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Colorectal Cancer Screening

M.D. Thesis

2007

Monica Ramona Mc Loughlin

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SUMMARY

Colorectal cancer is a major public health burden and is the most common cause of mortality from cancer in Europe. Over the last two decades robust evidence from randomised clinical trials and case-control series have confirmed that the mortality from colorectal cancer can be reduced by screening. The challenge over the next decade is how to implement this in clinical practice. This is what we set out to answer with this thesis.

Not all individuals are equal when it comes to screening and those with a family history of colorectal cancer are at a higher risk of developing colorectal cancer. These individuals with a moderate to high family history risk merit a more intensive screening approach with colonoscopy. We examined the feasibility of setting up a family screening clinic where after consultation with the individual a colonoscopy is offered on a dedicated screening list. Colonoscopy was performed in 405 individuals and revealed adenomatous polyps in 18.3% with 2% having high grade dysplasia and 2.2% having multiple polyps. Colorectal cancer was present in 1.5%.

For those at average risk of developing colorectal cancer most evidence points towards screening with faecal occult blood testing. As in any screening programme a compliance rate of over 60% is necessary for effectiveness. Little is known about the acceptance of colorectal cancer screening in Ireland. We organised a screening programme with faecal occult blood testing among 600 individuals and found a poor compliance of 28% among

those who agreed to participate. Obviously such a poor compliance would render any national screening programme ineffective. A public awareness campaign is necessary in Ireland to improve understanding of colorectal cancer and the success of screening.

With this in mind we carried out a questionnaire on the knowledge of colorectal cancer screening among Irish individuals. From our results, with the aid of a focus group, we developed an information leaflet on colorectal cancer screening. We found that this information leaflet helped to improve the awareness surrounding colorectal cancer. General Practitioners play a pivotal role in any screening programme and we were pleased therefore with their response to a questionnaire on colorectal cancer screening. The overwhelming majority of General Practitioners favours colorectal cancer screening and would participate in any national screening programme.

Finally we looked at a new screening tool for colorectal cancer, faecal tumour marker M2-PK. Although four randomised controlled trials involving over 300,000 individuals have found that faecal occult blood testing reduces colorectal cancer mortality by half among those who participate, faecal occult blood testing is often criticized for its low sensitivity. The holy grail of colorectal cancer screening is a non-invasive screening tool with a high sensitivity and specificity. In our study faecal tumour marker M2-PK may be such a tool with a sensitivity and specificity of over 90% for colorectal cancer.

Acknowledgements

I would like to state that this thesis is predominantly my own work: The study design, the collection and analysis of data, and the writing of this manuscript. However I had help from others.

Prof. Colm O'Morain generated the topic for this thesis and participated in the study design. He also reviewed the manuscript.

Ellen Shiel assisted in the laboratory providing advice on ELISA methodology.

Maria Campbell as Health Promotions Officer was an integral part of the Bowel Cancer Awareness Week. She helped form the focus group that developed our leaflets and posters and was present each day at our information stand.

Gerard O'Connor lent his expertise to the design of the faecal occult blood testing, in particular to the logistics of returning the kits in the post.

Dedication

I would like to thank Prof. Colm O'Morain for his help and guidance throughout this thesis, and indeed his support both personally and professionally. When I first met Prof. O'Morain he spoke of cancer screening and his enthusiasm and commitment to screening has remained undiminished. I considered myself fortunate back then to have the opportunity to work for him and with the passage of time I realise how fortunate I really was. When colorectal cancer screening is implemented in Ireland it will be due in no small part to his ceaseless work at an international and national level.

During my time in the Adelaide & Meath Hospital I worked with people who inspired me, certainly influenced me, helped me, sometimes just listened to me, shared a coca-cola, and whom I now consider friends. I smile as I find myself passing on their words of wisdom to others and laugh as I recount one of our many stories.

Finally I would like to thank my family, who have heard more about this thesis than I am sure they ever wanted to. Tricky yokes thesis to sum it up in true Leitrim style. To my parents Monica and Padraig Mc Loughlin thank you for all the love, support, and worry you harbour for each of us. Thank you to Norma and Tom, Lassarina, Sabina, and Padraig, who always know what I am about to say. And to my biased eye thank you and a big hug to the best nephew in the world Jack Byrne.

Abbreviations

Adelaide, Meath, and National Children's Hospital	AMNCH
Adenomatous polyposis coli	APC
American Gastroenterological Association	AGA
British Society of Gastroenterology	BSG
Colorectal Cancer	CRC
Construction Workers' Health Trust	CWHT
Deoxyribonucleic acid	DNA
Faecal occult blood test	FOBT
Familial adenomatous polyposis	FAP
Hereditary nonpolyposis colorectal cancer	HNPCC
Microsatellite instability	MSI
Mismatch repair	MMR
Odds Ratio	OR
Oesophagogastroduodenoscopy	OGD
Positron Emission Tomography	PET
Quality Adjusted Life Years	QALYS
Relative risk	RR
Standardized incidence ratios	SIR
Veterans Affairs	VA

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Chapter One

Introduction

Colorectal cancer

Colorectal cancer is the leading cause of mortality from cancer in Europe. In population-based studies the overall five-year survival from colorectal cancer is only sixty percent, which reflects the fact that a large number of patients present at a late stage.[1] Survival of cancer depends on the degree to which the cancer has spread. If colorectal cancer can be detected at an early stage, the prognosis is excellent and early colonic cancer has a five year survival in excess of 97%.[2]

Early colorectal cancer is defined as adenocarcinoma confined to the mucosa or submucosa. Under the Dukes staging this would correspond to Dukes A, invading through the muscularis mucosa but not through the muscularis propria. Under the TNM staging this would correspond with a T1 lesion, invading through the muscularis mucosa into the submucosa and a T2 lesion going beyond the submucosa into the muscularis propria, but not through the muscularis propria. Unfortunately only a relatively small proportion of colorectal cancers are found at an early stage. The risk of metastases increases as colorectal cancer invades into the submucosa. The risk of lymph node metastases for cancers invading superficially into the submucosa has been reported at between 2-3% compared with 8-12% for those carcinomas invading to the inner surface of the muscularis propria.[3 4]

Currently 80% of colorectal cancers are diagnosed when the cancer has spread beyond the bowel wall and as a result the average five year survival remains disappointingly low at 40%.[5 6] The only way to improve colorectal cancer survival figures is through screening and early detection, and studies have shown that early colonic cancers account for 20% of all lesions detected by screening among asymptomatic individuals.[7,8] Over the last two decades robust evidence from randomised clinical trials and case-control series have confirmed that the mortality from colorectal cancer can be reduced by screening. Indeed among those who participate in colorectal cancer screening the mortality from colorectal cancer has been halved.[9] The challenge over the next decade is how to implement this in clinical practice.

The European Council has stated that colorectal screening should be provided for all individuals aged 50-74 years in a quality assured programme.[10] The development of colorectal cancer from normal colonic mucosa through to adenomatous polyps, high grade dysplasia, and finally colorectal cancer is a slow process, taking over ten to fifteen years. As such colorectal cancer represents an ideal cancer for screening and early detection.

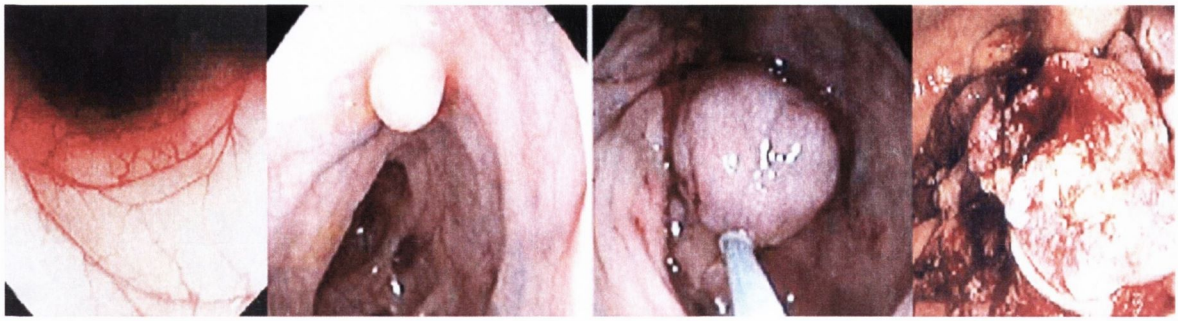
In addition to the reduction in mortality associated with earlier detection of colorectal cancer, screening asymptomatic individuals may lead to a reduction in the incidence of colorectal cancer through the removal of adenomatous polyps. There is no doubt that the removal of adenomatous polyps leads to a reduction in the incidence of colorectal cancer by a magnitude of between 76-90%.[11] However there is as yet scant evidence that

screening and subsequent removal of polyps will lead to a reduction in colorectal cancer incidence.

Adenomatous polyps and colorectal cancer

Molecular, genetic and clinical research indicate that colorectal cancer usually proceeds through a discontinuous process from normal mucosa, to increased cellular proliferation, to early benign adenoma, to adenoma with advanced histological features, and finally to invasive cancer and metastases.[12] Epidemiologic data show that there is a parallel prevalence of adenomas and cancers in both high and low incidence countries, with the average age of adenoma patients being about 7-8 years younger than that of colorectal cancer patients.

Small simple tubular adenomas are found in over 30% of older adults and have a very low malignant potential. Studies indicate that most remain static or may actually regress with time, whereas only a few grow and develop advanced histological features.[13] Small simple tubular adenomas contain only the earliest occurring genetic alterations found in more advanced adenomas, and only a few appear to develop the additional acquired genetic changes needed to stimulate accelerated cellular division, growth and dedifferentiation. Advanced adenomas are defined as those that are greater than 1cm, contain appreciable villous tissue, or high grade dysplasia.[14]. These advanced adenomas are much less common, but much more likely to progress to cancer. (See figure one)



Normal →→→→→→ Adenoma →→→→→→→→ Dysplasia →→→→→ CRC

APC →→→→ K-Ras →→→→ Loss of DCC →→→ P53

DNA methylation →→→→→→→→→→→→→→→→→

Figure one: Progression from normal colonic mucosa through adenomatous polyps, to high grade dysplasia, and colorectal cancer.

Direct colonoscopy screening studies report that the prevalence of advanced adenomas in asymptomatic adults over the age of 50 is 5% in women and 9% in men.[15] These advanced adenomas have a much higher malignant potential. In a retrospective review of patients with unresected polyps > 1cm, who had been followed by serial barium enema examinations over a six year period 83 (37%) of the polyps enlarged and 21 invasive cancers developed at a previous polyp site. The cumulative risk of malignancy at the site of an index polyp >1cm was 2.5% at 5 years, 8% at 10 years, and 24% at 20 years.[16]

A recent report suggested that the rate of carcinoma occurring in polyps is much less than previously thought and furthermore that the chance of malignancy in a polyp < 1cm was very low. In this retrospective review of 3,225 resected polyps the rate of adenocarcinoma detected was 0.07% for polyps <1 cm, 2.41% for polyps 1-2 cm, and 19.35% for polyps >2 cm.[17] Contradictory evidence was presented from a study of 1933 resected polyps < 1cm: Advanced histology including carcinoma was found in 10.1% of adenomas 5-10mm in size and in 1.7% of adenomas < 5mm. Carcinoma was found in 0.9% of adenomas 5-10mm in size.[18] In light of this polypectomy and histological evaluation of all polyps > 5mm would seen prudent.

Evidence that polypectomy reduces the incidence of colorectal cancer came initially from the National Polyp Study in the United States. This study addressed the issue that adenomatous polyps are the precursor of colorectal cancer and removing them would prevent colorectal cancer. Follow-up of 1,418 individuals who underwent a polypectomy showed a reduction in the incidence of colorectal cancer of 76 - 90%, when compared

with three reference groups.[11] Of the 3371 adenomatous polyps removed during the National Polyp Study, 7.7% showed moderate dysplasia and 6.2% showed high grade dysplasia, 2.5% severe dysplasia and 3.7% in situ carcinoma. The percentage of adenomas with high-grade dysplasia increased significantly with increased size with an odds ratio, OR, of 4.8 for adenomas 0.6-1 cm, and 20.3 for an adenoma > 1 cm. The percentage of adenomas with high-grade dysplasia also increased with increasing villous component with an OR of 5.9 for a 1-25% villous component and an OR of 20.2 for a 76-100% villous component. Patients with multiple adenomas were more likely to have an adenoma with high-grade dysplasia at 13.8% than patients with a single adenoma at 7.3%, giving an OR of 2.0 for multiplicity. The percentage of patients with high-grade dysplasia in an adenoma increased with patient age with an OR of 1.0 for those aged 40-49 years, 1.3 for those 50-59 years, 2.2 for those 60-69 years, 2.5 for those aged 70-70 years, and 3.6 for those aged more than 80 years compared to those aged less than 40 years. Interestingly there was no difference between men and women as regards the occurrence of high-grade dysplasia.[19] High-risk adenomas are thus those > 1cm, with villous component, and multiple adenomas.

Flat adenomatous polyps

In recent years Japanese studies propose the possibility of nonpolypoid or flat adenomas giving rise to subsequent colorectal cancer. These studies suggest that this may represent an alternative pathway to colorectal carcinogenesis that is different from the traditional polyp-cancer sequence. Specifically, it has been suggested that small flat adenomas have

a higher prevalence of high grade dysplasia and are more likely to rapidly advance to invasive cancer than adenomatous polyps.[20]

A prospective study of 211 patients assessed the prevalence of flat and depressed colorectal adenomas in the US. Flat and depressed adenomas were found in 22.7% and invasive cancer was present in 4.5% of these lesions in contrast with the adenomatous polyps detected which contained no cancer. The average size of all flat and depressed adenomas containing high-grade dysplasia or cancer, was significantly smaller than the adenomatous polyps containing high-grade dysplasia, 10.75mm vs. 20mm.[21]

The prevalence of flat and depressed colorectal cancer lesions in the UK was determined when a single endoscopist performed a high magnification colonoscopy with chromoscopy of 850 patients. A total of 285 flat adenomatous polyps were found, with high grade dysplasia in 44.6%. Of the adenomatous polyps high grade dysplasia was present in only 17%. Of the 14 protruberant carcinomas 93% were in the left colon and of the 10 flat carcinomas 90% were in the right colon. Of the protruberant adenomas with high grade dysplasia 95% were in the left colon in contrast 82% of the flat lesions with high grade dysplasia were found in the right colon. [22]

From these studies in Western populations there is a significant prevalence of flat and depressed adenomas and they appear to have a different biological behaviour than polypoid adenomas, with a high malignant potential and a propensity for developing in

the right colon. This may have a bearing on a putative reduction in colorectal cancer incidence with colorectal cancer screening secondary to polypectomy.[23]

To date in the majority of screening trials published, follow-up is not sufficiently long to clarify the effect of detecting and removing adenomas on colorectal cancer incidence. Those groups with an extended follow-up have produced conflicting data. Mandel et al followed up their Minnesota Colon Cancer Control Study for 18 years, and found 417 colorectal cancer cases developed in the annual screening group, 435 in the biennial screening group, and 507 in the control group. The cumulative incidence per 1000 of colorectal cancer was 32 in the annual screening group, 33 in the biennial screening group, and 39 in the control group. Over 18 years both annual and biennial screening with a rehydrated faecal occult blood test (FOBT) significantly reduced the incidence of colorectal cancer by 20% and 17% respectively.[24]

Kronberg et al continued their biennial screening to nine rounds and hence the Funen study has accumulated data for 17 years. The incidence of colorectal cancer was similar during the seventeen years between those screened and the controls and two theories were proposed by the authors for this. Firstly non-responders were not re-invited again, so that by the ninth round only 8558 subjects, or 43% of those initially screened, were included, and this may have had an impact on their mortality figures and colorectal cancer incidence. Indeed the mortality ratio for colorectal cancer increased from 0.79 after five rounds of screening with 14,203 screened to 0.84 after nine rounds of screening with just 8558 screened. Secondly as the putative reduction in colorectal incidence is due

to polypectomy the low sensitivity of the FOBT for adenomatous polyps is undoubtedly important. Improving the sensitivity by rehydration as was done by Mandel et al leads to an increased number of colonoscopies. In the Funen study 5.3% of those screened had a colonoscopy. However in the Minnesota study 28% of those with a biennial rehydrated FOBT and over 40% of those with an annual rehydrated FOBT had a colonoscopy. [25] Long-term follow-up is needed from other screening trials before we may claim that screening reduces the incidence of colorectal cancer in addition to reducing the mortality from colorectal cancer.

Risk stratification and colorectal cancer

Colorectal cancer screening in average risk individuals is advised from 50 years of age onwards. However certain individuals, with a higher risk of developing colorectal cancer, merit screening at a younger age. These high-risk individuals may be identified from their family history. One in nine individuals diagnosed with colorectal cancer have a family history of colorectal cancer. In Vastmanland county in Sweden 411 patients were diagnosed with colorectal cancer during a three year period. The family history of 400 of these individuals (97%) was obtained: Five patients (1.2%) were diagnosed as having hereditary nonpolyposis colorectal cancer, or HNPCC, eight (1.9%) had at least three relatives with colorectal cancer in a first- or second- degree relationship, and a dominant pattern of inheritance but no age specifications, and thirty four (8.3%) had at least one first-degree relative with colorectal cancer. No patient with familial adenomatous polyposis, FAP, was identified in this study. [26]

Familial adenomatous polyposis

FAP accounts for < 1% of cases of colorectal cancer and is autosomal dominant.[27] It arises from germline mutations of the adenomatous polyposis coli (APC) gene located on chromosome 5q21, however in 22-46% of cases it arises as a spontaneous mutation.[28] The APC gene is a tumour suppressor gene encoding a protein with a role in cell adhesion, signal transduction, and transcriptional activation. More than 300 different disease-causing mutations have been identified and can be found in 80-90% of FAP families. Age of presentation, density of colonic polyposis and highest cancer risk correlates with the mutation location with the most dense polyposis arising from mutations of the mid-portion of the gene.[29]

FAP is estimated to affect one in 10,000 individuals, male and female equally, and is nearly 100% penetrant. The defining feature of FAP is the appearance in childhood and adolescence of hundreds to thousands of adenomas throughout the colon, which will inevitably progress to colorectal carcinoma. In the stomach 50% will develop fundic glands polyps, usually in the fundus, sometimes in the body. They may increase in number but have little tendency for malignant transformation. Gastric adenomas occur in 6% and can present diffusely throughout the stomach, they may rarely be premalignant lesions. Adenomas of the small intestine are found in 33-92% of patients, and are usually multiple, sessile, and along the mucosal folds of the descending duodenum. The risk of dysplasia increases with the number, size and villous architecture. Although dysplasia in the peripapillary region is as high as 74% peripapillary carcinoma occurs in just 4%. The time interval for the development of peripapillary carcinoma ranged from 0.5 to 9 years.[30]

Duodenal polyposis can be classified into five stages according to criteria proposed by Spigelman with a 2.3% risk of cancer with 1-4 small tubular polyps and a 36.4% risk of cancer with > 20, large, or villous polyps.[31]

In attenuated FAP there are more than 20 cumulative colorectal adenomatous polyps with a more proximal distribution. There is an 80% lifetime risk of colorectal cancer and a later onset of disease with polyps presenting in mid to late 20s and colorectal cancer in the 50s. Roughly 10% of patients with attenuated FAP have germ-line mutations in APC.[32 33]

Recently germline mutations of the MYH gene have been identified in some patients with no identifiable APC gene mutation but with multiple colorectal adenomas. The MYH gene is a base excision gene that mediates oxidative damage to deoxyribonucleic acid, DNA; it appears to be autosomal recessive with bi-allelic mutations necessary for the mutation. Limited information is yet available on the spectrum of mutations in MYH. Age of occurrence of polyps is older than FAP, and polyps typically number < 100. Heterozygous mutations may marginally influence the risk of colorectal carcinoma.[34 35]

Genetic testing for APC is indicated in those with ≥100 colorectal adenomas, or those with ≥20 cumulative colorectal adenomas. If the disease-causing mutation is identified endoscopic screening can be directed at those who test positive for the mutation. If the mutation is not found, all first-degree family members should undergo endoscopic screening.

The American Gastroenterological Association, AGA, advises annual sigmoidoscopy beginning at age 10-12 years, and in the case of attenuated FAP colonoscopy beginning in the late teens or early 20s, depending on the age of polyp expression in the family.[36] The British Society of Gastroenterology, BSG, advises annual sigmoidoscopy from age 13-15 years until age 30 years, and at three to five year intervals thereafter until age 60 years. Oesophagogastroduodenoscopy, OGD, is advised at 3 yearly intervals from age 30, and more frequently if there is extensive polyposis.[37] Based on Spigelman's classification of duodenal polyps one proposed OGD schedule is 5 yearly intervals for 1-4 small tubular polyps, 3 yearly intervals for 5-20 tubulovillous polyps, and 1-2 yearly intervals with > 20 villous or large polyps.[30]

Hereditary nonpolyposis colorectal cancer

HNPCC accounts for nearly 2% of colon cancers, and results from inactivation of the DNA mismatch repair process by germline gene defects in the genes that encode key components of the mismatch repair complexes.[38] HNPCC is autosomal dominant with 80% penetrance and a lifetime risk for colon cancer of 80% by 70 years. Women with HNPCC are at a 10-fold increased risk of endometrial cancer at 40-60 years with a cumulative risk of 40-50% at age 70 years. Ovarian cancer occurs in 9%, gastric cancer in 5-20%, uroepithelial cancer in 1%.[39] A population carrier frequency of 1:3139 is estimated.[40]

The mismatch repair proteins, MMR, function as "DNA caretakers" to maintain the fidelity of genomic DNA during replication. The loss of MMR activity only occurs in cells that inactivate both alleles of the MMR gene. The genes involved are MLH1, MSH2, MSH6, MLH3, PMS1, PMS2, TGFBR2, and EXO1, with MLH1 and MSH2 accounting for greater than 95% of cases.[41] The effect of MMR loss is microsatellite instability, MSI. Microsatellites are short, repetitive sequences located throughout the genome, but primarily in introns, and insertions or deletions leads to genomic instability and a rapid accumulation of somatic mutations in oncogenes and tumour suppressor genes.

