for each polyp detected during the study period was obtained (**Table 3.1**)

Table 3.1 Characteristics of polyps detected during the study period

Variable number	Variable and information obtained
1	NHS Number (unique patient identifier)
2	Date of birth
3	Sex
4	Date of polypectomy (date when the procedure was performed)
5	Patient ID in the BCSP (unique patient identifier)
6	Polyp ID (unique ID for each polyp at endoscopic detection)
7	Polyp location (segment of colon where the polyp was found)
8	Estimated size of polyp in mm (polyp size estimated during endoscopy)
9	Histological ID (unique ID for each polyp in the histology report)
10	Polyp actual size in mm (polyp size measured during histology)
11	Polyp architecture (histological types)
12	Degree of dysplasia
13	Presence of carcinoma (yes/no)
14	Polyp morphology (sessile/pedunculated/flat)
15	Excision completeness
16	Centre ID (bowel cancer screening centre where colonoscopy was performed)

Note: BCSP = bowel cancer screening programme.

The methodology used to process and analyse the data is described in Chapter 5; the analysis of all adenomas is also described in Chapter 5.

3.5.2 Data sets for the analysis of surveillance outcome

Data about the participants and their investigations for both screening and surveillance staging were obtained. In addition, information about the adenomas detected at both screening and surveillance was gathered. The data obtained are described in **Tables 3.2** and **3.3**.

Table 3.2 Patient- and procedure-specific information

Variable number	Variable and information obtained
1	NHS number (unique patient identifier)
2	Patient ID in the BCSP (unique patient identifier)
3	Sex
4	Date of birth
5	Episode ID (unique ID for when a patient attends an investigation in the BCSP)
6	Episode type (screening/surveillance)
7	Confirmed date (date of the investigation)
8	Patient height (in metres, when available)
9	Patient weight (in kilograms, when available)
10	Screening centre code (centre for colonoscopy)
11	Greatest risk (outcome of the colonoscopy: normal or abnormal, LR/IR/HR adenoma, cancer)
12	Outcome of the result (subsequent management: surveillance/discharge/treatment)

Note: NHS = National Health Service; BCSP = Bowel Cancer Screening Programme; LR = low-risk; IR = intermediate-risk; HR = high-risk.

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Table 3.3 Information about adenomas obtained at screening and surveillance

Variable number	Variable and information obtained
1	NHS number (unique patient identifier)
2	Date of birth
3	Sex
4	Date of polypectomy (date when the procedure was performed)
5	Patient ID in the BCSP (unique patient identifier)
6	Episode type (screening/surveillance)
7	Episode ID (unique ID for an event when a patient attends an investigation, as recorded in the BCSP database)
8	Polyp ID (unique ID for each polyp at endoscopy)
9	Polyp location (segment of colon where the polyp was found)
10	Polyp estimated size in mm (as estimated during endoscopy)
11	Histological ID (unique ID for each polyp in the histology report)
12	Polyp actual size in mm (polyp size measured during histology)
13	Polyp architecture (histological types)
14	Degree of dysplasia
15	Presence of carcinoma (yes/no)
14	Polyp morphology (sessile/pedunculated/flat)
15	Excision completeness
16	Centre ID (bowel cancer screening centre where colonoscopy was performed)

Note: NHS = National Health Service; BCSP = Bowel Cancer Screening Programme.

The patient and procedure data set was used to derive datasets for screening and surveillance procedures. The surveillance dataset were then arranged sequentially in a fashion so that surveillance episodes were arranged chronologically. The multiple procedures in a same episode were arranged chronologically as well. Following this when screening and surveillance datasets were merged using unique pseudo anonymised subject

identifier number a comprehensive dataset was obtained demonstrating the screening and subsequent surveillance procedures for participants in the NHS BSCP.

The HR and the IR group subjects at screening were then only selected which generated two robust datasets demonstrating screening and surveillance episodes for these two groups.

The polyp data set was used in different way for valid analysis. For the descriptive part of the study to evaluate the colorectal adenomas and the prevalence advanced neoplasia in them the entire polyp data set was used and then subsequently screened to include polyps with complete information available for all histological variables. The process of selection has been elaborately described in the figures 5.1 and 5.2 subsequently.

For evaluation of the screening and surveillance outcome the polyp dataset was screened to derive separate screening and surveillance polyp data sets. For polyps detected in the same segment of the bowel in multiple sequential procedures in the same episode, with endoscopic mucosal resection being the procedure of polypectomy then it has been only counted once to avoid duplication in the data. The patient and procedure datasets for screening and surveillance then was merged with the screening and surveillance polyp datasets to derive four comprehensive datasets for HR and IR group subjects with screening and surveillance procedure and polyps to evaluate the outcome. These have been demonstrated in the figure 6.2 and 6.3 in chapter six.

For risk stratification analysis subjects with complete histological datasets for all polyps at screening and surveillance are only used and the data processing and merging has been explained in figure 7.1 in chapter seven.

After data merging at each step the a random ten percentage of the derived data was taken and checked with the pseudo-anonymized original data set obtained at source and to ensure absence of any mismatch before proceeding in to analysis.

The descriptive statistical outcomes have been documented with tables and figures. Proportions will be described in percentage up to two decimal points. Pearson's chi-square tests were used to test for significant differences in frequency data and a Student's *t*-test was used to compare adenoma size between pairs of different groups. After building valid models, binary logistic regressions were performed to determine the important predictor factors that determine the presence of advanced neoplasia in adenomas. Multinomial logistic regressions with valid models were performed to determine any important factors at screening that determine outcome at surveillance. The exact statistical analysis plans and models are discussed in the respective chapters.

3.6 Analysis software

Data were obtained in Microsoft Excel 2010 format. To process the data and merge the different sets of data, the Stata Statistical Software, Release 12 (Stata Corporation, College Station, TX, USA) was used. The statistical analyses were performed with IBM SPSS Statistics for Windows, Version 19.0 (IBM Corporation, Armonk, NY, USA).

The analyses were carried out with supervision provided by Dr Douglas Wilson, a statistician based at the Wolfson Research Institute of Health and Wellbeing, University of Durham. The exact tests and analysis performed are described in the relevant chapters.

3.7 Ethical considerations

The work described in this thesis was an evaluation of the BCSP. As such it was termed 'service evaluation' and prospective ethical approval was not necessary. Also, there was no allocation to intervention groups, nor was any randomization planned. Similar work within the field of breast cancer screening over the past 20 years had not necessitated prospective

ethical approval. The research project was discussed verbally with the local Regional Ethics Committee of The Health Research Authority based in Jarrow and formal ethics approval was not needed as the project is of a service evaluation nature. Ethical approval was obtained from the University Ethics committee for this work (Appendix 1). The use of BCSP data in this thesis has been sanctioned by the director of the NHS Screening Programmes and confirmation was obtained through electronic communication (Appendix 2).

3.8 Summary

By using the data sets obtained from the BCSP national database it was possible to evaluate the magnitude of advanced neoplasia detected by the BCSP.

Binary and multinomial regression methods were used to determine important predictors for advanced neoplasia in colorectal adenomas and to evaluate important factors at screening that predict surveillance outcome; comprehensive data cleaning and consolidation created a workable database with which to perform the analysis.

Chapter 4: Aims and objectives

4.0 Aims and objectives for the study of all adenomas in the BCSP

These included:

- detecting the extent of advanced neoplasia in the adenomas detected in the BCSP (adenomas containing HGD, VH, carcinoma, adenomas ≥10 mm);
- identifying the predictive factors that influenced the presence or absence of carcinoma in the adenomas of the FOBT-positive population;
- evaluating whether the adenomas of all size categories with advanced neoplasia were more common in the left side of the colon;
- identifying factors that predict the presence of advanced neoplasia in adenomas in different segments of the colon.

4.1 Aims and objectives for the study of surveillance outcome

These included:

- detecting the proportion of patients diagnosed with CRC and adenomas at surveillance with particular emphasis on first surveillance;
- determining the proportion of patients with AAs at screening and assessing for any significant difference in proportions between the IR and HR groups;
- detecting the proportion of patients with adenomas ≥10 mm at screening and evaluating any significant difference in proportions in between the two groups;
- assessing the difference in outcome between IR and HR groups at first surveillance and determining whether the difference was significant;
- determining the yield of colorectal neoplasia at second and third surveillance for IR and HR groups;

- comparing the yield of the proportion of patients with AAs between screening and first surveillance and between first and second surveillance to demonstrate the changing pattern and determine whether the differences were statically significant.

4.2 Aims and objectives for the study of surveillance risk re-stratification

These included:

- determining the magnitude of advanced neoplasia detected in IR and HR patients at screening;
- determining the magnitude of advanced neoplasia detected at surveillance;
- identifying the factors at screening that could predict the outcome at surveillance;
- identifying the effects of alternative surveillance intervals on the outcomes of surveillance of HR patients.

Chapter 5: Adenoma characteristics in the BCSP

5.0 Aims and objectives

These included:

- detecting the proportion of advanced neoplasia detected in the BCSP (adenomas containing HGD, VH, carcinoma, adenoma ≥10 mm);
- identifying the predictive factors that influence the presence or absence of carcinoma in the adenomas of the FOBT-positive population;
- evaluating whether adenomas with advanced neoplasia of all size categories were more common in the left side of the colon;
- identifying the factors predicting the presence of advanced neoplasia in adenomas in different segments of the colon.

5.1 Methodology

5.1.1 Data processing

During colonoscopy, polyps were assessed and data about each polyp was recorded in the BCSP database by the specialist nurse. The polyps were then resected, retrieved and sent for histological examination. The results of the histological examinations were then transcribed into the database. The BCSP national database was interrogated to capture all the lesions identified as polyps during colonoscopy for the period from June 2006 to May 2012. The information about each polyp is described in Chapter 3.

The data set was processed (**Figure 5.1** and **Table 5.1**) and cleaned to obtain a comprehensive database where all the variables for analysis were available for each of the adenomas (**Figure 5.2**).

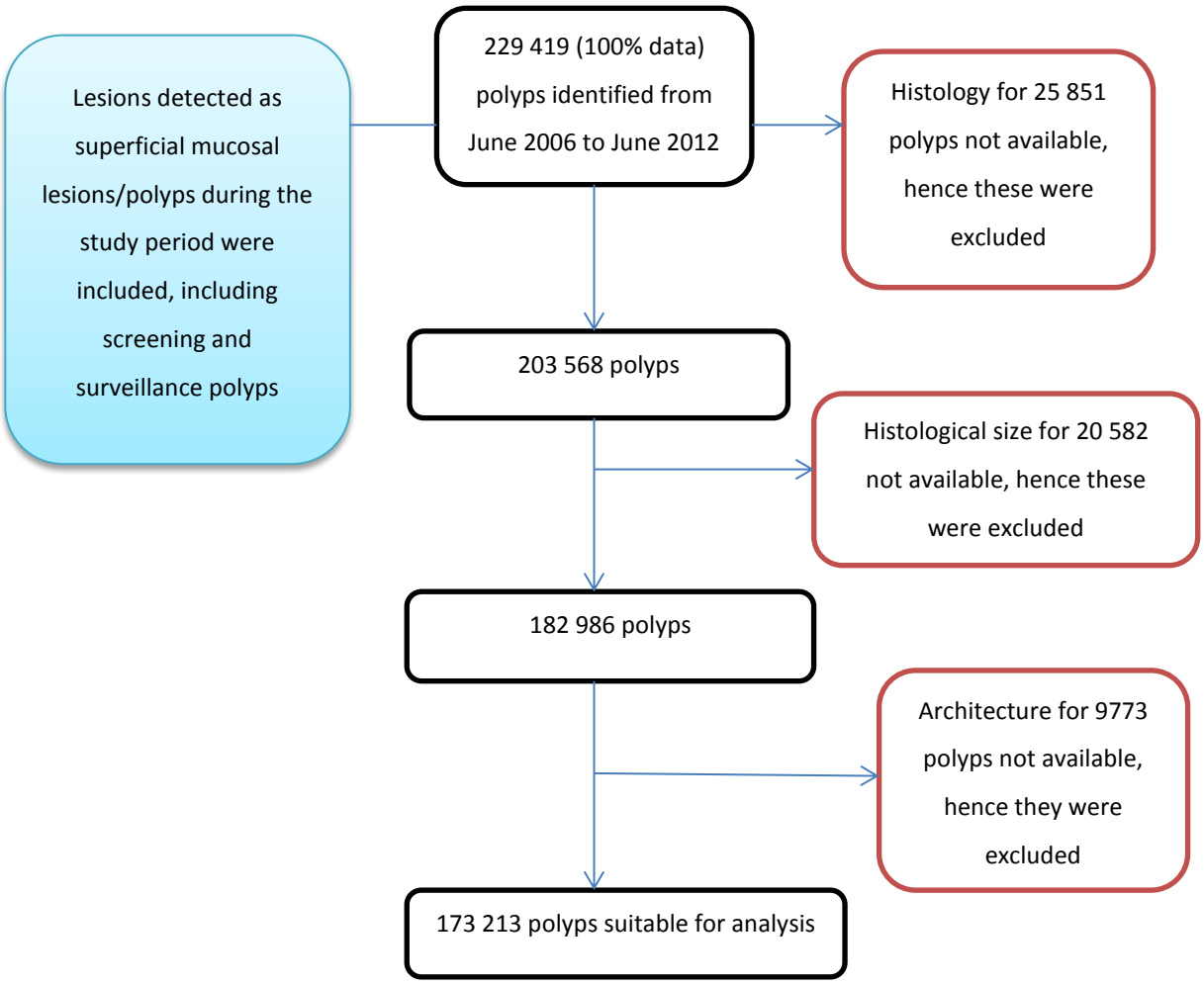

Figure 5.1 Data processing flow chart.

Table 5.1 Histological types recorded in the BCSP

Polyp architecture	**Number**	**%**
Tubular adenoma	96 980	55.99
Tubulovillous adenoma	36 061	20.81
Villous adenoma	2323	1.34
Hyperplastic	33 480	19.33
Serrated adenoma	1830	1.06
Other polyp	1821	1.05
Mixed HP/adenoma	430	0.25
Lipoma	117	0.07
Lymphoid	99	0.07
Endocrine tumour (carcinoid)	49	0.03
Stromal	23	0.01
Total	173 213	100

Note: HP = hyperplastic

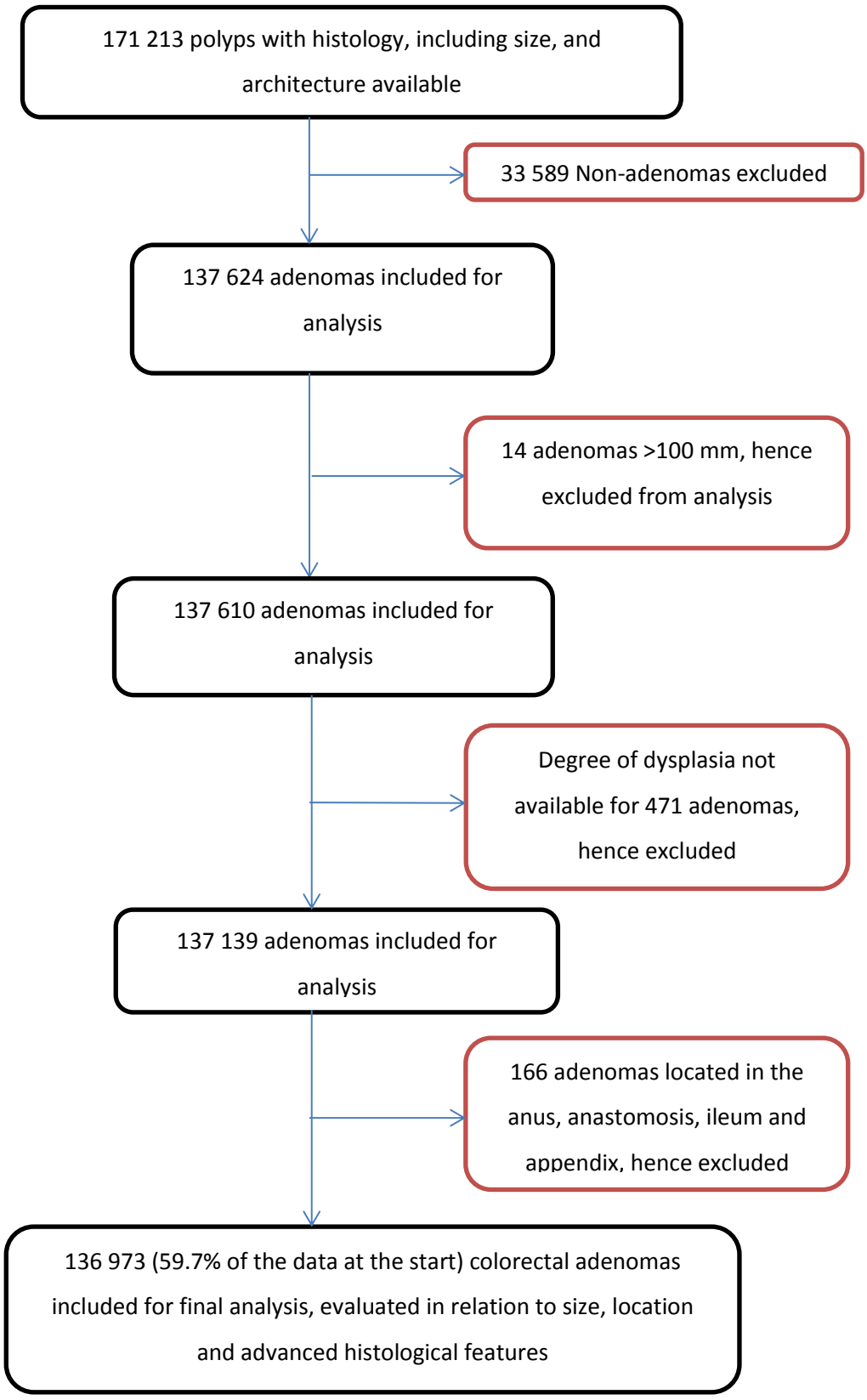

Figure 5.2 Data cleaning flow chart.

Note: NAA = non-advanced adenoma.

During the data processing, only colorectal adenomas with their complete histology data available were included and these led to inclusion of 59.7% of the total number of polyps to be included for the analysis leaving 40.3% of polyps being not included. These has been carefully thought off as statistical imputation to create corroborative value in comparison the polyps with complete data sets could not account for all biological and genetic variabilities that play in part in adenoma formation and progression. In comparison to the polyps with data set the polyps with missing data did not reveal any particular pattern, that could suggest a reason for missed information.

Histological size for any analysis involving the adenomas was chosen because it is the most appropriate and true measure of adenoma size. Adenomas >100 mm were excluded because this may be due to error during data input and because superficial mucosal lesions >100 mm are not very common. Adenomas located in the anus and appendix were excluded as these locations do not involve the large bowel. Adenomas located in the anastomosis were excluded because their segmental location in the bowel was altered as a result of surgical procedure. The final data set contained 136 973 adenomas whose information was recorded and used.

For analytical purposes, tubulovillous and villous adenomas were grouped together as villous. The large bowel was divided into six segments as shown in **Table 5.2**; all locations proximal to the splenic flexure (SF) were regarded as the right or proximal colon, and all locations distal to the transverse colon (TC) as the left or distal colon. For the purpose of segmental analysis, the SF and descending colon (DC) were considered as the same segment and the ascending colon (AC) and hepatic flexure (HF) as the same segment, because it was often anatomically difficult to distinguish between these adjacent parts in the colon.

The proportion of AAs and NAAs detected was measured and the AAs and adenomas with carcinoma were described together as adenomas with ACN for the purpose of segmental analysis.

Table 5.2 Segmental order of the bowel

Segmental number	Location in the bowel
Segment 1	Rectum
Segment 2	Sigmoid colon
Segment 3	DC and SF
Segment 4	TC
Segment 5	HF and AC
Segment 6	Caecum

Note: DC = descending colon; SF = splenic flexure; TC = transverse colon; HF = hepatic flexure; AC = ascending colon.

5.2 Results

5.2.1 Basic demography of patients with adenomas

During the study period June 2006 – August 2012 the total number of adenomas included for analysis was 136 973, obtained from 58 334 patients during screening or surveillance procedures in the BCSP. The majority of patients were men (39 503, 67.72% men; 18 831, 32.28% women) and the mean age at polypectomy was 66.22 years (range: 59.24–93.30; standard deviation (SD): 4.14).

5.2.2 Adenoma location

The segmental distribution of the adenomas is shown in **Table 5.3** and **Figure 5.3**.

Table 5.3 Location of adenomas

Location	Number	%
Rectum	14 830	10.83
Sigmoid colon	53 835	39.30
DC and SF	16 973	12.39
Transverse	18 580	13.56
AC and HF	21 076	15.39
Caecum	11 679	8.53
Total	136 973	100

Note: DC = descending colon; SF = splenic flexure; HF = hepatic flexure; AC = ascending colon.

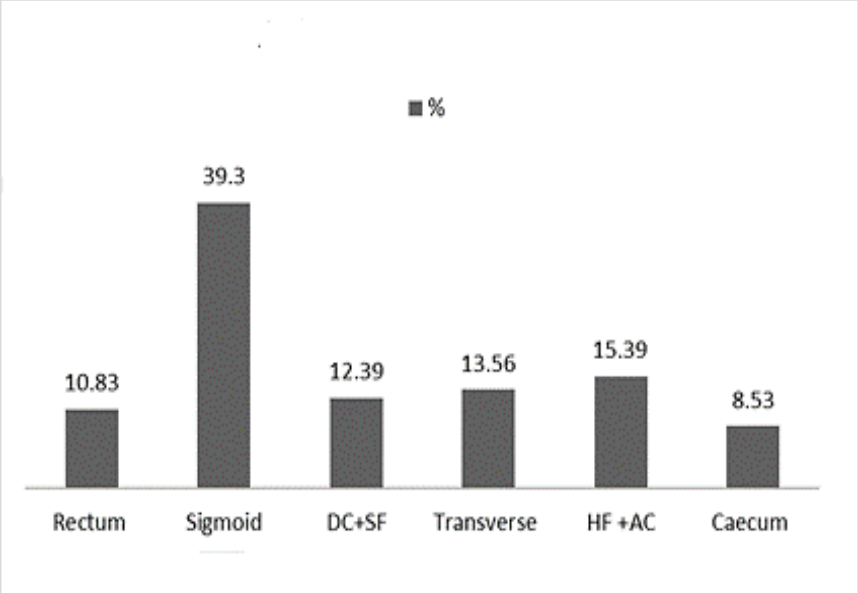

Figure 5.3 Segmental distribution of adenomas.

Note: DC = descending colon; SF = splenic flexure; HF = hepatic flexure; AC = ascending colon.

The majority of adenomas were located in the combined regions of the rectum and sigmoid colon (50.13%). The majority of adenomas were detected in the distal colon (62.52%).

5.2.3 Size distribution of adenomas

Adenomas were divided into different size cohorts according to increasing size. The proportions of adenomas of different size groups are described in **Figure 5.4**.