Many colon cancers demonstrate mutations in a small percentage of microsatellite repeats but if a tumour shows 30-40% or more markers that are unstable it is scored as MSI-high, if less than 30-40% of markers are unstable the tumour is designated as MSI-low. A panel of five mononucleotide and dinucleotide microsatellite loci are used to detect MSI, namely BAT25, BAT26, D2S123, D5S346, and D17S250.[42] Immunohistochemistry can also detect mismatch repair gene defects with loss of expression of the MLH1 or MSH2 genes in 100% of those with MSI-high, and normal expression of MLH1 or MSH2 in 93% of those with MSI-stable.[43] The decision to conduct either MSI testing or immunohistochemistry resides in local expertise.

Adenomas from patients with HNPCC are few in number, are predominantly on the right side of the colon, and progress towards carcinoma more rapidly than in the general population. In a study of 249 carriers of HNPCC and 247 controls, adenomas were

identified in 70.3% of the carriers and 29.2% of the controls. The adenomas in the carriers occurred at an earlier age, were larger, had a higher proportion of villous components, and/or high grade dysplasia. Immunohistochemistry for hMLH1 and anti-PMS2 on those known carriers of an hMLH1 germline mutation, and hMSH2 on those known carriers of hMSH2 germline mutations was carried out on 31 adenomas from 22 of the carriers. The MMR proteins were found to be absent in 23 of the adenomas. The 8 adenomas with MMR protein staining showed low-grade dysplasia. The MMR gene defect is thus involved in the early development and malignant transformation of adenomatous polyps in HNPCC.[44]

Paradoxically, although patients with HNPCC are affected by colon cancer at young ages and have tumours with histopathological features that suggest aggressive tumour behaviour, the clinical outcomes for HNPCC patients with colon cancer are typically better than outcomes for patients with sporadic colon cancer. HNPCC patients with colorectal cancer have an improved 5-year survival (76% vs. 54%) on a stage-for-stage basis compared with patients with sporadic cancers.[45] MSI tumours have an increased number of lymphoid aggregates in the peritumoural tissue, and it is thought these may slow tumour progression via IL-4 and TNF-α production.

In an attempt to standardize diagnostic criteria for HPNCC the Amsterdam criteria was developed in 1991.[46] As knowledge of the clinical and histological features of HNPCC developed the Bethesda guidelines were formed in 1996.[47] In 2002 the revised Bethesda guidelines outlined recommendations for identifying individuals with HNPCC and

criteria for MSI testing.[48] Under the revised Bethesda guidelines tumours should be tested for MSI if colorectal cancer is diagnosed in a patient who is less than 50 years of age; regardless of age in the presence of synchronous/metachronous colorectal cancer or a HNPCC-associated tumour including endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain; colorectal cancer in a patient under 60 years of age with the MSI-high histology of a tumour with infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern; when colorectal cancer is diagnosed in one or more first-degree relatives with a HNPCC-associated tumour, with one of the cancers being diagnosed under 50 years of age; when colorectal cancer is diagnosed in two or more first- or second-degree relatives with a HNPCC-associated tumour, regardless of age.

If immunohistochemical staining or microsatellite testing confirms MSI, germ-line testing of MSH2/MLH1 is recommended. If the mutation is identified, at-risk relatives should be referred for genetic counseling and endoscopic screening if the mutation is present. If no germ-line mutation is found relatives should be referred for endoscopic screening. Germline MMR mutations are found in 45-60% of families meeting HNPCC criteria, and finding MSI in patients with colorectal cancer increases the likelihood of finding germline MMR mutations to over 60%. The Bethesda guidelines have a good sensitivity of 96%, but only a moderate specificity of 27% for identifying MSI-high patients.[49 50]

The AGA recommend that individuals with HNPCC should have a colonoscopy every 1-2 years beginning at aged 20-25 years, or 10 years earlier than the youngest age of colon cancer diagnosis in the family, whichever is the earlier.[36] The BSG recommend biennial colonoscopy starting at aged 25 years, or 5 years younger than the first cancer case in the family, whichever is the earlier, and continuing to 75 years of age. In families with cases of gastric cancer biennial OGDs should begin at aged 50 years of age, or five years less than the first gastric cancer case in the family, whichever is the earlier.[37] In women annual surveillance for endometrial cancer should begin between 25 and 35 years with annual pelvic examination and transvaginal ultrasound scan.[51]

Familial colorectal cancer

While relatives of patients with rare genetic syndromes such as FAP and HNPCC certainly benefit from an intensive screening programme, the majority of "familial" colorectal cancer is seen in first-degree relatives of patients with colorectal cancer. From population studies it is estimated that 9.4% have a first-degree relative with colorectal cancer.[52] Whether or not these individuals should be screened, when screening should occur, and how frequently screening should be is far less clear cut.

Autopsy and retrospective studies have demonstrated a two- to three- fold increased risk of colorectal cancer and adenomatous polyp development in this population.[53 54] Case control studies based upon hospital records or registry data have also demonstrated an increased prevalence of adenomatous polyps and cancers among first-degree relatives of patients with colorectal cancer.[55 56] These studies were limited in that they included

only symptomatic patients. Several endoscopic studies have documented a high prevalence of adenomatous polyps in asymptomatic first degree relatives of colorectal cancer patients. Most of these studies were retrospective and without a control population.[57,58 59] Four of these studies were prospective but again lacked a control population.[60,61,62,63] Two studies used flexible sigmoidoscopy.[64,65] (See table one)

Guillem et al were the first to evaluate colonoscopic findings in asymptomatic individuals with and without a family history of colorectal cancer: They compared the detection rate of neoplasms in 181 asymptomatic first-degree relatives of colorectal cancer patients with that in 83 asymptomatic individuals in a prospective trial. The overall detection rate of adenomatous polyps in the family-risk group was 14.4% and in the control group 8.4%. The first-degree relatives developed colonic adenomas at an earlier age than the controls, and this difference was most striking in men. Logistic regression analyses revealed that age, male sex, and first-degree relative status were independent risk factors for the presence of colonic adenomatous polyps with a relative risk, RR, of 2.32, 2.86, and 3.49 respectively. In first-degree relatives a greater proportion of the polyps were proximal to the splenic flexure than in controls, 48% vs. 25%, and the proportion of polyps with marked cytological atypia appeared to be greater in first-degree relatives than in controls, 18% vs. 13%. Those with two or more first-degree relatives afflicted with cancer had a higher risk of developing a colonic adenoma than those with just one first degree relative, 23.8% vs. 13.1%. The exact relationship of the index case also had an affect, for those whose first degree relative with cancer was a sibling the risk of finding an adenoma was higher than those whose first degree relative with cancer was a parent, 24% vs. 9%.[66]

STUDY	ADENOMAS FOUND IN THOSE WITH A FIRST-DEGREE RELATIVE WITH CRC	ADENOMAS FOUND IN THOSE WITHOUT A FAMILY HISTORY OF CRC
Gryska et al, 1987[60]	63% of 49 individuals	
Grossman et al, 1988[61]	18% of 154 individuals	
McConnell et al, 1990[62]	12% of 125 individuals	
Baker et al, 1990[59]	27% of 201 individuals	
Luchtefeld et al, 1991[67]	10.6% of 143 individuals	5.8% of 137 individuals
Guillem et al, 1992[66]	14.4% of 181 individuals	8.4% of 83 individuals
Meagher et al, 1992[68]	46% of 429 individuals	
Stephenson et al, 1993[69]	13% of 92 individuals	10% of 30 individuals
Wu CS et al, 1995[70]	9.9% of 213 individuals	
Bazzoli et al, 1995[71]	69% of 39 individuals	36% of 358 individuals
Pariente et al, 1998[72]	23.2% of 185 individuals	17.3% of 370 individuals
Hunt et al, 1998[73]	8% of 137 individuals	
Dowling et al, 2000[74]	14% of 236 individuals	
Syrigos et al, 2002[75]	11% of 249 individuals	

Table one: Adenomatous yield in prospective colonoscopy studies of individuals with a first degree relative with colorectal cancer.
CRC: colorectal cancer

Prospective studies of colonoscopic screening in individuals with two or more affected first degree relatives have generally been small. (See table two.) Adenomas found at colonoscopy have ranged from 24% of 21 individuals, to 36% of 18 and 39 individuals.[66] [63] [64] Stephenson et al found adenomas in 10% of 20 people with either two or more relatives affected or a relative younger than 45 years affected.[69] A large report found neoplasia in 19.5% of 202 individuals with three or more affected relatives and in 11% of 132 individuals with two first degree relatives or a relative aged under 45 years.[76] Hunt et al found adenomas in 11% of 83 people with either two or more relatives with colorectal cancer, a first degree relative with colorectal cancer under the age of 50 years, or both a first and second degree relative with colorectal cancer, one of whom was less than 50 years of age.[73]

Aitken et al in a case-control study of 1023 individuals undergoing colonoscopy compared family history of colorectal cancer between the 141 patients with adenomas and the 882 individuals with normal colonoscopies. Patients with just one first-degree relative in this study were found to be at no greater risk for adenomas than those without a family history.[77] From these studies it can be concluded that individuals with only one first-degree relative with colorectal cancer have a lower risk of colon neoplasia than those with more than one first-degree relative affected with colorectal cancer. Whether or not to screen these individuals remains debatable

STUDY	ADENOMAS FOUND IN INDIVIDUALS WITH AN AFFECTED RELATIVE WITH CRC	INCLUSION CRITERIA OF STUDY
Orrom et al, 1990[63]	36% of 18 individuals	> 2 first-degree relatives with CRC
Houlston et al, 1990[76]	19.5% of 202 individuals 11% of 132 individuals	> 3 first-degree relatives with CRC > 2 first-degree relatives with CRC and one < 45 years
Guillem et al, 1992[66]	24% of 21 individuals	> 2 first-degree relatives with CRC
Meagher et al, 1992[68]	45% of 194 individuals 67% of 55 individuals	> 1 relative with CRC > 1 first-degree relative with CRC
Hunt et al, 1998[73]	13% of 110 individuals 11% of 83 individuals	> 3 first-degree relatives with CRC > 2 first-degree relatives with CRC and one < 50 years of age

Table two: Adenomatous yield in prospective colonoscopy studies of individuals with more than one first degree relative with colorectal cancer.
CRC: colorectal cancer

Bazzoli et al set out to determine if asymptomatic patients with only one first-degree relative with colon cancer should have a colonoscopy. Over a two year period in Bologna colonoscopies were performed on 397 asymptomatic patients, 39 of whom had a first-degree relative with colorectal cancer. Adenomatous polyps were found in 155, 69%, of patients with one first-degree relative with colorectal cancer and in only 36%, of those without a family history. Multiple logistic regression analysis of risk factors associated with adenomatous polyps revealed an adjusted odds ratio of 1.4 for male sex, 1.6 for age over 50 years old, and 1.9 for one first-degree relative having colorectal cancer. This study confirmed previous reports that patients with a family history of colorectal cancer have an increased risk of developing adenomatous polyps, but more specifically it shows that even individuals with only one first-degree relative with colorectal cancer should be screened.[71]

Pariente et al in a larger study substantiated these findings. They performed a colonoscopy in 185 first-degree relatives of patients with colorectal cancer and compared the findings of 370 individuals without a family history of colorectal cancer. Adenomas were found in 23.2% of the family history group and 17.3% of the controls, OR of 1.5 for all adenomas, 2.5 for large adenomas. The characteristics of the index cancer patient influenced the prevalence of high-risk adenomas in the first-degree relatives with an OR of 5.2 when the index case was less than 65 years, an OR of 2.2 when the index case was 65-75 years, and an OR of 1.9 when the index case was greater than 75 years[72]

The influence of the index cases age is in accordance with findings from St John et al. In a case-control study medical histories were sought from 7493 first-degree relatives of patients with colorectal cancer and 1046 individuals without a family history of colorectal cancer. The reported diagnosis of colorectal cancer were confirmed in 79% of instances. The OR of developing colorectal cancer was 1.8 for those with one affected relative compared to those with no family history of colorectal cancer. This increased to an OR of 3.7 when the affected relative was less than 45 years of age.[78]

Similarly the risk of developing colorectal cancer for individuals with a family history of colorectal cancer was obtained prospectively from two ongoing studies, the Nurses' Health Study and the Health Professionals Follow-up Study. A history of colorectal cancer in a first-degree relative was reported by 3007, 9.4%, of the 32,085 men and by 8727, 10.0%, of the 87,031 women. During the study period, colorectal cancer was diagnosed in 148 of the men and 315 of the women. Of these 463 participants with colorectal cancer, 17% had previously reported a family history of colorectal cancer. For men with a family history, the age-adjusted RR of colorectal cancer was 1.64, and for women with a family history, the age-adjusted RR was 1.77. Furthermore, the RR associated with a family history of colorectal cancer was not altered by multivariate adjustment for known or suspected environmental risk factors for the disease. The RR among study participants with two or more affected first-degree relatives was 2.75 and for participants under the age of 45 years who had one or more affected first-degree relatives, the RR was 5.37.[79]

A recent population based study assessed the risk of colorectal cancer associated with a family history. Familial risk was estimated from a cohort analysis of the relatives of 767 patients who developed colorectal cancer between 1993 and 1998 in Calvados. A trained interviewer asked all participants about their family history of cancer, and the diagnosis was confirmed in 78% of cases. The expected numbers of cancers were calculated from Calvados incidence rates of colorectal cancer. The risk of developing colorectal cancer for those with a family history of colorectal cancer was 1.54 compared to those without a family history. This risk appeared to be greater, but not significantly so, for first degree relatives than for second degree relatives, RR 1.71 compared with RR 1.22.[80]

A systematic review and meta-analysis of published case-control and cohort studies, between 1958 and 1999, which have quantified familial risk of colorectal cancer, was performed by Johns, et al. (See figure 2) Twenty case-control studies reporting the risk of colorectal cancer in relatives of colorectal cancer were identified. Ten of these used controls ascertained from the general population, and 10 used hospital patient controls. In total 16,225 patients who had first degree relatives with colorectal cancer and 29,755 matched controls were included. Seven studies excluded cases with FAP or premalignant bowel disease. In eight studies diagnoses of colorectal cancer in relatives were confirmed wherever possible. Seven cohort studies reporting the risk of colorectal cancer in 125,327 relatives of colorectal cancer cases were identified. Six of these studies were retrospective. An attempt was made in all to verify cancer diagnoses in relatives.

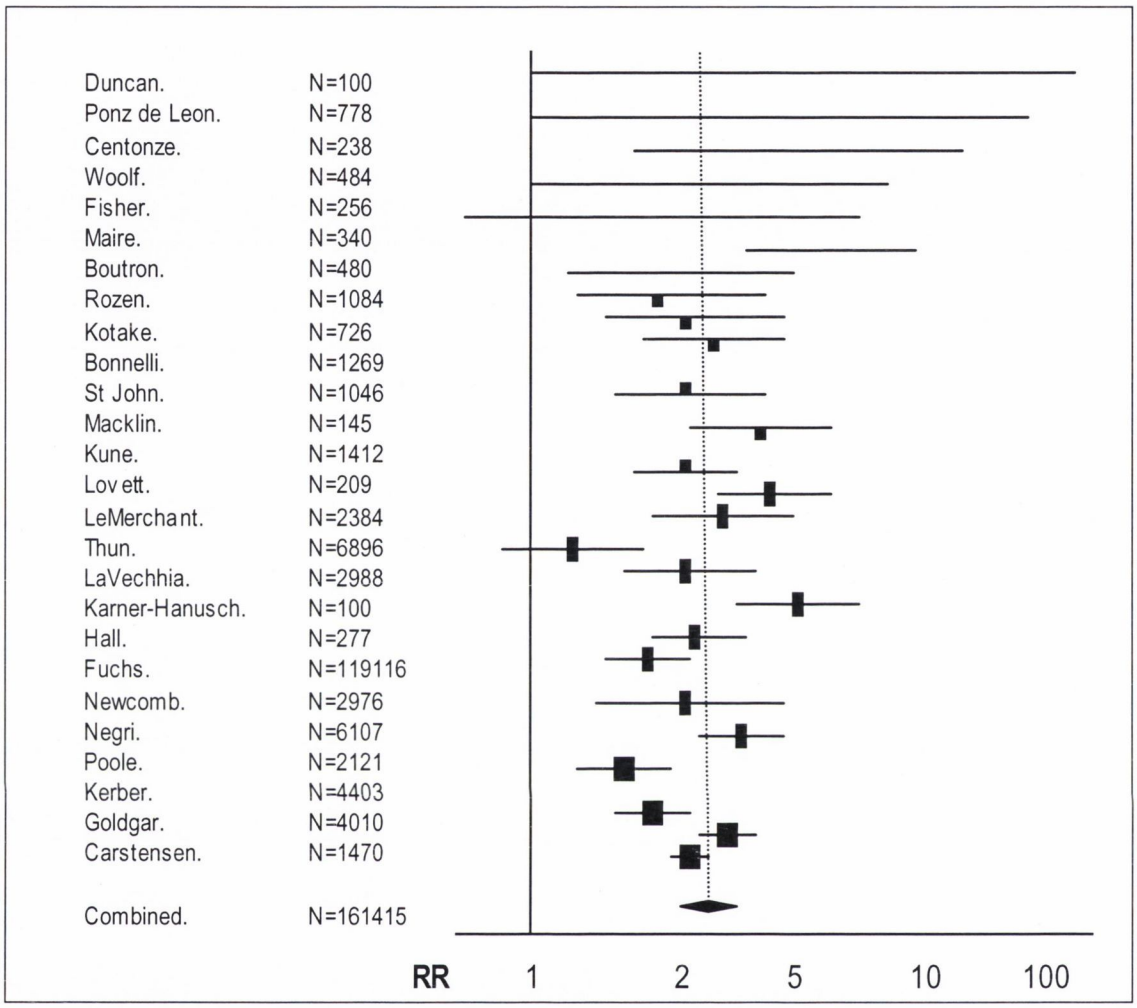


Figure two: Funnel plot of relative risk of colorectal cancer associated with having at least one first-degree relative with colorectal cancer.

Horizontal lines represent 95% confidence intervals. Each box represents the relative risk point estimate and its area is proportional to the weight of the study. The diamond and broken lie represent the overall summary relative risk estimate. The unbroken vertical line is at the null value where relative risk is 1.

Using all studies, the pooled RR is 2.25 for developing colorectal cancer among individuals with a first degree relative with colorectal cancer. Eleven of the studies distinguished between colon cancer with a RR of 2.42, and rectal cancer with a RR of 1.89. There was no statistically significant difference between right and left sided colorectal cancer. Fourteen studies reported separate parent-offspring and sibling familial colorectal cancer risks. The estimates of parent-offspring RR ranged from 1.3 to 10, with a pooled RR of 2.26. For siblings the RR ranged from 1.8 to 11 with a pooled RR of 2.57. Six studies reported the risk of colorectal cancer associated with having more than one affected first-degree relative, with the RR ranging from 2.2 to 9.4 and the pooled RR being 4.25. Seven studies reported risks of colorectal cancer by age at diagnosis of colorectal cancer in the index case, and in all the risks were greatest for those relatives of cases diagnosed young. The pooled RR of colorectal cancer is 3.87 in relatives of cases diagnosed > 45 years, 2.25 between 45 and 59 years, and 1.82 in those > 59 years. In addition nine studies reported the risk of colorectal cancer associated with adenomas in a first degree relative, and found a RR of 1.99. This meta-analysis provides strong evidence for screening those with a first-degree relative with colorectal cancer, the moderate risk "familial" group.[81]

Since then attempts have been made to clarify the appropriate age at which to begin screening in moderate-risk individuals. Colorectal neoplasia is rare under the age of 50 years and the appropriateness of colonoscopy at less than 50 years of age in individuals at moderate risk may be questioned. This view was supported in a cohort of 232 asymptomatic individuals with a strong family history of colorectal cancer, where

neoplastic lesions were detected by colonoscopy in 33 participants (14%), four had an advanced adenoma and two had cancer. Only one advanced adenoma was detected in a participant below the age of 50 years.[74] In contrast a cohort of 249 asymptomatic individuals who had one or two first-degree relatives with colorectal cancer colonoscopy detected neoplastic lesions in 27 (11%), fourteen had an advanced adenoma and no cancers were detected. Nearly half of the adenomas detected, 44.4%, were discovered in asymptomatic individuals who were <50 years old.[75] In light of these contradictory findings further studies are needed to determine if screening should begin in those < 50 years old.

Studies have also revealed that screening intervals for individuals at moderate risk due to their family history should be shorter than those for average risk individuals. Colonoscopy was performed on 436 asymptomatic individuals and adenomas were found in 172 of these. A repeat colonoscopy was then offered at 3 years to all. Polyps were found in 9 individuals who had an initial normal colonoscopy: 2 of these had no family history of colorectal cancer and 7 had a family history of colorectal cancer. Polyps were found in 46 individuals who had a previous polypectomy: 26 had no family history and 20 had a family history of colorectal cancer. Multivariate analyses showed that adenoma size >10mm, tubulovillous pathology, severe dysplasia, and a first-degree relative with colorectal cancer were significant risk factors for the presence of adenomas 3 years later.[82] Similar findings were demonstrated in a three year endoscopic follow up of 87 patients with adenomas. All polyps found initially > 9 mm were removed, with smaller polyps being left in situ. Repeat colonoscopy at three years revealed that a familial

history of colorectal cancer led to a fourfold higher risk of adenoma growth, but no increased adenoma incidence.[83]

The etiology of the increased family risk of colorectal cancer, whether environmental or hereditary, has been addressed in studies. According to a Nordic twin study 60% of colorectal cancer is due to environmental effects, 35% to hereditary factors, and 5% to shared environmental effects.[84] The question was examined further from the nationwide Swedish Family-Cancer Database which included all individuals born in Sweden after 1931 and their biological parents, totaling over 10 million individuals. A total of 37,873 colorectal cancers were recorded in offspring and parents from 1991 to 2000. The standardized incidence ratios, SIRs, in offspring when a parent had colorectal cancer were 1.78.