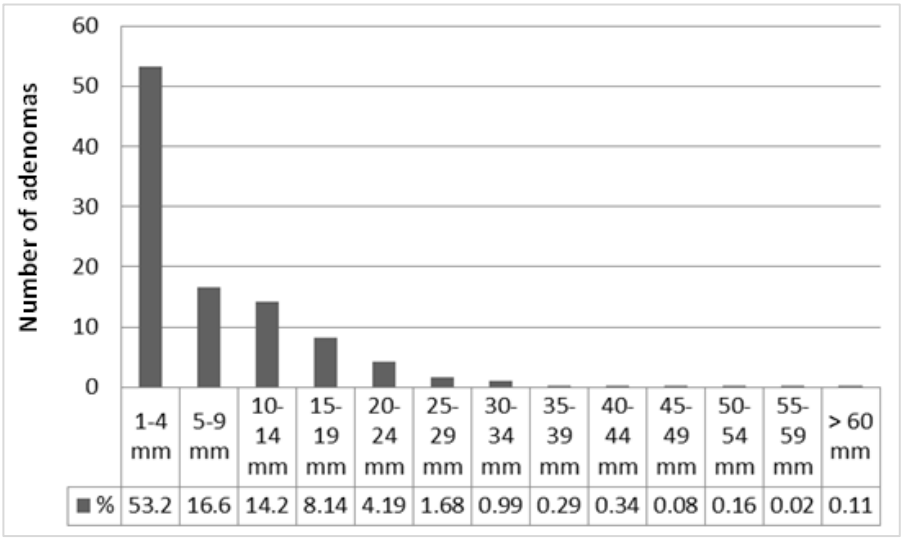

Figure 5.4 Size distribution of adenomas.

The majority of adenomas detected by the BCSP were smaller adenomas <5 mm (53.2%) in size. Diminutive adenomas and sub-centimetre adenomas accounted for 69.8% of all adenomas removed.

5.2.4 Advanced histological features in the different size categories

To determine the prevalence of advanced histological features (HGD, VH, carcinoma), adenomas were divided into 5-mm size categories. Then, the proportion of adenomas in each category containing those features was estimated (**Table 5.4** and **Figure 5.5**).

Table 5.4 Percentage of adenomas with an advanced histology

Size (mm)	Total number	HGD *N*	HGD %	Villous *N*	Villous %	Cancer *N*	Cancer %
1–5	72 815	599	0.8	6489	8.9	79	0.1
6–9	22 776	896	3.9	6406	28.1	182	0.8
10–14	19 468	2320	11.9	9928	51.0	539	2.8
15–19	11 152	2193	19.0	7198	64.5	598	5.4
20–24	5737	1519	26.5	4119	71.8	389	6.8
25 –29	2295	723	31.5	1773	77.3	200	8.7
30–34	1358	483	35.6	1076	79.2	139	10.2
35–39	397	154	38.8	334	84.1	50	12.6
40–44	464	177	38.1	386	83.2	42	9.1
45–49	111	50	45.0	94	84.7	10	9.0
50–54	214	94	43.9	176	82.2	32	15.0
55–59	33	15	45.5	27	81.8	4	12.1
≥60	153	62	40.5	135	88.2	18	11.8
Total	136 973	9285	6.8	38 141	27.8	2282	1.7

Note: HGD = high-grade dysplasia.

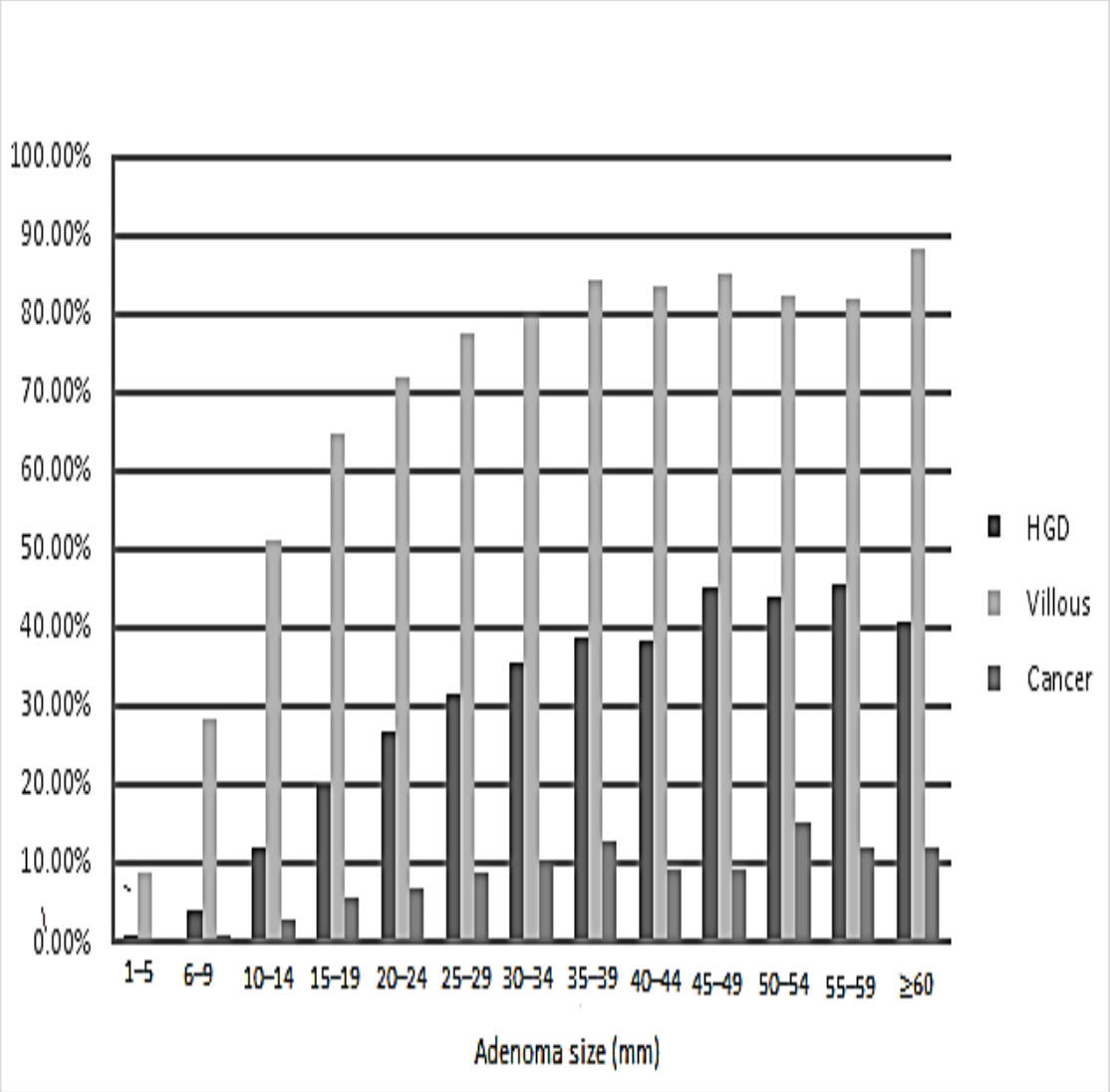

Figure 5.5 Percentage of adenomas with advanced histology.

Note: HGD = high-grade dysplasia.

Adenomas containing the highest proportion of HGD were 55–59 mm in size. Adenomas containing the highest proportion of cancer were 50–54 mm in size. Adenomas containing the highest proportion of VH were of 50–54 mm in size (**Figure 5.5**). The proportion of adenomas containing advanced histological features increased with the increasing size of the adenoma up to 35 mm and then plateaued.

5.2.5 Magnitude of detection of advanced adenomas

Table 5.5 shows the number and proportion of AAs (adenomas with HGD or VH, size ≥10 mm) detected. The majority of adenomas were NAAs (81 846, 59.75%), while the remaining 55 127 (40.25%) were AAs. The majority of AAs (41 382, 75.06%) were ≥10 mm in size. Of the remaining sub-centimetre AAs, a significant proportion (12 895, 23.4%) were AAs due to a villous component. Only 850 (1.54%) were AAs due to the presence of HGD.

Table 5.5 Detection of advanced adenomas

Adenoma type	Number	%
NAA	81 846	59.8
AA	55 127	40.2
Total	136 973	100

Note: NAA = non-advanced adenoma; AA = advanced adenoma.

In the BCSP, the majority of the adenomas detected and resected were NAAs.

5.2.6 Analysis of adenomas containing cancer

5.2.6.1 Analysis plan

A total of 2282 adenomas containing cancer were included in the final data set used for analysis. These analyses were performed to obtain information about the location of malignant adenomas in the colon, their size and distribution between the sexes. The proportions of adenomas were analysed to see whether there were any differences between the proportions of adenomas with or without carcinoma in men and women, and between proximal and distal sites in the colon.

Univariate and multivariate logistic regression analyses were carried out to determine the significant factors that could influence the development of carcinoma in adenomas; then, the OR with 95% CIs for these significant factors was calculated.

5.2.6.2Location of adenomas containing carcinomas

Table 5.6 shows the location of adenomas that contained carcinomas.

Table 5.6 Location of adenomas with cancer

Location	***N***	**%**
Sigmoid colon	1623	71.1
Rectum	449	19.7
DC	105	4.6
TC	27	1.2
SF	23	1.0
AC	37	1.6
HF	10	0.4
Caecum	8	0.4
Total	2282	100

Note: DC = descending colon; TC = transverse colon; SF = splenic flexure; AC = ascending colon; HF = hepatic flexure.

The majority (90.8%) of adenomas containing carcinomas were situated in the rectosigmoid region. The majority (95.6%) of adenomas containing carcinomas were located in the left side of the colon.

5.2.6.3Size distribution of adenomas with carcinomas

Malignant adenomas were divided into different size cohorts; the proportion of malignant adenomas in the different size cohorts is shown in **Table 5.7**.

Table 5.7 Size distribution of adenomas with carcinomas

Size (mm)	***N***	**%**
1–5	79	3.5
6–9	182	8.0
10–14	539	23.6
15–19	598	26.2
20–24	389	17.0
25–29	200	8.8
30–34	139	6.1
35–39	50	2.2
40–44	42	1.8
45–49	10	0.4
50–54	32	1.4
55–59	4	0.2
>60	18	0.8
Total	2282	100

The majority (66.8%) of adenomas containing carcinomas were 10–24 mm in size.

5.2.6.4 Sex distribution of malignant adenomas

Adenomas were categorized according to the sex of the participants; then, the proportion of adenomas containing carcinomas was measured for each sex (**Table 5.8**).

A Pearson's chi-square test was performed to assess the significance of the difference between proportions (**Table 5.9**).

Table 5.8 Proportion of malignant adenomas in men and women

Adenoma type	**Men** ***N*** **(%)**	**Women** ***N*** **(%)**
Adenoma	99 665 (98.5)	35 026 (98.0)
Adenoma with carcinoma	1562 (1.5)	720 (2.0)
Total	101 227(100)	35 746 (100)

Table 5.9 Pearson's chi-square test results

Test performed	χ^2	df	Two-tailed *P*-value
Pearson's chi-square	35.794	1	<0.001

Note: df = degrees of freedom.

The proportion of adenomas containing carcinomas was higher in women and the difference was statistically significant.

5.2.6.5Sex and location distribution analysis for adenomas with cancer

Adenomas were categorized into groups according to their proximal or distal location. Location in the SF, DC, sigmoid colon and rectum was considered as distal; the remaining locations were considered as proximal. In each group, the proportion of adenomas with carcinomas and their distribution between the sexes were measured. Pearson's chi-square tests were used to measure whether there was any significant difference in the proportion of adenomas with cancer between men and women, incorporating both proximal and distal locations. The results of the analysis are shown in **Table 5.10**.

Table 5.10 Location and sex distribution of AAs with and without carcinomas

Location	**Sex**	**Adenoma *N* (%)**	**Adenoma with carcinoma *N* (%)**	**χ^2**	**df**	***P***
Distal	Female	22 224 (97.0)	693 (3.0)	25.88	1	<0.001
Distal	Male	61 214 (97.6)	1507 (2.4)			
Proximal	Female	12 802 (99.8)	27 (0.2)	2.75	1	0.097
Proximal	Male	38 451 (99.9)	55 (0.1)			
Total	Female	35 026 (98.0)	720 (2.0)			
Total	Male	99 665 (98.5)	1562 (1.5)			
		134 691	2282			

Note: df = degrees of freedom.

Compared to adenomas detected in men, adenomas detected in women had a higher proportion of carcinoma in the distal colon, and this difference was statistically significant.

There was no significant difference in the proportion of adenomas containing carcinomas in the proximal colon and between men and women.

5.2.6.6Age group and sex distribution of adenomas with carcinomas

Adenomas were divided according to the patient's age at the time of the polypectomy. The proportion of adenomas with cancer was measured for both sexes in the four age groups. A Pearson's chi-square test was performed to evaluate the significance in the different proportions of malignant adenomas between the two sexes in all four age group. The results are described in **Table 5.11**.

Table 5.11 Age group distribution of adenomas containing carcinomas

Age, years	Sex	Adenoma *N* (%)	Adenoma with carcinoma *N* (%)	χ^2	df	*P*
60–65	Female	13 316 (98.0)	278 (2.0)	15.7	1	<0.001
	Male	39 349 (98.5)	619 (1.5)			
66–70	Female	14 826 (98.0)	309 (2.0)	19.17	1	<0.001
	Male	42 282 (98.5)	650 (1.5)			
71–75	Female	6326 (98.2)	118 (1.8)	2.14	1	0.14
	Male	16 730 (98.4)	265 (1.6)			
>75	Female	557 (97.4)	15 (2.6)	0.41	1	0.52
	Male	1276 (97.9)	28 (2.1)			

Note: df = degrees of freedom.

In patients up to 70 years of age, adenomas detected in women had a higher proportion of malignancy than adenomas from men and the difference was statistically significant.

There was no significant difference in the proportion of adenomas containing carcinomas between men and women above the age of 70 years.

5.2.6.7Factors that predict the presence of carcinomas in adenomas

The factors assessed in the model were patient- and adenoma-specific characteristics. Adenoma-specific factors included: the presence of VH, HGD, distal location and increasing size. Adenomas were divided into three size categories (<6 mm, 6–9 mm and >9 mm). Patient-specific factors included female sex and increasing age.

The distribution of adenoma- and patient-specific factors is described in **Table 5.12**.

Table 5.12 Adenoma- and patient-specific factors

Adenoma-specific factors						
Number	*HGD* N *(%)*	*VH* N *(%)*	*Distal location* N *(%)*	*<5 mm* N *(%)*	*6–9mm* N *(%)*	*>9mm* N *(%)*
136 491 (adenomas)	7258 (5.4)	36 621 (27.3)	83 438 (61.1)	72 736 (54.0)	22 594 (16.5)	39 361 (29.3)
2282 (adenomas with cancer)	2027 (88.8)	1520 (66.6)	2200 (96.4)	79 (3.5)	182 (8.0)	2021 (88.6)
Patient-specific factors						
Number	*Men* N *(%)*	*<66 years* N *(%)*	*66–70 years* N *(%)*	*71–74 years* N *(%)*	*>74 years* N *(%)*	
136 491 (adenomas)	99 665 (73.0)	52 665 (38.6)	57 108 (42.4)	23 056 (17.1)	1833 (1.3)	
2282 (adenomas with cancer)	1562 (68.4)	897 (39.3)	959 (42.0)	383 (16.8)	43 (1.9)	

Note: HGD = high-grade dysplasia; VH = villous histology.

A univariate analysis was performed followed by a multivariate analysis to detect important predictive factors in logistic regression. The results are described in **Tables 5.13** and **5.14**. The Wald test calculates a *z* statistic for each coefficient in the logistic model, which is squared and has a chi-square distribution; the OR is a measure of the association between exposure and outcome; it represents the odds that an outcome will occur given a particular exposure, compared to the odds the outcome will produce in the absence of that exposure/reference.

Table 5.13 Result of the univariate logistic regression for adenoma- and patient-specific factors determining cancer in adenomas

Factors	**Wald test**	**OR (df = 1)**	**Lower 95% CI**	**Upper 95% CI**	***P***
HGD	5347.87	139.5	122.2	159.3	<0.0001
VH	1398.37	5.34	4.89	5.83	0.008
Distal location	619.19	16.48	13.21	20.55	0.002
Female sex	35.58	1.31	1.2	1.4	<0.001
6–9 mm	220.46	7.41	5.69	9.66	<0.001
>9 mm	1127.06	47.27	37.45	59.2	<0.001

Note: OR = odds ratio; df = degrees of freedom; CI = confidence interval; HGD = high-grade dysplasia; VH = villous histology.

The univariate analysis model for age alone is not significant in predicting the presence of cancer in adenomas in the three different age groups and hence it is not included.

In univariate analysis, HGD, presence of VH, distal location, increasing size and female sex showed significant ORs for the presence of carcinomas in adenomas.

Table 5.14 Results of the multivariate logistic regression for adenoma- and patient-specific factors determining cancerous adenomas

Factors for cancer	**B**	**Wald**	***P***	**OR**	**Lower 95% CI OR**	**Upper 95% CI OR**
HGD	4.175	3283.447	**<0.001**	**65.049**	**56.39**	**75.03**
VH	−0.018	0.125	0.724	0.982	0.88	1.08
Distal location	1.141	91.285	**<0.001**	**3.129**	**2.47**	**3.95**
Female	0.154	9.076	**0.003**	**1.16**	**1.05**	**1.28**
60–64 years (Ref)						
65–69 years	−0.045	0.744	0.388	0.956	0.863	1.059
70–74 years	0.125	3.251	0.071	1.133	0.989	1.298
>74 years	0.14	0.614	0.433	1.15	0.811	1.632
<6 mm (Ref)						
6–9 mm	1.019	51.791	**<0.001**	**2.771**	**2.099**	**3.657**
>9 mm	1.553	149.786	**<0.001**	**4.728**	**3.687**	**6.063**

Note: OR = odds ratio; CI = confidence interval; HGD = high-grade dysplasia; VH = villous histology.

Controlling for all other factors, the presence of HGD, distal location and increasing size had significantly higher ORs for malignant adenomas.

An adenoma detected in a woman would be 1.1 times more likely to contain a carcinoma than an adenoma detected in a man. This higher OR for women was statistically significant (*P* = 0.003) but was not a very strong determining factor (95% CI = 1.05–1.28).

5.2.7 Adenomas with advanced neoplasia in the right (proximal) and left (distal) colon

An adenoma with advanced neoplasia is described as one that contains any of the following characteristics: HGD, VH and carcinoma. All adenomas were categorized into three groups according to their size as determined by histological examination (<6 mm, 6–9 mm and >9 mm).

5.2.7.1Are adenomas with advanced neoplasia more common in the left or right colon?

The number and proportion of advanced neoplasia for the different size categories and the two different locations were measured. A Pearson's chi-square test was used for each size category to determine the significance of the differences in proportion between the right and left side of the colon (**Table 5.15** and **Figure 5.6**).

Table 5.15 Distribution of adenomas with advanced neoplasia in the three size categories and proximal and distal locations

Size (mm)	**LA (*N*)**	**LA (%)**	**LAN (*N*)**	**LAN (%)**	**RA (*N*)**	**RA (%)**	**RAN (*N*)**	**RAN (%)**
<6	29 926	89.1	3677	10.9	35 976	91.7	3236	8.3
6–9	10 143	65.9	5238	34.1	5733	77.5	1662	22.5
>9	11 706	31.9	24 948	68.1	2165	45.8	2563	54.2

Note: LA = left-sided adenoma; RA = right-sided adenoma; LAN = left-sided advanced adenoma, RAN = right-sided advanced adenoma.

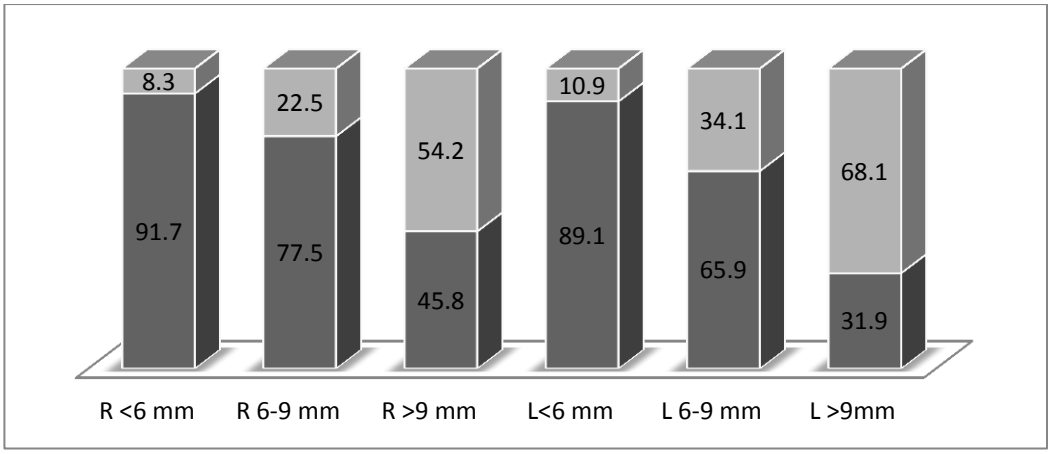

Figure 5.6 Distribution of ACN in all size categories.

Note: ACN = advanced colorectal neoplasia.

The proportion of adenomas with advanced neoplasia was greater in the left than the right side of the colon in all size categories. There was a statistically significant increased proportion of adenomas with advanced neoplasia in the left colon, in each size category, as shown by the chi-square test in **Table 5.16**.

Table 5.16 Chi-square test statistics

Size (mm)	**LA *N* (%)**	**LACN *N* (%)**	**RA *N* (%)**	**RACN *N* (%)**	**χ^2 (df = 1)**	***P***
<6	29 926 (89.1)	3677 (10.9)	35 976 (91.7)	3236 (8.3)	152.06	<0.001
6–9	10 143 (65.9)	5238 (34.1)	5733 (77.5)	1662 (22.5)	316.59	<0.001
>9	11 706 (31.9)	24 948 (68.1)	2165 (45.8)	2563 (54.2)	360.1	<0.001

Note: LA = left-sided adenoma; LACN = left-sided advanced colorectal neoplasia; RA = right-sided adenoma; RAN = right-sided advanced colorectal neoplasia; df = degrees of freedom.

5.2.7.2Are adenomas with advanced neoplasia smaller in the right than left colon?

The differences in size between right- and left-sided adenomas were measured with the Student's *t*-test for all adenomas first and then for ACNs. The results of the *t*-test and the size distribution are shown in **Tables 5.17** and **5.18**, and **Figures 5.7** and **5.8**.

Table 5.17 Difference in mean adenoma size between the left and right side for all adenomas

Location	***N***	**Mean size (mm)**	**SD**	**MD**	**95% CI of MD**	***t***	***P***
Left	85 638	9.71	7.857	4.898	4.83–4.96	143.87	<0.0001
Right	51 335	4.81	4.743	–	–	–	–

Note: SD = standard deviation; MD = mean difference; CI = confidence interval.