A total of 253,476 pairs of spouses met the entrance criteria of living together for at least 30 years, there was no increased risk for a spouse of developing colorectal cancer. This is perplexing in light of the effect of dietary habits or lifestyle on colorectal cancer. However spouse correlation may not be sensitive for environmental effects that exert their action early in life. The overall SIR for risk in a sibling when a sibling had colorectal cancer was 6.89 for right-sided colon, 1.81 for left-sided colon, and 1.96 for the rectum. This could be due to environmental effects in early life or hereditary factors. If environmental factors were important siblings with a small age difference would have a higher risk than those with a large age difference. However the increased risk of

colorectal cancer among those whose sibling had colorectal cancer was independent of the age difference thus indicating a hereditary effect.[85]

The accumulating evidence for familial risks is acknowledged in guidelines for colorectal cancer screening. The BSG recommend that individuals with one first degree relative affected by colorectal cancer aged less than 45 years, or with two affected first degree relatives should have a colonoscopy at consultation about family history or between the ages of 35-40 years, whichever is the later, and a repeat colonoscopy at 55 years.[37] The AGA adopted a broader strategy and recommend that individuals with a first-degree relative with colon cancer when less than 60 years, or with two first-degree relatives diagnosed with colorectal cancer at any age should have screening colonoscopy starting at age 40 years or 10 years younger than the earliest diagnosis in the family, whichever comes first. The colonoscopy should then be repeated every 5 years.[36]

Family history is thus used in the clinical setting to inform decisions regarding the use of colonoscopic surveillance. However this approach places considerable importance on the accuracy of family history information, and this is usually gathered by interview with a family member. Underreporting of family history has been observed and the stigma associated with bowel symptoms may mean that colorectal cancer is discussed less readily in families.[86] There is also evidence that systematic recall bias may arise from the fact that people with a raised awareness of a particular cancer may be more likely to report a positive family history.[87]

Mitchell et al assessed the accuracy of a family history of colorectal cancer reported by relatives compared with the actual diagnosis of colorectal cancer among relatives. A clinical nurse specialist conducted face to face interviews with 199 colorectal cancer patients and 133 healthy individuals. The family histories obtained from these individuals encompassed 5637 first and second degree relatives. The family history provided was linked to a computerised cancer registry data to determine the accuracy. The cancer registry data revealed a total of 148 confirmed cases of colorectal cancer among first-degree relatives or second-degree relatives, of which only 62 were reported correctly by the interviewees. The interviewees had a sensitivity of 56% and a specificity of 99% for reporting colorectal cancer among first-degree relatives.

For reporting colorectal cancer among the second-degree relatives the interviewees had a sensitivity of 27% and a specificity of 99%. This indicates that a large proportion of colorectal cancer cases go unreported by family relatives. Five of the interviewees reported a family history that met criteria indicating a need for surveillance, but only two of these five families were confirmed by the cancer registry data. The cancer registry data through record linkage identified a further four interviewees who warranted surveillance, who did not report a family history of such. Therefore only two of six families, who should have been recommended for surveillance, were identified at interview. The sensitivity of interview in terms of identifying appropriate individuals for surveillance is 33%. These interviews were conducted under ideal circumstances by a trained clinical nurse specialist during a lengthy consultation at the interviewee's own

home. Reporting inaccuracies may be more extreme where family history is taken in a busy clinic.[88]

This was confirmed by Church et al, who reviewed the charts of two hundred in-patients to determine the level of family history noted. In the initial review a family history of colorectal cancer was sought in only 45 of the 100 charts, with an accuracy of 80% for colorectal cancer. In the second review four years later the recording of family history of colorectal had increased to 61 of the 100 charts, but the accuracy for colorectal cancer had not improved much at 74%.[89]

Consideration should be given as to how often a family history of cancer is sought, how detailed a history is obtained, and how accurate that information received is. If we wish to be serious about screening those individuals at increased risk of colorectal cancer due to their family history then specifically asking about this should be as routine as soliciting a family history for cardiovascular risk factors. Most individuals are aware of their family history of cardiovascular disease and in an analogous manner routine questioning of a colorectal cancer history will increase the accuracy. The benefit of repeated questioning was demonstrated in a study of 125 patients who underestimated their family history risk of colorectal cancer. Further questioning via telephone and a mailed questionnaire seeking a family history of colorectal cancer led to a reduction in those who reported having no family history from 31.2% to 13.5%, and an increase in those identified as HNPCC from 3.2% to 8.8%.[90]

A zealous campaign to increase the frequency and accuracy with which a family history of colorectal cancer is sought, while indicated, must be tempered by the knowledge that with an increasing public awareness there will be an increasing demand from the public, concerned about their risk and seeking investigations. Indeed screening clinics in the UK have seen a six fold increase in colorectal cancer family history referrals over the last few years, not all being necessary.

Over two years the appropriateness of such referrals was explored in a clinic attended by 448 individuals. In total 79 patients were classified as HNPCC, 53 of these individuals were over 30 years and had a colonoscopy. Of the 190 individuals deemed to be at moderate risk 123 had a colonoscopy. 152 individuals were low-risk and did not have a colonoscopy. Therefore after review about one third of patients who were referred for colorectal risk assessment did not meet increased risk criteria and were not eligible for a colonoscopy.[91] The benefits of a familial colorectal cancer clinic may be considerably diluted if individuals are screened on the basis of their perceived risk rather than their actual risk based on their family history.

Average risk individuals

The benefit of colorectal cancer screening in average risk individuals is often lost in the myriad screening options and recommendations available. Although there is now a consensus that colorectal cancer screening will reduce mortality there is no consensus on the best screening tool. The four possible screening options cited in various guidelines are FOBT, sigmoidoscopy, colonoscopy, barium enema, or a combination thereof. Cost-effective analysis do not help distinguish between the strategies with the median incremental cost-effectiveness ratios being €9950/life-year saved, €13,200/life-year saved, and €10,000/life-year saved, for FOBT, sigmoidoscopy, and colonoscopy respectively compared with no screening.[92] Thus all screening options are well within the $50,000 per life year saved that society is willing to pay.[93]

The US Agency for Health Care Policy and Research, and the American Cancer Society place equal emphasis on all four options.[36 94] Only one body, the American College of Gastroenterology, recommend colonoscopy above all other tests for colorectal cancer screening in average risk individuals.[95] Conversely the US Preventive Services Task Force concluded that there was no evidence that the increased accuracy of colonoscopy offsets the additional complications, inconvenience, and cost and could not recommend it over other screening methods for colorectal cancer.[96] Similarly the Canadian Task Force on Preventive Health Care found that there was insufficient evidence to recommend colonoscopy for colorectal cancer screening, but good evidence to support FOBT or sigmoidoscopy.[97]

The European Union reveals equal disparity in practice. Italy, Germany, and Poland have implemented national colorectal cancer screening programmes using colonoscopy, but uptake is disappointingly low at less than 10%. [98-100] In France a population-based study of over 91,000 individuals has confirmed the feasibility of FOBT screening and a national screening programme utilizing FOBT is to be implemented.[101] In the UK the feasibility of FOBT screening was confirmed in a pilot study of two sites covering a population of one million people.[102] However the follow-up of a sigmoidoscopy screening trial is awaited before a decision is made on which screening modality to implement nationally in the UK.[103]

Double contrast barium enema

As can be anticipated from such diverse attitudes on screening options there are drawbacks to each. Although double contrast barium enema is recommended for screening no published studies of its efficacy exist as a screening tool. The sensitivity of barium enema for polyps > 1cm is low at 48% when compared with colonoscopy, as shown in the National Polyp Study in the US.[104] The sensitivity of barium enema for colorectal cancer is 82.9%, and that of colonoscopy for colorectal cancer is 95%, with an odds ratio of 3.93 for a missed cancer by barium enema compared with colonoscopy, as shown by a retrospective multi-centre study of 2193 consecutive cases of colorectal cancer.[105] Despite the presence of barium enema in screening guidelines its place lies for those individuals who have had a failed colonoscopy rather than as a screening tool. Even here its position is being usurped by virtual colonoscopy.

Sigmoidoscopy

Two thirds of adenomas and cancers are located in the rectum and sigmoid colon, which is within reach of the flexible sigmoidoscopy, a procedure which takes only five minutes, requires no sedation and only a self-administered enema to clear the bowel, making it an attractive screening option. Retrospective case controlled studies provide evidence that sigmoidoscopy prevents colorectal carcinoma. The use of sigmoidoscopy in 261 patients who died of colorectal carcinoma was contrasted with that of 868 control patients. The OR for exposure to sigmoidoscopy was 0.3 for the control group when compared with the group with colorectal cancer.[106] This conclusion is supported by that of a larger case-controlled study involving 16351 patients with colorectal cancer and 16,351 patients in the Veterans Affairs (VA) system. Compared with controls, patients with colorectal cancer were less likely to have had an endoscopic procedure of the large bowel before being diagnosed with cancer, OR 0.51 for colon cancer and OR 0.44 for rectal cancer.[107] Four population-based flexible sigmoidoscopy trials were carried out on the strength of existing evidence.

In Norway 799 individuals aged 50-59 years were randomized to flexible sigmoidoscopy or no screening. All who had polyps detected at sigmoidoscopy went on to have a full colonoscopy and polypectomy. During the 13 year follow up a reduction in colorectal cancer incidence of 80% and in colorectal mortality of 50% was observed in the screened group. Very high acceptance rates for sigmoidoscopy were achieved at 81%, a figure that might be difficult to achieve elsewhere.[108]

In the UK 354,262 individuals aged 55-64 years were invited to participate in a flexible sigmoidoscopy screening trial with only 55% responding positively. Participants were then randomized to flexible sigmoidoscopy screening or a control group. Attendance among those assigned screening was 70% giving an overall acceptance rate of 33.6% for flexible sigmoidoscopy. Those with high risk distal lesions were referred for colonoscopy. The detection rate for cancer was 3.5 per 1000 and long-term follow-up is awaited on the effect on colorectal cancer incidence and mortality.[103]

An Italian trial invited 1170 individuals, aged 55-59 years, living in Turin to participate in a flexible sigmoidoscopy screening trial. The uptake was low with just 24%, 278 individuals complying. Long-term follow-up is awaited again.[109]

The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial in the US enrolled 77,465 individuals aged 55-74 years. A total of 64 658 subjects, 83.5%, underwent screening flexible sigmoidoscopy, with 23.4% of these having a polyp or mass. The detection rate for cancer, for each 5-year age group, was 1.1-2.5 for women and 2.4-5.6 for men per 1000 screened, and of the 169 cancers detected 130, 77%, were stage I or II. Again follow-up data is awaited.[110]

The sensitivity of flexible sigmoidoscopy for colorectal cancer is 70-80% but concerns have been raised at the risk of missing proximal lesions in the colon. Lieberman and Weiss report on 2885 individuals who underwent colonoscopy with the information obtained from examination of the rectum and sigmoid colon used as a surrogate for the

results of a flexible sigmoidoscopy. Advanced colonic neoplasia was found in 10.6% of individuals and sigmoidoscopy identified only 70.3% of these.[111] In a tandem study colonoscopy was performed in 1463 women. Although the incidence of advanced colonic neoplasia was lower in women at 4.9%, flexible sigmoidoscopy identified only 34.7% of these lesions.[112]

Imperial et al in a study of nearly 2000 individuals undergoing screening colonoscopy addressed the issue of advanced proximal neoplasia among those with no distal polyps, that is those individuals whose sigmoidoscopy would not indicate the need for a colonoscopy yet who harbour advanced proximal neoplasia in their proximal bowel. The prevalence of proximal neoplasia among individuals with no distal polyps was 1.5%, among those with distal hyperplastic polyps 4%, among those with distal tubular adenomas 7.1%, and among those with distal advanced neoplasms 11.5%. In total nearly half, 23 of the 50 individuals, with advanced proximal neoplasia had no distal polyps.[113]

A study of 1,988 asymptomatic individuals attempted to define predictors of proximal neoplasia in those without distal adenomatous pathology. Comparing the 55 patients with isolated advanced proximal neoplasia with the 1,933 patients without, they were significantly older at 64.5 years vs. 57 years; more likely to have a family history of colorectal cancer at 21.8% vs. 13.4%; more likely to be current smokers at 25.5% vs. 19.4%.[114]

The fear of missing isolated advanced proximal neoplasia has led some to believe that screening flexible sigmoidoscopy is as illogical as screening only one breast during mammography, and has become a very persuasive argument against using flexible sigmoidoscopy as a screening tool.[115] In reality no screening programme is ever one hundred percent effective and only 2-5% of asymptomatic individuals are believed to have isolated advanced proximal neoplasia.[116]

The real concern surrounding sigmoidoscopy is its acceptance rate and its invasiveness as a screening test in asymptomatic individuals. In studies, which represent the ideal clinical situation, the acceptance rate varies from 24-80%.[108 103 110] Screening sigmoidoscopy is an invasive procedure and is associated with risks which may not be acceptable in an asymptomatic individuals: a perforation rate of 1 in 25,000, bleeding in 3.2%, and pain in 14%.[117 118]

Colonoscopy

Evidence-based guidelines place greatest weight on large-scale randomized trials, but the corroboration for colonoscopy comes from small case-control studies or indirect evidence where the primary aim of the study did not set out to determine the efficacy of colonoscopy in screening for colorectal cancer. In the landmark US National Polyp Study after an initial clearing colonoscopy, where all polyps were removed, 1418 patients were re-colonoscoped every three years for an average follow-up time of 5.9 years. Only five asymptomatic early-stage cancers were detected during follow-up, and this low incidence of metachronous cancer was compared to that of three different reference

populations. The effect of removing all adenomas was to reduce the incidence of subsequent cancer by between 76% and 90%. This was the first time that a well-designed, controlled, prospective study demonstrated that colonoscopic removal of all adenomas in the colon and rectum successfully interrupted the adenoma-carcinoma sequence and prevented most cancers from developing.[11]

A recent European study confirmed the findings of the US National Polyp Study. A multi-center Italian study followed 1693 patients, after resection of at least one adenoma >5mm in diameter for a mean of 10.5 years. They found that the incidence of metachronous cancer, compared with that of a reference population , was reduced by 75%, with six colorectal cancer cases occurring in the cohort compared with an expected 17.7 colorectal cancer cases.[119]

Case-control studies have evaluated the feasibility of colonoscopy in colorectal cancer screening. A colonoscopy screening study conducted at thirteen VA medical centres enrolled 3196 individuals. A total of 1171 individuals, 37.5%, had adenomatous polyps. Advanced disease that is an adenoma greater than 10mm, or with villous features or high-grade dysplasia, or invasive cancer was present in 329 individuals, 10.5%. In total 2.6% of individuals had cancer or adenoma with high-grade dysplasia and most of these, 73.5% were identified before there was nodal involvement or distal spread.[120]

Over 500 asymptomatic Chinese subjects, with a mean age of 56 years, responded to advertisements to participate in colorectal cancer screening, and underwent colonoscopy.

Advanced colonic lesions were found in 63 subjects, 12.5%, 4 invasive cancers, 35 tubular adenomas with moderate or severe dysplasia, 15 large tubular adenomas, and 9 villous adenomas.[121]

It should be borne in mind that both these studies enrolled individuals who wished to participate in colorectal cancer screening, and population-based studies reveal that the acceptance rate for colonoscopy as a screening tool is less than 20%.[122 123]

The sensitivity of colonoscopy for colorectal cancer is over 95% in retrospective studies of patients who developed colorectal cancer, and 96.7% in prospective FOBT screening trials.[105 124] Back-to-back colonoscopy studies reveal that the miss rates for polyps > 1cm is 0-6%, and for polyps < 1cm 15-27%.[125 126] Back-to-back colonoscopy may however overestimate the sensitivity of colonoscopy, and colonoscopy may not be the gold standard we believe it to be. Using advanced technology and intensive bowel preparation, virtual colonoscopy followed by colonoscopy reveals that the sensitivity of colonoscopy for polyps more than 10mm was 92.3%, with a miss rate of 12%. Sensitivities for polyps more than 8mm were 91.5%, and for polyps more than 6mm 87.5%. Two polyps were malignant, both were detected on virtual colonoscopy and one was missed on colonoscopy before the results of the virtual colonoscopy was revealed.[127]

To maintain colonoscopy as a gold standard colonoscopy technique becomes of crucial importance. In particular the quality of bowel preparation and colonoscopy withdrawal times have been identified as factors impacting on colonoscopy detection rates.[128-130]

Improving the quality of colonoscopy techniques is estimated to reduce interval cancers by up to 50%.[131]

Aside from sensitivities another key issue with regard to colonoscopy screening is associated complications. As colonoscopy is invasive it is associated with risks and a retrospective review of 6066 colonoscopies performed in one Swedish county from 1979 to 1995 analysed this. The overall morbidity was 0.4%, 0.2% for diagnostic colonoscopy and 1.2% for therapeutic colonoscopy. The most frequent complications were bleeding in 0.2% and perforation in 0.1%. There was no mortality.[132] Although the risk associated with a single colonoscopy is small the cumulative risk of repeat screening colonoscopy may outweigh the benefit obtained from screening colonoscopy.[133]

Inadequate screening capacity is also an important barrier to colorectal cancer screening. Colonoscopy is the final pathway of all colorectal cancer screening. Depending on which faecal test is used 2-15% of participants will need a colonoscopy.[134] Between 5-10% of participants undergoing screening flexible sigmoidoscopy screening will need a colonoscopy.[135] If colonoscopy is used as the screening option then the potential annual demand for screening colonoscopy can be calculated: Most importantly compliance with any screening test is never 100%; it is unlikely that compliance would exceed 60%, a figure reached with mammography. Some patients with serious medical problems would not be candidates and recruitment for the VA study suggests that this would be 5% and

up to 25% of patient will already have had a colonoscopy. Thus 45-50% of those aged 50-70 years can be expected to attend for colonoscopy.[136]

In 2002 in the US 2.8 million flexible sigmoidoscopies and 14.2 million colonoscopies were performed with a potential available capacity of 6.7 million flexible sigmoidoscopies and 8.2 million colonoscopies.[137] Sufficient capacity exists to screen the unscreened population with FOBT within one year. To screen the unscreened population with flexible sigmoidoscopy using all available capacity would take six year, and using half the available capacity ten years. Using all the available capacity it would take five years to screen the unscreened population with colonoscopy, and using half the available capacity four years.[138]

A large multi-centre prospective study in the UK assessed the availability and quality of colonoscopy in a cross-section of gastroenterology centres in the UK. A total of 9223 colonoscopies were carried out over a four month period in 68 endoscopy units in three National Health Service regions. The mean number of colonoscopies performed was 142 in the district general hospitals and 213 in the teaching hospitals, and caecal intubation was disappointingly low at 76.6%. The conclusion from this study was that the infrastructure for colorectal cancer screening by means of endoscopy is not in place in place in the UK yet.[139]

Faecal Occult Blood Testing

There are a number of problems with FOBT which may limit its use in population based screening programmes. The sensitivity of FOBT varies with the protocol used. The sensitivity of FOBT for CRC ranges from 26-69%, and for adenomas 9-36% [111 134 140] Of those with a positive unrehydrated FOBT 5-18% will have a cancer and 20-40% will have a large polyp or cancer.[8 141] Furthermore efforts to increase sensitivity in the Minnesota trial by rehydration resulted in an unacceptably high false positive rate without any gain in the number of cancers detected. The Minnesota trial did reveal that with annual testing, the programme sensitivity for detecting cancer is as high as 90% with faecal occult blood testing.[142]

In addition although FOB screening might be expected to detect adenomas, all three published trials showed that screening had no effect on cancer incidence. In all cases reduced mortality was secondary to earlier detection and treatment of established colorectal cancers in the screened population.[143] The Nottingham group have followed up their cohort for 11 years and to date there is no reduction in the incidence of colorectal cancer among those screened.[144] The Funen group after 17 years of follow up have a similar incidence of colorectal cancer among those screened and those not.[25] However the Minnesota group, which showed the largest reduction in colorectal cancer mortality, revealed that over 18 years both annual and biennial screening with FOB significantly reduced the incidence of colorectal cancer.[24]

Compliance with FOB testing is a problem. In clinical practice many patients who enroll in screening programmes that use FOB testing do not undergo more than one test.[145] In the two European population-based studies only 60% of eligible subjects participated in the first screening round and 40% in all the screening rounds.[8 141]

Guaiac-based FOBT depend on faecal blood to catalyze the phenolic oxidation of guaiac in the presence of hydrogen peroxide to produce a blue chromogen. Unfortunately there can be false positives: The peroxidase present in many fresh fruit and vegetables, animal haemoglobin and myoglobin may all cause a false positive. In addition high-dose supplements of vitamin C will inhibit the guaiac reaction leading to a false negative result. A recent review has suggested that dietary restriction is not required when using guaiac-based FOBT and this will have important implications for compliance with screening.[146] The most commonly used guaiac tests are the Hemoccult II and Hemoccult-SENSA. Although Hemoccult II was used with rehydration in the Minnesota trial to increase sensitivity it was associated with a high rate of false positive tests compared with un-rehydrated Hemoccult II.[142] Hemoccult-SENSA has a higher sensitivity but a higher false positive rate than Hemoccult II.

Promising developments for FOBT are the immunochemical tests based on reversed passive haemagglutination and specific for human haemoglobin, which have a higher sensitivity and specificity compared with the guaiac tests. Immunochemical FOBTs include Heme Select, Monahaem, and InSure. Immunochemical testing has evolved further due to the development of the latex agglutination method which gives a

quantitative result using an automated analytical procedure. As a result the positivity threshold can be varied to achieve an increased sensitivity with lowered specificity or a decreased sensitivity with an increased specificity. The optimal positivity threshold depends on the ability or capacity of the health care system to evaluate positive tests with colonoscopy. It represents a balance between the costs incurred due to evaluation of false positive FOBTs if the specificity is decreased compared with the improved cancer detection rate if the sensitivity is increased. [147]

Immunochemical FOBTs may be used on a single sample collection, without the need for dietary restriction, thus potentially increasing compliance.[148] However one noteworthy study has shown that the sensitivity of immunochemical FOBT increases from 56% for one day collection, to 83% with a two day collection, and 89% with a three day collection.[149] Thus three-day stool collection appears the most prudent even for immunochemical FOBT.