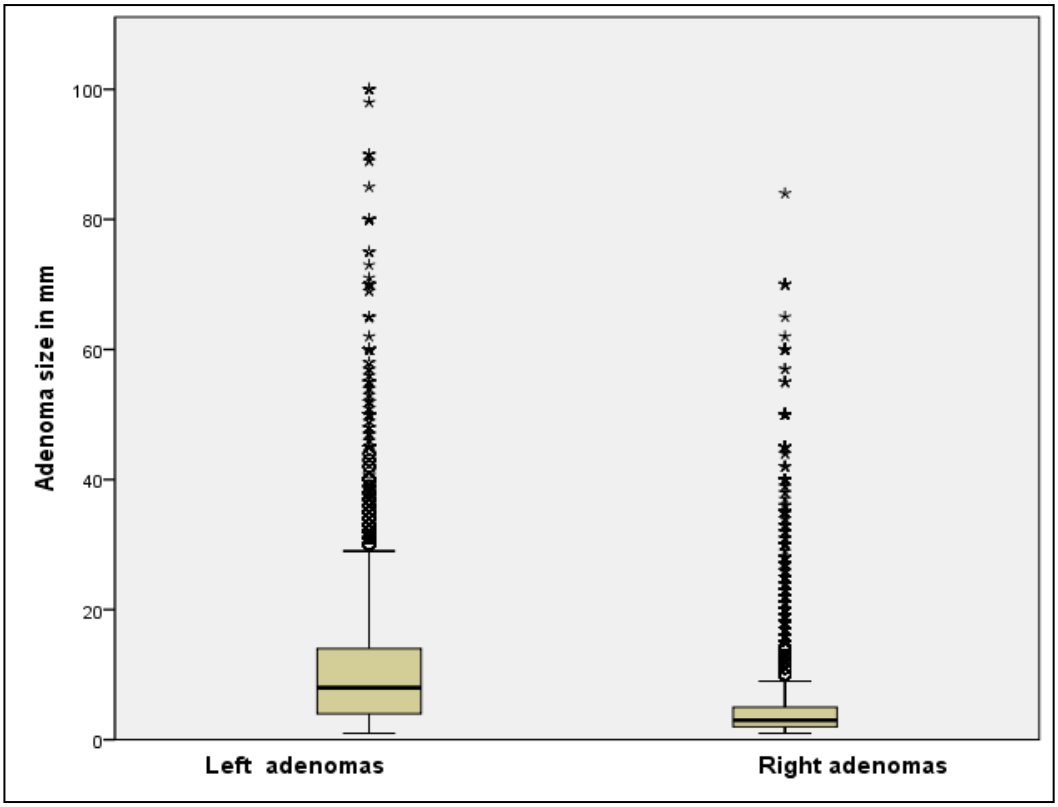

Figure 5.7 Box plot showing the size of left- and right-sided adenomas.

The rectangle represents 50% of the cases, the line in the middle of the box represents the median value, the whiskers represent the maximum and minimum values and the dots above the whiskers represent the outliers, in this case larger adenomas.

Table 5.18 Difference in mean size between left- and right-sided ACNs

Location	Number	Mean Size (mm)	SD	MD	95% CI of MD	*t*	*P*
Left	33 863	14.54	8.66	5.29	5.07–5.50	47.55	<0.0001
Right	7461	9.25	8.7	–	–	–	–

Note: ACN = advanced colorectal neoplasia; SD = standard deviation; MD = mean difference.

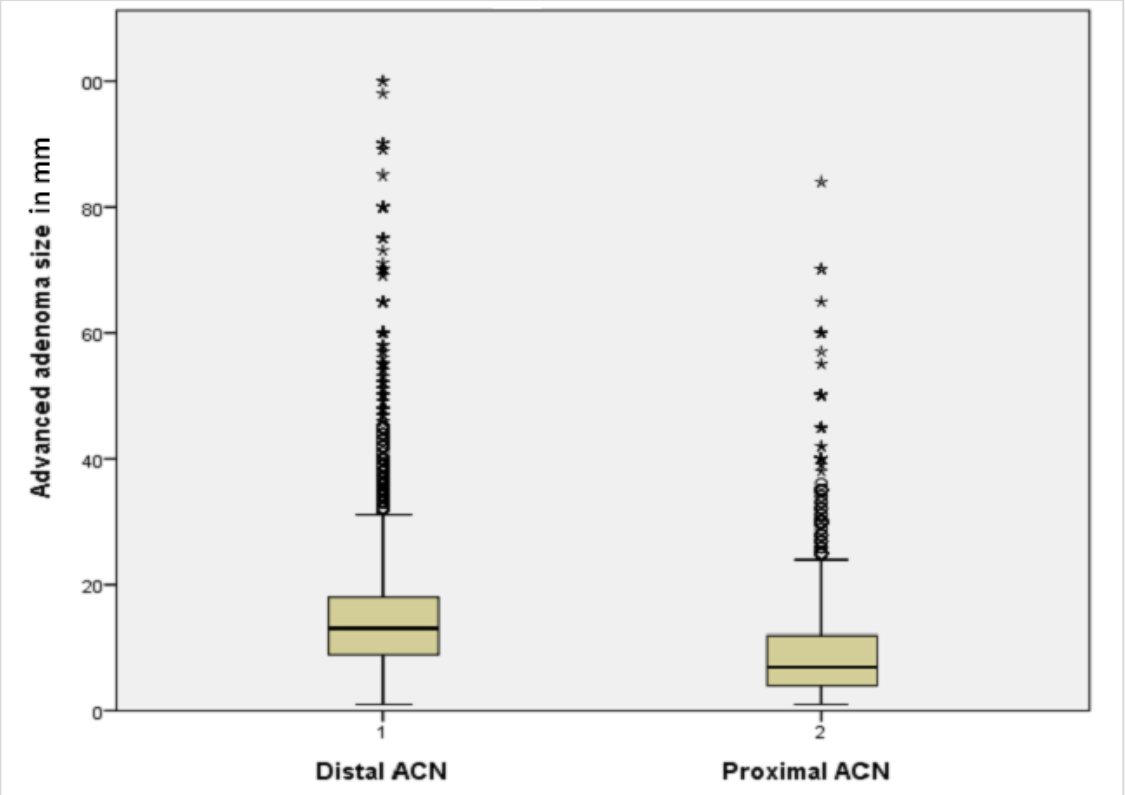

Figure 5.8 Box plot showing the size of left/distal and right/proximal ACN.

Note: ACN = advanced colorectal neoplasia.

All left-sided adenomas were larger than right-sided adenomas; any differences in size were statistically significant.

5.2.7.3Relationship between adenomas with advanced neoplasia and their size, location, patient sex and age when detected

The distribution of the predictor factors for adenomas with and without advanced neoplasia was measured with univariate and multivariate logistic regression analyses to identify important predictors of ORs with a 95% CI (**Tables 5.19** and **5.20**).

Table 5.19 Distribution of patient- and adenoma-specific factors (sex, location and size) in adenomas with and without advanced neoplasia

Number	Men *N* (%)	Women *N* (%)	Right colon *N* (%)	Left colon *N* (%)	<6 mm *N* (%)	6–9 mm *N* (%)	>9 mm *N* (%)
A = 95 649	71 624 (74.9)	24 025 (25.1)	43 874 (45.9)	51 775 (54.1)	65 902 (68.9)	15 789 (16.6)	13 871 (14.5)
ACN = 41 324	29 603 (71.6)	11 721 (28.4)	7461 (18.1)	33 863 (81.9)	6913 (16.7)	6900 (16.7)	27 511 (66.6)

Note: A = adenoma without advanced neoplasia; ACN = advanced colorectal neoplasia.

Table 5.20 Results of univariate analysis showing the ORs of the predictor factors for CAN

Factors	Wald test	OR (df = 1)	Lower 95% CI of OR	Upper 95% CI of OR	*P*
Female sex	157.44	1.18	1.15	1.21	<0.001
Left colon	8822.6	3.84	3.73	3.73	<0.001
6–9 mm	5494	4.14	3.99	4.3	<0.001
>9 mm	32 209	18.9	18.31	19.52	<0.001

Note: OR = odds ratio; df = degrees of freedom; CI = confidence interval.

Increasing size and left-sided location were independently associated with a statistically significant increased risk for the presence of advanced neoplasia in adenomas (**Tables 5.21** and **5.22**).

Table 5.21 Multivariate logistic regression result showing the determining factors for ACN

Factors for ACN	B	Wald test	*P*	OR	Lower 95% CI OR	Upper 95% CI OR
Left location	0.462	750.52	**<0.001**	1.58	1.53	1.64
Right location (ref)						
Female sex	0.16	42.11	**<0.001**	1.10	1.07	1.14
Male sex (ref)						
<6 mm (ref)						
6–9 mm	1.335	4713	**<0.001**	3.8	3.65	3.94
>9 mm	2.766	25592	**<0.001**	15.89	15.36	16.44

Note: ACN = advanced colorectal neoplasia; OR = odds ratio; CI = confidence interval.

Controlling for all other factors, when adenomas were located in the left colon they were 1.5 times more likely to show ACN compared to adenomas in the right colon. Controlling for all other factors, size was an independent predictor for adenomas to have features of ACN. Adenomas of 6–9 mm and >9 mm in size were 3.5 and 15 times, respectively, more likely to have ACN features than adenoma of <6 mm size. Female sex also was a significant, independent predictor for adenomas to display advanced neoplasia (OR = 1.10; 95% CI = 1.07–1.14).

5.2.7.4When compared to left-sided adenomas, do most right-sided adenomas with advanced neoplasia belong to the sub-centimetre size categories?

To answer this question, adenomas with ACN were grouped into three different size categories; then, a binary logistic regression analysis was performed where the dependent variable was location and the predictor variables were the size categories of adenomas with

ACN. ORs were adjusted for age and sex. The distribution of size categories and results of the regression analysis are described in **Table 5.22**.

Table 5.22 Distribution of size category for left- and right-sided ACNs

Size (mm)	LACN (*N*)	LACN (%)	RACN (*N*)	RACN (%)
<6	3677	10.9	3236	43.4
6–9	5238	15.5	1662	22.3
>9	24 948	73.7	2563	34.4
Total	33 863	100	7461	100

Note: LACN = left-sided advanced colorectal neoplasia; RACN = right-sided advanced colorectal neoplasia.

The majority of right-sided ACNs (65.7%) were <10 mm, and the majority of left-sided ACNs (73.7%) were >9 mm. This difference was statistically significant (χ^2 = 764.2; *P*<0.0001).

5.2.7.5How did adenomas with advanced neoplastic features differ in the different segments of the large bowel?

Adenomas were categorized according to their location in the colon. The proportion of advanced neoplasia in each segment was measured (**Table 5.23** and **Figure 5.9**).

Table 5.23 Proportion of advanced neoplasia in the different colonic segments

Adenoma type	**Rectum *N* (%)**	**Sigmoid colon *N* (%)**	**DC&SF *N* (%)**	**TC *N* (%)**	**HF&AC *N* (%)**	**Caecum *N* (%)**
Without AN	8564 (57.7)	29 636 (55.0)	13 575 (80.0)	16 405 (88.3)	17 776 (84.3)	9693 (83.0)
With ACN	6266 (42.3)	24 199 (45.0)	3398 (20.0)	2175 (11.7)	3300 (15.7)	1986 (17.0)
Total	14 830	53 835	16 973	18 580	21 076	11 679

Note: AN = advanced neoplasia; ACN = advanced colorectal neoplasia; DC&SF = descending colon and splenic flexure; TC = transverse colon; HF&AC = hepatic flexure and ascending colon.

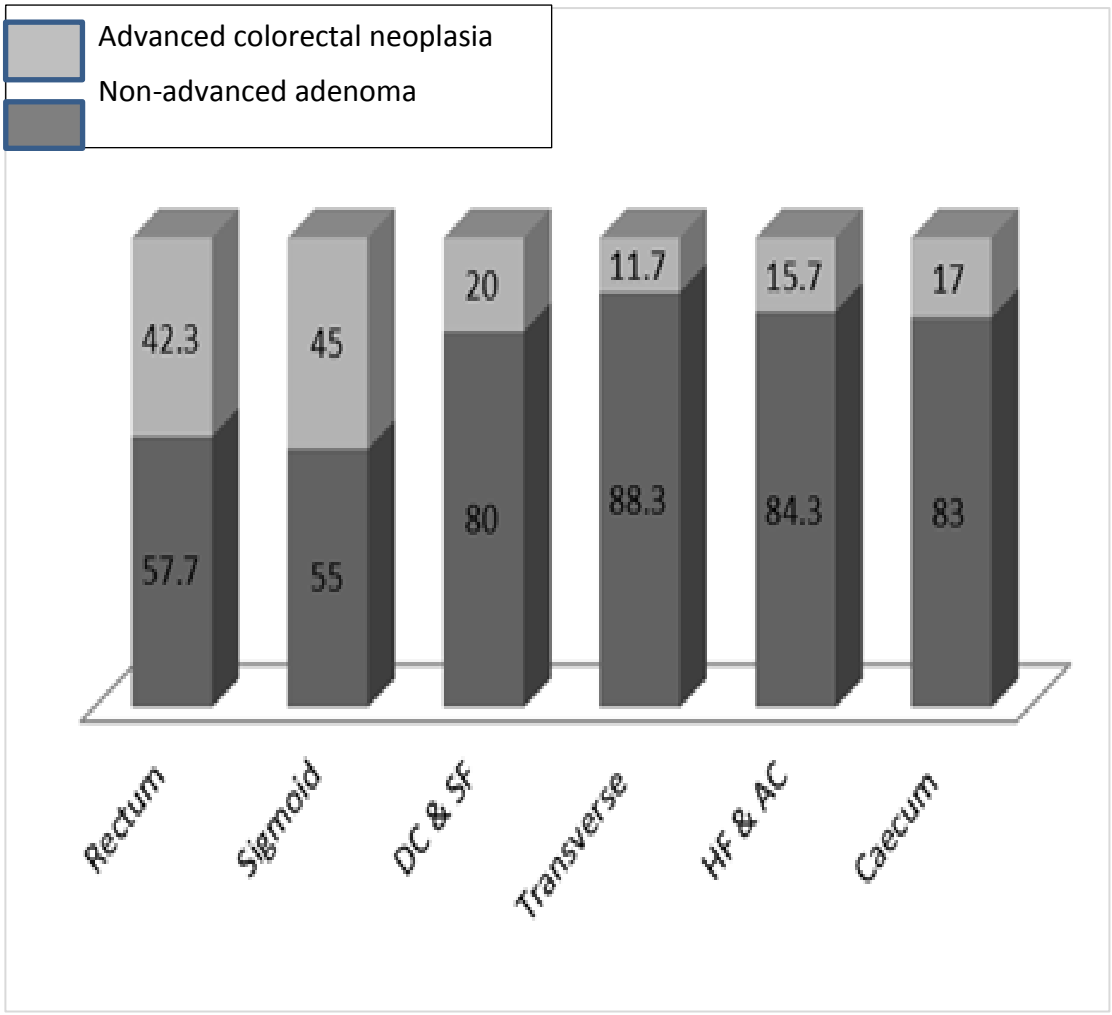

Figure 5.9 Advanced neoplasia in adenomas located in different segments of the colon.

Note: ACN = advanced colorectal neoplasia; DC&SF = descending colon and splenic flexure; HF&AC = hepatic flexure and ascending colon.

Adenomas in the sigmoid colon had the highest proportion of advanced neoplasia. The proportion of advanced neoplasia was lowest in adenomas located in the TC. The proportion of advanced neoplasia in adenomas declined from the sigmoid up to the TC and then showed a rise through the rest of the two proximal segments.

5.2.7.6How did the location of an adenoma predict the presence of advanced neoplastic features?

Multivariate logistic regression was performed where the dependent factor was the presence or absence of advanced neoplasia, and the predictor variables were segmental location, sex, age and size of the adenoma. Location and sex were modelled into the regression analysis as categorical variables. Location in the caecum and male sex were considered as references for this analysis. Participants age and size of the adenoma were entered into the regression analysis as continuous variables, to measure changes in ORs for advanced neoplasia with each unit increase of age (years) and size (mm).

The results of the regression analysis are shown in **Table 5.24**.

Table 5.24 Results of logistic regression: advanced neoplasia versus segmental location

Location	**B (coefficient)**	***z* (Wald test)**	***P***	**OR**	**95% CI OR**
Rectum	0.714	461.76	<0.0001	2.04	1.91–2.18
Sigmoid	0.405	187.53	<0.0001	1.49	1.41–1.58
DC&SF	−0.091	6.83	0.009	0.91	0.85–0.97
TC	−0.394	116.79	<0.0001	0.67	0.62–0.72
HF&AC	−0.112	10.95	0.001	0.89	0.83–0.95
Caecum (ref)					
Female sex	0.093	34.05	<0.0001	1.09	1.06–1.13
Age (years)	0.002	1.109	<0.0001	1.003	1.001–1.005
Adenoma size (mm)	0.192	1895	<0.0001	1.21	1.20–1.21

Note: OR = odds ratio; CI = confidence interval; DC&SF = descending colon and splenic flexure; TC = transverse colon; HF&AC = hepatic flexure and ascending colon.

An adenoma located in the rectum was twice as likely to have advanced neoplasia compared to an adenoma located in the caecum. Compared to adenomas located in the caecum, adenomas located in the AC, HF, TC, SF and DC showed lower ORs for advanced neoplasia (the coefficients were negative and the ORs did not exceed the value of 1). An adenoma from a female patient had a higher probability of having advanced neoplasia (OR = 1.09). Adenomas located in the TC had the lowest odds for advanced neoplasia, when all other factors were controlled for.

5.3 Discussion

Numerous studies of the natural history of adenomas have shown that only a minor proportion of colorectal adenomas develop into CRC [8, 35]. Adenomas that continue to grow and become AAs have the highest malignant potential. From the perspective of bowel cancer screening, it is important to identify the factors associated with the presence of ACN, so that this knowledge helps the screening endoscopist to identify and remove these lesions.

Several studies have reported on the magnitude of detection of advanced neoplasia in a screened population. In a cross-sectional analysis performed on a population- based colonoscopy screening programme, Regula et al. [42] reported that 5.6% of participants had advanced neoplasia. This study analysed the results of 50 148 screening colonoscopies in Poland over a four-year period, from October 2000 to December 2004. Brenner et al. [50] also reported the prevalence of AAs in a screened population. They derived their data from a national screening colonoscopy database of 840 149 participants. AAs were detected in 7.5% of patients aged 60–64 years and in 8.4 and 9.2% of patients aged 65–69 and 70–74 years, respectively. A systematic review performed to study the distribution of advanced neoplasia in 20 562 screened individuals used data from four different studies and demonstrated that AAs were only detected in 1155 individuals (5.6%) [45]. Although these studies performed a

'per-participant' analysis, it is clear that only a small proportion of participants had advanced neoplasia; also, the majority of these studies were based on screening programmes where colonoscopy was the screening tool.

In this thesis, only adenomas that had been resected were analysed where the BCSP had a complete data set from a FOBT screening programme. 'Per-adenoma' analysis demonstrated that the majority of adenomas detected were NAAs (81 846; 58.2%) (see **Table 5.5**). This is in keeping with the findings of the other screening studies. The relatively higher proportion of AAs compared to previous studies was because only patients with adenomas were included and a per-adenoma analysis was performed. In addition, the population studied was a FOBT-positive cohort.

The majority of adenomas (50.1%) detected in the BCSP were located in the rectum and sigmoid colon and 76.59% of all adenomas were located in the distal colon (see **Table 5.3** and **Figure 5.3**). The distribution of adenomas in the BCSP population is in keeping with the epidemiological studies that have demonstrated similar distributions [33, 112]. The distributions of adenomas in the BCSP population follows the pattern described in those epidemiological studies describing the natural history of colorectal adenoma and also perhaps represent the fact that these are derived from FOBT population and left sided adenomas with bleeding would be identified more in during the screening.

The prevalence of an advanced histology in adenomas of different size categories has also been well documented [45, 113–116]. These studies evaluated various patient- and adenoma-specific factors that are important determinants for the presence of advanced histological features in adenomas. The adenoma data in the NPS was derived from 3371 adenomas (1867 patients); the size and extent of the villous component of the adenoma were the major independent risk factors associated with HGD [112]. The increased detection

of HGD in distal adenomas was attributed to increased size and villous component rather than location. The sex of the participants was not associated with HGD in this study. The multiplicity of factors influencing HGD was also dependent on size and VH.

Lieberman et al. [113] studied 13 992 asymptomatic individuals who had a screening colonoscopy; 45% of them had polyps. The study identified an advanced histology in 1.7% of the 1–5-mm group, and in 6.6 and 30.6% of the 6–9-mm and >9-mm groups, respectively.

Otake et al. [114] studied the cumulative incidence of advanced neoplasia during follow-up in patients who had diminutive (<5 mm) adenomas at screening and had been referred for polypectomy. Only 2.8% of patients with diminutive polyps demonstrated advanced histology, but the incidence was significantly higher in those who had multiple (>3) adenomas.

Gschwantler et al. [115] studied patient and adenoma characteristics associated with HGD and invasive carcinoma/colorectal adenomas. Their study included 4216 patients and 7590 adenomas were removed from them. They concluded that adenoma size was the most important risk factor for the presence of advanced histological features. In this study, the percentages of advanced histology detected were 3.4, 13.5 and 38.5% for adenomas with a diameter <5 mm, 5–10 mm and >10 mm, respectively. No CRC was detected in adenomas with a diameter <5 mm. Their multivariate analysis identified size, left-sided location, VH and age as risk factors for advanced histology. Sex and multiplicity of adenomas failed to demonstrate any influence.

Nusko et al. [116] studied a number of patient- and adenoma-specific characteristics to determine their influence on the risk of developing CRC in all adenomas. They performed a ‘per-adenoma’ analysis that included a total of 11 188 adenomas removed during the period from 1978 to 1993. Adenoma size proved to be the most important factor followed by

left-sided location. They did not find CRC in adenomas <6 mm size (5027 adenomas). They also demonstrated that with increasing size there was a right-sided shift (that is, more cancers were found in right-sided adenomas) as a result of the interaction between location and size. They also demonstrated complex interaction between sex and a multiplicity of factors predicting for higher risk of CRC in adenomas.

Increasing size and distal location were factors associated with advanced histology and carcinoma in the studies mentioned here.

In a complex interaction model, a patient's age and sex were identified as factors determining malignant transformation of the benign colorectal adenomas. In contrast to two of the studies mentioned earlier [115, 116], a very small proportion of adenomas <6 mm in size (79/72 815; 0.1%) were shown to contain a focus of cancer (see **Table 5.4** and **Figure 5.5**). This perhaps shows that some of the CRCs developed *de novo* from the epithelium and some developed cancer through a different carcinogenesis pathway than the adenoma–carcinoma sequence, where increasing size is a driving factor in developing a malignant focus. This pathway was described as a *de novo* pathway; according to this hypothesis, CRC can also develop *de novo* from normal mucosa. This pathway is well described in the Western and Japanese literature [117–120]. It is an increasingly recognized entity, with more diminutive CRC cases being described recently [121]. In a study from the UK, Rembacken et al. [122] looked at flat and depressed colorectal lesions and reported that 6% of flat adenomas <10 mm showed early CRC signs. The FOBT-positive screening cohort discussed in this thesis represents a population at high risk of developing CRCs; the adenomas detected in this population represented adenomas that developed either through the conventional adenoma–carcinoma sequence or through the *de novo* pathway. For this reason, in the multivariate analysis, size and HGD were separate independent factors used to identify risk

factors associated with malignant adenomas because HGD could be a size-independent risk factor for developing CRC.

Adenoma size appeared to be a crucial factor associated with advanced histology; accurate estimation of adenoma size is also important for risk stratification and surveillance planning. Wide variation in optical size estimation has been reported among experienced endoscopists, which in turn adversely affected surveillance intervals [123, 124]. Histological size is the most accurate available estimation of adenoma size; it was used in the BCSP and was also used for the analysis in this thesis. The analysis performed in this work was on a per-adenoma rather than per-person basis, which helped to develop an understanding of the assessment of each individual adenoma from an endoscopist's perspective.

The distribution of advanced histology demonstrated that the proportion of adenomas containing advanced histological features increased with increasing size of the adenomas up to 35 mm, after which it plateaued (see **Figure 5.5**).

The proportion of advanced histology in diminutive (<6 mm) and small adenomas (6–9 mm) was measured. HGD was present in 0.8 and 3.9% of diminutive and smaller adenomas and VH was present in 28.1 and 8.9% of smaller and diminutive adenomas. VH accounted for the majority of advanced histology in sub-centimetre adenomas. The proportion of adenomas with malignancy was very low in these two groups (0.1% in diminutive and 0.8% in smaller adenomas). These findings are similar to those of other studies which measured advanced histology in sub-centimetre adenomas and also found that VH accounted for the majority of advanced histology [125].

This is an important finding because a very low prevalence of advanced histology was

reported in another study by Gupta et al. [126]; this could have important implications for the potential practice of 'predicting, resecting and discarding' diminutive colon polyps. This

study included 2361 adenomas; their sensitivity analysis revealed that the frequency of advanced histological features varied from 0.2 to 0.7% within diminutive polyps, and from 1.5 to 3.6% within small polyps. The proportion of advanced histology is much greater in the adenomas detected in a FOBT-positive population.

The multivariate analysis described in this thesis demonstrated that HGD, increasing adenoma size, distal location and female sex were independent risk factors associated with carcinoma (see **Table 5.14**). Also, the proportion of adenomas containing cancer was higher in the adenomas of female patients and the difference in proportion was significant for malignant adenomas detected in the left or distal colon. In the BCSP, after the first 1 million FOBT tests, more CRC was found in men (men *vs*. women, 11.6 *vs*. 7.8%) [107]. The findings of more adenomas containing cancer when they are still identifiable as polyps in female patients (in this study) perhaps reflect the fact that more CRCs in women were detected in the BCSP when lesions were still confined as superficial mucosal lesions and/or locally confined as polyps. VH did not achieve any significance as an associated factor for the presence of carcinomas in adenomas either in univariate or in multivariate analysis.

The differences between right- and left-sided AAs have been previously studied. Researchers reported that right-sided AAs were smaller that their left-sided counterparts and hence easier to miss during colonoscopy. Gupta et al. [127] performed a cross-sectional analysis of the histology performed at a single centre providing services to more than 1900 endoscopists in 43 states in the USA. They studied 233 414 polyps removed from 142 686 patients. They demonstrated that size distribution was similar in the right and left side of the colon for all polyps; however, in the case of AAs and adenomas with HGD or cancer, right-sided adenomas were significantly smaller in size (adenomas with HGD and CRC: right *vs*. left, 8.2 *vs*. 12.4, $P<0.001$; AAs: right *vs*. left, 7.6 *vs*. 11.1; $P<0.001$). Their findings suggested

that colonoscopy inconsistently protects against right-sided CRC as smaller AAs were easy to miss. This fact was further augmented by the evidence in another study which demonstrated a greater likelihood for missed and recurrent adenomas in the proximal colon [128].

For this thesis, the author had the opportunity to address these issues and the results have demonstrated that diminutive (<6 mm), small (6–9 mm) and larger adenomas (≥10 mm), and adenomas detected in the left colon had significantly higher proportions of ACN (see **Tables 5.14** and **5.15**, and **Figure 5.6**). Size distribution and the mean size of left-sided adenomas were significantly larger than right-sided adenomas in this cohort and this was true for all adenomas and ACN (see **Tables 5.16** and **5.17** and **Figures 5.6** and **5.7**). When ACNs were considered, only then did the majority of right-sided ACNs belong to the sub-centimetre category (see **Table 5.22**), in contrast to the left side where the majority of ACNs were of ≥10 mm. This was purely because all adenomas in the left side were larger and hence had a higher proportion of advanced histology in each size category; this further supported the fact that the malignant potential of the left-sided colonic epithelium is more than that of the right colon.

The fact that malignant adenomas were detected in different segments of the distal colon in varying proportions (see **Table 5.6**) and the evidence from the existing literature that distal segments of the colon were more exposed to carcinogens [81], raise the question about the biological differences in different segments of the colon, which could be explained in terms of the varied malignant potential of each segment.

A segmental analysis was performed to answer this question. The distribution of ACNs demonstrated that the sigmoid colon had the highest proportion of ACN and the transverse had the lowest (see **Table 5.23** and **Figure 5.8**). The multivariate analysis performed with a valid model confirmed that segmental locations were significant and independent risk

factors determining the presence of advanced histological features in adenomas, along with adenoma size and sex of the patient (see **Table 5.24**). These findings suggest that left sided colonic epithelium is biologically different and more tumorigenic and further studies including cytogenetic analysis into right and left sided colorectal adenomas could answer this question. NHS BCSP provides a unique opportunity to perform this which in turn can lead into individualistic management and surveillance protocol depending on different cytogenetic abnormalities in different segments of colon.

Chapter 6: Surveillance follow-up

6.0 Introduction

In the BCSP, the BSG guidelines for adenoma surveillance are followed except that the LR group is called back for biennial FOBT screening instead of having surveillance colonoscopy after five years. The HR and IR groups, who underwent continuing surveillance in the BCSP for the study period between June 2006 and August 2012, are analysed in this chapter.

6.1 Aims and objectives

The main aims included:

- detecting the proportion of patients diagnosed with CRC and adenomas at surveillance with particular emphasis on the results at first surveillance;
- determining the proportion of patients with AAs at screening and assessing any significant difference in prevalence between the HR and IR groups;
- detecting the proportion of patients with adenomas ≥10 mm size at screening and evaluating any significant difference in prevalence between the two groups;
- assessing any differences in outcomes between the HR and IR groups at first surveillance and determining whether any difference was significant;
- determining the yield of colorectal neoplasia at second and third surveillance for the HR and IR groups;
- comparing the incidence of patients developing AAs between screening and first surveillance and between first and second surveillance to demonstrate the changing pattern and determine whether any differences are statically significant.

6.2 Methods

Three data sets were obtained from the national database. They contained all the participant information, the procedure used and polyp details. The information obtained has been discussed in Chapter 3 (Methodology). The data were processed to create two separate data sets, the first set containing the participant- and procedure-specific data on the screening episodes, and the second set containing similar participant- and procedure-specific data on the surveillance episodes. The data sets containing the polyp details were further divided into two separate data sets. The first set had all the information for the polyps detected and resected during the screening episodes; the second set contained similar polyp data at screening and surveillance. The data sets containing the participant and procedure details were merged with the polyp data sets to obtain two comprehensive, workable data sets that contained relevant information about each participant, procedure and polyps for both screening and surveillance episodes. The surveillance episodes were chronologically sequenced for each and every participant to identify multiple surveillances against each participant. The comprehensive screening and surveillance data sets were then merged to obtain the final data set. This contained all the data required for each participant with regard to their screening and subsequent surveillance episodes.

For the analyses of the yield of AAs at screening, and at first and second surveillance, participants with available histology for their adenomas were included and the HR and IR groups were combined to assess the difference in yield of AAs between screening and first surveillance episodes and also between first and second surveillance.

The data were processed and merged using the Stata Statistical Software, Release 12.1 (StataCorp LP, College Station, TX, USA) and the analyses were performed with IBM SPSS Statistics for Windows, Version 20.0 (IBM Corporation, Armonk, NY, USA). The differences of

proportions were statistically evaluated by performing a Pearson's chi-square test and McNemar's test whenever appropriate, and the results are shown in tables in this chapter.

6.3 Data processing

6.3.1 Participant and procedure data

These are summarized in **Figure 6.1**.

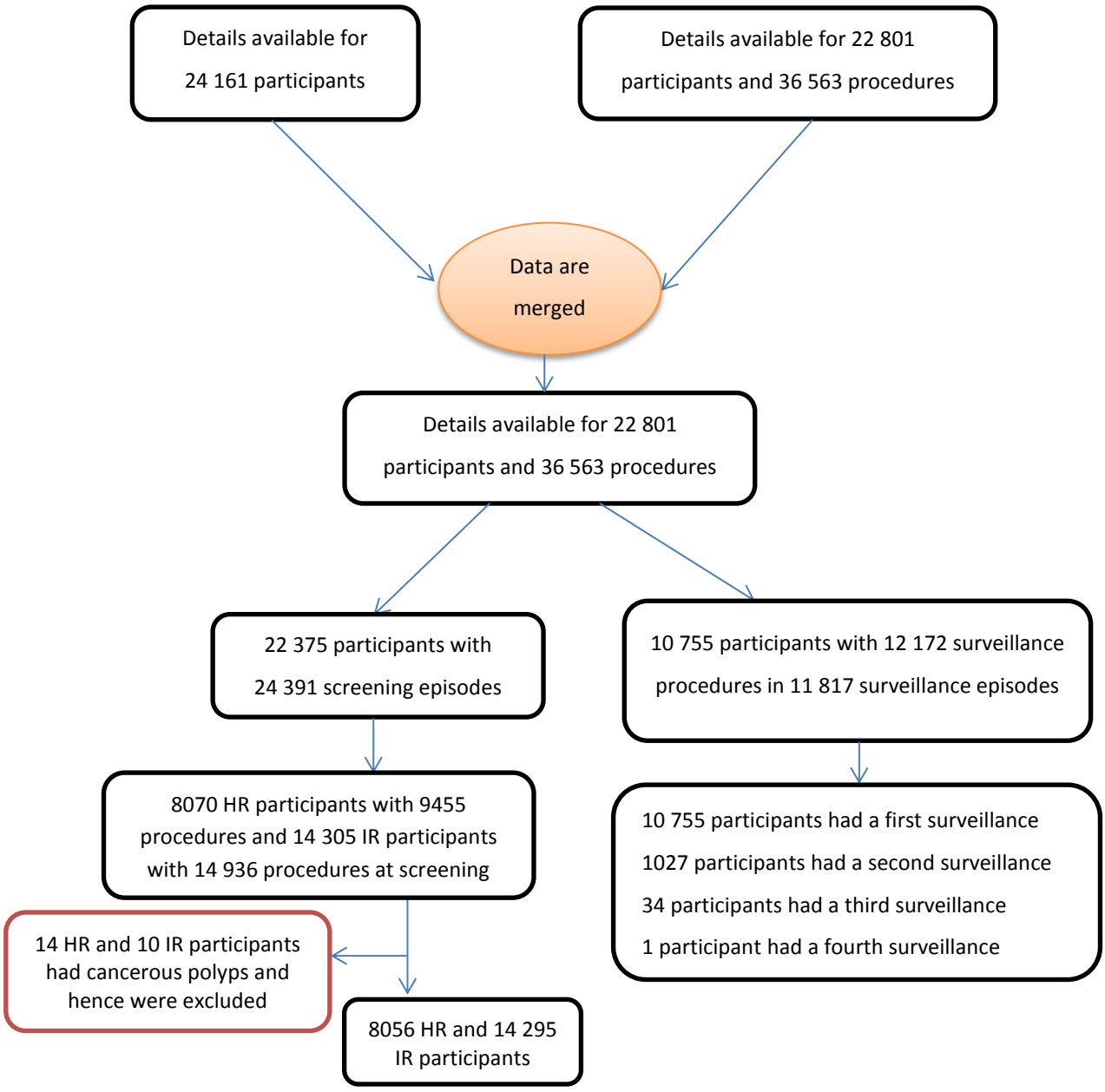

Figure 6.1 Participant- and procedure-specific data.

Note: HR = high-risk; IR = intermediate-risk.

6.3.2 Polyp data

The database was interrogated for all polyps detected at screening and surveillance for participants who were stratified as HR and IR groups during the study period. The data sets of the polyps detected at screening and surveillance were integrated with the data sets containing the participant- and procedure-specific data, and then analysed to obtain the final results.

6.4 Results

6.4.1 Outcome of surveillance of high-risk participants

Participants identified as belonging to the HR group at the screening colonoscopy, who underwent surveillance during the study period, were included. The path of HR participants during their surveillance episodes is shown in **Figures 6.2** and **6.3**.

For the analysis of the yield of ACN at surveillance, participants with CRC and participants with histology data were included, combined and used as the denominator.

Of the HR group at first surveillance, 39 had CRC. A total of 3361 participants in the HR group had adenomas and 2953 of them had histology data. In the IR group, 20 had CRC at first surveillance; 1896 had adenomas of which 1782 had histology data. Serrated adenomas were detected in a very small number of participants (31 in the HR group and 14 in the IR group) at first surveillance; they were excluded from the analysis because they represent a very small group and has a different pathways for polyp development and progression.

8046 participants at screening

(August 2006–August 2012)

Male: 6138; female: 1908

Age, years: mean: 65.79; median: 65.29; SD: 4.44; range: 60.05–88.38

Histology available: 7879 participants

Participants with three or more ≥10-mm adenomas: 1026 (13.11%) (*N* = 7826)

Participants with <10-mm and ≥10-mm adenomas: 5590 (71.43%) (*N* = 7826)

Participants with five or more <10-mm adenomas: 1210 (15.46%) (*N* = 7826)

AAs: 7140 (90.62%); non-AAs: 686 (8.70%); serrated adenoma: 21 (0.27%); incomplete data: 32 (0.41%) (*N* = 7879)

5579 participants completed first surveillance (August 2007–August 2012)

Male: 4240; female: 1339

Age, years: mean: 66.48; median: 66.41; SD: 3.56; range: 60.75– 84.79

Time lag surveillance–screening, years: mean: 1.2; median: 1.05; range: 0.15–5.05

Percentile of screening–first surveillance lags, years: 25%: 1.00; 50%: 1.05; 75%: 1.17; 99%: 3.51

4507/5579 (80.78%) had surveillance within three months (±) of expected date

Histology available for 3763 participants with adenomas: 2922

Participants with ≥10-mm adenomas: 120 (4.11%) (*N* = 2922)

Participants with <10-mm and ≥10-mm adenomas: 217 (7.43%) (*N* = 2922)

Participants with <10-mm adenomas: 2585 (88.46%) (*N* = 2922)

AAs: 738 (19.61%); non-AAs: 2184 (58.04%); serrated adenomas: 31 (0.83%); others: 810 (21.52%) (hyperplastic, inflammatory, non-polyp, other polyp) *N* = 3763

Greatest risk outcome at first surveillance (*N* = 5579)

Cancer	HR	IR	LR	Abnormal	Normal	No result
39	441	1085	1835	1167	989	23
(0.7%)	(7.90%)	(19.45%)	(32.89%)	(20.92%)	(17.73%)	(0.41%)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

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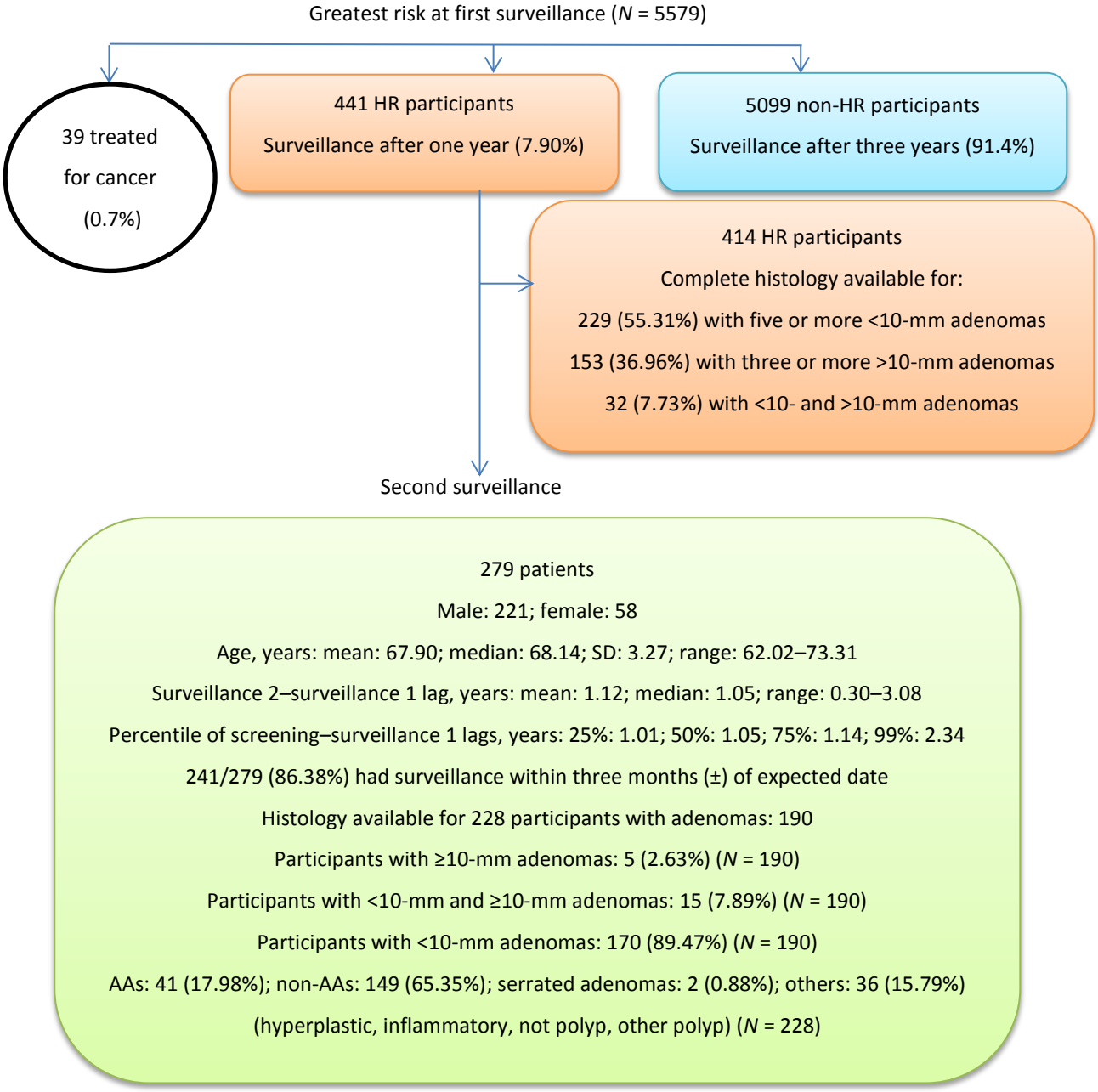

Greatest risk at second surveillance (*N* = 279)

Cancer	HR	IR	LR	Abnormal	Normal	No result
2	43	59	101	43	28	3
(0.72%)	(15.41%)	(21.15%)	(36.2%)	(15.41%)	(10.04%)	(1.07%)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

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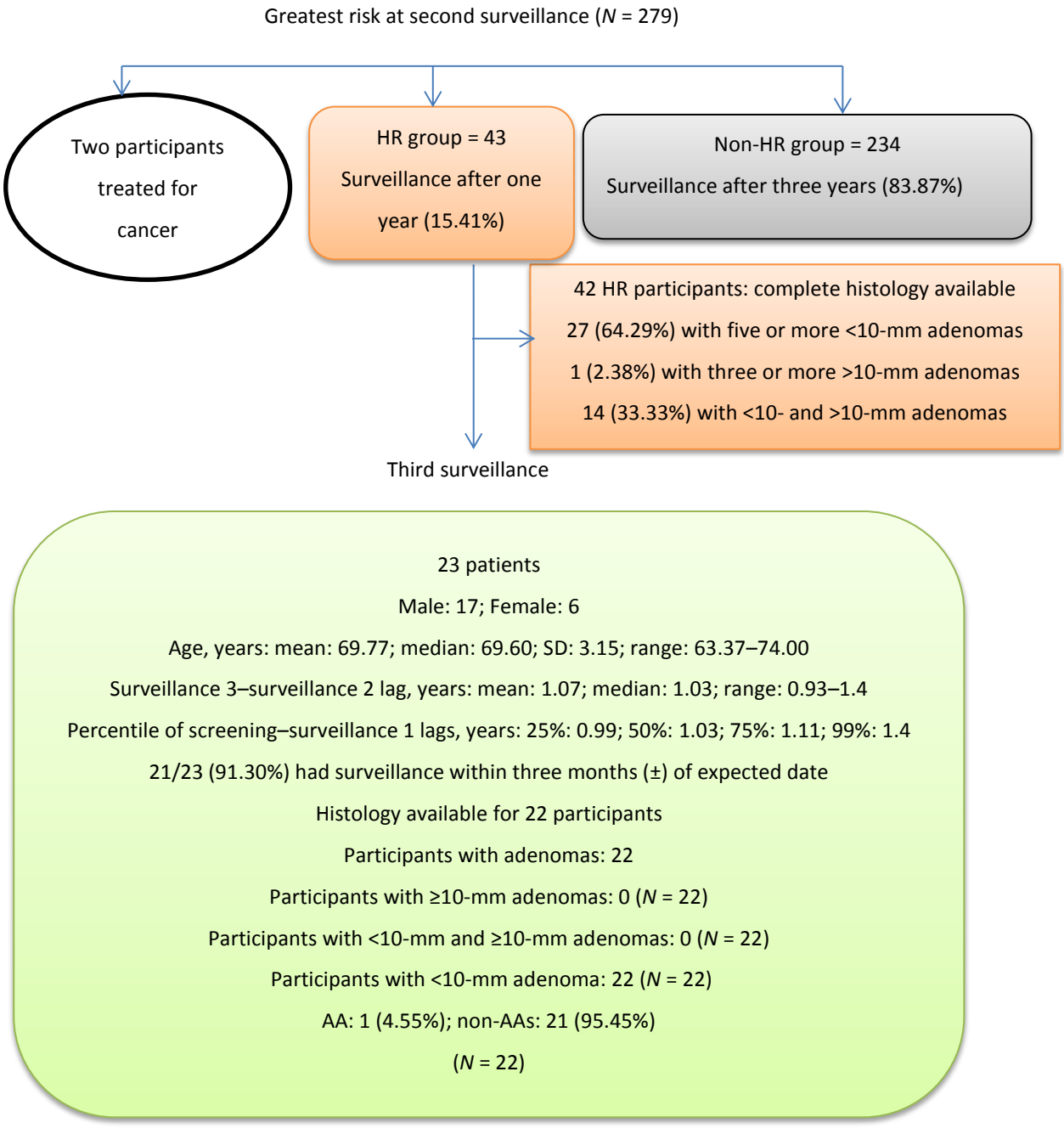

HR	IR	LR	Abnormal	No result
6	3	11	1	2
(26.09%)	(13.04%)	(47.83%)	(4.34%)	(8.70)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