The sensitivity and specificity of the guaiac-based FOBTs and immunochemical FOBTs have been compared in several studies. In a population of 23,000 a colorectal cancer screening programme used a guaiac-based FOBT from 1980-85 and an immunochemical FOBT from 1985-1993. A positive guaiac-based FOBT occurred in 5.7% and a positive immunochemical FOBT in 2.7%. The OR of dying of colorectal cancer was 0.19 for those screened with the immunochemical test during the previous one year, and 0.36 for those screened with the guaiac-based test during the previous one year.[150]

Sensitivity, specificity and the positive predictive value of Hemoccult II, Hemoccult Sensa, and Heme Select were assessed in a large population based study of over 10,000 individuals over a one year period. A positive FOBT was found in 2.5% with Hemoccult II, 3% with a combination of Hemoccult Sensa and Heme Select, 5.9% with Heme Select, and 13.6% with Hemoccult Sensa. The sensitivity was lowest with Hemoccult II at 37.1%, the combination of Hemoccult Sensa and Heme Select had a sensitivity of 65.6%, Heme Select 68.8%, and Hemoccult Sensa 79.4%. Specificity was 86.7% with Hemoccult Sensa, 94.4% with Heme Select, 97.3% with the combination of Hemoccult Sensa and Heme Select, and 97.7% with Hemoccult II.[134] Therefore the immunochemical FOBT Heme Select improves on Hemoccult II screening, with more carcinoma and polyps detected and only a slight increase in colonoscopies performed. A two-tier approach in which Heme Select is used to confirm a positive guaiac-based Hemoccult Sensa also improves on Hemoccult II screening. However the two-tier approach will most certainly affect compliance and so may be ill-advised.

A review of FOBT screening population studies revealed that test positivity is highest with rehydrated Hemoccult II, followed by Hemoccult SENSA, immunochemical FOBT and un-rehydrated Hemoccult II. Specificity on the other hand is highest for rehydrated Hemoccult II, followed by immunochemical FOBT, Hemoccult SENSA, and Hemoccult II. The sensitivity of immunochemical FOBT is in the range of 70-90% with specificity of 95% in the majority of studies.[151] Immunochemical FOBT appears to be superior to the guaiac-based FOBT.

Never-the-less it is the large randomized guaiac-based FOBT trials that provide the majority of evidence for colorectal cancer screening. No randomized controlled trials exist for the immunochemical FOBTs, and it is unlikely that such large studies will occur in the future. If a test is truly more accurate, as the immunochemical FOBT appears to be over the guaiac-based FOBT then perhaps randomized trials are not necessary. New data on immunochemical FOBTs are expected in the near future but to date no long-term follow-up studies of immunochemical FOBT screening programmes have been published.

Evidence for Faecal Occult Blood Testing

In the Minnesota trial, 46,551 volunteers aged between 50 and 80 years were randomised to screening using annual FOBT, biennial FOBT, and a control group. Because of the nature of the participants compliance was high with 90% completing at least one screening, all the screenings were completed by 46.2% of the annual group and 59.7% of the biennial group. The positivity rate was 2.4% for un-rehydrated FOB and 9.8% for rehydrated FOB. During the study period 38% of those screened annually and 28% of those screened biennially had at least one colonoscopy. The incidence of colorectal cancer was almost identical in the three groups, 323 in the annual screening, 323 in the biennial screening group, and 356 in the control group. However the cumulative annual mortality rate from colorectal cancer was lower in the annually screened group, 5.88 per 1000, than in the biennially screened group, 8.33 per 1000, and the control group, 8.83 per 1000.

Early cancer or stage A was found in 30.2% of the annual screened group, 26.6% of the biennial screened group, and 22.3% of the control group. Advanced cancer or stage C and D was found in 31.9% of the annual screened group, 38.3% of the biennially screened group, and 37.3% of the control group. Mandel et al demonstrated a reduced mortality of 33% among the annually screened patients compared with the control population, after 13 years of follow-up. Cumulative colorectal cancer mortality however was only 6% lower in the biennially screened group than in the control group.[142]

In the Nottingham trial 152,850 individuals aged 50-74 years were randomly assigned to a biennial screening group with an un-rehydrated FOBT or to a control group. To keep the false-positive rate to a minimum a repeat test was sent to individuals with up to four positive squares, with instructions to restrict their diet. Individuals with five or more positive squares at the first test or those with one or more positive squares at the retest were offered colonoscopy. Acceptance of screening ranged from 29% to 74% according to the general practice screened, with 38.2% completing all the FOBT, 21.4% completing at least one, and 40.4% not completing any. 2.1% of people needed colonoscopy after their first FOB screen, and 1.2% needed colonoscopy on rescreening FOBTs. In total 4% of all individuals who underwent FOBT had a positive result and required colonoscopy.

As a result 236 individuals were diagnosed with colorectal cancer and 710 individuals were diagnosed with adenomas. 249 interval cancers presented, 400 cancers were diagnosed in non-responders, and 856 cancers were diagnosed in the control group. A further 8 cases of colorectal cancer were diagnosed in the screening group during endoscopic follow-up of a screen-detected lesion. The proportion of early stage A tumours was significantly higher in the screening group than in the control group, 20% vs. 11%, whereas the proportion of advanced tumours stage C and D was significantly lower in the screening group than in the control group 46% vs. 52%. The number of verified deaths attributable to colorectal cancer was lower in the screening group than in controls, 360 vs. 420. In summary, Hardcastle demonstrated that despite a low

compliance, of approximately 50%, and a relatively short follow-up time, of median 7.8 years, a 15% reduction in mortality was shown using biennial FOBTs.[8]

In the Funen trial 30967 people were assigned to biennial screening and 30966 were assigned to the control group. Colonoscopy was offered to those individuals with one or more positive squares. During the five rounds of screening the positivity rate was 0.8-1.4% and overall 4.3% of the screened population underwent colonoscopy. In the screened group 120 colorectal cancers were detected and 270 adenomas were detected. 195 colorectal cancers occurred in non-responders, 148 interval cancers occurred and 483 cancers developed in the control group.

The proportion of early stage A cancer was higher in the screening group than in the control group 22% vs. 11%, and the proportion of advanced cancer stage C and D was lower in the screened group than in the control group 39% vs. 47%. The number of deaths due to colorectal cancer was lower in the screened group than in the control group, 182 vs. 230. In summary Kronborg demonstrated that biennial screening by FOBT with a compliance of 67%, over 10 years of follow up could reduce colorectal cancer mortality by up to 18%.[141]

Meta-analysis by Towler et al in 1998 of all trials to date, indicated that mortality from colorectal cancer is reduced by approximately 16% in those randomised to screening. The four randomised controlled trials, involving about 330,000, and two non-randomised trials, involving 113,000 people, were evaluated. (See figure three) For most trials the

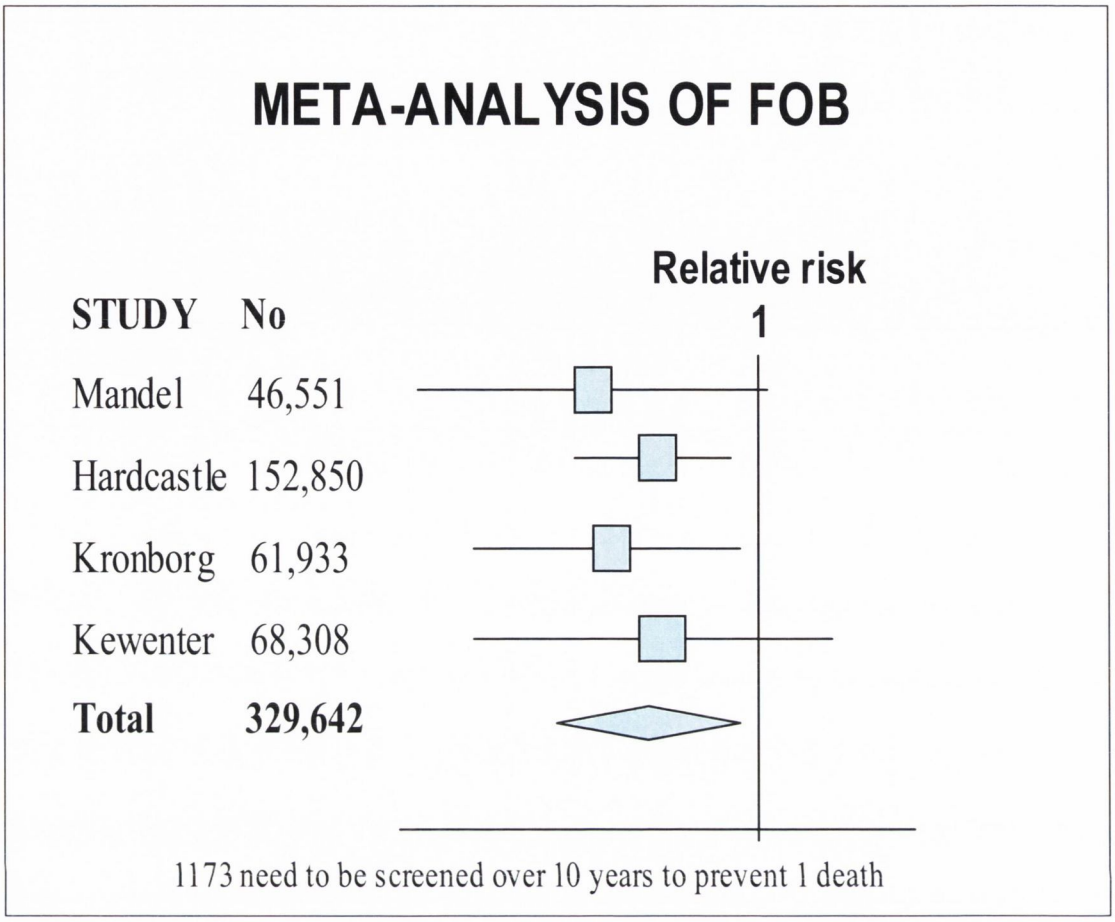


Figure three: Funnel plot of relative risk of colorectal cancer associated with faecal occult blood testing.
Horizontal lines represent 95% Confidence Intervals. Each box represents the relative risk point estimate. The diamond represents the overall summary estimate with Confidence intervals given by its width. The unbroken vertical line is the null value (RR=1)

FOBT were not rehydrated resulting in a low test positivity rate of 0.8-2.4%, but a higher positive predictive value for colorectal cancer 5.6% to 17.7%, with a sensitivity of 46% for colorectal cancer. The rehydrated test gave a higher positivity rage of 4.8%-9.8% but the positive predictive value was 2.2%-4.2%, with a sensitivity of 92% for colorectal cancer. The percentage of people who completed at least one FOBT ranged from 60% to 90%, with higher compliance in the American trials than in the European trials.
The four randomised controlled trials revealed a reduction in mortality ranging from 12% to 33%.

The New York study showed a 37% reduction in mortality with annual screening among those attending for the first time, but an 18% reduction in mortality among regular attendees. The Burgundy trial had yet to publish their mortality figures at the time of the meta-analysis, but have recently published their findings: In accordance with the other European trials biennial screening with un-rehydrated FOBT led to a 16% reduction in mortality after an 11-year follow up in individuals aged 45-74 years. Reduction in colorectal mortality was 33% among those adhering to screening.[101]

The meta-analysis revealed that FOBT screening leads to an overall reduction in colorectal cancer mortality of 16%. Adjusting for compliance gives a 23% reduction in colorectal mortality. Overall if 10,000 people were offered screening 8.5 deaths from colorectal cancer would be prevented over 10 years. Put another way, the number needed to screen in order to prevent one death from colorectal cancer over 10 years is 1173 (741-2807). The number of colonoscopies or sigmoidoscopies performed could range from

20-800 per life prolonged according to the results of the screening trials. The number needed to be screened to prevent one colorectal cancer death was 747 in Nottingham, 44838/60; 470 in the Danish trial, 20,672/40; and 360 in the Minnesota trial, 14034/39.

In the Minnesota trial 49% of patients who developed colorectal cancer were identified through screening. In the European trials screening detected 27% of the patients who developed colorectal cancer.[9] The programme sensitivities are 92% for annual rehydrated FOBT and 81% for annual un-rehydrated FOBT with corresponding specificities of 90% and 98%. The programme sensitivity for biennial un-rehydrated FOBT is 47-66% with specificity of 86-97%.

The question of how long the effect of a once-off intervention with FOBT lasts was answered in a study from China. Once-off screening with an immunochemical FOBT was carried out among 94,423 individuals and 97,838 unscreened individuals served as the control group. Over a seven year follow-up the cumulative mortality of the screened group was 14.7% lower than the control group. The protective benefit of screening lasted for five years.[152]

No screening test is ever one hundred percent effective and an important concern is the emergence of cancer among individuals with a negative test. A negative test may give a false sense of reassurance and lead individuals to ignore developing symptoms. This was assessed by a study from Calvados, France. FOBT screening was carried out among 165,000 people aged 45-74 years and all cancers in the area were identified from the

cancer registry. From the cancer registry 988 cancers were diagnosed: 16% occurred after a positive FOBT, 10.5% occurred after a negative FOBT, 36.3% occurred in non-responders to the FOBT campaign, and 37.3% occurred before screening with FOBTs began.

The Dukes Staging of colorectal cancer did not differ significantly amongst those with a negative FOBT from those of the non-responders or those pre-screening. Of those who developed cancer after a positive FOBT 45.4% were Dukes Stage A. In contrast of those who developed cancer after a negative FOBT or in non-responders or pre-screening Dukes stage A occurred in 28%, 24.6%, and 23.6% respectively. Importantly patients and physicians do not seem to be falsely reassured by a negative FOBT and are watchful of symptoms.[153]

However it is clear that there is a need for a non-invasive test for colorectal cancer with a higher sensitivity and specificity.

Faecal calprotectin

Faecal calprotectin in initial studies displayed potential as a screening tool for colorectal cancer. The overall sensitivity and specificity of calprotectin for colorectal cancer and adenomatous polyps was 37-79% and 63-72%.[154 155] However faecal calprotectin is also raised in inflammatory diseases of the intestinal tract.[156] The largest trial to date of faecal calprotectin involving 2321 patients emphasized the fact that faecal calprotectin has no place in colorectal cancer screening.[157]

Faecal DNA

A non-invasive diagnostic approach is the detection of molecular alterations in faecal DNA as neoplasms continuously exfoliate large populations of viable colonocytes, unlike the sparse and largely apoptotic cells shed from normal mucosa.[158] The identification and characterisation of the genetic changes in the malignant transformation from normal mucosa to adenoma, to high-risk adenoma and carcinoma in the bowel have progressed rapidly over the last three decades.[159-161] Two major classes of genes, oncogenes and suppressor genes are involved. Oncogenes are genes whose products, including peptide growth factors, growth factor receptors, signal transduction factors, tyrosine kinase, and transcription-regulatory proteins, normally promote cell growth. Tumour suppressor genes, which usually produce nuclear-regulatory proteins, regulate cell growth.

The mutations in the APC gene occur in 60% of patients with sporadic colorectal cancer, and are thought to be the earliest genetic mutation in colorectal cancer progression. APC can be detected in the faeces of 57% of patients with colorectal cancer.[162] One-third to

one-half of patients with adenocarcinoma of the colon carry a mutant allele of K-ras genes and this can be detected in the stool.[163] [164] An acquired defect of p53, or loss of the wild-type allele tends to be a late event in colorectal carcinoma, and occurs in 50-70% of cases, this can be detected in the stool.[165]

A number of genes are involved in MMR such as hMSH2, hMLH1, hPMS2, hMSH3, and hMSH6. Loss of MMR leads to greatly elevated frequencies of point mutations and MSI frameshifts and this can be detected in the faeces.[166] High-integrity or L-DNA is found in the stool of over 60% of patients with colorectal cancer. Longer template DNA is an epigenetic phenomenon consistent with the known abrogation of apoptosis. DNA in normal stool exists in short fragments, where in patients with colorectal cancer dysplastic cells produce longer DNA.[161]

All faecal DNA markers are affected by the relatively low frequency of single marker alterations in colorectal cancer. The sensitivity of the non-invasive molecular diagnosis of colorectal cancer could be improved by considering as broad a panel of markers as possible. A multitarget assay panel of DNA changes has a sensitivity of just over 50-60% and a specificity of 94-96% for colorectal cancer. [167-169]

The two main obstacles with faecal DNA are cost and methodology. Sample stability and difficulties extracting sufficient DNA need to be overcome to improve sensitivity.[170] Current guidelines limit faecal DNA to those who refuse to have invasive screening done.[171] However if fecal DNA testing is found to be effective and cost-effective, it

could have a significant impact on colorectal cancer screening practices. To make fecal DNA comparable with colonoscopy the screening interval would need to decrease to 2 years and the cost of testing decrease to $195.[172]

Virtual colonoscopy

Computed tomographic colonography, also known as virtual colonoscopy, is a recently developed, minimally invasive imaging modality for the detection of colorectal neoplasia, in which thin-section spiral computed tomography is used to generate two-dimensional axial images. Three dimensional images are subsequently reconstructed by means of software with dedicated algorithms, either surface rendering, or more recently volume rendering, in order to produce endoscopic-like images.

Virtual colonoscopy has a high accuracy in the detection of colorectal carcinomas and polyps larger than 6 mm, although the results in the literature have been quite varied. Sensitivities for detecting patients with polyps ≥10 mm have ranged from 32 to 96% and specificities have ranged from 74 to 98%. Sensitivities for detecting polyps 6 – 9 mm in size have ranged from 39 to 94% and specificities have ranged from 63 to 95%.[127 173 174] The reasons for such wide variations are uncertain but appear to involve variation in ability to recognize polyps, learning curve effects, bias in performance and interpretation associated with low prevalence, and differing technical approaches.

Using advanced technology, including bowel preparation, software, interpretation and training, ideal circumstances can achieve a sensitivity of 94% and specificity of 96% for

detecting large polyps greater than 1cm. The average image interpretation time was 19.6 minutes. The sensitivity of colonoscopy for polyps more than 10mm was 92.3%, for polyps more than 8mm 91.5%, and for polyps more than 6mm 87.5%.[127]

It must be remembered that virtual colonoscopy is "minimally invasive" as opposed to "non-invasive" It involves bowel preparation, similar to that for colonoscopy, and air insufflation via the rectum. Virtual colonoscopy with "faecal-tagging" may eliminate the need for bowel preparation. In a recent study faecal tagging was achieved by ingesting 20 ml of contrast agents at each of five principal meals during the 48 hours preceding virtual colonoscopy and proved successful with a sensitivity for polyps > 8 mm of 95.5%, and for polyps > 6 mm 86%. Adverse reactions to the iodine contrast occurred in 19.3% and consisted of nausea, vomiting, skin reactions, and diarrhoea.[175] Further studies of faecal tagging are necessary to confirm this finding but it may improve acceptability.

Currently patients report more pain and discomfort during virtual colonoscopy rather than during conventional colonoscopy. This is no doubt influenced by the sedation patients routinely receive with conventional colonoscopy. Never-the-less it underscores the fact that virtual colonoscopy is minimally as opposed to non-invasive.[176]

The biggest problem for virtual colonoscopy is that it may be implemented too widely without sufficient regard for current technological problems that affect sensitivity. A much lower sensitivity of 55% is reported for virtual colonoscopy under conditions that

mimic current practice. A multi-center trial revealed a sensitivity of virtual colonoscopy for lesions at least 6 mm was 39% and for lesions at least 10 mm was 55%. Virtual colonoscopy missed 2 of 8 cancers. The accuracy of virtual colonoscopy varied considerably between centers and did not improve as the study progressed, there was no evidence of a "learning curve". All radiologists had performed at least 10 virtual colonoscopy cases and had 5 reviewed before starting the study. Only one of the centers had substantial prior involvement and had the best results with sensitivity of 82%. The sensitivity for all other centers combined was only 24%.[177]

There also remains controversy as to what size polyp should be interpreted by those reading virtual colonoscopy for referral for conventional colonoscopy. Most polyps in the 6-9 mm range are adenomatous polyps and studies suggest may harbour invasive cancer in 0.9% of cases.[18 178] Current guidelines from the American College of Gastroenterology on colorectal cancer screening recommends that patients with polyps $\geq$ 6 mm on virtual colonoscopy should be referred for conventional colonoscopy and polypectomy.[171] The cost-effectiveness of virtual colonoscopy as a screening tool for colorectal cancer will depend on the intervals recommended. In order to have comparable cost-effectiveness to conventional colonoscopy virtual colonoscopy would have to be recommended at 10 yearly intervals.[179]

Positron emission tomography

Positron emission tomography, PET, is based on the knowledge that malignancy leads to an alteration in cellular biochemical reactions. ^{18}F labeled 2-fluoro-2-deocy-D glucose, ^{18}FDG, is used as a tracer and relies on the increased glucose consumption of malignant cells. The tracer is converted into a monophosphate by the enzyme hexokinase and leads to intracellular trapping; following radioactive decay its distribution can be mapped. This ability to image cellular biology has led to its application in the non-invasive assessment of cellular proliferation.

The potential of PET for colorectal cancer screening has been assessed in 3210 asymptomatic individuals. PET colorectal cancer screening is hampered by the physiological uptake demonstrated in the bowel. However increased uptake with an intensity equal to or exceeding the level of uptake in the brain and bladder were considered abnormal and interpreted as intraluminal neoplasia. A subsequent colonoscopy revealed neoplasia in 20: 2 tubular adenomas > 1cm, 12 villous adenomas, and 6 cancers. Although it is possible to differentiate neoplasia by an increased rate of glycolysis it has limited applicability as a screening tool.[180]

Faecal Tumour M2-PK.

Tumour cells are capable of surviving and proliferating under unfavourable conditions, namely a poor supply of oxygen and nutrients. A key control enzyme regulating this is the glycolytic enzyme pyruvate kinase. Pyruvate kinase is responsible for net energy production within the glycolytic pathway with the transfer of phosphate from

phosphoenolpyruvate to ADP and the formation of ATP and pyruvate. This enzyme regulates the exit of the glycolytic pathway and determines the relative amount of glucose that is channeled into synthetic processes or used for glycolytic ATP production.