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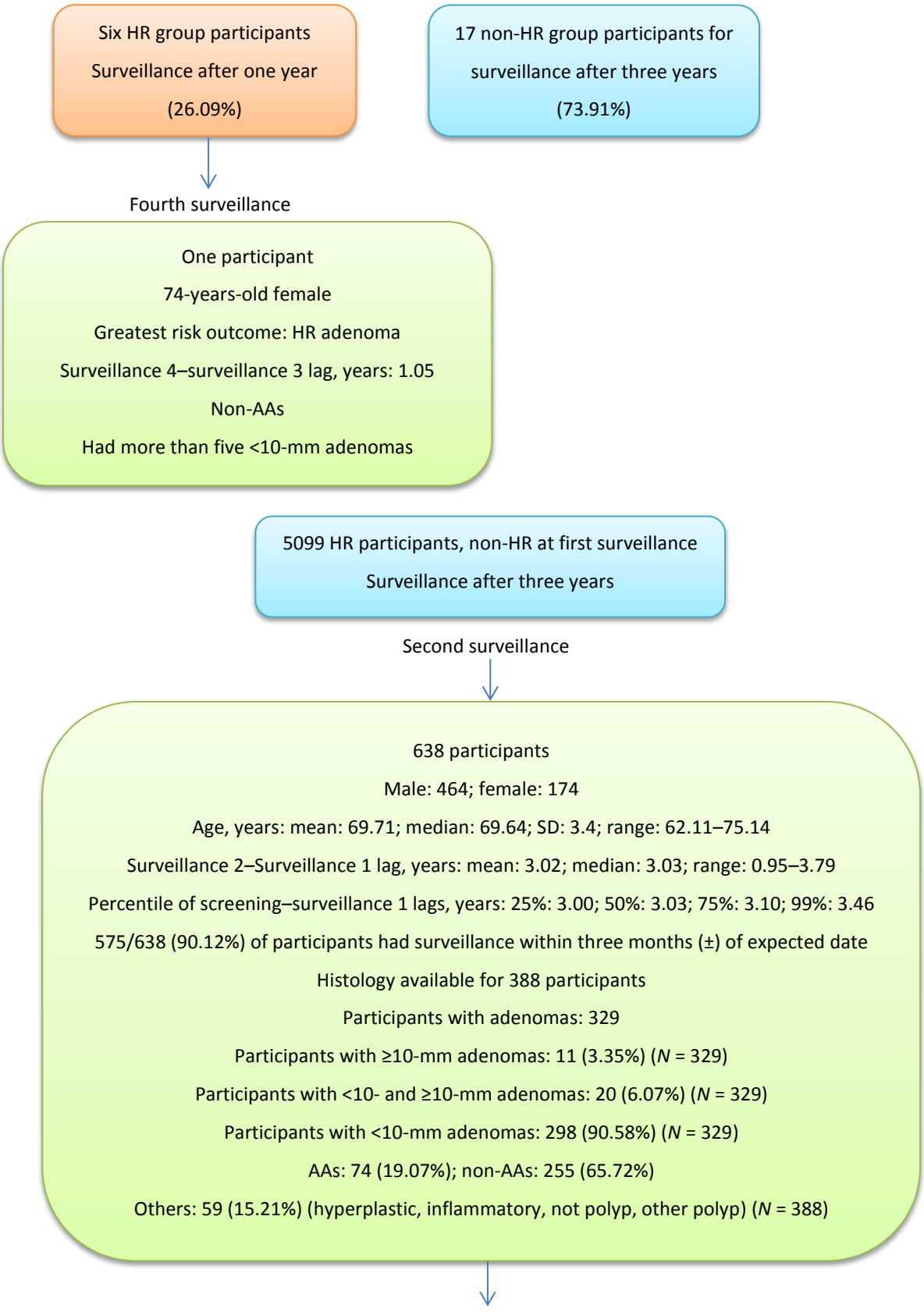

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Greatest risk outcome at second surveillance (*N* = 638)

Cancer	HR	IR	LR	Abnormal	Normal	No result
5	34	67	224	165	131	12
(0.78%)	(5.33%)	(10.4%)	(35.11%)	(25.76%)	(20.43%)	(1.88%)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

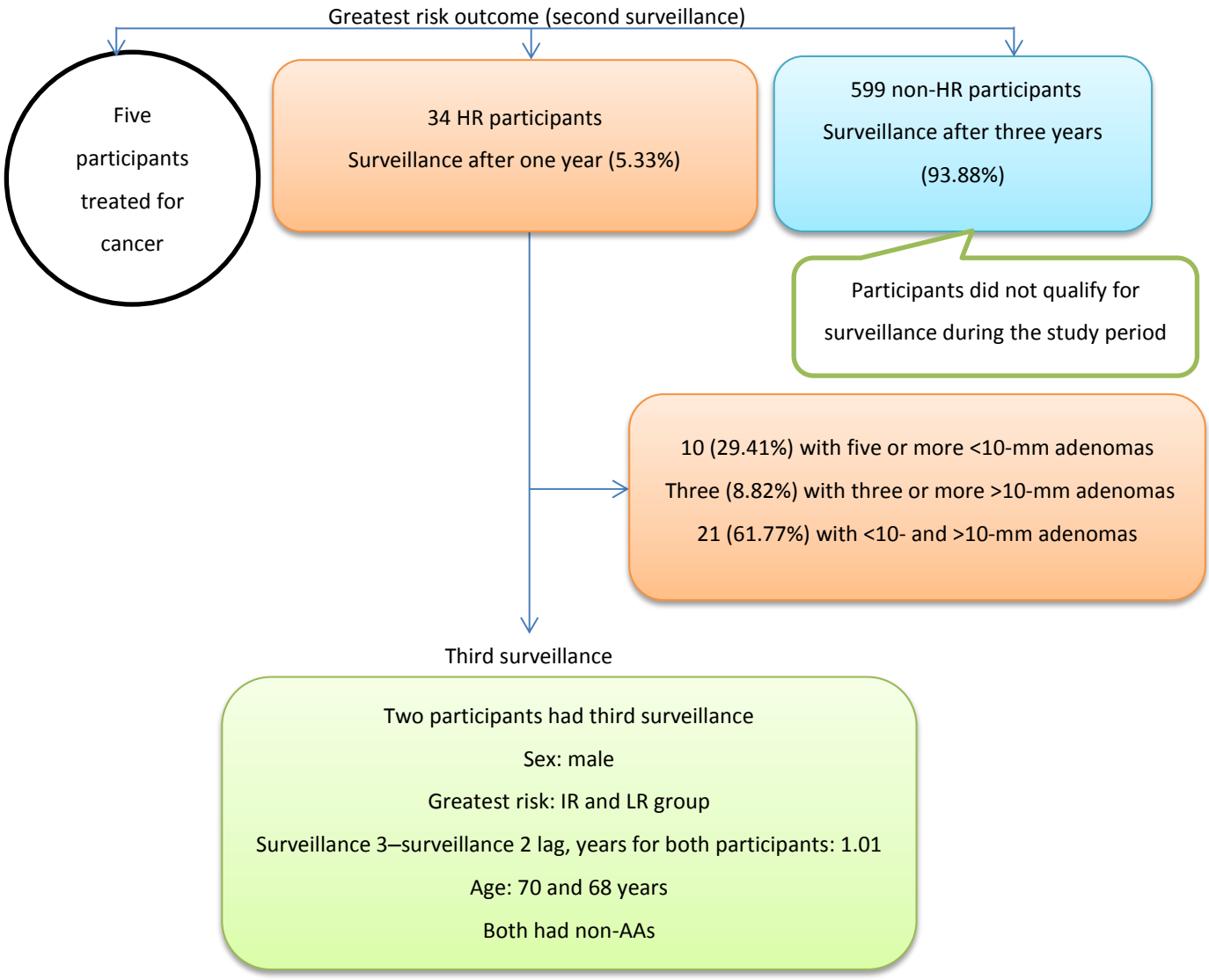
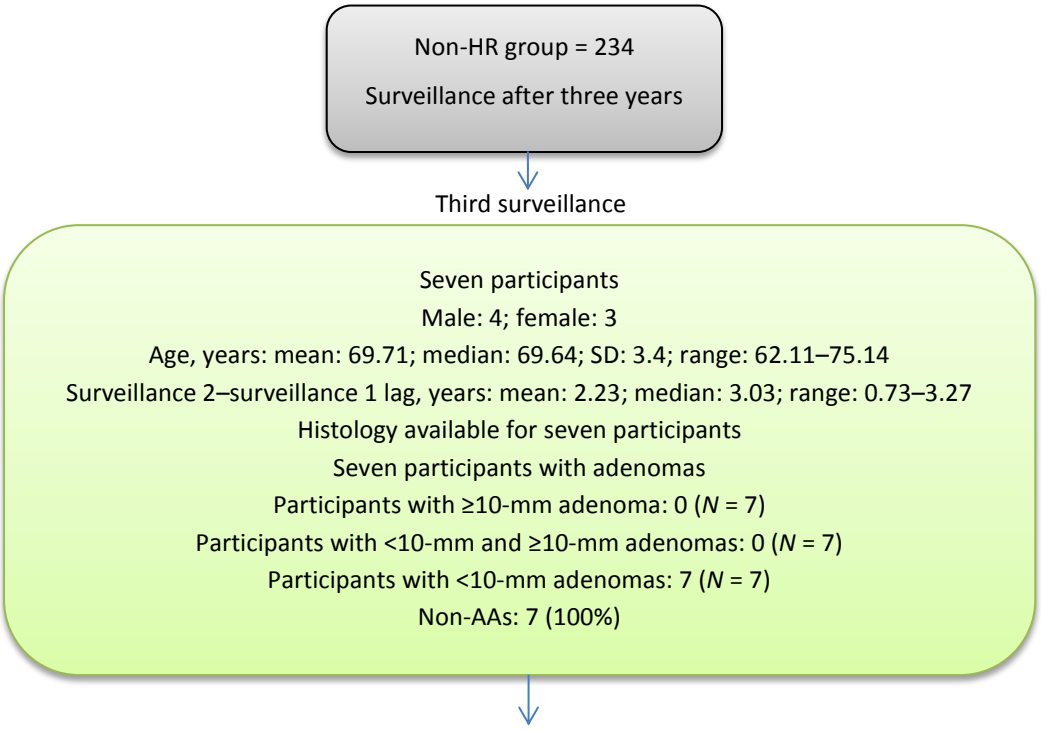


Figure 6.2 HR group surveillance outcome: per-participant analysis.



HR	IR	LR
1 (14.29%)	1 (14.29%)	5 (71.42%)

Figure 6.3 HR group at screening and first surveillance, and non-HR group at second surveillance.

Note: Participants did not qualify for further surveillance during the study period. HR = high-risk; IR = intermediate-risk; LR = low-risk.

6.4.2 Outcome of surveillance for IR participants

Participants identified as IR at the screening colonoscopy, and who underwent surveillance procedures during the study period and had a complete data set with regard to their screening, surveillance and adenomas, were included. The screening data sets were merged with the surveillance data set to identify individuals who had a complete data set for both screening and surveillance colonoscopies. All were included in the analysis. The pathway of IR participants during their surveillance episodes is shown in **Figure 6.4**.

14 295 IR participants at screening
Male: 9177; female: 5118
Age, years: mean: 65.43; median: 65.15; SD: 4.39; range: 59.94–88.73
(August 2006–August 2012)
Histology available for 13 925
Participants with one or two ≥10-mm adenomas: 8087 (58.80%) (*N* = 13 753)
Participants with <10-mm and ≥10-mm adenomas: 3336 (24.26%) (*N* = 13 753)
Participants with three or four <10-mm adenomas: 2330 (16.94%) (*N* = 13 753)
AAs: 12 202 (87.63%); non-AAs: 1551 (11.28%); serrated lesions: 119 (0.85%);
incomplete data sets: 53 (0.24%)
(*N* = 13 925)

4723 IR participants completed their first surveillance

4723 participants completed their first surveillance (August 2007–August 2012)
Male: 3029; female: 1694
Age, years: mean: 68.36; median: 68.32; SD: 3.47; range: 61.03–81.61
Screening–surveillance 1 lag, years: mean: 2.98; median: 3.04; range: 0.51–5.07
Percentile of screening–surveillance 1 lags, years: 25%: 3.00; 50%: 3.04; 75%: 3.11; 99%: 3.78
3967/4723 (83.99%) had surveillance within three months (±) of expected date
Histology available for 2456 participants
Participants with adenomas: 1778
Participants with ≥10-mm adenomas: 121 (6.8%) (*N* = 1778)
Patients with <10-mm and ≥10-mm adenomas: 87 (4.89%) (*N* = 1778)
Participants with <10-mm adenomas: 1570 (88.31%) (*N* = 1778)
AAs: 385 (15.67%); non-AAs: 1393 (56.72%); serrated adenomas: 14 (0.58%); others: 664 (27.03%)
(hyperplastic, inflammatory, not polyp, other polyp) (*N* = 2456)

Greatest risk outcome at first surveillance (*N* = 4723)

Cancer	**HR**	**IR**	**LR**	**Abnormal**	**Normal**	**No result**
20	144	368	1384	1729	1042	36
(0.42%)	(3.05%)	(7.79%)	(29.3%)	(36.61%)	(22.06%)	(0.77%)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

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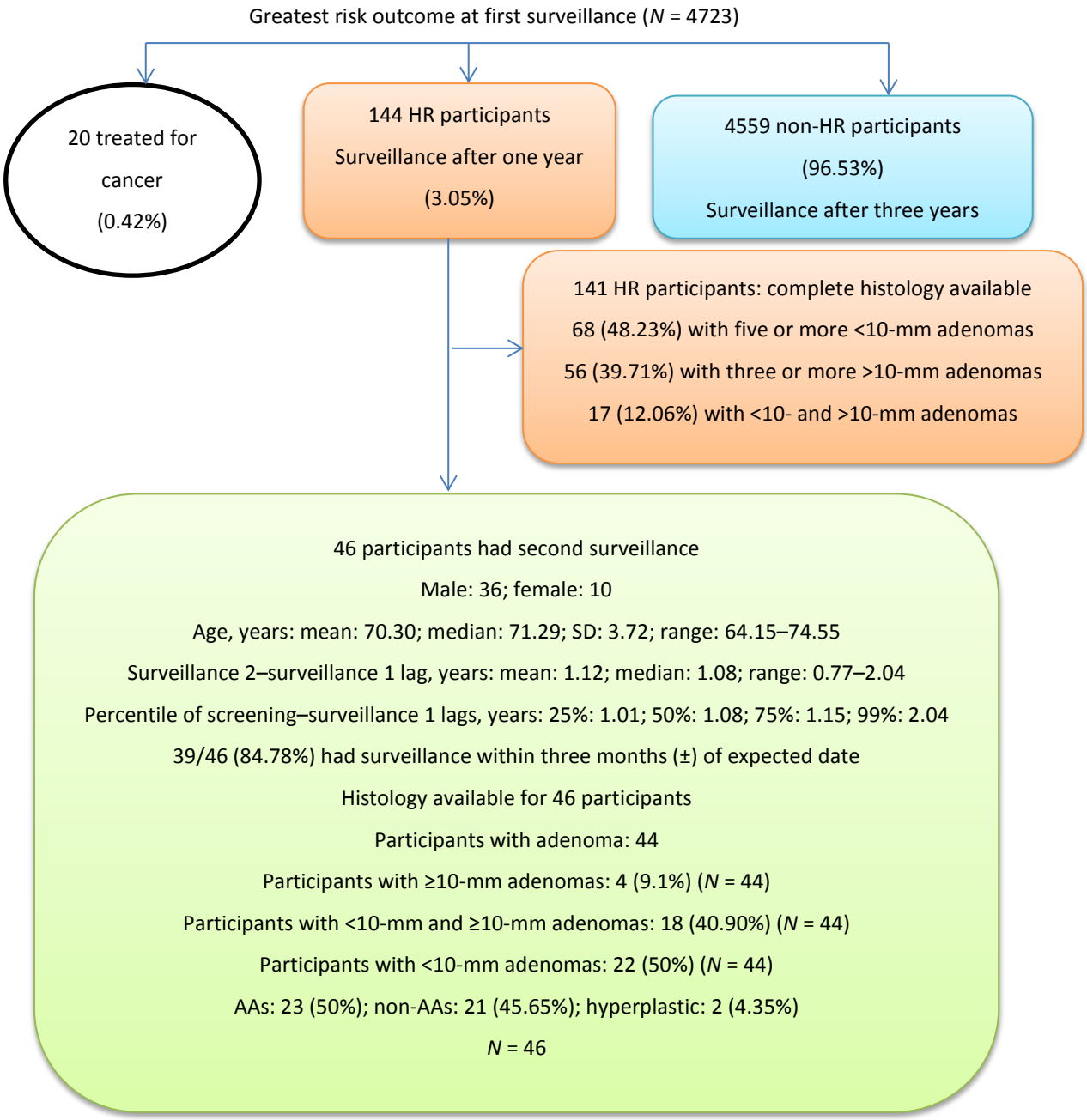

Greatest risk outcome at second surveillance (*N* = 46)

Cancer	HR	IR	LR	Abnormal	Normal	No Result
1	5	6	17	9	7	1
(2.17%)	(10.87%)	(13.04%)	(36.96%)	(19.57%)	(15.22%)	(2.17%)

Note: HR = high-risk; IR = intermediate-risk; LR = low-risk.

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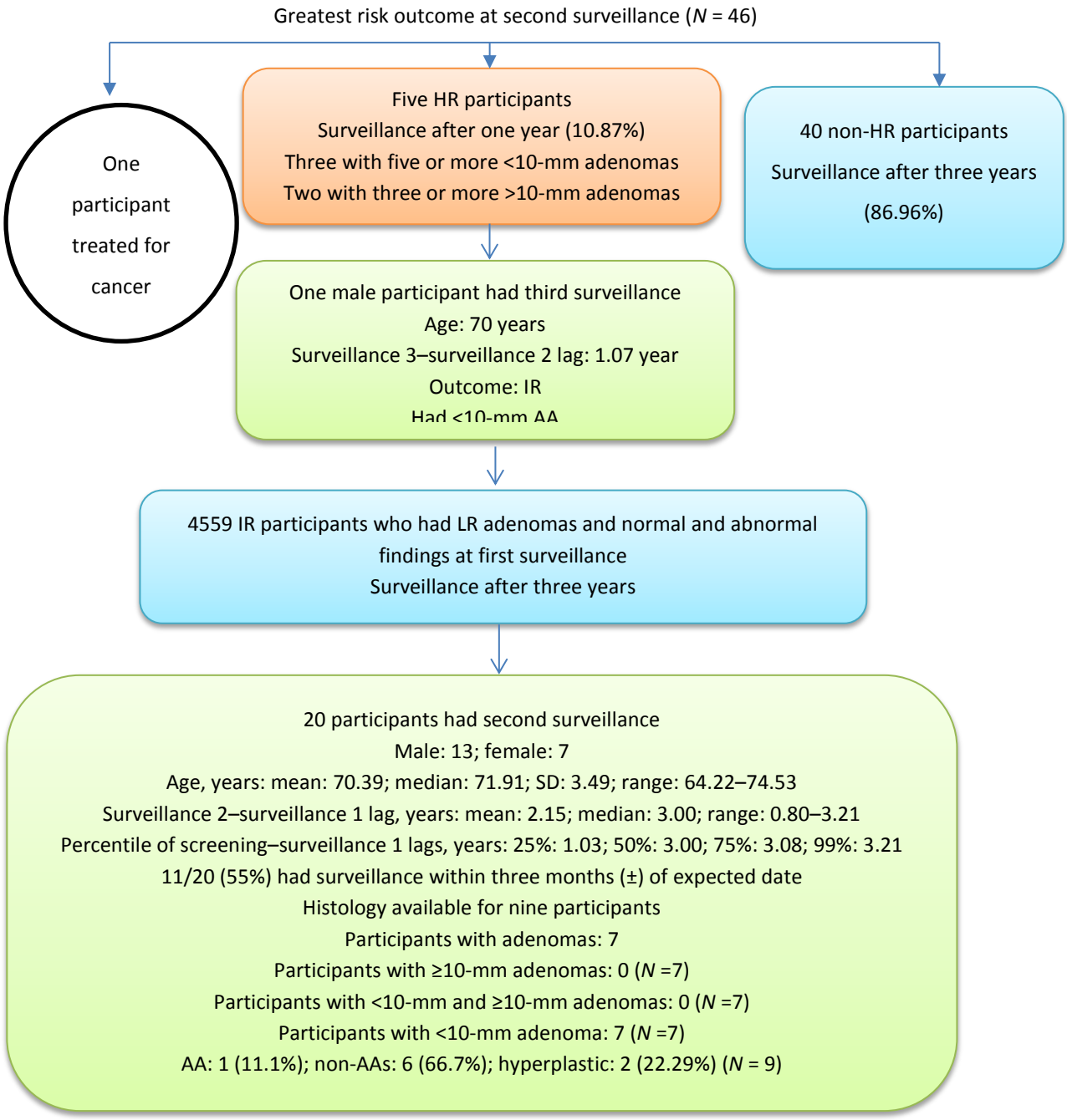

Greatest risk outcome at second surveillance (*N* = 20)

HR	LR	Abnormal	Normal
1	6	8	5
(5%)	(30%)	(40%)	(25%)

Note: HR = high-risk; LR = low-risk.

Participants after their second surveillance did not qualify for third surveillance within the study period.

Figure 6.4 HR group surveillance outcome: per-participant analysis.

6.4.3 Demography of the population studied

A total of 8056 HR individuals participated in the screening. Mean age was 65.7 years; the majority of participants were male (76.2%). Overall, 5579 completed their surveillance during the study period and the mean age at first surveillance was 66.4 years. With regard to the surveillance procedures, 75% were performed within one year of the screening colonoscopy; 99% of participants completed their surveillance by 3.5 years after screening. A delay in timing the surveillance colonoscopy could be due to a variety of reasons, including delayed participation during surveillance and change of residence.

For the IR group, 14 295 participants were identified during the screening colonoscopy. Mean age at screening was 65.4 years, and the majority of participants were male (64.2%). A total of 4723 IR participants completed their first surveillance during the study period and the mean age at surveillance was 68.3 years. Of these, 75% completed their first surveillance 3.11 years after screening and 99% completed first surveillance 3.78 years after screening.

6.4.4 Detection of advanced adenomas at screening

The total number and proportion of HR and IR participants who had AAs at screening were measured. A chi-square test was then performed to evaluate whether there was any significant difference in the detection of AAs at screening between the two groups. The results are shown in **Tables 6.1** and **6.2**.

Table 6.1 Detection of AAs at screening

Risk group	With histology	AA *n* (%)	NAA *n* (%)	Serrated adenoma *n* (%)	Partial data set *n* (%)
HR	7879	7140 (90.62)	686 (8.70)	21 (0.27)	32 (0.41)
IR	13 925	12 202 (87.63)	1551 (11.28)	119 (0.85)	53 (0.24)

Note: AA = advanced adenoma; NAA = non-advanced adenoma; HR = high-risk; IR = intermediate-risk.

Table 6.2 Pearson's chi-square test result showing the difference in proportion of patients in the HR and IR groups having AA at screening

χ^2	df	*P*
44.74	1	<0.001

Note: HR = high-risk; IR = intermediate-risk; AA = advanced adenoma; df = degrees of freedom.

In the HR group, there was a higher proportion of participants with AAs compared to the IR group at screening (90.62 *vs.* 87.63%), and the difference in proportion was statistically significant. BCSP participants in the HR group had significantly more AAs than participants in the IR group.

6.4.5 Detection of adenomas ≥10 mm

Adenomas ≥10 mm were AAs by definition. The proportion and number of participants with adenomas ≥10 mm at screening were detected, and are described in the **Table 6.3**.