Pyruvate kinase is expressed as different isoenzymes depending on the metabolic requirements, and the varying isoenzymes control the phosphometabolite pools and the interaction between glycolysis, glutaminolysis, and serinolysis: M1-PK is found in tissues with high rates of energy consumption and low phosphometabolite pools such as brain and muscle; M2-PK is found in proliferating tissues with a high capacity for nucleic acid synthesis such as embryonic cells, adult stem cells, and tumour cells.[181] M2-PK occurs in a dimeric form with a low affinity for its substrate, phosphoenolpyruvate, and in a tetrameric form with a high affinity for phosphoenolpyruvate.[182]

In tumour cells the dimeric form of M2-PK increases and this change from the tetrameric form to the dimeric form is induced by oncoproteins. The oncoproteins $pp60^{v\text{-}src}$ kinase and HPV-16 E7 have been shown to induce this dimerisation.[183] [182] The dimerised form of M2-PK, called tumour M2-PK, leads to an accumulation of all phosphometabolites above pyruvate kinase which are then channeled towards synthetic processes such as nucleic acid, amino acid and phospholipids synthesis. (See figure four.) Tumour cells also require energy and this results in high rates of glycolysis and glutaminolysis.[181] To overcome this tumour cells have reduced mitochondrial pyruvate consumption and produce pyruvate and energy from the amino acid glutamine via glutaminolysis.

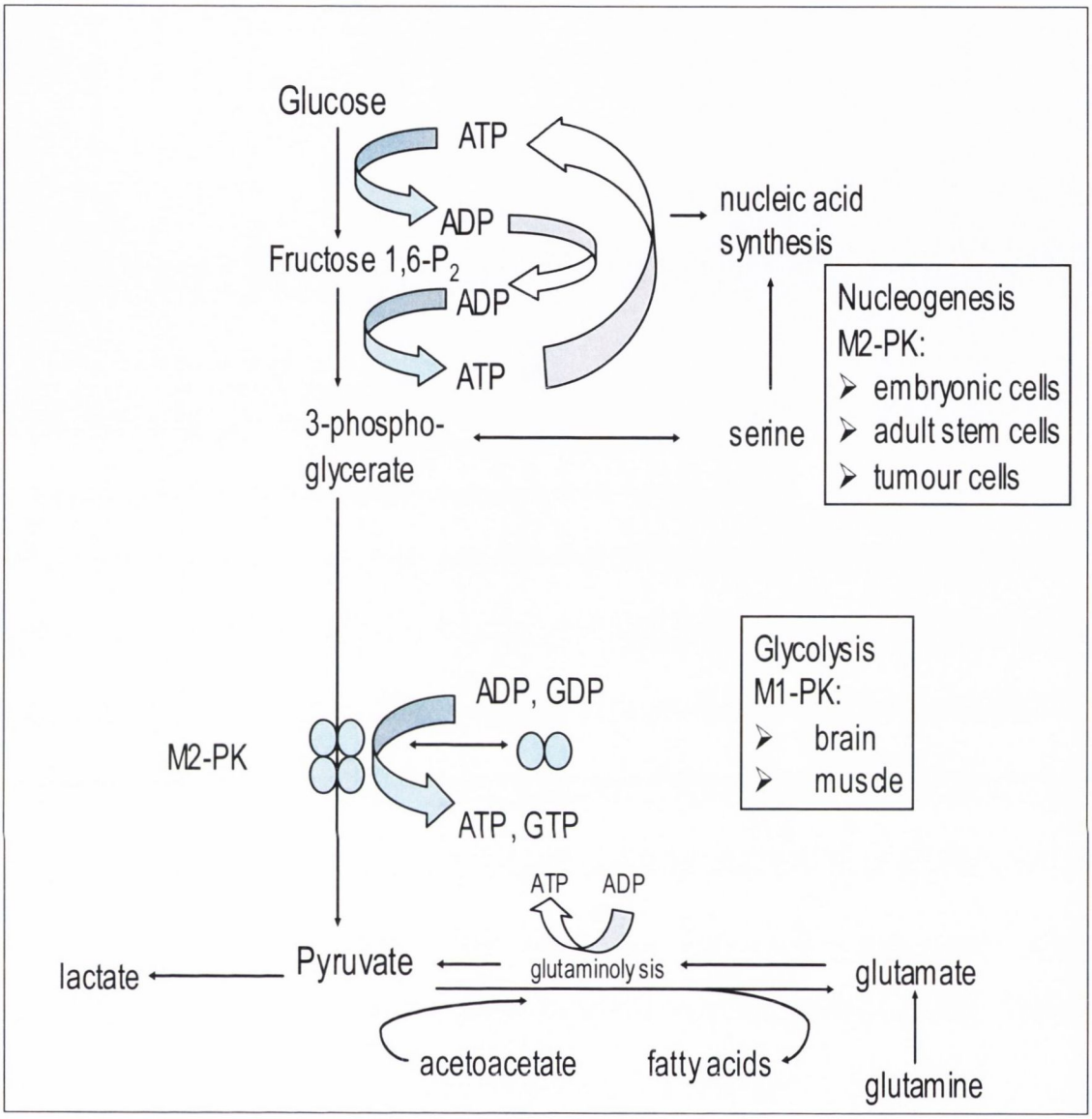


Figure four: M2-PK

Glutaminolysis is dependent on oxygen supply, unlike the glycolytic energy production by pyruvate kinase which is independent of oxygen. In solid tumours, with poor vascularisation tumour cells may have reduced oxygen, glucose or other nutrients. Under such conditions glutaminolysis becomes inhibited and M2-PK switches back to the tetramer form under the influence of accumulating levels of fructose 1,6-P_2. This allows the tumour to switch between anabolism and catabolism depending on oxygen and nutrient supply.[184] Human tumour cells also produce energy via a mechanism known as serinolysis where serine is converted to 3-phosphoglycerate and then to pyruvate and lactate.[182]

Determinations of tumour M2-PK in EDTA-plasma samples of patients with gastrointestinal tumours revealed an upregulation of tumour M2-PK in oesophageal, gastric, colonic, and rectal carcinomas. In a group of 34 patients with colorectal cancer, 20 patients with oesophageal or gastric cancer, 14 patients with pancreatic or biliary cancer, 22 patients with inflammatory bowel disease, and 60 healthy controls tumour M2-PK was determined in EDTA plasma samples. The mean M2-PK value was 30.3 u/ml for gastrointestinal cancer, 12.5 U/ml for inflammatory bowel disease, and 6.5 U/ml for healthy controls. Among the gastrointestinal cancers the level was highest among pancreatic and biliary cancer at 58.6 U/ml, colorectal cancer had a mean value of 34.4 U/ml and gastric and oesophageal cancer had a mean value of 19.2 U/ml.

In colorectal cancer the sensitivity of tumour M2-PK at a cut-off of 18 U/ml was 67.6% compared with a sensitivity of 71% for CEA and 55.2% for Ca19-9.[185] Tumour M2-PK

can be detected and quantified in the faeces of patients with gastrointestinal cancer. Stool samples of 21 patients with colorectal cancer, 8 patients with colorectal adenomas and 49 healthy control subjects were analysed for tumour M2-PK. A mean tumour M2-PK level of 19U/ml was found for colorectal cancer, higher for colon cancer at 31.9 U/ml than for rectal cancer at 12.5 U/ml. In comparison adenomas had a mean tumour M2-PK level of 5.1 and controls 2.0 U/ml.[186]

In a recent study from Germany 60 patients with colorectal cancer and 144 patients without colorectal cancer provided stool samples for the determination of tumour M2-PK. There was a significant difference in tumour M2-PK levels, using a cutoff level of 4 U ml, the sensitivity for colorectal cancer was 73% and the specificity was 78%. In addition the stage of the tumour, both by Dukes' classification and TNM revealed a strong correlation between the amount of faecal tumour M2-PK and staging: sensitivities of 57% for T1, 59% for Dukes' A, and 78% for T4, 90% for Dukes' D.[187]

Conclusions

Colorectal cancer is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe.[188] Over the last decade the effectiveness of colorectal cancer screening has been established in international studies. The goal over the next decade is to implement organized colorectal cancer screening programmes. Many challenges exist: raising public awareness, raising political awareness, optimizing utilization of available financial and

clinical resources. The screening programmes adopted will differ from country to country depending on local resources, public will, and political willingness.

Aims

The aim of this thesis is to consider colorectal cancer screening in an Irish setting, both that of high-risk individuals and average-risk individuals:

- The feasibility of colonoscopy screening for high-risk individuals.
- Public awareness of colorectal cancer and how this may be increased with an information campaign.
- The support that might be expected from general practitioners in a screening programme.
- The compliance with an FOBT programme in Ireland.
- Assessing a novel screening tool for colorectal cancer screening, tumour M2-PK.

Chapter two

High risk individuals

Introduction

The risk of finding polyps and tumours at colonoscopy increases with age and is highest in those > 69 years of age, with an OR of 2.7, compared with those < 50 years of age.[189] Based on a family history of colorectal cancer it is possible to identify a group of individuals at a higher risk of developing colorectal cancer where screening at an earlier age is indicated. The clinical syndromes familial adenomatous polyposis and hereditary non-polyposis colorectal cancer account for 2-3% of colorectal cancer and unambiguous screening guidelines exist for these individuals.[30 51] Those at a moderate risk on the basis of their family history account for nearly a third of all colorectal cancer cases but are a more diverse group with ambiguous screening guidelines.[37 36] The benefit of screening those at moderate risk was most recently demonstrated in a 16-year prospective follow-up study. Screening colonoscopy in those with a moderate family history led to an 81% reduction in mortality from colorectal cancer.[190] From a population-based study of colorectal cancer cases in a Swedish county it is estimated that follow-up of relatives is required in every ninth individual with colorectal cancer, if both high and moderate familial risk is considered.[26]

I assessed the colonoscopy findings in those deemed to be at a higher risk of developing colorectal cancer based on their family history.

Methods

A family screening clinic was commenced to screen individuals at moderate risk of developing colorectal cancer based on family history. Individuals were deemed to be at moderate risk if they had one first-degree relative with colorectal cancer at any age; or more than one first-degree relative with colorectal cancer with none aged less than 50 years. All patients diagnosed with colorectal cancer in the hospital were invited to provide contact details of their first-degree relatives; their relatives were then sent appointments for the clinic. In addition general practitioners could refer individuals with a family history of colorectal cancer.

While there was no upper age limit a lower age limit of ten years younger than the index case at diagnosis was implemented. Individuals were assessed and after discussion on the risks and benefits were referred for a colonoscopy. A dedicated endoscopy screening list at weekly intervals was established to accommodate the screening colonoscopies. If colonoscopy was unsuccessful a barium enema was performed. Any polyps found at colonoscopy were removed endoscopically and sent for histological assessment. Those individuals with adenomatous polyps were subsequently scheduled for surveillance colonoscopy.

If any cancers were detected the cancer was initially staged by computerised tomography for colonic lesions, and by computerised tomography, endoscopic ultrasound and magnetic resonance imaging for rectal lesions. For curative colonic carcinoma surgical resection was offered followed by adjuvant chemotherapy in those subsequently found to

have tumour spread beyond the bowel or node positive disease. For curative rectal cancer total mesorectal excision was offered with down-staging pre-operative chemoradiotherapy for those with transmural or node positive disease.

Statistical analysis was carried out using the continuity correction for Pearson Chi-square on the SPSS software package.

Results

In total 405 of 476 (85%) individuals attended for colonoscopy over a three year period. The female to male ratio was 56.3% to 43.7%, with an average age of 48.34 years. (See table three.) Colonoscopy was incomplete in 4 individuals and a barium enema was performed in these individuals, a 98.7% colonoscopy completion rate. The colonoscopy was normal in 289 individuals (71.3%); hyperplastic polyps were present in 36 individuals (8.9%), adenomatous polyps in 74 individuals (18.3%) with high grade dysplasia being present in 8 of these individuals (2%), and cancer was present in 6 individuals (1.5%).

Of the 74 individuals with adenomatous polyps, multiple polyps were found in 9 (2.2%) tubular adenomas were present in 54 individuals, tubulovillous adenomas in 19 individuals, and villous adenomas in 2 individuals. Lesions were found in the caecum in 19.5%, ascending colon in 8.9%, transverse colon in 3.5%, descending colon in 13.3%, sigmoid in 31.8%, and rectum in 23%, with only 22% of individuals with right-sided lesions also having lesions on the left-side of the colon. (See figure five.)

	Individuals screened N=405
Sex:	
Female	**228 (56.3%)**
Male	**177 (43.7%)**
Age:	
Average	**48.34 years**
Range	**23-75 years**
% < 45 years	**39.5%**
% 46-60 years	**47.4%**
% > 60 years	**13.1%**
Referrals:	
GP referrals	**190 (46.9%)**
In-hospital referrals	**215 (53.2%)**
Cigarettes:	
Current smoker	**152 (37.5%)**
Ex-smoker	**24 (6%)**
Non-smoker	**229 (56.5%)**
First-degree relatives with CRC:	
One	**319 (78.8%)**
Two	**66 (16.3%)**
Three	**20 (4.9%)**
Index patient's relationship:	
Sibling	**248 (61.2%)**
Parent	**157 (38.8%**
Index patient's age:	
Average	**53.5 years**
Range	**27-82 years**
% < 45 years	**22.9%**
% 46-60 years	**50.1%**
% > 60 years	**20.6%**

Table three: Demographics of individuals screened.

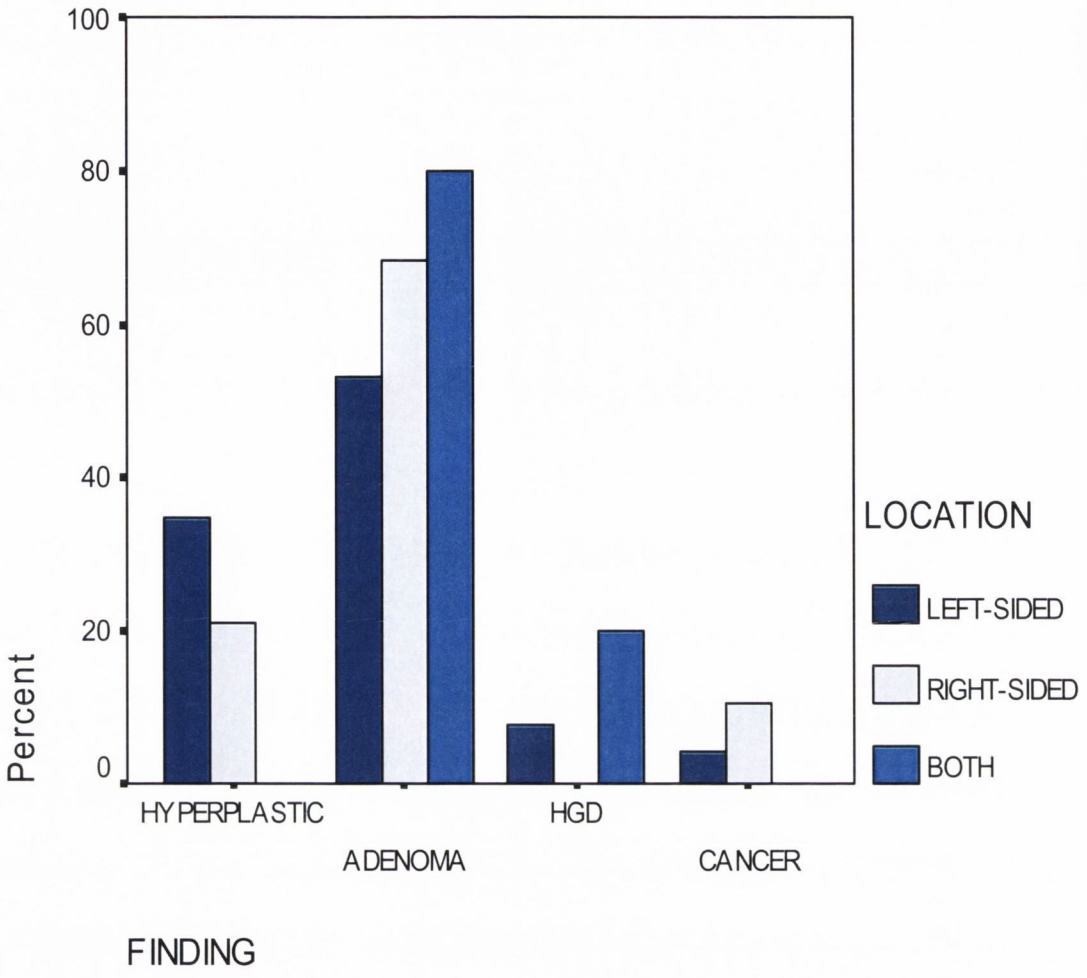


Figure five: Location of findings at colonoscopy.

More males than females had cancer or high-grade dysplasia at 8 compared with 6; however the numbers were too small to make this difference significant. (See figure six.) When adenomatous polyps, high-grade dysplasia and cancer were taken into account there was a statistically significant difference between males and females with 44 males having polyps, high-grade dysplasia or cancer, compared with 36 females, $p = 0.033$. The majority of individuals was non-smokers at 56.5%, 6% were ex-smokers, and just over a third, 37.5%, were current smokers. (See figure seven.) However smoking habit had no significant influence on the presence or absence of polyps or cancer.

Age did have a significant influence on colonoscopic findings. (See figure eight.) For those individuals aged less than 45 years of age 142 (88.7%) had no significant findings on colonoscopy, 18 (11.2%) had significant abnormalities detected with 2 having cancer or high-grade dysplasia and the remaining 16 having adenomatous polyps without high-grade dysplasia; For those aged 45-60 years 147 (76.5%) had no significant findings, 45 (23.4%) had significant abnormalities with 7 having cancer or high-grade dysplasia and 38 adenomatous polyps without high-grade dysplasia.; For those aged over 60 years no significant abnormalities were found in 36 (67.8%), 17 (32%) had significant findings with 5 having cancer or high-grade dysplasia and the remaining 12 having adenomatous polyps without high-grade dysplasia. There was a statistically significant difference between those aged less than 45 years and those aged more than 45 years for the presence of adenomatous polyps, high-grade dysplasia, and cancer with a p value of 0.001. However for cancer alone there was no significant difference with a p value of 0.077, perhaps due to the small numbers.

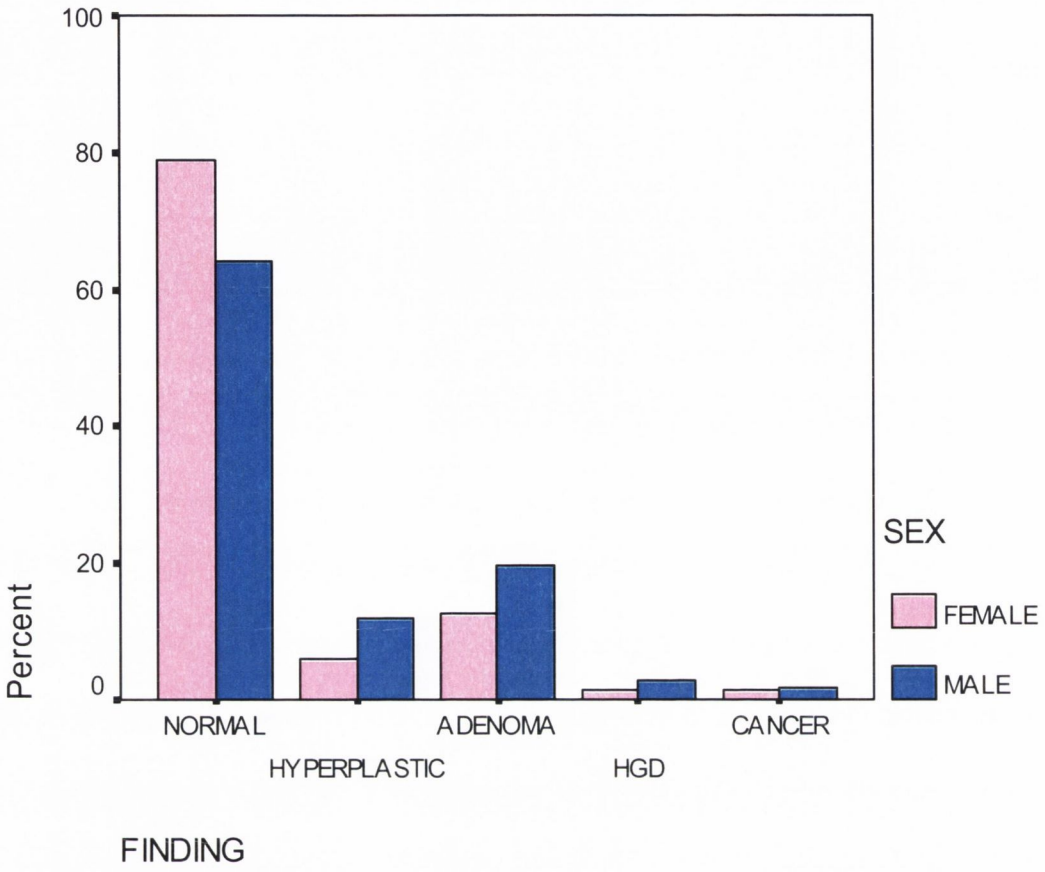


Figure six: Colonoscopy findings among males and females

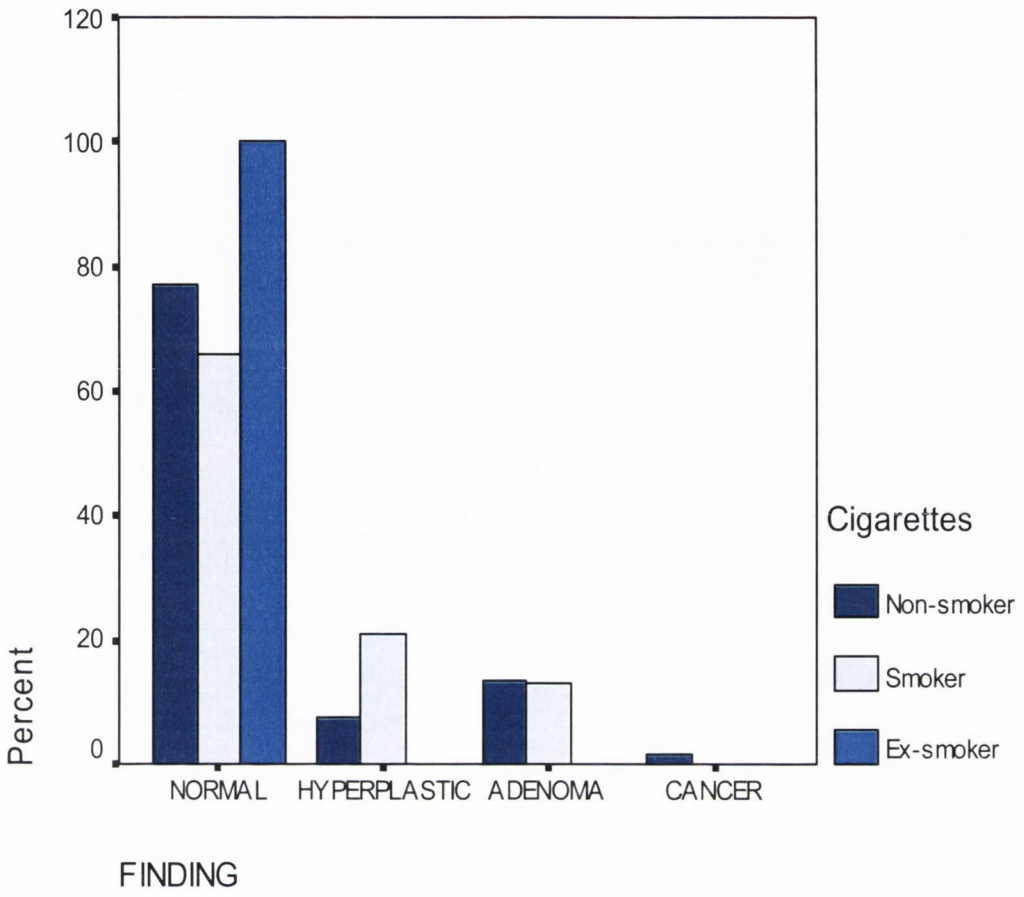


Figure seven: Smoking and colonoscopy findings.