Table 6.3 Number of patients with ≥10-mm adenomas

Risk group	Patients with histology available	Patients with ≥10-mm adenomas *n* (%)
HR	7879	6616 (84.54)
IR	13 925	11 423 (83.06)

Note: HR = high-risk; IR = intermediate-risk.

Most participants in both HR and IR groups had adenomas ≥10 mm at screening, but a higher proportion of HR participants had larger adenomas (84.54 *vs.* 83.06%) and this difference was statistically significant (χ^2 = 13.03; *P* = 0.002).

6.4.6 Detection of colorectal neoplasia and CRC

6.4.6.1 Detection of colorectal neoplasia and CRC at first surveillance

The number of HR and IR participants attending their first surveillance colonoscopy were studied and the proportion with CRC, adenomas and other findings was measured. Participants included in the 'Other' category were those whose surveillance colonoscopy did not detect any adenomas (normal/abnormal findings like diverticulosis, haemorrhoids, outcome not yet recorded in the system). The results are shown in **Table 6.4**.

Table 6.4 Outcome of first surveillance

Risk group at screening	Total no. patients at first surveillance	CRC *n* (%)	Adenoma *n* (%)	Other *n* (%)
HR	5579	39 (0.7)	3361 (60.24)	2179 (39.06)
IR	4723	20 (0.42)	1896 (40.14)	2807 (59.98)
Total	10 323 (100)	59 (0.57)	5257 (50.92)	4986 (48.51)

Note: CRC = colorectal cancer; HR = high-risk; IR = intermediate-risk.

A very small proportion of participants were detected as having CRC. There was no significant difference in the detection of CRC between HR and IR participants at their first surveillance (χ^2 = 137.5; *P* = 0.08). The majority of HR participants had adenomas at first surveillance (60.24%), whereas the majority of IR participants did not have a colorectal adenoma at first surveillance (59.98).

A higher proportion of HR participants had adenomas (60.24 *vs.* 40.14%) at first surveillance compared to the IR group, and this difference was statistically significant (χ^2 = 413.5; *P*<0.001). A higher proportion of IR participants did not have any adenomas compared to HR participants (59.98 *vs.* 39.06%) and the difference was statistically significant (χ^2 = 425.2; *P* = <0.001).

6.4.6.2 Detection of colorectal neoplasia and CRC at second surveillance

HR and IR participants were stratified into different risk categories according to the findings of their first surveillance procedure; they then went on to have their second surveillance procedure. This is illustrated in **Figures 6.3** and **6.4**. The results are summarized in **Table 6.5**.

Table 6.5 Outcome of second surveillance

Risk group at screening	**Total no. patients at second surveillance**	**CRC *n* (%)**	**Adenoma *n* (%)**	**Other *n* (%)**
HR	917	7 (0.76)	528 (57.58)	382 (41.66)
IR	66	1 (1.56)	35 (53.03)	20 (45.41)
Total	983 (100)	8 (0.81)	563 (57.27)	402 (41.92)

Note: CRC = colorectal cancer; HR = high-risk; IR = intermediate-risk.

The majority of participants (57.27%) had colorectal adenomas after the second surveillance. Only a very small proportion of participants had CRC at second surveillance (0.81%). There was no significant difference in the proportion of participants with adenomas at second

surveillance between participants stratified as HR or IR at screening (57.58 *vs.* 53.03%; χ^2 = 108.6; *P* = 0.52).

6.4.6.3 Detection of colorectal neoplasia at third surveillance

Table 6.6 summarizes the detection of colorectal dysplasia at third surveillance.

Table 6.6 Detection of colorectal neoplasia at third surveillance

Risk group at screening	**Total no. patients at second surveillance**	**CRC *n* (%)**	**Adenoma *n* (%)**	**Others *n* (%)**
HR	33	0	29 (87.8)	4 (12.2)
IR	1	0	1	0

Note: CRC = colorectal cancer; HR = high-risk; IR = intermediate-risk.

6.4.7 Reduction of advanced adenoma

AAs were recognized as the potent precursor pathology that could develop into colorectal carcinoma. Detection of participants with AAs was measured at screening and also at first and second surveillance.

The significance of the reduction of participants with AAs was analysed with the McNemar's test. The findings of the analyses are described in the next sections.

6.4.7.1 Advanced adenoma detection at screening vs. first surveillance (HR and IR groups combined)

Table 6.7 shows the distribution of participants with AAs at screening and first surveillance.

Table 6.7 Distribution of patients with AAs at screening and first surveillance

Screening *n* (%)	**AAs at first surveillance *n* (%)**	**AAs at first surveillance (%)**	**Total**
AAs: 5474 (89.9)	1080 (19.73)	4394 (80.27)	5474 (100%)
NAAs: 611 (10.1)	107 (17.51)	504 (82.49)	611 (100%)
Total: 6085 (100)	1087 (19.51)	4890 (80.49)	6085

Note: AA = advanced adenoma; NAA = non-advanced adenoma.

There was a significant reduction in the number of participants with AAs at screening (89.9 *vs.* 19.73%; McNemar's test; *P*<0.001).

Polypectomies performed during screening had a sustained effect on the reduction of AAs.

6.4.7.2 Advanced adenoma detection in first vs. second surveillance

Table 6.8 shows the distribution of participants with AAs at first and second surveillance.

Table 6.8 Distribution of patients with AAs at first and second surveillance

First surveillance *n* (%)	**AAs at second surveillance *n* (%)**	**No. AAs at second surveillance (%)**	**Total**
AAs: 197 (35.3)	39 (19.8)	158 (80.2)	197 (100%)
NAAs: 361 (64.7)	71 (19.67)	290 (80.33)	361 (100%)
Total: 558 (100)	110 (19.71)	448 (80.29)	558

Note: AA = advanced adenoma; NAA = non-advanced adenoma.

There was a reduction in the proportion of participants with AAs from second to third surveillance (35.3 *vs.* 19.71%) and the reduction was significant (McNemar's test; *P*<0.001). Continuing surveillance is effective in reducing the number of patients with AAs.

6.5 Discussion

6.5.1 Yield of CRC at surveillance

The detection and resection of colorectal adenomas during colonoscopy is an effective and powerful tool to reduce the incidence of CRC. There are several long-term follow-up studies that support this view.

Winawer et al. [46] followed a cohort of 1418 patients with sporadic colorectal adenoma for an average period of 5.9 years. These were the participants of the NPS, an RCT evaluating the effectiveness of surveillance on patients discovered to have one or more colorectal adenomas. The incidence of CRC during the follow-up period was compared with three reference groups; in two of them, colorectal adenomas were not removed, while the third reference group was derived from a population-based registry. Although 1210 patients were followed up until the end of the study period, only five (0.41%) asymptomatic, early-stage CRCs were detected during follow-up. The number of CRCs expected with regard to the three reference groups were 48.3, 43.4 and 20.7; thus, a significant reduction in CRC incidence (90, 80 and 76% compared to the three groups; $P<0.001$) was achieved.

Zauber et al. [10] followed up the NPS patients further (median follow-up period = 15.8 years) and noted a significant reduction in mortality from CRC compared to the general population. This study demonstrated an even longer-term protective effect of colonoscopy and polypectomy.

Brenner et al. [82] performed a population-based case-control study and showed that a colonoscopy performed within the preceding 10 years was associated with a 77% lower risk of developing CRC.

This evidence suggests that colonoscopy and polypectomy should reduce the incidence of CRC during follow-up and also confer a protective effect from mortality from CRC. Thus, the

protective effect of the high-quality colonoscopy offered by the BCSP at surveillance should in turn translate into a lower incidence of CRC and AAs. There should be a subsequent and significant gradual reduction in the incidence of AAs and CRC in the cohort undergoing ongoing surveillance.

In the BCSP follow-up, a very small proportion of participants were diagnosed with CRC at first surveillance (0.7% in the HR group and 0.42% in the IR group) and there was no significant difference between the two groups. Considering the two groups together, there were only 39 CRCs among the 10 323 participants (0.57%) who completed first surveillance. These results reflect the protective effect of polypectomy with regard to developing future CRC in HR and IR groups. The small number of cases of CRC after one and three years of screening could either represent missed lesions during screening or *de novo* CRC that did not develop along the adenoma–carcinoma sequence.

6.5.2 Yield of advanced colorectal neoplasia and advanced adenoma

Lee et al. [129] reported the results of a 12-month surveillance of the HR group in the BCSP (August 2006–April 2010). Their study included 1760 HR participants; of these 1340 completed their first surveillance during that period. There were 14 CRCs (0.8%) detected at surveillance, which is similar to the findings of this thesis. Their ACN yield was 6.6% (116/1760).

In the current study, histology was available for 2922 HR participants with adenomas at surveillance of which 25.2% (738/2922) had AAs. Considering that 39 HR participants had CRC at surveillance and 2179 HR participants had no colorectal neoplasia, the proportion of HR participants with ACN in this study was 15.1% (777/5140). This higher detection of ACN compared to the study by Lee et al. [129] could be because a larger cohort was studied over

a longer period of time and also because histology data were available for 87.9% (2953/3361) of patients with adenomas, but not for all participants.

For the IR group in this study, histology results were available for 1778 participants with adenomas at first surveillance and 21.6% (385/1778) of them had AAs. In this group, at first surveillance 20 participants had CRC and 2807 participants did not have any colorectal neoplasia. The proportion of the IR group who had ACN at first surveillance was 8.8% (405/4605). Combining the HR and IR groups together, the proportion of patients with ACN at surveillance was 12.1% (1182/9745).

AA formation is an important intermediate point in the natural history of adenomas before they develop into CRC. Detection and removal of these lesions are of prime importance to reduce the incidence of CRC. Many studies have estimated the risk of developing AAs during adenoma surveillance. In a meta-analysis, Martínez et al. [65] studied the risk of developing AAs and CRC after polypectomy. Their study included 9167 participants with sporadic colorectal adenomas from eight different prospective North American studies. Participants were followed up for a long period, with a median follow-up of 47.2 months. The mean age of participants was 62 years and 71.2% were male. Six of the studies involved were RCTs. All the adenomas detected during the initial colonoscopies were removed. ACN was detected in 11.8% (1082/9167) of patients and CRC was detected in 58 (0.6%) patients at their first surveillance. Although the study population differed from the FOBT-positive screened population and the surveillance procedures were performed at different intervals, these results provide some insight into the occurrence of ACN after polypectomy during follow-up in a study setting where all the participants had a complete baseline clearing colonoscopy and then underwent a specific surveillance schedule. In this study, the detection of ACN

during surveillance (11.8%) is not very different to the detection of ACN for the combined HR and IR groups at first surveillance (12.1%) in the BCSP.

In 2012, Martínez et al. [99] performed another pooled analysis to evaluate the risk of developing ACN at one year after initial colonoscopy and polypectomy. The study was originally set up to compare the ACN yield for the same cohort of patients with the American and British surveillance guidelines. The study included data from four North American prevention trials, where a colonoscopy was included in the surveillance protocol one year after the initial examination. Overall, 3226 participants were included in the final analysis; their median age was 64 years (range = 50–70 years). The follow-up colonoscopy was performed at a median of 12.8 months. In the group that fulfilled the BSG HR group criteria at baseline examination, 18.7% had ACN at surveillance after one year (95% CI = 14.8–22.5). The detection of ACN in the HR group in the BCSP was 15.1%. Although according to the baseline risk factors both studies represent similar groups, the procedures were not carried out within the setting of a screening programme. Colonoscopy quality indicator data were not part of the North American study and were not collected, whereas the examinations performed in the BCSP were more demonstrably high-quality colonoscopies. The lower detection of ACN in the BCSP cohort is probably because of complete clearance of adenomas at baseline. Hence, reducing the probability of missed lesions leads to a lower incidence of ACN at surveillance at one year in this HR group.

More recently, Vemulapalli et al. [130] evaluated the effect of using the British guidelines on a cohort of patients with adenomas in North America. This included 1414 patients with colorectal adenomas who had a follow-up colonoscopy more than 200 days after the baseline examination; 377 patients could be stratified as the UK HR group and, at first surveillance, 36 (9.54%) had ACN and two (0.5%) had CRC. The ACN yield is lower than in the

BCSP in this HR group. However, this was a single-centre study and did not include patients who underwent surveillance procedures elsewhere. This limitation would result in a restricted view of the outcome. Also, colonoscopy quality indicator data were not mentioned and therefore outcomes may not match the higher yield of BCSP surveillance.

Saini, Kim and Schoenfeld [89] performed a meta-analysis and systematic review to evaluate the incidence of AAs at the three-year surveillance in patients who had been categorized as either HR or LR during their baseline colonoscopy according to the American guidelines. Although the group under study was different compared to the different risk groups in the BCSP, it did provide some insight about AA incidence at the three-year surveillance. They selected 15 trials for the meta-analysis and found a variable AA incidence rate during surveillance. Four of the studies included in this meta-analysis provided the data on the incidence of adenomas at surveillance.

One of these four studies was performed by Noshirwani et al. [88]. They tried to evaluate the need for a three-year surveillance after baseline colonoscopy and polypectomy. This was a retrospective study from the Cleveland Clinic Foundation Adenoma Registry database. In the study, there were two groups equivalent to the UK HR group. One of these groups were patients with three adenomas (along with one >10-mm adenoma) and 21.3% of them had AAs at the three-year surveillance. The other group consisted of patients with more than three adenomas (along with one >10-mm adenoma) and 34.5% of them had AAs at the three-year surveillance. These two groups were equivalent to the HR group in the BCSP. AA incidence at the first-year surveillance for the BCSP HR group was 14.4% (738/5140). The higher incidence in the North American study was because surveillance was performed after a longer duration in the HR group and possibly also because of higher-quality procedures performed in the BCSP, where a better clearance could be achieved. There were also groups

equivalent to the UK IR group in that study. The first group had three small adenomas and the second group had two adenomas, one of them being >10 mm. Overall, 8.5% of the first and 10.3% of the second group had AAs at the three-year surveillance. In the BCSP, 8.4% (385/4605) of IR patients had AAs at their first surveillance, three years from their initial screening, and the AA yield between the UK and the North American groups was not significantly different.

6.5.3 Difference in outcome between HR and IR groups at first surveillance

Only a very small proportion of participants were diagnosed with CRC at first surveillance in both groups (HR group = 0.7%; IR group = 0.42%) and there was no significant difference in the detection of cancer. A significantly higher proportion of HR participants had adenomas at first surveillance compared to the IR group (60.24 *vs.* 40.14%; $P<0.001$). The non-neoplastic yield was significantly higher in the IR group compared to the HR group (59.98 *vs.* 39.06%; $P<0.001$).

These findings suggested that the current risk stratification strategy, which relies on population-based studies, often involving symptomatic patients, is effective in categorizing the FOBT-positive screened population into different risk groups. This model is effective in stratifying the HR and IR groups in the BCSP population with the HR group demonstrating a significantly higher yield of colorectal adenomas at follow-up.

The CRC yield in the IR group at first surveillance was very low and the majority of participants (59.98%) did not have any colorectal neoplasia. Therefore, the interval between screening and first surveillance for this group could be safely prolonged.

6.5.4 Detection of advanced adenomas during continuing surveillance

Colonoscopy and polypectomy have been associated with a reduced mortality risk from CRC during prolonged follow-up in a number of studies. This is primarily because of the identification and removal of AAs that have the highest potential to develop into CRC. Adenoma surveillance provides the opportunity to identify and remove subsequent AAs and NAAs and thereby reduce the incidence and mortality from CRC.

The reduction in incidence and mortality from CRC during surveillance was demonstrated in the studies that followed up the cohort from the NPS [10, 46]. In the initial follow-up study, 1418 patients were followed up for an average period of 5.9 years with a total follow-up period of 8401 person-years and a significant reduction in the incidence of CRC achieved at the third, sixth and seventh year – 90, 88 and 76%, respectively (P<0.001) – compared to the reference group [46]. The long-term study followed up a larger cohort of 2602 patients from the NPS for a total of 37 073 person-years (median = 15.8 years); there was a 53% reduction in mortality from CRC [10].

A colonoscopy-associated reduction in CRC incidence and mortality was also reported in population-based studies. A population-based, case-controlled study from Germany demonstrated that a colonoscopy performed within a 10-year period was associated with a 77% lower risk of developing CRC [97] The study also demonstrated the protective effect on left- and right-sided CRC. A large population-based study from Norway followed up 40 826 patients with colorectal adenomas (median follow-up = 7.7 years) and demonstrated that colorectal mortality was lower in patients with NAAs and moderately higher in patients with AAs compared to the general population [83].

An effective adenoma surveillance programme that reduces the incidence and mortality from CRC ideally should be effective in demonstrating a significant reduction in the incidence

of AAs during the sequential stages of continuing surveillance. This thesis provided a unique opportunity to demonstrate this reduction.

The outcome of the first surveillance has been discussed previously. During the study period, 917 HR and 66 IR participants underwent second surveillance examinations in the BCSP (see **Table 6.5**). They underwent second surveillance at different time intervals depending on their latest risk categorization and based on the findings at the first surveillance colonoscopy. The majority of these individuals (563/983; 57.3%) had adenomas at second surveillance and a very small proportion had CRC (8/983, 0.81%). This higher yield of colorectal adenomas at the second surveillance colonoscopy reflected the fact that a significant proportion of participants in this cohort were categorized as HR at first surveillance. During the study period, only 34 participants underwent their third surveillance; this did not reflect the overall outcome of third surveillance because the majority of IR participants, who were categorized as the non-HR group at their first surveillance, were scheduled to have their second surveillance after three years from their first surveillance; this was beyond the limit of the time frame of the current study.

The AA yield was compared between screening and first surveillance and also between first and second surveillance. The HR and IR groups were combined and participants with histology data were included in this analysis. The majority of participants with adenomas at screening had AAs (5474/6085; 89.9%), whereas the majority of participants at first surveillance had NAAs (4890/6085; 80.4%). The reduction in the proportion of participants with AAs was significant (89.9 *vs.* 19.51%; $P<0.001$; see **Table 6.7**).

Similar comparative analyses were performed between the outcomes of first and second surveillance. A total of 558 participants were included; after their first surveillance, they completed their second surveillance and had adenomas with histology data available. The

majority of these participants had NAAs at first (361/558; 64.7%) and second surveillance (448/558; 80.3%); there was a significant reduction in the proportion of participants with AAs at second surveillance (19.71 *vs.* 35.3%; *P*<0.001; see **Table 6.8**). These results demonstrate that continuing surveillance with colonoscopy and polypectomy was successful in reducing the burden of AAs in the screened population, which is crucial to the effort of reducing the incidence and mortality from CRC in this population.

The effects of continuous surveillance and the yield of advanced neoplasia have been studied by Imperiale et al. [131] who followed up a cohort of 945 patients with colorectal adenomas to evaluate the predictive risk factors for developing ACN at second surveillance. It was a single-centre retrospective study that included patients with colorectal adenomas. At the index colonoscopy, 36.9% (349/945) of patients had AAs; however, at first and second surveillance only 8.9% (84/945) and 5.9% (56/945) patients were found to have AA. The study involved a symptomatic population but demonstrated a reduction in AAs at subsequent surveillances.

6.6 Summary and conclusion

This thesis has demonstrated the outcome of continuing adenoma surveillance in the BCSP. A very small proportion of patients presented with CRC at first surveillance. The current adenoma surveillance guidelines were effective for stratifying a screening cohort, demonstrating a higher AA yield in the HR group at first surveillance. The majority of the IR group had a non-neoplastic yield at first surveillance, indicating that the surveillance interval for this group could be safely prolonged. Continuing surveillance demonstrated a significant reduction in the proportion of patients with AAs, indicating the long-term effectiveness of polypectomy for the screening cohort.

Chapter 7: Surveillance strategy

7.0 Introduction

This chapter focuses on the different key characteristics studied and then established as significant factors in predicting the detection of ACN at surveillance in patients with colorectal adenoma; their relevance in predicting advanced neoplasia in the BCSP population are evaluated.

7.1 Aims and objectives

These included:

- determining the magnitude of advanced neoplasia detected in HR and IR patients at screening;
- determining the magnitude of advanced neoplasia detected at surveillance;
- identifying the factors at screening that could predict outcome at surveillance;
- identifying the effects of alternative surveillance intervals on the outcomes of surveillance of IR and HR patients.

7.2 Methodology

7.2.1 Analysis

The data for all the HR and IR participants who had their screening and surveillance procedures done during the study period were included. For participants at screening, only those where all adenomas were retrieved and histological results were available were included for final analysis because the number and histological features of adenomas at screening were included for analysis. Participants who had completed their first surveillance were included because during the study period the majority of surveillance procedures were first surveillance procedures. Participants who had polyp data at first surveillance were

included as the available data were sufficient for categorization of surveillance outcome. The outcomes of the first surveillance procedures were categorized into four different groups: normal (no adenoma detected); participants with NAAs; participants with AAs; and participants with CRC.

The intervals between screening and surveillance were measured. The HR group was categorized into two different subgroups. In the first subgroup, first surveillance was performed within two years of screening; in the second group the surveillance interval was longer than two years. Similar categorization was done for the IR group according to a surveillance interval of four or more years. The effects of different surveillance intervals on the outcomes were determined for both HR and IR groups.

7.2.2 Data cleaning flow chart

Figure 7.1 describes the data cleaning process.

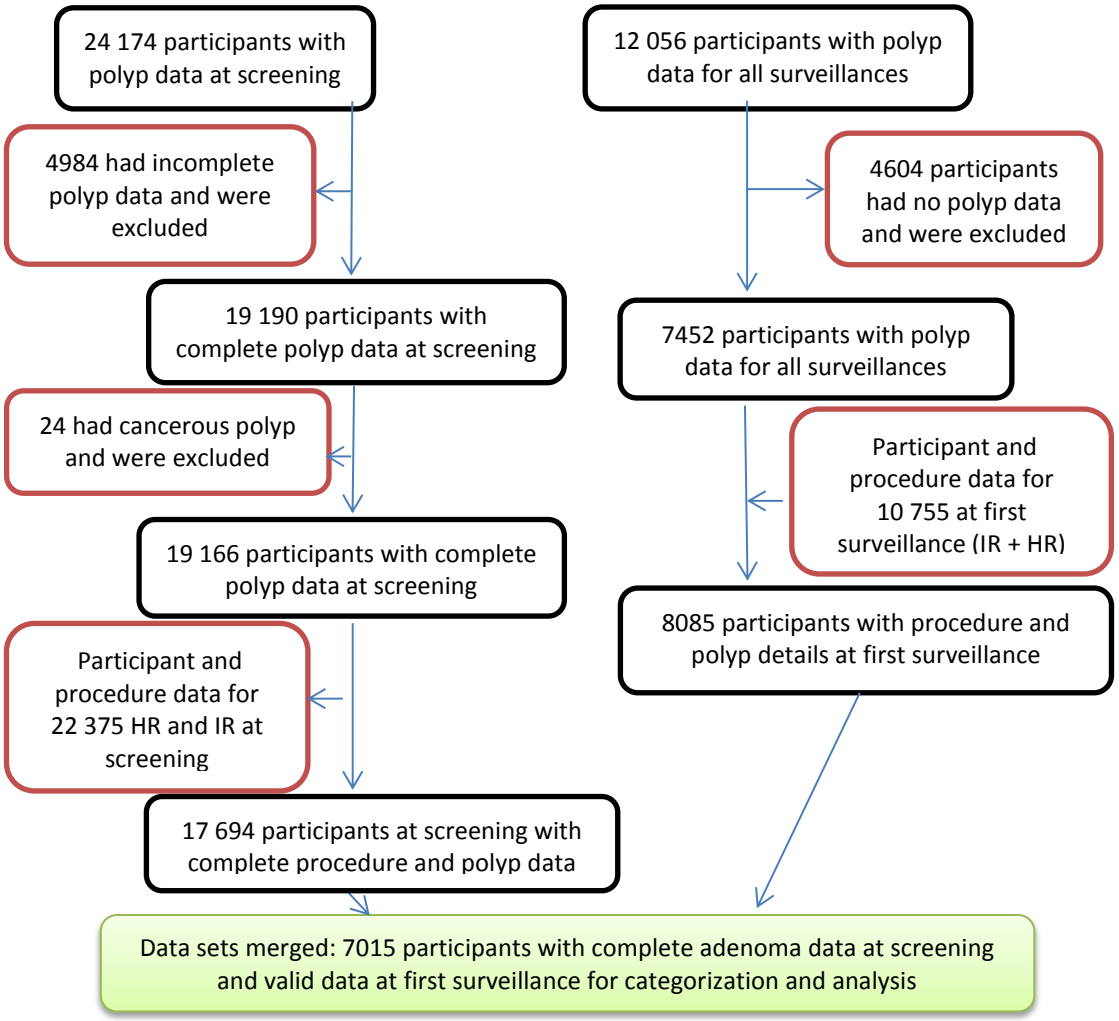

Figure 7.1 Flow chart showing the data cleaning process.