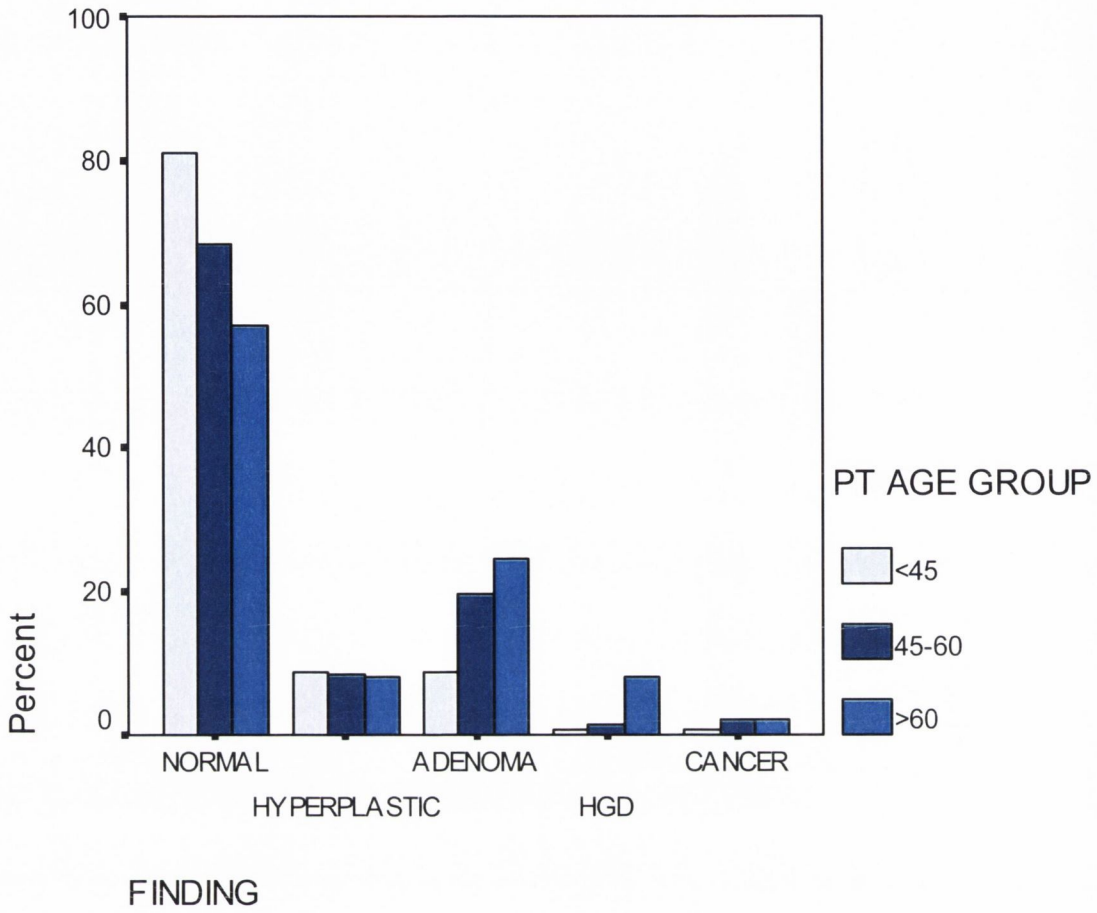


Figure eight: Colonoscopic findings relative to patients' age.

(HGD = high grade dysplasia)

There was no significant difference between those aged 45-60 years and those aged over 60 years for the presence or absence of adenomatous polyps, high-grade dysplasia, or cancer. If we limited colonoscopy to only those aged 45 years or more we would have avoided colonoscopy in 160 individuals. However we would have missed one adenocarcinoma, one tubulovillous adenoma with high-grade dysplasia, one villous adenoma, one tubulovillous adenoma, and fourteen tubular adenomatous polyps including one with multiple polyps. On the other hand if we limited colonoscopy to only those aged 40 years or more we would have avoided colonoscopy in 87 individuals and we would have missed only two individuals with tubular adenomatous polyps.

Somewhat surprisingly the age of our index patient had no significant bearing on the detection of lesions at colonoscopy among their first-degree relatives. (See figure nine.) Our index patients ranged in age from 27 to 82 years with an average age of 53.5 years. Among the first-degree relatives of those index patients aged less than 50 years no significant finding was found in 129 (82.7%), adenomatous polyps without high-grade-dysplasia were found in 22 (14.1%), and high-grade dysplasia or cancer was found in 5 (3.2%) individuals. For those first-degree relatives of index patients aged greater than 50 years no significant finding was found in 196 (78.7%), adenomatous polyps without high-grade dysplasia were found in 44 (17.7%), high-grade dysplasia or cancer was found in 9 (3.6%) individuals. The age of our index patient had no significant effect on the presence or absence of adenomatous polyps, high-grade dysplasia and cancer with a p value of 0.856.

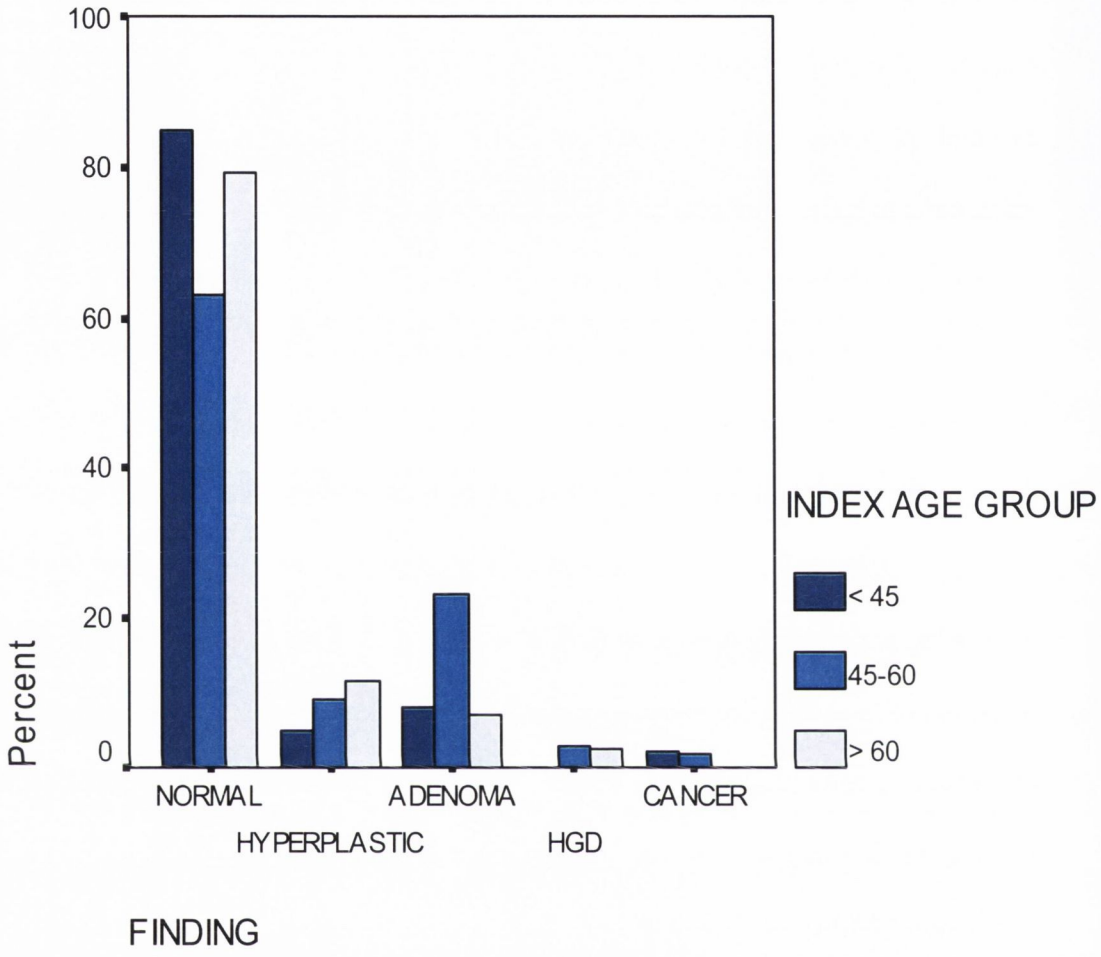


Figure nine: Colonoscopic findings relative to index patients' age.

(HGD = high grade dysplasia)

We found that the relationship of the index patient to the first-degree relative was important, with those who had a sibling with colorectal cancer more likely to have an adenomatous polyp, high-grade dysplasia, or cancer than those who had a parent with colorectal cancer, p= 0.001. (See figure ten.)

While 86 of our screened individuals had more than one first-degree relative with colorectal cancer, none met the criteria for Hereditary Nonpolyposis Colorectal Cancer. Interestingly we found no statistically significant difference between those who had one first-degree relative with colorectal cancer and those with more than one first-degree relative with colorectal cancer with a p value of 0.371.

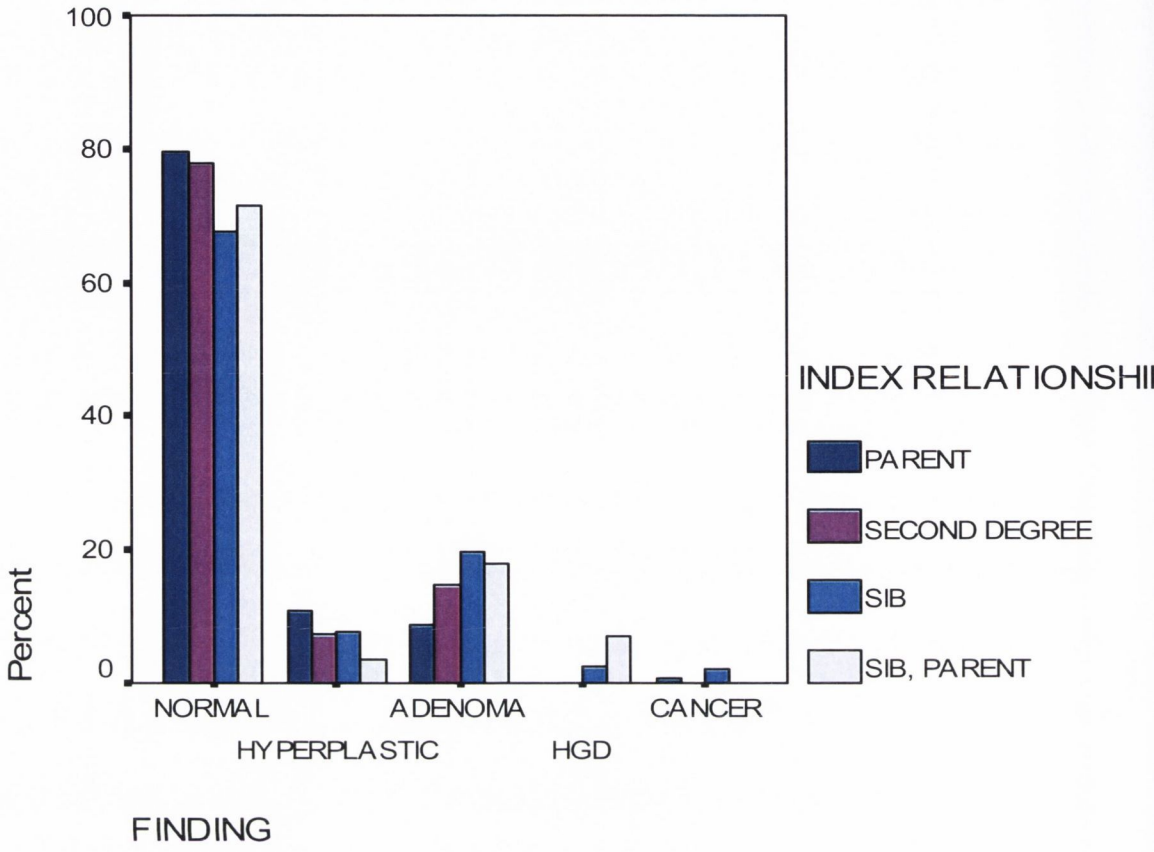


Figure ten: Colonoscopy findings according to relationship to index patient.

Discussion

In conclusion in this study of individuals with a moderate familial colorectal cancer risk we found adenomatous polyps in 18.3% with high-grade dysplasia in 2% of these, multiple polyps in 2.2%, and colorectal cancer in 1.5%. There is currently no colorectal cancer screening in Ireland for average risk individuals. However data from the National Cancer Registry of Ireland reveals an annual incidence of just under 2,000 for colorectal cancer with a European age-standardised rate of 40.09.[191] The age-standardised rate of colorectal cancer in our moderate risk population is 420 thus confirming they represent a group at higher risk of colorectal cancer than those without a family history of colorectal cancer.

Our findings are supported by a meta-analysis of 20 published case-control and 7 cohort studies which revealed a pooled relative risk of 2.25 for developing colorectal cancer among individuals with a first degree relative with colorectal cancer.[81] We found no increased risk for those with more than one affected first-degree relative compared with those with one affected relative, and no increased risk associated with the age of the index patient. This contrasts with the meta-analysis which found a pooled relative risk of 4.25 for those having more than one affected first-degree relative, and a pooled relative risk of 3.87 in relatives of cases diagnosed < 45 years and 1.82 in those > 59 years.[81] This difference may be explained by a failure to exclude those with HNPCC from the meta-analysis. None of the individuals in our study fulfilled criteria for HNPCC. Since this meta-analysis was published a large prospective colonoscopy study of 249 first-

degree relatives has failed to show a difference in the incidence of neoplasia according to the number of affected first-degree relatives.[75] And a recent population-based study showed no significant increased risk of developing colorectal cancer among individuals with a first-degree relative with colorectal cancer according to the index patient's age.[80]

We found that cancer or adenomatous polyps occurred more often when the affected relative was a sibling rather than a parent. We had found that the age of the screened individuals did have an influence on the colonoscopy findings with those aged less than 45 years of age significantly less likely to have cancer or adenomatous polyps compared with those over 45 years of age. Those with an affected parent were younger, mean age 42 years, than those with an affected sibling, mean age 51, which may account for the increased risk when the index case was a sibling rather than a parent. However the above meta-analysis contained fourteen studies reporting parent-offspring and sibling-sibling relative risk: The pooled relative risk for colorectal cancer when a parent was affected was 2.26, and when a sibling was affected was 2.57, supporting an increased relative risk when the index case is a sibling rather than a parent.

Smoking has been associated with an increased risk of colorectal neoplasia and in a cross-sectional study of 1988 patients attending for screening colonoscopy there was a statistically significant association between pack-years and the probability of a patient having significant colorectal neoplasia or any colorectal adenomatous neoplasia.[192] However in our study there was no significant difference in the presence of colorectal neoplasia among those who were current smokers, ex-smokers, or non-smokers.

Our data shows a significantly increased yield from screening colonoscopy as the age of the individual increased. Similar findings have been revealed in prospective colonoscopic studies of individuals with a moderate family risk of developing colorectal cancer.[66 72 190] We therefore do not believe there should be an upper age-limit for screening colonoscopy in those with a first-degree relative with colorectal cancer. However increasing the age at which individuals had their screening colonoscopy to 40 years would have eliminated the need for 87 colonoscopies, and the loss of detecting two tubular adenomatous polyps.

In conclusion in this study of individuals with a moderate familial colorectal cancer risk we found adenomatous polyps in 18.3% with high-grade dysplasia in 2% of these and multiple polyps in 2.2%, and colorectal cancer in 1.5%. The age of the index case and the number of first-degree relatives with colorectal cancer did not have a significant impact on the presence of neoplastic lesions. We recommend colonoscopy screening in all those with a first-degree relative with colorectal cancer, and our findings show that screening may begin after 40 years of age. In addition we find that screening should not be limited based on the index patient's age, individuals with a first degree relative with colorectal cancer at any age benefit from screening.

Chapter three

Average-risk individuals

Colorectal cancer is a major public health burden. It is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe.[188] The evidence that screening for colorectal cancer leads to earlier detection and improved survival is now incontrovertible and has led to a consensus that colorectal cancer screening will reduce mortality.[8 11 106-108 141 142]

For any screening programme to be effective an acceptance rate of over 60% is necessary. Little is known about the acceptability of colorectal cancer screening in Ireland. I decided to determine the acceptability of FOBT screening for colorectal cancer in an Irish population.

Method

Ethical approval was granted from the ethics committee of the Adelaide, Meath, and National Children's Hospital and St James Hospital. An FOBT screening pack was offered to 600 individuals, aged over 50 years, at two different work sites. The two sites chosen were the Adelaide Meath and National Children's Hospital, AMNCH, and the Construction Workers' Health Trust, CWHT. Individuals over the age of 50 years of age received information about colorectal cancer and were offered FOBT screening. The

completed FOBT kits were returned to the Department of Gastroenterology, AMNCH, and analysed centrally.

In AMNCH this took place during a week-long "Bowel Cancer Awareness Week". In the lead up to this week information leaflets and posters on colorectal cancer were designed in conjunction with the Health Promotion Unit and the Photography Department. During this week posters were displayed throughout the various departments and wards in the hospital and a stand was manned in the main concourse, adjacent to the canteen. All individuals over the age of 50 years were invited to participate in colorectal cancer screening, and the FOBT kits were given only to those who expressed interest.

The CWHT have a membership of 10,000 and their nurses visit the various building sites providing a health check with blood pressure monitoring, cholesterol, and glucose. A one-day training course on colorectal cancer symptoms, signs, and screening was held for the CWHT nurses. Following this the nurses offered FOBT kits to individuals who wished to be screened for colorectal cancer during their health check.

The FOBT screening pack consisted of an information leaflet on colorectal cancer, three guaiac-based FOBT kits and three stool applicators, an instruction leaflet on the utilization of the FOBT kits, and a biohazard return envelope.

The information leaflet and the instruction leaflet were designed with the aid of the Health Promotion Officer. The aim was to provide relevant and easily understood information on colorectal cancer symptoms and risk factors, and simple clear instructions on how to use the FOBT kits. Preliminary leaflets were designed and then reviewed by a working group of non-medical personnel. Following the input of the working group a final version of the information and instruction leaflet was prepared and brought back to the working group. The working group approved of our final version (see appendices).

The guaiac-based FOBT Hemoccult II was used. No dietary restrictions were necessary and no medications were stopped prior to completing the FOBT kits. Stool samples were collected on three separate days, with the three FOBT kits and applicators for each separate day. Name, contact details, and the date the kit was used were written on the back of the kit prior to usage. The stool samples could not touch the toilet water and the stool applicator was used to apply a sample of stool to each of the two windows on the FOBT kit visible when the flap of the kit was peeled back. The flap was then closed. The kits could keep for several months unopened but once completed had to be returned within 14 days for testing.

A positive FOBT depended on fecal blood to catalyze the phenolic oxidation of guaiac in the presence of hydrogen peroxide to produce a blue chromogen. If any one of the six windows produced a blue colour the FOBT was deemed positive. All individuals with a negative FOBT were informed of the result, but advised to seek further medical opinion

if they developed any symptoms in the future. All individuals with a positive FOBT were informed of the result and offered a colonoscopy.

Colonoscopy was performed at the gastroenterology department in AMNCH. Any polyps found at colonoscopy would be removed and sent for histological assessment. If adenomatous polyps were confirmed the individual would then enter a surveillance colonoscopy programme. If a colorectal cancer was found at colonoscopy individuals would be staged with computerised tomography for colonic cancer, and magnetic resonance imaging and endoscopic ultrasound scan for rectal cancer. If the cancer was believed to be resectable curative surgery would be offered together with adjuvant or preoperative chemoradiotherapy as found to be appropriate.

Results

In AMNCH 300 individuals agreed to participate in colorectal cancer screening and were offered FOBT kits. Of these 300 individuals only 89, 29.6%, completed and returned their FOBTs: 66 females and 23 males. None of the 89 FOBT kits were positive and no colonoscopy was necessary.

In the CWHT the FOBT kits were offered to 300 individuals. Only 73 individuals agreed to participate and of these individuals only 15, 20.5%, completed and returned their FOBTs: all males. Two individuals with a positive FOBT have had a colonoscopy which was normal.

Overall the positivity rate of the FOBT was 1.9%.

Discussion

Our compliance rate with FOBT among individuals who agreed to participate was 28%: 29.6% in AMNCH and 20.5% in CWHT, much lower than we had anticipated. The positivity rate of the FOBT at 1.9% is in keeping with other studies for an unrehydrated guaiac-based FOBT, but with the small numbers involved no colorectal lesions were detected.[9] In view of this no conclusions of the sensitivity and specificity of FOBT in an Irish setting can be reached.