Note: HR = high-risk; IR = intermediate-risk.

7.3 Predictive factors for analysis

The adenoma- and patient-specific factors associated with the detection of colorectal adenomas and ACN during surveillance have been discussed in details in the literature review (Chapter 2, Section 2.8) and will be briefly mentioned here.

The NPS demonstrated that age, number of adenomas and size of the largest adenoma at enrolment were independent risk factors for predicting any adenoma detected during the first surveillance colonoscopy; however, the only factor predicting the detection of adenomas with advanced pathological features was the number of adenomas at onset (≥3 adenomas: OR = 6.9; 95% CI = 2.6–18.3; P<0.001) [48].

Noshirwani et al. [88] showed that the number and size of baseline adenomas were significantly associated with the detection of ACN at surveillance (having ≥4 adenomas or any adenoma with advanced pathological features; P<0.001).

In their pooled analysis, Martínez et al. [65] identified male sex, increasing age, number and size of adenomas, proximal location and villous architecture at baseline as independent risk factors for metachronous advanced neoplasia.

The number and size of adenomas, the presence of HGD and VH, and proximal location of adenomas at the index colonoscopy were shown in different studies to be important factors associated with the detection of AAs at surveillance [77, 89, 91, 100, 132].

Along with adenoma- and patient-specific factors, procedure-related factors were also shown to be associated with the detection of AAs at surveillance. Poor bowel preparation and poor colonoscopy reach (cecal intubation) have been shown to be important factors associated with the detection of AAs at surveillance [100]. In a recent population-based, case-control study from Germany, Brenner et al. [96] showed that procedure-related factors were more important than polyp characteristics for the stratification of CRC risk after

colonoscopic polyp detection in the community setting. In a study performed in a tertiary centre, Seo et al. [133] looked at the practice factors important for local recurrence and detection of metachronous AAs after polypectomy. In this study, 917 patients with 1206 AAs were followed up for a median duration of 28.5 months. Piecemeal resection and the presence of two or three of the diagnostic criteria for AAs (≥10 mm, HGD, VH) were significantly associated with local recurrence (adjusted hazard ratio = 2.46; 95% CI = 1.11–5.48; *P* = 0.027 for the presence of 2/3 criteria of AAs and piecemeal resection) *vs.* en bloc resection (adjusted hazard ratio = 6.96; 95% CI = 1.58–30.71; *P* = 0.010). Male sex, the number of adenomas (>3) and the presence of all three diagnostic AA criteria were significantly associated with AA detection at surveillance.

Therefore, in this thesis, the sex of participants, the number of adenomas at the screening colonoscopy and the presence of advanced histology (VH and HGD) were studied to identify their importance with regard to the detection of AAs at first surveillance.

The dependent variable was the outcome at first surveillance, which was categorized into four different groups: participants with normal results; participants with NAAs; participants with AAs; and participants with CRC. Participants with normal results were the reference group for the multinomial logistic regression.

7.4 Results

7.4.1 Patient demographics

In total, 5001 (71.3%) of the 7015 participants were male, and the mean age was 65.27 years (SD = 3.45; range = 60.06–80.04; median = 65.21). Overall, 3672 (52.3%) participants were HR at screening and the rest were IR at screening.

7.4.2 Distribution of advanced neoplasia at screening

The distribution of advanced neoplasia is shown in **Table 7.1**.

Table 7.1 Distribution of advanced neoplasia at screening

Advanced neoplasia	**Participants with HGD** ***N*** **(%)**	**Participants with VH** ***N*** **(%)**	**Participants with adenoma >10 mm** ***N*** **(%)**
Present	1028 (14.7)	4057 (57.8)	5508 (78.5)
Absent	5881 (83.8)	2985 (42.2)	1287 (18.3)
Missing values	106 (1.5)	0	220 (3.1)
Proximal location	958 (13.6)	6045 (86.2)	12 (0.2)

Note: 14.7% participants had HGD at screening; 57.8% had VH at screening; 78.5% had adenomas ≥10 mm size during screening; and 13.6% had an adenoma in proximal colon during screening. HGD = high-grade dysplasia; VH = villous histology.

7.4.3 Distribution of the number of adenomas at screening

Table 7.2 shows the number of adenomas per participant at screening.

Table 7.2 Adenomas per participant at screening

Number of adenomas	**Number of participants**	**%**
1	1418	20.2
2	1388	19.8
3	1393	19.9
4	1025	14.6
≥5	1791	25.5

Just over one quarter of participants (25.5%) had five adenomas at screening; 20.2% had one adenoma; 19.9% had three adenomas; and 19.8% had two adenomas. Participants with four adenomas at screening had the lowest proportion (14.6%).

7.4.4 Outcomes at first surveillance

Participants were categorized into four groups according to the outcomes at surveillance. The groups were those with a normal result, those with a NAA, those with an AA and those with CRC. The group with normal results was chosen as the reference group for logistic regression analysis. **Table 7.3** shows the distribution of outcome at first surveillance.

Table 7.3 Distribution of outcome at first surveillance

Outcome at first surveillance	Number of participants	%
Normal	620	8.8
NAA	5566	79.3
AA	786	11.2
CRC	43	0.6

Note: NAA = non-advanced adenoma; AA = advanced adenoma; CRC = colorectal cancer.

At first surveillance, the majority of participants had NAAs (79.3%) and the lowest proportion of participants had CRC (0.6%).

7.4.5 Univariate regression analysis: the effect of predictive factors

Univariate multinomial logistic regression analysis was performed to evaluate the individual effect of each predictor. The results of the analysis are shown in **Table 7.4**.

Table 7.4 Results of the univariate multinomial regression analysis

Predictor	**Reference**	**NAA OR (95% CI)**	**NAA *P***	**AA OR (95% CI)**	**AA *P***	**CRC OR (95% CI)**	**CRC *P***
Male gender	Present	0.94 (0.78–1.13)	0.55	1.55 (1.2–1.9)	**<0.001**	0.92(0.47–1.8)	0.83
Female gender (Ref)	Ref	–	–	–	–	–	–
VH	Present	0.88 (0.74–1.05)	0.16	0.90 (0.72–1.13)	0.164	0.63 (0.31–1.3)	0.2
No VH (Ref)	Ref		–	–	–	–	–
HGD	–	1.05(0.76–1.45)	0.73	0.87 (0.57–1.31)	0.5	0.91 (0.27–3.09)	0.89
No HGD (Ref)	Ref	–	–	–	–	–	–
Number of adenomas (1-Ref)[a]	Ref	–	–	–	–	–	–
5	–	1.1 (0.84–1.43)	0.47	1.7 (1.2–2.5)	**0.002**	2.4 (0.9–6.06)	**0.05**
4	–	0.92 (0.69–1.2)	0.6	1.74 (1.21–2.5)	**0.002**	1.72 (0.6–4.9)	0.3
3	–	1.06 (0.8–1.3)	0.6	1.2 (0.91–1.6)	**0.01**	1.8 (0.7–4.5)	0.21
2	–	0.96 (0.7–1.1)	0.7	1.2 (0.91–1.6)	0.16	1.02 (0.38–2.7)	0.96
Adenoma ≥10 mm	Present	0.92 (0.77–1.1)	0.37	0.68 (0.55–0.85)	**0.001**	0.62(0.32–1.2)	0.16
Adenoma <10 mm (Ref)	Ref	–	–	–	–	–	–
Proximal location	Present	1.2 (0.9–1.6)	0.06	2.1 (1.5–2.9)	<0.001	1.9 (0.86–4.3)	0.1

Note: [a]1-Ref = participants with one adenoma. OR = odds ratio; CI = confidence interval; NAA = non-advanced adenoma; AA = advanced adenoma; CRC = colorectal cancer; VH = villous histology; HGD = high-grade dysplasia.

According to the univariate analysis, male sex increased the odds of having an AA at first surveillance. Having three or more adenomas at screening or having an adenoma ≥10 mm at screening also increased the odds of having an AA at first screening.

7.4.6 Multivariate regression analysis: the effect of predictive factors

A multivariate analysis was performed to determine the main effects of the predictor variables on the surveillance outcomes, by using forced entry of factors into the regression analysis. The results are shown in **Table 7.5**. (The significant findings are shown in bold).

Table 7.5 Results of the multivariate analysis

Predictor factor	**Normal**	**NAA OR (95% CI)**	**NAA *P***	**AA OR (95% CI)**	**AA *P***	**CRC OR (95% CI)**	**CRC *P***
Male gender	Present	0.94 (0.77–1.14)	0.56	1.39 (1.07–1.8)	**0.01**	0.84 (0.41–1.7)	0.64
Female gender (Ref)	Ref	–	–	–	–	–	–
VH	Present	0.83 (0.67–1.02)	0.08	1.06 (0.81–1.4)	0.63	0.62 (0.26–1.4)	0.27
No VH (Ref)	–		–	–	–	–	–
HGD	Present	1.14 (0.82–1.6)	0.42	1.08 (0.7–1.68)	0.71	1.3 (0.37–4.7)	0.66
No HGD (Ref)	–	–	–	–	–	–	–
Number of adenomas (1-Ref)	Ref	–	–	–	–	–	–
5	Present	1.16 (0.85–1.59)	0.32	2.9 (2.05–4.3)	**<0.001**	2.2 (0.81–6.2)	0.11
4	Present	1.01 (0.73–1.3)	0.95	1.74 (1.1–2.6)	**0.007**	1.7 (0.59–5.4)	0.3
3	Present	1.05 (0.8–1.3)	0.7	1.4 (0.99–2.03)	**0.05**	1.3 (0.46–3.7)	0.6
2	Present	0.93 (0.7–1.1)	0.5	1.2 (0.91–1.7)	0.15	1.02 (0.38–2.7)	0.96
Adenoma ≥10 mm	Present	0.98 (0.79–1.2)	0.88	0.85 (0.64–1.3)	0.2	0.86 (0.38–1.9)	0.73
Adenoma <10 mm (Ref)	Ref	–	–	–	–	–	–
Proximal location	Present	1.2 (1.9–2.7)	0.1	1.8 (1.3–2.6)	**<0.001**	1.8 (0.74–4.3)	0.18

Note: OR = odds ratio; CI = confidence interval; NAA = non-advanced adenoma; AA = advanced adenoma; CRC = colorectal cancer; VH = villous histology; HGD = high-grade dysplasia.

Male sex and the detection of 3–5 adenomas, and any adenoma in the proximal colon, were significant predictors for detecting advanced adenomas at first surveillance.

7.5 Effect of surveillance interval on outcomes at first surveillance

In the data set used to analyse predictor factors at surveillance, 3107 participants were stratified as HR at screening. The surveillance interval for them varied beyond one year in the programme. Any deviations from the BSG guidelines were because of practical reasons related to: communicating with participants; participant compliance; participants changing residence; and developing a workforce in the early stages of the screening programme.

HR participants were divided into three different groups according to the surveillance intervals of <1.5 year, 1.5–3 years and >3 years. The group with the surveillance interval of <1.5 year was the group where surveillance procedures could be performed according to the BSG guidelines. This group was used as the reference group in the regression analysis when evaluating whether increasing the surveillance interval would have any effect on the surveillance outcomes. The results are shown in **Tables 7.6–7.8**.

Table 7.6 Distribution of surveillance interval for HR participants

Surveillance interval (years)	Number (%)
<1.5	3107 (84.6)
1.5–3	286 (7.8)
>3	278 (7.6)

The majority of HR participants had their surveillance within one and a half years.

Table 7.7 Distribution of surveillance outcome in the three HR groups

Surveillance <1.5 years			**Surveillance 1.5–3 years**		**Surveillance >3 years**	
Outcome	Count	%	Count	%	Count	%
Normal	279	9.0	14	5.0	13	4.5
NAA	2405	77.4	195	70.1	218	76.2
AA	399	12.8	67	24.1	55	19.2
CRC	24	0.8	2	0.7	0	0.0
Total	3107	100%	278	100%	286	100%

Note: NAA = non-advanced adenoma; AA = advanced adenoma; CRC = colorectal cancer.

The majority of HR participants had NAAs in all three surveillance interval groups.

Table 7.8 Results of the regression analysis

Outcome	**Surveillance interval (years)**	**Coefficient**	***Z***	***P***	**OR**	**95% CI**
NAA	>3	0.665	5.179	**0.023**	1.94	1.09–3.4
NAA	1.5–3	0.48	2.858	0.091	1.61	0.92–2.8
NAA	Reference (<1.5)	–	–	–	–	–
AA	>3	1.085	11.625	**0.001**	2.958	1.59–5.5
AA	1.5–3	1.208	15.782	**<0.001**	3.346	1.84–6.07
AA	Reference (<1.5)	–	–	–	–	–
CRC	>3	−19.428	–	–	–	–
CRC	1.5–3	0.507	0.417	0.518	1.661	0.36–7.74
CRC	Reference (<1.5)	–	–	–	–	–

Note: OR = odds ratio; CI = confidence interval; NAA = non-advanced adenoma; AA = advanced adenoma; CRC = colorectal cancer.

Compared to standard surveillance, when surveillance took place after three years for a HR participant the odds for the detection of AAs and NAAs increased significantly without increasing the odds for CRC.

Compared to standard surveillance, when surveillance took place between one and a half and three years for a HR participant, the odds for detection of AAs increased significantly without increasing the odds for CRC.

These results provide an opportunity to reassess and possibly increase the surveillance interval and use the colonoscopy workforce more appropriately. Surveillance procedures could safely be reduced, thus allowing the use of a finite, skilled workforce in a cost-effective manner.

The majority of the IR group had a non-neoplastic yield at first surveillance, signifying that the surveillance interval for this group could be safely prolonged.

Continuing surveillance showed a significant reduction in the proportion of patients with AAs, thereby indicating the long-term effectiveness of polypectomy in the screening cohort.

7.6 Discussion

In the BCSP population, male sex, the number of the adenomas and the proximal location of any adenoma at screening were associated with an increased risk of detecting AAs at first surveillance in the HR and IR groups. Increasing adenoma size and the presence of advanced histological features were not associated with increased detection of AAs at first surveillance.

In the univariate analysis, multiple adenomas (≥3), proximal location, male sex and increasing size (≥10 mm) were associated with the detection of AAs at first surveillance; however, in the multivariate analysis, adenoma size failed to reach significance. The

association between the number of adenomas at screening and the detection of AAs at surveillance is similar to the findings of the NPS [48] and the other studies mentioned previously. The evidence derived from population-based studies is valid when stratifying the BCSP population into different risk groups according to the number of adenomas detected at screening. The BCSP population belongs to the 60–74-year age group, where colorectal adenomas are common and patients with multiple adenomas could continue to develop metachronous adenomas in the future [46, 77, 134]. Also, the presence of multiple adenomas at baseline increases the likelihood of AAs detected at surveillance because of missed lesions at the initial colonoscopy; this has been proved by tandem colonoscopy studies [78, 135].

Proximal location of adenomas at screening was associated with the detection of AAs at surveillance, which has also been demonstrated by other studies [65, 101, 135]. This association in the BCSP population may represent a cohort of patients with adenomas of different tumour biology with the potential for developing metachronous lesions at surveillance.

In contrast to other studies, the presence of advanced histological features did reach a significant association with the detection of AAs at surveillance, which indicates that the current BSG strategy of risk stratification without histological characteristics is valid for the BCSP population. It also demonstrates that the subjective variations that have been reported and studied when assessing HGD and VH [136, 137] are often associated with a lack of definite objectivity and hence have failed to demonstrate any significant ORs for AAs at surveillance.

The HR group, who had their first surveillance after one and a half or three years after screening, did not show any higher OR for CRC at first surveillance; this reinforced the

established protective role of polypectomy [46]. The OR for CRC did not increase in any of the delayed surveillance HR groups, but the OR for AAs and NAAs increased. This means that the surveillance interval can be safely increased in this group without any additional increased risk of CRC. The fact that the time required for developing invasive carcinoma from an adenoma requires 5–20 years [30] illustrates that increasing the surveillance interval after a clearing colonoscopy is safe. Also, the high-quality colonoscopy that was delivered within the setting of the BCSP provides better examination and clearance; hence, the surveillance interval could safely be prolonged in the HR group. The current European guidelines recommended a surveillance interval of three years for HR patients within the setting of high-quality colonoscopy [16]. An increase in the interval would allow the cost-effective use of a skilled resource.

Chapter 8: Discussion and conclusions

8.0 Introduction

This chapter summarizes the major findings of this thesis and their relevance in the background of existing evidence in the literature and their implications. It also discusses any improvements that could be incorporated in future work of a similar nature and the direction of future research in the field of colorectal adenoma surveillance. Finally, it includes personal reflections from the experience gained during the period of the work.

8.1 Main findings

The main findings are enumerated below.

1. In the BCSP population, the majority of the adenomas were located in the combined regions of the rectum and sigmoid colon (50.13%) and most were detected in the distal colon (62.52%) (see Table 5.3 and Figure 5.3). The distribution of adenomas in the BCSP population is in keeping with the epidemiological studies that have demonstrated similar distributions [33, 112]. The distributions of adenomas in the BCSP population follows the pattern described in those epidemiological studies describing the natural history of colorectal adenomas. Also, it is important to remember that these data represented subjects who were derived from a FOBT-positive population and thus left sided adenomas with bleeding are more likely to be picked up than from an undifferentiated, unscreened population.

2. The proportion of adenomas containing advanced histological features increased with increasing size of the adenoma up to 35 mm, which was followed by a plateauing trend signifying the increasing neoplastic potential with increasing size. The prevalence of advanced histology in adenomas of different size categories has also been well documented [45, 113–116]. These studies evaluated various patient and adenoma-specific factors that

are important determinants of the presence of advanced histological features in adenomas. One of the consistent findings is the increased prevalence of advanced histological features with increasing adenoma size, reflecting progressive tumorigenesis of colorectal adenomas.

3. Segmental location of the adenomas was associated with a significant different potential to have ACN. An adenoma located in the rectum was twice as likely to have advanced neoplasia compared to an adenoma located in the caecum; adenomas located in the caecum, AC, HF, TC, SF and DC demonstrated lower ORs for advanced neoplasia. Adenomas located in the TC demonstrated the lowest odds for having advanced neoplasia.

There are several studies [115, 116] which have identified that left sided location is an independent risk factor for adenomas to acquire advanced histological features. The results in this thesis indicated that even in the left sided colon different segments of the large bowel had different potentials for adenomas to develop ACN. This signifies that in the FOBT positive BCSP cohort of subjects, the different segments of colon have different tumorigenic potential. This could be due to complex interaction of faecal loading, differential segmental gut microbiota, differential exposure of carcinogens to different segment of bowel [81] leading to different carcinogenic mutations. This would need further evaluation with studies involving histological and cytogenetic assessment of the colorectal adenomas from different segments of large bowel. These facts emphasised that the adenomas in the different segments of the left side of the large bowel would need more thorough examination and evaluation during screening colonoscopies due to a higher probability of harbouring CAN.

4. All left-sided adenomas were larger than right-sided adenomas and this was also true for adenomas with advanced neoplasia. The differences in size were statistically significant. The proportions of adenomas with advanced neoplasia were located more in the left side of the colon than the right side in all size categories and the difference was statistically significant.

This illustrates the fact that, in the BCSP population, left-sided adenomas had more advanced histological features.

The differences between right- and left-sided AAs have been previously studied. Researchers reported that right-sided AAs were smaller that their left-sided counterparts and hence easier to miss during colonoscopy. Gupta et al. [127] performed a cross-sectional analysis of the histology performed at a single centre providing services to more than 1900 endoscopists in 43 states in the USA. They studied 233 414 polyps removed from 142 686 patients. They demonstrated that size distribution was similar in the right and left side of the colon for all polyps; however, in the case of AAs and adenomas with HGD or cancer, right-sided adenomas were significantly smaller in size (adenomas with HGD and CRC: right vs. left, 8.2 vs. 12.4, P<0.001; AAs: right vs. left, 7.6 vs. 11.1; P<0.001). Their findings suggested that colonoscopy inconsistently protects against right-sided CRC as smaller AAs were easy to miss. This fact was further augmented by the evidence in another study which demonstrated a greater likelihood for missed and recurrent adenomas in the proximal colon [128].

We addressed these issues and the results have demonstrated that diminutive (<6 mm), small (6-9 mm) and larger adenomas ($\geqslant$10 mm), and adenomas detected in the left colon had significantly higher proportions of ACN (see Tables 5.14 and 5.15, and Figure 5.6). Size distribution and the mean size of left-sided adenomas were significantly larger than right-sided adenomas in this cohort and this was true for all adenomas and ACN (see Tables 5.16 and 5.17 and Figures 5.6 and 5.7). When ACNs were considered, only then did the majority of right-sided ACNs belong to the sub-centimetre category (see Table 5.22), in contrast to the left side where the majority of ACNs were of $\geqslant$10 mm. This was purely because all adenomas in the left side were larger and hence had a higher proportion of advanced histology in each size category; this further supported the fact that the malignant potential

of the left-sided colonic epithelium is more than that of the right colon. The probability of a missed lesion in the right colon would be similar for all right sided adenomas (AAs and NAAs) as they are generally smaller than the left sided adenomas. The risk of missed lesions in right-sided colonic adenomas is not a phenomenon in isolation for advanced adenomas only in BCSP population. This implies a careful examination of right sided bowel during screening colonoscopy. Further research is needed in this field by studying various protected time slots for extubation times in different segment of bowel to identify the optimal time to enhance the detection of advanced adenoma in BCSP in right side of the large bowel.

5. The presence of HGD, distal/left sided location, increasing size and female sex represented significantly higher ORs for the presence of carcinomas in adenomas which had been detected as polyps during colonoscopy in the BCSP, thereby demonstrating important factors associated with cancerous polyps.

There are several studies which have looked into the important determinants for the presence of advanced histological features in adenomas. Increased prevalence of advanced histology with increasing size of the adenoma is reported I several studies [45, 113-116].

Gschwantler et al. [115] has demonstrated size, left-sided location, VH and age as risk factors for advanced histology. But gender and multiplicity of adenomas failed to demonstrate any influence in that study.

In the National Polyp Study (examined 3371 adenomas from 1867 patients) the size and extent of the villous component of the adenoma were the major independent risk factors associated with HGD [112]. The increased detection of HGD in distal adenomas was attributed to increased size and villous component rather than location. The sex of the

participants was not associated with HGD in this study. The multiplicity of factors influencing HGD was also dependent on size and VH.

In another study Nusko et al. [116] performed a 'per-adenoma' analysis that included a total of 11 188 adenomas removed during the period from 1978 to 1993. Adenoma size proved to be the most important factor followed by left-sided location. They also demonstrated complex interaction between sex and a multiplicity of factors predicting for higher risk of CRC in adenomas.

In contrast to In contrast to two of the studies mentioned earlier [115, 116], a very small proportion of adenomas <6 mm in size (79/72 815; 0.1%) were shown to contain a focus of cancer (see **Table 5.4** and **Figure 5.5**). This perhaps shows that some of the CRCs developed de novo from the epithelium and some developed cancer through a different carcinogenesis pathway than the adenoma–carcinoma sequence, where increasing size is a driving factor in developing a malignant focus. This pathway was described as a de novo pathway; according to this hypothesis, CRC can also develop de novo from normal mucosa. This pathway is well described in the Western and Japanese literature [117–120].

Adenoma size appears to be a crucial factor associated with advanced histology in the current literature which is also the finding of this current study. The distribution of advanced histology demonstrated that the proportion of adenomas containing advanced histological features increased with increasing size of the adenomas up to 35 mm, after which it plateaued (see Figure 5.5). The left sided location and HGD is also found to be important factors as in other studies. The importance of female gender in NHS BCSP is perhaps reflecting the fact of increased life expectancy of female population in UK, but this area needs more research among the NHS BCSP population.

6. A very small proportion of patients had CRC at first surveillance and in subsequent surveillance procedures and hence, the current screening interval is safe.

Winawer et al. [46] followed a cohort of 1418 patients with sporadic colorectal adenoma for an average period of 5.9 years. These were the participants of the NPS, an RCT evaluating the effectiveness of surveillance on patients discovered to have one or more colorectal adenomas. The incidence of CRC during the follow-up period was compared with three reference groups; in two of them, colorectal adenomas were not removed, while the third reference group was derived from a population-based registry. A significant reduction in CRC incidence (90, 80 and 76% compared to the three groups; $P<0.001$) was achieved.

Similar results were demonstrated with continuing follow up with NPS study patient cohort over a longer period of time (median follow-up period = 15.8 years) and a significant reduction in mortality from CRC compared to the general population. Brenner et al. [82] performed a population-based case-control study and showed that a colonoscopy performed within the preceding 10 years was associated with a 77% lower risk of developing CRC.

This evidence suggests that colonoscopy and polypectomy is leading to the reduction of incidence of CRC during follow-up and also confers a protective effect from mortality from CRC. Thus, the protective effect of the high-quality colonoscopy offered by the BCSP at during screening and surveillance is translating in to a low incidence of CRC and AAs during surveillance.

Ongoing surveillance demonstrated a significant reduction in the proportion of patients with AAs indicating the long-term effectiveness of polypectomy in the screened cohort. Advanced neoplasia detected at second surveillance was of a very small magnitude.

7. The results during the first surveillance in this thesis demonstrated a higher yield of AAs in the HR group at first surveillance compared to the IR group and thus establishing the fact that the current surveillance stratification strategy is effective. The majority of the IR group had a non-neoplastic yield at first surveillance, signifying that the surveillance interval for this group could be safely prolonged.

8. The risk stratification analysis has demonstrated in this thesis that the number of adenomas (≥3), proximal location and male sex demonstrated higher ORs for detection of AAs at first surveillance in both HR and IR groups. This supports the validity of the current guidelines for the BCSP cohort.

These findings are similar to the findings of others. Martínez et al. [65] studied the risk of developing AAs and CRC after polypectomy. Their study included 9167 participants with sporadic colorectal adenomas from eight different prospective North American studies. Participants were followed up for a long period, with a median follow-up of 47.2 months. Male gender, number and size of prior adenomas the presence of villous features, and proximal location were the factors which were found to be significantly associated with an increased risk for metachronous advanced neoplasia.

Similar findings of multiplicity and size of the adenoma being the significant factors were also identified in other studies [88, 48, 78, 135].

Proximal location of adenomas at screening was associated with the detection of AAs at surveillance, which has also been demonstrated by other studies [65, 101, 135]. This association in the BCSP population may represent a cohort of patients with adenomas of different tumour biology with the potential for developing metachronous lesions at surveillance.

Thus the evidence derived from population-based studies is valid when stratifying the BCSP population into different risk groups according to the number of adenomas detected at screening.

9. An increased surveillance interval (up to three years) in the HR group was not associated with any risk of increased detection of CRC at surveillance but was associated with increased detection of AAs; hence, the surveillance interval in this group can safely be prolonged.

The small number of HR group patients who had their surveillance after three years did not reveal any significant increased detection of CRC. This reflects the protective effect of the polypectomy and also suggests that the surveillance interval could be safely increased beyond 12 months. However, the increased detection of AAs in the group with surveillance interval more than three years suggests new onset metachronous lesions and hence, increasing surveillance interval in this group would need participant involvement in shared decision making prior to plan for future surveillance.

8.2 Opportunities and limitations

The BCSP database provided a unique opportunity to capture the data and information that were collected contemporaneously. Epidemiological risk factors (for example, smoking/alcohol consumption, family history of CRC) and metabolic factors (for example, body mass index, diabetes) associated with colorectal adenomas could have been incorporated in the current study to evaluate their importance in the screened population. If the data regarding acetylsalicylic acid and non-steroidal anti-inflammatory drug use in this population were available and incorporated, then their protective effect in the screened population could have been assessed.

Detection and removal of colorectal adenomas require high-quality colonoscopy, and good bowel preparation is an important part of that. Although the colonoscopies performed in the

BCSP are of a high quality and delivered in a quality control setting with continuing governance, there were variations in performance and the performance indicators and variability in bowel preparations could have been included in the model to assess their importance in risk stratification analysis.

The data collected for this thesis is a reflection of practice amongst the screening colonoscopists practising during the time period of this study. Alhough they all achieved certain performance indicators, there are likely to have been performance differences and a further study including their adenoma detection rates and withdrawal times for each colonoscopy procedure would help to make the analysis more robust and could quantify and equilibrate for such differences.

The missing data about the polyp histology led to loss of 40.3% polyps, which could not be included for analysis for descriptive part of the study (chapter 5). This is a weakness of this work, but was an unavoidable strategy for analysis and statistical imputation could not account for complex biological factors responsible for development and progression of polyps. A comparison between adenomas detected in screening and surveillance could have demonstrated the true prevalence and incidence of colorectal adenoma in the NHS BCSP population and any fundamental difference among screening and surveillance polyps.

Furthermore the quality of the data in any database research depends in the accuracy of the data. Missing data in the database for this research accounts for an unknown degree of variation in the results; ideally prospective further research is needed to re-inforce the findings of this work.

There could have been patients in NHS BCSP diagnosed with interval cancers during the study period who were not included in the surveillance database due to lack of participation

in adenoma surveillance. Incorporation of interval cancer data could have demonstrated strength or weakness of the quality of the screening colonoscopies in BCSP and could have also demonstrated valid risk factors in screening population indicative of interval cancer.

The overall numbers of participants in their second surveillance, particularly with respect to IR group are low in this study, restricting the ability to reach valid conclusions about the need of continuing surveillance. This could have been possible by extending the study period for at least three more years but this this was beyond the academic duration of this research and could not be done. The overall observation of the adenoma surveillance in this retrospective study demonstrated gradual diminished incidence of advanced adenomas and detection of very small numbers of colorectal cancers. This provides the reassurance to perform future randomised controlled trials with different surveillance intervals among HR and IR group to identify new evidenced based guidance for NHS BCSP which could be safe, and cost effective. This could also lead to a new era where surveillance intervals can be decided by shared decision making with more participation from the people screened. The current recommendations are didactic and not based on patient participation. These approaches would also require qualitative research looking into decision making processes involving the participants in NHS BCSP.

8.3 Personal reflection

This was a fascinating journey for me over a period of almost four years. It improved my understanding of database management and the rigorous methods of data processing and the transformation of a raw database to analysable data sets. The various courses and modules I took taught me to use a range of statistical software packages and their particular usefulness at various stages of data processing and analysis. My experience of working continuously with an expert statistician demonstrated the effectiveness and the need of

collaboration between clinicians and scientists to perform useful clinical research that can improve patient care. The continuous time struggle between my clinical and research workload and deadlines highlighted the need for protected academic time to perform a research activity.

Overall, this study was very satisfactory and demonstrated the safety of current practice in the BCSP, the validity of the current surveillance guidelines for the BCSP population and the safety of increasing surveillance intervals for both IR and HR groups, which will be more cost-effective.

8.4 Future research

The results from this study demonstrate that the surveillance interval could probably be safely prolonged in both HR and IR groups. This assures the safety of performing a prospective RCT for different surveillance intervals both for HR and IR groups. The magnitude of detection of advanced neoplasia was minimal at second surveillance and the number of patients reaching their third surveillance was minimal.

To address the problematic knowledge gap, and wide variability in adenoma surveillance in guidelines in different countries, a large group of investigators in Sweden, Norway, Poland, the Netherlands and Spain have decided to undertake a large-scale multicentre randomized trials for colorectal adenoma surveillance and the project is named as “European Polyp Surveillance Trials (EPoS)” (138). This study has three arms. This study has started to recruit patients in April 2015, constitute two parallel-group randomized controlled trials: EPoS I for patients with low-risk adenomas; EPoS II for patients with high-risk adenomas. EPoS III is an observational study for patients with serrated polyps. The primary end point in EPoS I, II, and III will beCRC incidence over 10 years. CRC incidence will be compared in the different arms in EPoS I and II, as well as across EPoS I and II, and compared with EPoS III. The secondary

end points will also be compared in the different arms in EPoS I and II, across EPoS I and II, and compared with EPoS III, and these will include cost effectiveness, yield of adenomas and serrated polyps with different subtypes during follow up period and major adverse events in surveillance colonoscopy. This study in future will provide further evidence to develop a new cost effective and safe surveillance guideline.

Continuing adenoma surveillance programmes and their success will need participation from the BCSP population. Research is needed focussing on shared decision making for surveillance planning. Though the programme is based on available evidence, new onset co-morbidities could be an important issue in this age group of (60 to 74 years) subjects and hence their perspectives need to be included, and hence share decision making tools need to developed through qualitative research in NHS BCSP, involving the participants.

A further study of the BCSP population is needed to capture a sufficient number of HR and IR patients completing their second and third surveillances. Since the programme was started in 2006, the second half of 2016 would provide sufficient data to perform that study; if the advanced neoplastic yield is minimal, then the BCSP population can safely be assessed with a screening tool after first surveillance rather than undergoing second surveillance, and that would be safe and cost-effective.

There are opportunities and a need to evaluate the epidemiological and metabolic factors and assess their association with advanced neoplasia during index screening procedures and during surveillance to weigh their importance in risk stratification, and including the cytogenetic factors in it could led to develop a new era in adenoma surveillance where individualistic evidence based surveillance guideline formulation is a possibility.

Another limitation of this study was that results derived the FOBT positive NHS BCSP population of a defined age group and hence the results would not be translated in real

terms to adenoma surveillance for non-BCSP, symptomatic populations. Further research looking into the adenoma surveillance into a symptomatic population would be needed to validate that.

Publications

Majumdar D, Lee TJ, Nickerson C, et al. Outcome of 3 year surveillance colonoscopy in patients with intermediate risk adenomas: analysis of the NHS Bowel Cancer Screening Programme National Database. *Gut*. 2011; 60(Suppl 1): A6.

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Majumdar D, Hungin AP, Wilson DW, et al. OC-044 Predictors of advanced neoplasia at surveillance in screening population – A study of all high and intermediate risk group subjects in first six year of NHS BCSP. *Gut*. 2014; 63(Suppl 1): A21–A22.

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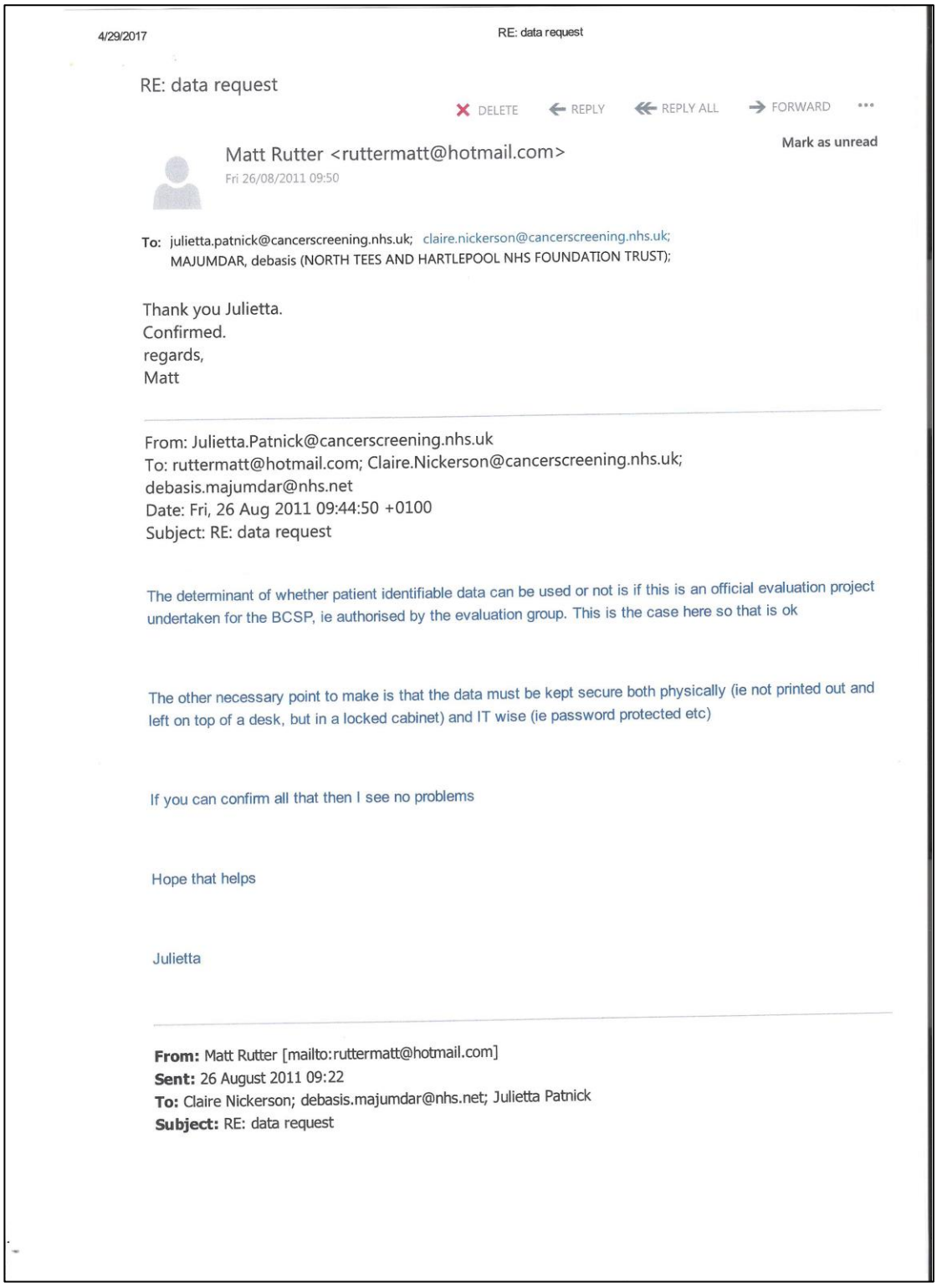
Appendix 1



4/29/2017 RE: data request

RE: data request

DELETE REPLY REPLY ALL FORWARD ...

Mark as unread

Matt Rutter <ruttermatt@hotmail.com>
Fri 26/08/2011 09:50

To: julietta.patnick@cancerscreening.nhs.uk; claire.nickerson@cancerscreening.nhs.uk; MAJUMDAR, debasis (NORTH TEES AND HARTLEPOOL NHS FOUNDATION TRUST);

Thank you Julietta.
Confirmed.
regards,
Matt

From: Julietta.Patnick@cancerscreening.nhs.uk
To: ruttermatt@hotmail.com; Claire.Nickerson@cancerscreening.nhs.uk; debasis.majumdar@nhs.net
Date: Fri, 26 Aug 2011 09:44:50 +0100
Subject: RE: data request

The determinant of whether patient identifiable data can be used or not is if this is an official evaluation project undertaken for the BCSP, ie authorised by the evaluation group. This is the case here so that is ok

The other necessary point to make is that the data must be kept secure both physically (ie not printed out and left on top of a desk, but in a locked cabinet) and IT wise (ie password protected etc)

If you can confirm all that then I see no problems

Hope that helps

Julietta

From: Matt Rutter [mailto:ruttermatt@hotmail.com]
Sent: 26 August 2011 09:22
To: Claire Nickerson; debasis.majumdar@nhs.net; Julietta Patnick
Subject: RE: data request

Dear Majumdar

I am happy to confirm that you are working on behalf of the national office of the bowel cancer screening programme on evaluation projects for the national programme. Your immediate supervisor is Dr Matt Rutter who chairs the national evaluation group

I look forward to working with you in the future

Julietta

From: majumdar debasis (NORTH TEES AND HARTLEPOOL NHS FOUNDATION TRUST) [mailto:debasis.majumdar@nhs.net]
Sent: 12 January 2011 13:48
To: Julietta Patnick
Cc: Claire Nickerson; ,
Subject: Permission to get data

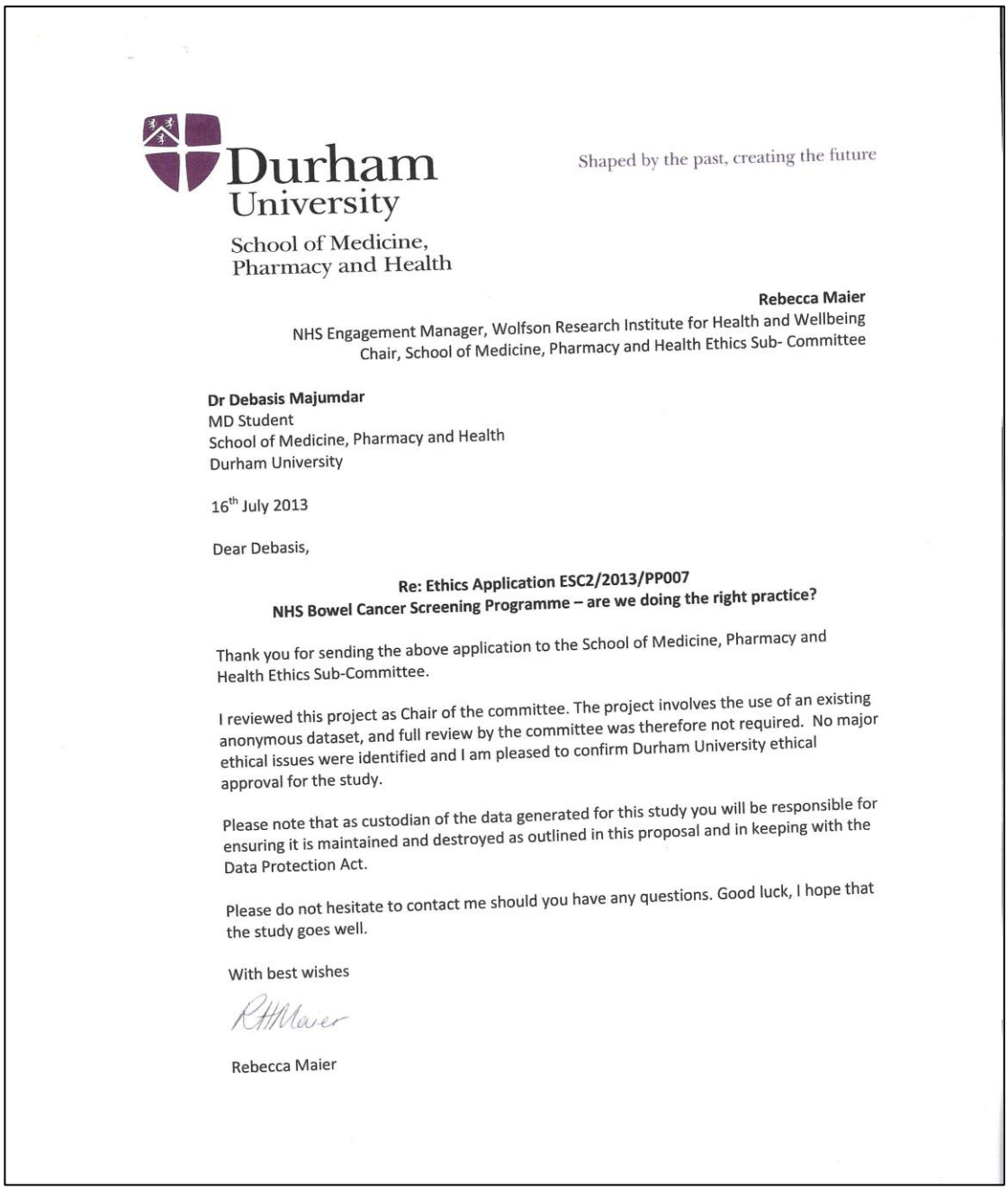
Dear Ms. Patnick,
I have started working in North Tees as Endoscopy Research Fellow after Tom Lee and planned to work on BCSP 3 yearly surveillance outcome under Dr. Rutters guidence.
I'd be grateful if you could give permission to analyse national data, as happened with Tom.
If you could kindly give the nod by return email that would be wonderful please.
Thanks and regards,

Dr. Debasis Majumdar
Endoscopy Research Fellow
University Hospital of North Tees.

****
****

This message may contain confidential information. If you are not th

Appendix 2



Durham University

School of Medicine, Pharmacy and Health

Shaped by the past, creating the future

Rebecca Maier
NHS Engagement Manager, Wolfson Research Institute for Health and Wellbeing
Chair, School of Medicine, Pharmacy and Health Ethics Sub- Committee

Dr Debasis Majumdar
MD Student
School of Medicine, Pharmacy and Health
Durham University

16th July 2013

Dear Debasis,

Re: Ethics Application ESC2/2013/PP007
NHS Bowel Cancer Screening Programme – are we doing the right practice?

Thank you for sending the above application to the School of Medicine, Pharmacy and Health Ethics Sub-Committee.

I reviewed this project as Chair of the committee. The project involves the use of an existing anonymous dataset, and full review by the committee was therefore not required. No major ethical issues were identified and I am pleased to confirm Durham University ethical approval for the study.

Please note that as custodian of the data generated for this study you will be responsible for ensuring it is maintained and destroyed as outlined in this proposal and in keeping with the Data Protection Act.

Please do not hesitate to contact me should you have any questions. Good luck, I hope that the study goes well.

With best wishes

RHMaier

Rebecca Maier