Colorectal cancer is definitely a disease people don't want to talk about, in a place people don't want to think about. The major barrier identified with colorectal cancer screening again and again is embarrassment.[193 194] Education and public awareness is the key to supporting screening. Efforts were made in this study to improve education and public awareness. This information campaign was more intensive in AMNCH with a week-long "Bowel Cancer Awareness Week". Because of the dispersed nature of the workers with the CWHT this intensive campaign was not possible: Individuals received information on only the one occasion when they visited the site nurse for their health check. This was reflected in the compliance rates of 29.6% in AMNCH and 20.5% in CWHT providing encouragement that a public awareness campaign can influence compliance. A more prolonged public awareness campaign with involvement of the national media and high-profile campaigners would undoubtedly influence compliance further. Lessons can be

learnt both from national campaigns in other countries and the experience of our colleagues in BreastCheck.

Members of the medical and nursing profession also have an important role to play as advocates for colorectal cancer screening. Physician recommendation is one of the key elements in influencing colorectal cancer screening uptake.[194 195] General practitioners, GPs, were not involved in our screening programme, yet studies from both the UK and France reveal that compliance can vary from under a third to over three-quarters depending on the GP's practice involved.[8 196] This has been presumed to reflect the GP's enthusiasm for and recommendation of colorectal cancer screening. Achievement of high levels of colorectal cancer screening uptake is possible when efforts to encourage screening are sustained and are incorporated into the routine preventive health care available.[197]

In conclusion although our compliance rate with FOBT was disappointingly low at 28% we have shown that a more intensive public awareness campaign did yield higher compliance rates: 29.6% versus 20.5%. As demonstrated internationally with colorectal cancer screening and nationally with BreastCheck a national public awareness campaign with high-profile support and advocacy from the healthcare profession should improve uptake further to acceptable levels.

Chapter four

A national screening programme

Introduction

Colorectal cancer is a major public health problem and is the leading cause of morbidity and death from cancer in Europe, with the incidence steadily increasing in both males and females.[198] In Ireland 1730 patients with colorectal tumours are diagnosed each year with 925 deaths occurring.[191] Evidence from several studies reveal that mortality can be reduced by screening and cost-effectiveness analyses have shown that screening for colorectal cancer, even in the setting of imperfect compliance, significantly reduces mortality, with costs in favor of or comparable to, other already implemented cancer screening procedures.[8 92 141 142]

Successful implementation of a screening programme is a two-step process: instigating the screening programme and achieving high compliance rates. Colorectal cancer screening without sufficient compliance can never be cost effective and will not influence prognosis significantly.[199 200] The awareness of the Irish public regarding the risks of colorectal cancer and its symptoms are among the lowest in the European Community, which might adversely affect compliance with any screening programme. In a questionnaire which involved a sample population of 1000 adults from 21 countries only a third of Irish people were aware of the risk factors for colorectal cancer; less than three

quarters realized that a diet high in fruit and fiber reduced the risk of colorectal cancer. Awareness of colorectal cancer in Ireland was the fifth lowest in Europe with just over 10% very aware of colorectal cancer and 65% somewhat aware.[201] Increased awareness of the nature and course of the disease will likely influence acceptance of, response to, and compliance with a screening protocol.

Furthermore screening uptake is shown to be significantly influenced by physician recommendation.[193 194] Indeed recommendation by general practitioners (GPs) is cited as the primary motivation for compliance by those participating in screening, at 58.7%, with leaflets in the mail influencing 36.95%, and surprisingly the impact of media influencing just 9.65%. Compliance with faecal occult blood screening, FOBT, was as low as 32.4% when mailed to participants and followed with a reminder letter, but reached 81.4% when the test was proposed by GPs.[202]

Uptake of colorectal cancer screening needs to be over 60% to be effective and a public awareness campaign is fundamental to any screening programme to help achieve this. Given the low awareness of colorectal cancer in Ireland we wanted to determine if a public awareness campaign would increase knowledge of colorectal cancer. The role of GPs in any screening programme is vital, both to increase knowledge and awareness of colorectal cancer and to encourage participation in screening. We sought to determine the attitudes of GPs towards colorectal cancer screening, and the degree of support that might be anticipated in a national screening programme.

Materials & Method

A questionnaire was sent out to 1,500 employees of the Adelaide & Meath Hospital. (See attached to appendices.) Demographic details and area of work were sought; the knowledge of the risk factors and symptoms of colorectal cancer and beliefs surrounding colorectal cancer screening were ascertained using a previously validated questionnaire. This questionnaire was formerly validated in a study involving 1,000 individuals across 21 countries in Europe, including Ireland.[201]

With the aid of the Health Promotion Officer a working group composed of non-medical personnel was assembled to design posters and information leaflets on colorectal cancer that would catch the attention of an Irish population and provide relevant and easily understood information on colorectal cancer symptoms and risk factors. A week long "Bowel Cancer Week" was then held in the hospital commencing with a reception to launch the posters and information leaflets. During the week posters were displayed throughout the hospital and an information stand was manned in the hospital concourse. At this stand information leaflets were provided to both the staff and public, and any questions on colorectal cancer were answered. After the information week the questionnaire was re-sent to all staff to establish if the information campaign had increased awareness of colorectal cancer or altered the perception of colorectal cancer screening.

A second questionnaire was sent to 600 GPs in Ireland assessing knowledge, belief and practices regarding colorectal cancer screening. (See attached to the appendices.) Along

with demographic details knowledge surrounding current screening tools was ascertained; the sensitivity and reduction in mortality associated with screening programmes utilizing faecal occult blood testing, FOBT, sigmoidoscopy, colonoscopy, or barium enema. The support for a national screening programme for colorectal cancer was sought and potential barriers identified. Whether colorectal cancer screening was currently discussed or offered to patients and colorectal cancer risk stratification of patients was determined. An initial draft of the questionnaire was sent to 50 GPs. No ambiguous questions were identified and the questionnaire was then sent to the remaining 550 GPs. A reminder and second questionnaire was sent out to all GPs two months after the first questionnaire to increase the response rate.

Statistical analysis was carried out using SPSS software.

Results

Posters and information leaflets

An information leaflet on colorectal cancer and a number of posters intended to stimulate interest in colorectal cancer were designed and presented to the working group. The benefit of the non-medical working group was revealed in the number of alterations and clarifications required in the information leaflet. And what medical personnel viewed as a catchy slogan and poster on colorectal cancer was neither instantly appealing nor memorable to the working group. (See table four.) The working group took it upon themselves to design a better poster.

SLOGAN SUGGESTED	GROUP REACTION
No BUTS think of your GUT	Made group think of the smoking ban instead.
The guts of the matter	Felt it was interesting and might catch attention but would need further explanation.
How fab are your abs	Men did not like it, women liked it, thought it would be best for a younger age group.
Keep tabs on your abs	Thought it was catchy, what image to put with it was difficult.
Bottoms up	Felt it suggested an alcohol awareness campaign.
Don't flush it all away	Wanted no mention of bowel motions. Wanted no picture or cartoon of a toilet.
Know your crap	Some found the word crap offensive, felt it would be best for a younger age group
Gut sense	Felt it was alright but did not want a picture or cartoon of the bowel.
Do you know your colon :	Felt it was the best of the choices available.

Table four: Slogans on posters suggested to the group.

The slogan, "Are you a regular guy?" grew from a pun on the word stool with a bar stool representing a bowel motion. The relevance of a change in bowel habit to colorectal cancer then became "Are you a regular guy? Know the facts on Bowel Cancer" with the poster a photograph of three men at a bar. Although the men in the group felt this would work the women felt excluded by the phrase, "Are you a regular guy?", and found the bar scene unappealing. In the end the women came up with the slogan, "Look after your own! Know the facts on Bowel Cancer" with the poster a sketch of a female bottom. The working group felt that two different posters would be needed to appeal to both sexes.

Staff questionnaire

The first questionnaire yielded 757 (50%) respondents: 314 (41%) < 30 years, 252 (33%) 30-40 years, 181 (24%) 40-50 years, 1 (1%) > 50 years; 648 (87%) female and 99 (12%) male. 1% declined to give age or sex. As regards their background (246) 32% were administration or clerical staff, (134) 18% allied health – from departments of physiotherapy, speech and language, occupational therapy, social work, and radiology, (242) 32% clinical – medical or nursing personnel, (120) 16% services, and 2% did not provide their work area.

Overall 49% of respondents were aware that colorectal cancer is the most common cancer in Europe, and as shown in figure eleven there was no significant statistical difference between age < 40 years and > 40 years; male or female; clinical personnel or non-clinical personnel. With regard to knowledge of risk factors for colorectal cancer

459, 60%, recognized that life style played a role, 593, 78%, recognized family history was important, 537, 71%, realized that increasing age led to an increasing risk of colorectal cancer, and 289, 39%, knew that men were at a higher risk than women for colorectal cancer. (See table five for breakdown according to age, sex, and occupation.)

Symptoms of colorectal cancer were correctly identified by 523, 69%, with 160, 21%, unsure, and 59, 8%, not recognizing warning symptoms for colorectal cancer. From a health promotion view point the promising result was that 665, 88% realized that increasing fruit and vegetable intake reduced the risk of colorectal cancer with just 21, 3%, not aware, and 62, 8%, unsure. Exercise was not as well recognized as a protective factor with just 360, 48%, aware that it reduced the risk of colorectal cancer, 141, 18%, not aware, and 245, 32%, unsure.

Although only 331, 43%, knew that colorectal cancer develops over many years and so is one of the most successfully treated cancers, 619, 82%, felt if it was diagnosed early it could be treated easily. With regard to screening 574, 76%, stated that screening would reduce mortality by half, yet only 409, 54%, knew there was a simple screening test: 78, 10% thought there wasn't a simple screening test, and 340, 45%, were unsure. An overwhelming 723, 96%, felt embarrassed discussing bowel symptoms with their doctor and delayed doing so. Somewhat more reassuringly 664, 88%, said they would avail of a simple screening test.

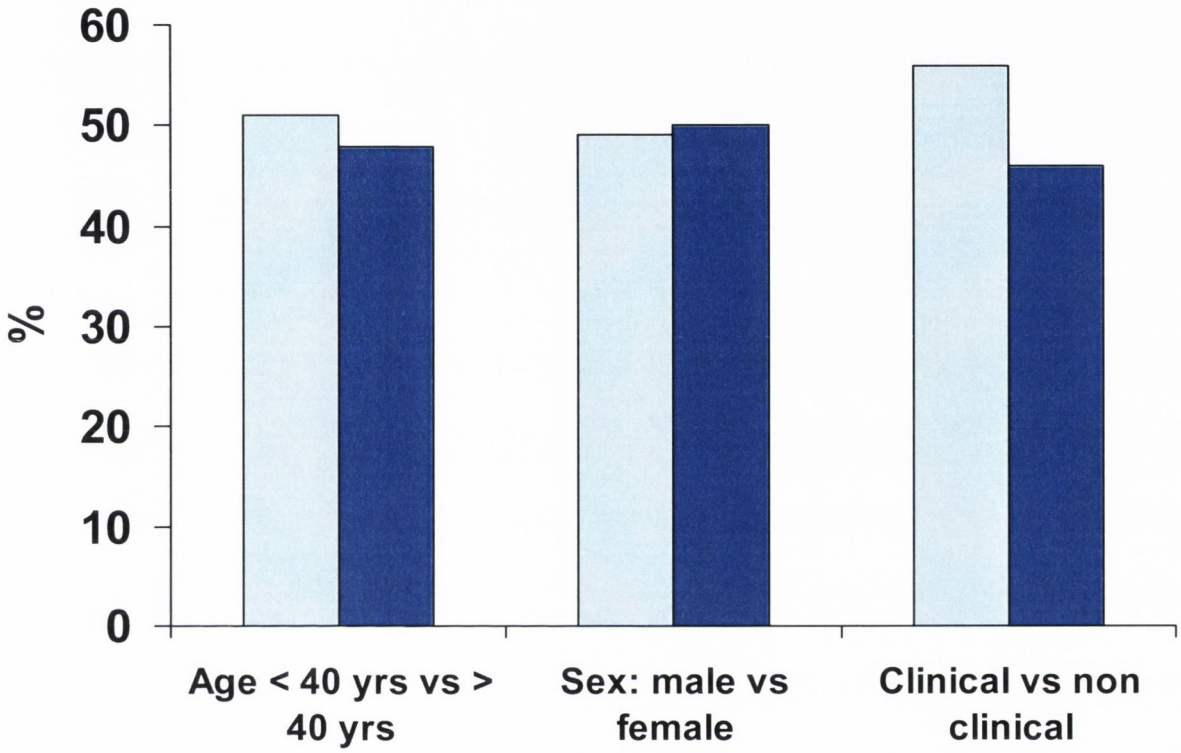


Figure eleven: Those who correctly answered the question, "What is the most common form of cancer in Europe", according to age, sex, and occupation.

	AGE		GENDER		OCCUPATION	
	< 40 yrs n=566	> 40 yrs n=182	Male n=99	Female n=648	Clinical n=242	Non-clinical n=500
RISKS FOR CRC:						
Family history	79%	80%	66%	81%	86%	76%
Increasing age	73%	69%	73%	72%	82%	67%
Gender	37%	41%	45%	38%	47%	35%
REDUCING CRC RISK:						
Altering lifestyle	63%	60%	61%	62%	72%	56%
Increased fruit & veg	87%	91%	86%	89%	87%	90%
Increased exercise	48%	49%	55%	47%	52%	47%
SYMPTOMS OF CRC:						
Change in bowel	72%	67%	62%	71%	85%	62%
Blood in stool	92%	90%	80%	93%	96%	89%
Weight loss	92%	90%	80%	93%	96%	90%
TOO EMBARASSED TO GO TO DOCTOR:	96%	96%	88%	98%	97%	96%
SCREENING FOR CRC:						
Easily treated if diagnosed early	82%	84%	93%	90%	93%	89%
CRC takes many years to grow	43%	57%	40%	45%	52%	40%
Simple screening tool available	53%	57%	56%	55%	59%	52%
Routine screening can half the number who die	75%	78%	72%	78%	75%	77%
WOULD YOU AVAIL OF SCREENING:	86%	92%	92%	88%	86%	90%

Table five: Break-down of correct answers according to age, gender, and occupation.

The repeat questionnaire administered after the "Bowel Cancer Awareness Week" yielded 302 (20%) respondents: 80 (26%) were under 30 years, 96 (32%) were 30-40 years, 75 (25%) were 40-50 years, and 50 (17%) were over 50 years; 254 (84%) were female and 44 (15%) were male. Their background was administration/clerical staff in 107 (35%) cases, allied health in 62 (21%), clinical in 82 (27%), and services in 49 (16%).

The repeat questionnaire revealed an improvement in colorectal cancer knowledge with 57% now recognizing that colorectal cancer is the most common cancer in Europe. (See figure twelve.) Risk factors associated with colorectal cancer were increasingly recognized with 218, 72% identifying that life style played a role, 245, 82%, aware of family history, 236, 78%, now realized that increasing age led to an increasing risk of colorectal cancer, and 132, 44%, knew that men were at a higher risk than women for colorectal cancer. (See table six for breakdown according to age, sex, and occupation.)

Encouragingly for early detection 228, 75%, were now aware of the symptoms of colorectal cancer with just 39, 13%, unsure, and 24, 8%, not recognizing warning symptoms for colorectal cancer. On a more negative note 281, 93%, still felt they would delay going to their doctor because of embarrassment over the symptoms. More were aware of the benefits of a healthy lifestyle with 273, 90%, stating fruit and vegetables would reduce the risk of colorectal cancer and 179, 59% wise to the benefits of exercise.

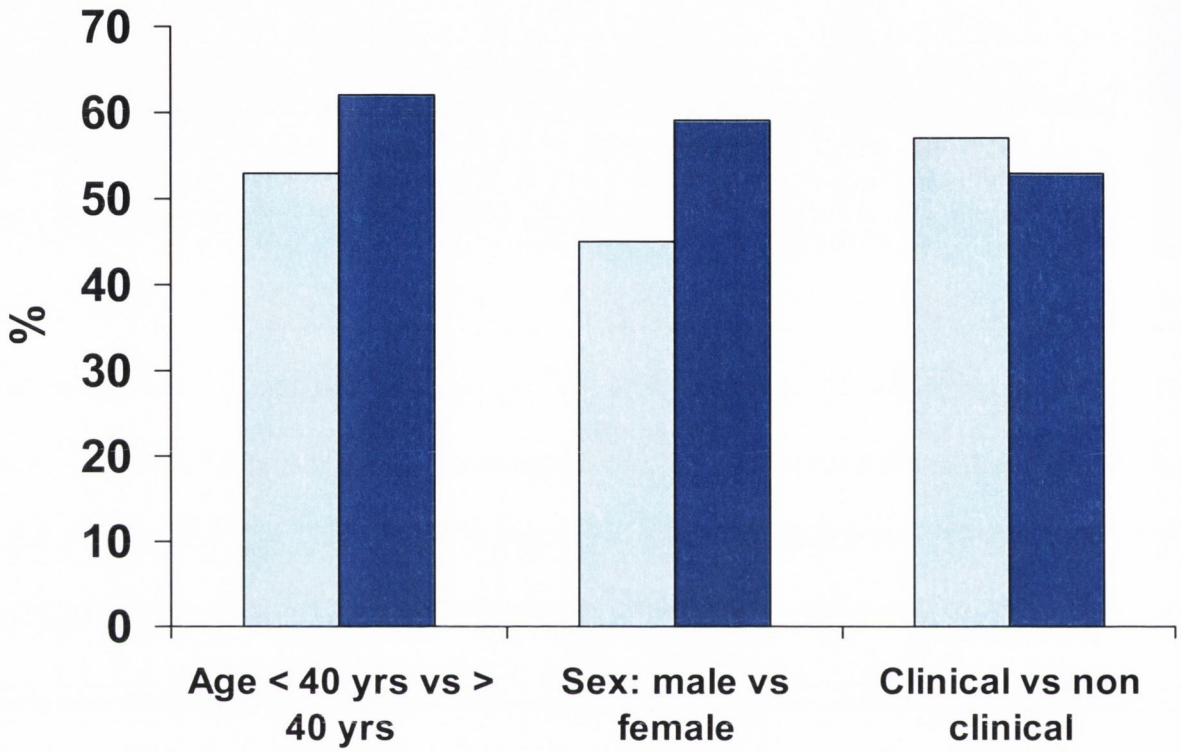


Figure twelve: Those who correctly answered the question, "What is the most common form of cancer in Europe", according to age, sex, and occupation on repeat questionnaire.

	AGE		GENDER		OCCUPATION	
	< 40 yrs n=176	> 40 yrs n=125	Male n=44	Female n=254	Clinical n=82	Non-clinical n=218
RISKS FOR CRC:						
Family history	85%	76%	79%	82%	86%	79%
Increasing age	77%	80%	84%	78%	89%	74%
Gender	43%	44%	54%	41%	49%	42%
REDUCING CRC RISK:						
Altering lifestyle	75%	62%	45%	59%	57%	57%
Increased fruit & veg	90%	92%	88%	92%	96%	89%
Increased exercise	58%	63%	60%	60%	63%	59%
SYMPTOMS OF CRC:						
Change in bowel	76%	80%	80%	80%	90%	74%
Blood in stool	90%	93%	81%	93%	97%	88%
Weight loss	90%	93%	81%	93%	97%	88%
TOO EMBARASSED TO GO TO DOCTOR:	95%	93%	88%	95%	94%	95%
SCREENING FOR CRC:						
Easily treated if diagnosed early	88%	93%	93%	90%	93%	89%
CRC takes many years to grow	55%	68%	56%	61%	63%	59%
Simple screening tool available	72%	81%	77%	76%	76%	76%
Routine screening can half the number who die	88%	90%	83%	90%	85%	91%
WOULD YOU AVAIL OF SCREENING:	87%	91%	93%	88%	88%	89%

Table six: Break-down of correct answers according to age, gender, and occupation on repeat questionnaire

The "Bowel Cancer Awareness Week" improved knowledge of colorectal cancer with 179, 59%, aware that colorectal cancer develops over many years and 270, 89%, believing that if diagnosed early it could be treated easily. There was also an enhanced awareness of screening with 227, 75%, aware of a simple screening tool and 265, 88%, aware that this would reduce colorectal cancer mortality by half.

GP questionnaire

The questionnaire was returned by 433, 72%, of the GPs. Their ages ranged from 29-85 years with a mean of 50 years; 67.7% were male and 32.3% female. (See table seven.) The years spent working as a GP ranged from 1-55 years with a mean of 21.56 years. The majority of practices were urban with 2-4 doctors in attendance. A receptionist was employed by 88.4%, a secretary by 80.5%, and a nurse by 77.5%, with 84.7% of practices computerised.

Colorectal cancer screening was discussed with patients by 80.7% of GPs: 4.6% discussed screening with all their patients, 77.2% with those felt to be at high-risk, 4.6% only with those patients that asked, and 13.5% with those at high risk and those that asked. Screening for colorectal cancer was offered by 72.9% of GPs: 4.7% offered screening to all patients, 57.3% only to those at high-risk, 5.6% to those that asked, and 32.4% to those at high-risk and those that ask.

Several vignettes representing patients at low, average, or high risk of developing colorectal cancer were presented. Low risk was attributed by 67.6% to an asymptomatic 45 year old patient. An asymptomatic 65 year old patient was felt to be at average risk by 70.3%, however 26.2% felt such an individual was at a high risk.

CHARACTERISTICS:	N (%)
Age: Mean Range	50.09 yrs 29-85 yrs
Sex: Male Female	293 (68%) 140 (32%)
Years as GP: Mean Range	21.56 yrs 1-55 yrs
Practice: Urban Rural Mixed	187 (33%) 137 (32%) 109 (25%)
GPs in practice: Single 2-4 5-6 > 6	144 (33%) 238 (55%) 43 (10% 8 (2%)

Table seven: Demographic details of GP respondents

Colorectal cancer risk is increased by having a family history of colorectal cancer and nearly all, 99.3% identified a family history of hereditary nonpolyposis colorectal cancer as being at high risk with only 0.7% ascribing this family history to average risk, 96.1% attributed a high risk to a patient with just one first-degree relative with colorectal cancer albeit at an early age of 45 years, and 47.5% attributed a high risk to a patient with one first degree relative with colorectal cancer aged 65 years.

Ulcerative colitis over time increases the risk of colorectal cancer and 91.6% identified a patient with ulcerative colitis for 15 years as being at high risk, with 8.4% considering this average risk. For a patient with ulcerative colitis for only 5 years 36.5% thought this was high risk and 59% average risk.

The majority of GPs felt there was a need for a national screening programme at 88.1%, 2.4% were unsure and 9.5% felt there was no need currently. With respect to which screening tool to use in a national programme, colonoscopy was the preferred method of screening at 35.4%, followed by FOBT at 18.1%, virtual colonoscopy at 10.4%, and sigmoidoscopy at 3.8%, 3.5% were unsure of the best screening tool and the remainder preferred a combination of screening tools. (See table eight.)

As regards the sensitivities of each screening tool colonoscopy was felt to be the most sensitive with 72.2% believing its sensitivity lay in the range of 75-100%, and FOBT was thought to be the least sensitive with 39.2% believing its sensitivity lay in the range of 0-25%. (See table nine.)

SCREENING TOOL PREFERRED	PERCENTAGE
Colonoscopy	35.4%
FOBT	18.1%
Virtual colonoscopy	10.4%
Sigmoidoscopy	3.8%
FOBT, colonoscopy	11.9%
Colonoscopy, virtual colonoscopy	6.2%
FOBT, virtual colonoscopy	1.8%
FOBT, colonoscopy, virtual colonoscopy	1.5%
FOBT, sigmoidoscopy, colonoscopy	1.5%
Colonoscopy, barium enema	1.2%
Sigmoidoscopy, colonoscopy	0.8%
FOBT, colonoscopy, barium enema	0.8%
FOBT, sigmoidoscopy	0.8%
Colonoscopy, virtual colonoscopy, barium enema	0.8%
Barium enema, virtual colonoscopy	0.8%
FOBT, sigmoidoscopy, colonoscopy, virtual colonoscopy, barium enema	0.8%
Colonoscopy, virtual colonoscopy, sigmoidoscopy	0.4%
Unsure	3.5%

Table eight: GP's preferred screening tool.

SCREENING TOOL	SENSITIVITIES			
	0-25%	25-50%	50-75%	75-100%
FOBT	39.2%	40.3%	16%	4.4%
Sigmoidoscopy	9.6%	41.2%	36.8%	12.4%
Colonoscopy	0%	1%	26.9%	72.1%
Barium enema	1.4%	22.9%	50.7%	25%
Virtual colonoscopy	0.8%	9.1%	39.9%	50.2%

Table nine: Presumed sensitivities for each screening tool.

There was no surprise therefore that colorectal cancer mortality reduction was perceived as greatest with colonoscopy and least with FOBT. (See table ten.) A one-way analysis of variance showed that perceived sensitivity and colorectal cancer mortality reduction associated with FOBT had a significant effect on which screening tool was chosen for a national screening programme. The perceived sensitivity associated with sigmoidoscopy, colonoscopy, or barium enema had no significant effect on the screening tool selected. The perceived mortality reduction associated with colonoscopy did however have a significant effect on the choice of screening tool.

Participation in a national screening programme was not significantly affected by age, sex, years in general practice, the type of practice i.e. whether urban, rural or mixed, or the size of the practice. Interestingly participation was not affected by how sensitive each of the screening tools was deemed or by how much colorectal cancer mortality was perceived to be reduced by the screening tools.

The main barrier to a national screening programme was considered to be a lack of resources by 93.4%. Other significant barriers identified were a lack of national guidelines by 85.9%, and lack of time by 82.2%. The evidence for colorectal cancer screening was thought to be sufficient by 67% of GPs, however just over half of GPs were happy with current screening tools with 45.8% finding them inadequate.

SCREENING TOOL	MORTALITY REDUCTION				
	0-25%	25-50%	50-75%	75-100%	Unsure
FOBT	51.3%	35%	10.6%	1.1%	1.9%
Sigmoidoscopy	16.7%	48.3%	29.3%	3.8%	1.9%
Colonoscopy	2.7%	22.1%	50.8%	22.5%	1.9%
Barium enema	12.3%	38.8%	37.3%	9.6%	1.9%
Virtual colonoscopy	5.9%	24%	47.5%	19%	3.6%

Table ten: Presumed mortality reduction with each screening tool

An obvious concern for 59.8% was the worry that symptomatic patients might face longer delays. As regards the pitfalls of screening GPs were split on this, 46.8% being concerned over false negatives and another 49.1% being concerned over false positives.

Despite these obstacles the vast majority of GPs, 93.9%, said they would participate in a colorectal cancer screening programme, and 90.8% said they themselves would avail of colorectal cancer screening.

Discussion

An effective screening programme needs all involved to buy into it. The general population needs to be aware that when diagnosed early colorectal cancer can be treated very easily, that the mortality from colorectal cancer can be halved through screening, and that a simple screening tool exists that can be carried out at home. GPs have a fundamental role in encouraging participation in screening and their willingness to support colorectal cancer screening is necessary for success.

The staff questionnaire revealed fair to good knowledge of the predisposing factors and symptoms of colorectal cancer, 39-78%. Although over three-quarters, 76%, optimistically believed that screening would reduce colorectal cancer mortality just 54% were aware of a simple screening test. Similar to our results a pan-European questionnaire revealed that only a third of Irish people were aware of the risk factors for colorectal cancer and less than three quarters realized that a diet high in fruit and fiber reduced the risk of colorectal cancer. Awareness of colorectal cancer in Ireland was the

fifth lowest in Europe with just over 40% aware that colorectal cancer developed slowly over many years and less than 75% aware that colorectal cancer was easily treated if diagnosed early.[201] Our questionnaire revealed similar levels of awareness surrounding colorectal cancer.

Interestingly we found that nearly all individuals would delay attending a doctor due to embarrassment over symptoms. In contrast the pan-European survey found that just under three-quarters of Irish respondents would be too embarrassed to go to their doctor with symptoms.[201]

The repeat questionnaire following the information campaign revealed an improvement in colorectal cancer screening knowledge. The success of screening will ultimately depend on the success of measures to improve compliance. Interventions designed to increase screening uptake have focused on education, risk perception strategies, and perceived benefits with successful treatment of early diagnosis.[194] We have shown that awareness of colorectal cancer can be enhanced and this should lead to improved compliance and hence success of any colorectal cancer screening programme.

A national screening programme for colorectal cancer was supported by 88% of GPs. With GP recommendation one of the major influencing factors in colorectal cancer screening uptake this level of support is crucial for the success of a colorectal cancer screening programme.[194 195 202] Although colorectal cancer screening is currently discussed by most GPs with their patients in 95.3% of cases this is only with patients felt

to be at high-risk or those who ask about screening. With the implementation of a colorectal screening programme our questionnaire suggests that GPs would discuss screening with all their patients.

Our questionnaire revealed that the preferred screening tool was colonoscopy at 35% with FOBT being favoured by 18%. However the sensitivity of FOBT was under-estimated and this may have influenced the choice of screening tool.

A major concern of GPs was the impact the screening programme might have on symptomatic patients with 59.8% worried about longer delays for symptomatic patients. This is a genuine concern as the introduction of screening programmes invariably leads to increased presentation of symptomatic patients due to the increased levels of public awareness of symptoms. In-built into any screening programme must be the capacity to deal with the increase in symptomatic patients.

In the UK FOBT screening pilot colonoscopy workload increased by up to 80% during some months. In addition to the expected increase from "pilot" colonoscopies there was an increase in "symptomatic" patients. Despite the provision of dedicated screening colonoscopy sessions hospitals were unable to maintain a 2-4 week waiting time for "pilot" colonoscopies. In all areas FOBT screening were suspended on occasion due to pressure on endoscopy services.[102] From this it was recommended by the UK CRC screening pilot evaluation team that waiting times for symptomatic patients should be reduced to 2-4 weeks before commencement of screening.

Quality assurance is another key element of any screening programme. This was highlighted by the GPs in our survey with half of the respondents concerned about false positives and false negatives.

Overall though the main barrier to a screening programme was felt by GPs to be a lack of resources and just over 70% of GPs stated that additional staff and incentives to participate would be required. One-third of our respondents were single-practice GPs and just over half worked in practices with 2-4 GPs: One-fifth had no secretary, one-tenth had no receptionist, and over one-tenth were not computerised. The Department of Health and Children in Ireland have recognised the poor infra-structure in the community and in their strategic management approach outlined in *Primary Care Strategy 2001* and *Quality and Fairness 2001* have emphasized how they will improve this. Primary care teams and primary care networks are being developed and will enable GPs to support screening programmes.

In addition the Department of Health and Children in their 2006 *Strategy for Cancer Control in Ireland* highlighted that the aging of our population will result in an approximate doubling in the number of people who will develop cancer in Ireland over the next 15 years and advocated the need for a comprehensive cancer control policy programme: a whole population, integrated and cohesive approach to cancer involving prevention, screening, diagnosis, treatment, and supportive and palliative care. In line with the *Primary Care Strategy 2001* it states that GPs are pivotal in the coordination of

the wide variety of services that patients may use and are a key partner in the delivery of effective secondary care services.

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Chapter five

A novel screening marker

Introduction

Colorectal cancer is the leading cause of mortality from cancer in Europe. In population-based studies the overall five-year survival from colorectal cancer is only sixty percent, which reflects the fact that a large number of patients present at a late stage [1]. Survival from cancer depends on the degree to which the cancer has spread and early colonic cancer has a five year survival in excess of 97% [2]. Colorectal cancer screening has been shown to reduce mortality. The most robust evidence supports faecal occult blood testing with a reduction in mortality of 12-33% [9]. However the sensitivity of faecal occult blood testing for colorectal cancer ranges from 26-69%, and for adenomas ranges from 9-36% [111 134 140]. The ideal screening tool for colorectal cancer should be non-invasive with a high sensitivity and specificity and should reliably detect the adenomatous pre-malignant stage.

A potential screening tool for colorectal cancer is the measurement of the dimeric form of faecal pyruvate kinase type M2, or tumour M2-PK. Tumour cells are capable of surviving and proliferating under unfavourable conditions, namely a poor supply of oxygen and nutrients. A key control enzyme regulating this is the glycolytic enzyme pyruvate kinase which determines the relative amount of glucose that is channeled into synthetic processes or used for energy production. Pyruvate kinase is expressed as different isoenzymes depending on the metabolic requirements, and tumour M2-PK, a dimeric form of pyruvate kinase, leads to an accumulation of phosphometabolites which

are channeled towards synthetic processes such as nucleic acid, amino acid and phospholipid synthesis.[181] Tumour cells then obtain energy via glutaminolysis, an oxygen-dependent process. Under conditions of reduced oxygen supply glutaminolysis becomes inhibited and M2-PK switches back to the tetramer form. This allows the tumour to switch between an anabolic or catabolic state depending on oxygen and nutrient supply.[184]

Using the manufacturer's cut-off value of 15 U/ml, tumour M2-PK in EDTA-plasma samples has been shown to have a sensitivity of 50-76.5% with a specificity of 89-90%.[185 203 204] Hardt et all reported a sensitivity of 67.5% and specificity of 96.7% using a higher cut-off level of 18 U/ml, whereas at a cut-off of 19.8 U/ML Schneider et al found 47.8% sensitivity at 95% specificity.[185 205] The sensitivity of tumour M2-PK in EDTA-plasma samples has been consistently demonstrated to be comparable or greater than that of serum CEA.[185 203 204] Tumour M2-PK can also be detected and quantified in the faeces of patients with gastrointestinal cancer. [186] Our aim was to assess the accuracy of faecal tumour M2-PK as a screening tool for colorectal cancer.

Materials and Methods

Ethical approval was obtained from the Medical Ethics Committee. Asymptomatic patients scheduled for a screening colonoscopy were recruited from the colorectal screening clinic and symptomatic patients with a diagnosis of colorectal cancer, prior to surgery or chemoradiotherapy, were recruited from the gastroenterology clinic. All

patients provided a stool sample, which reached the laboratory within 24 hours and was stored at -80°C until analysed.

Stool extraction was carried out using the commercially available ScheBo® Tumor M2-PK™ Quick-Prep™ dosing device. The stool sample extract was then diluted 1:3 in washing buffer. Faecal tumour M2-PK was measured with a commercially available ELISA (ScheBo® Tumor M2-PK Stool Test). After incubation of the stool samples for one hour on the ELISA plate coated with a monoclonal antibody to human Tumour M2-PK, a biotinylated second monoclonal antibody, anti-Tumour M2-PK bio, was added for a further 30 minutes. POD-Streptavidin, consisting of a complex of peroxidase and streptavidin, binds to the biotin moiety during the next 30 minutes of incubation. A substrate solution, 3,3′5,5′-tetra-methyl benzidine (TMB), is then added for 15 minutes and the peroxidase oxidizes TMB, turning it yellow. This colour reaction is stopped by adding an acidic solution and the concentration of oxidized TMB is determined photometrically at an optical density of 450 nm with a microtiter plate reader between 5 and 30 minutes after addition of the stop solution. The test kit allows the quantification of faecal tumour M2-PK between the range of 1 to 30 units/ml (U/ml) and a cut-off of 4 U/ml is used with values above this considered positive.

Guaiac-based faecal occult blood tests were used. A sample of stool was applied to each of the two windows of the faecal occult blood test. A positive test depended on fecal blood to catalyze the phenolic oxidation of guaiac in the presence of hydrogen peroxide

to produce a blue chromogen. If any one of the windows produced a blue colour the test was deemed positive

Statistical analysis was performed by the Mann Whitney U-test using the SPSS statistical package.

Results

Stool samples from 162 patients were collected: 97 of these patients had a normal colonoscopy, 30 patients had adenomatous polyps, and 35 patients had colorectal cancer. The patients ranged in age from 23 years to 85 years with a mean age of 51 years; 45% were male and 55% were female. (See table eleven.)

Faecal tumour M2-PK levels ranged from 0.8 to 4 U/ml with a mean of 2 U/ml for those with a normal colonoscopy, 2 to 34 U/ml with a mean of 8 U/ml for those with adenomas, and 4 to 52 U/ml with a mean of 26 U/ml for those with colorectal cancer. (See figure thirteen.) There was a statistically significant difference between faecal tumour M2-PK levels for those with a normal colonoscopy when compared to those with either adenomas and carcinoma using the Mann-Whitney U test ($p<0.001$) Similarly there was a statistically significant difference in faecal tumour M2-PK levels between those with adenomas and those with carcinoma ($p<0.001$).

	NORMAL N= 97	ADENOMAS N=30	COLORECTAL CANCER N=35
Age: Mean Range	 46.6 yrs 23-71 yrs	 53 yrs 40-70 yrs	 68.6 yrs 52-85 yrs
Sex: M:F	42%:58%	50%:50%	60%:40%
Colon: Right Left	 Normal Normal	 8 adenomas 22 adenomas	 7 cancers 28 cancers
Polyps: TA TVA		 23 7	
Cancer: Dukes A Dukes B Dukes C Dukes D			 4 12 15 4

Table eleven: Demographics and characteristics of patients.
(TA = tubular adenoma, TVA = tubulovillous adenoma)

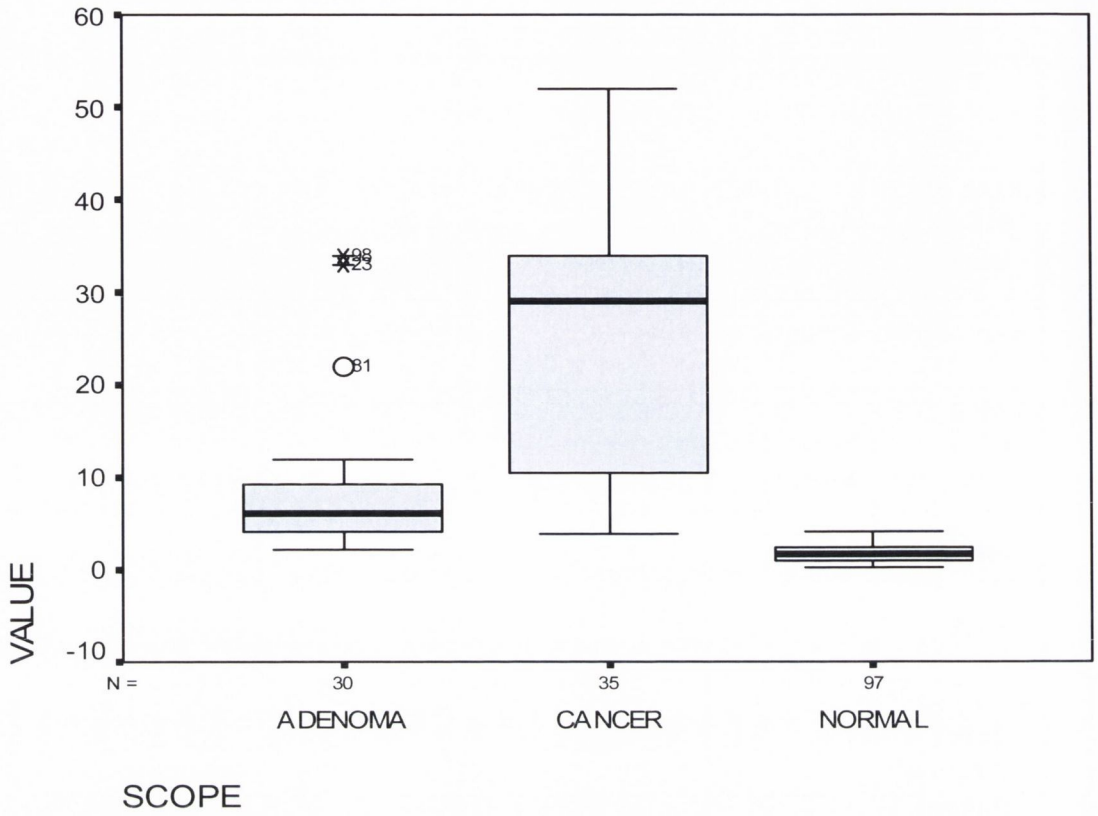

Figure thirteen: Faecal tumour M2-PK levels for those with normal findings, adenomatous polyps, or colorectal carcinoma on colonoscopy.

There was no statistical difference in faecal tumour M2-PK levels and the Dukes staging of colorectal cancer. The mean faecal tumour M2-PK levels for Dukes stage A was 20.85 U/ml, for Dukes stage B 33.95 U/ml, Dukes stage C 22.75 U/ml, and Dukes stage D 19.6 U/ml. There was also no statistical difference in faecal tumour M2-PK levels and the type or size of adenomatous polyp. The mean faecal tumour M2-PK levels for tubular adenomatous polyps was 7.92 U/ml and for tubulovillous adenomatous polyps was 9.16 U/ml. For polyps > 1cm the mean faecal tumour M2-PK level was 8.99 U/ml and for those < 1cm the mean faecal tumour M2-PK level was 8.21 U/ml.

Using a cut-off of 4U/ml faecal tumour M2-PK was found to be positive in 2/97 of those with a normal colonoscopy, 23/30 of those with adenomas, and in 34/35 of those with colorectal cancer. One of our patients with colorectal cancer had a negative faecal tumour M2-PK, and this patient had a Dukes A rectal adenocarcinoma. Of our patients with adenomatous polyps 7 had a negative faecal tumour M2-PK: four of these had tubular adenomas, two in the caecum, one in the descending colon, and one in the rectum; and three had a tubulovillous adenoma all in the rectum, all seven were less than 1cm in size. The sensitivity of faecal tumour M2-PK for colorectal cancer was 97% and for adenomas 76%, and the specificity of faecal tumour M2-PK was 98%. The sensitivity of faecal tumour M2-PK for colorectal cancer was 97% and for adenomas 76%, and the specificity of faecal tumour M2-PK was 98%.

The faecal occult blood test was found to be positive in none of the 97 patients with a normal colonoscopy. The faecal occult blood test was positive in 2/30 of those with adenomas, and in 7/35 of those with colorectal cancer. (See table twelve.) The sensitivity of faecal occult blood testing for colorectal cancer was 20% and for adenomas 7%, and the specificity of faecal occult blood testing was 93%.

Discussion

We have shown in this study that faecal tumour M2-PK has a high sensitivity of 97% for colorectal cancer and a specificity of 98%. For adenomatous polyps the sensitivity of faecal tumour M2-PK was 76% with a specificity of 98%. There was no statistically significant difference in faecal tumour M2-PK positivity with the type or size of polyps detected, or the colorectal cancer stage. The sensitivity of faecal occult blood testing for colorectal cancer was 20% with a specificity of 93% and for adenomas the sensitivity was 7% with a specificity of 93%. Our results are encouraging for faecal tumour M2-PK in colorectal cancer screening and highlight the lack of sensitivity of a once-off faecal occult blood testing

Tumour M2-PK in plasma samples has a sensitivity of 50-76.5% with a specificity of 89-90% at a cut-off level of 15 U/ml for colorectal cancer.[185 203 204] Hardt et al reported a sensitivity of 67.5% and a specificity of 96.7% using a cut-off level of 18 U/ml, whereas at a cut-off of 19.8 U/ML Schneider et al found 47.8% sensitivity and 95% specificity.[185 205]

TEST	NORMAL N=97	TA N=23	TVA N=7	DUKES A N=4	DUKES B N=12	DUKES C N=15	DUKES D N=4
Faecal tumour M2-PK +ve	2	19	4	3	12	15	4
FOBT +ve	0	1	1	1	2	3	1

Table twelve: Faecal tumour M2-PK and Faecal Occult Blood Testing positivity rates and colon findings.
(TA = tubular adenoma, TVA = tubularvillous adenoma)

The tumor M2-PK levels in plasma have also been shown to correlate with cancer stage. In a study of 54 patients with colorectal cancer the mean tumor M2-PK concentration of Dukes A was 16.6 U/ml, of Dukes B 22 U/ml, and of Dukes C 48 U/ml [204].

The detection of tumour M2-PK in the faeces of patients with colorectal cancer heightened interest in its use as a screening tool. In a study of 21 patients with colorectal cancer, 8 patients with colorectal adenomas and 49 healthy controls a mean faecal tumour M2-PK level of 19U/ml was found for colorectal cancer, 5.1 U/ml for adenomas and 2 U/ml for controls. The mean faecal tumour M2-PK level was higher for those with colon cancer at 31.9 U/ml compared to those with rectal cancer at 12.5 U/ml [186]. This corresponds with the results of our study where we found a mean faecal tumour M2-PK level of 26 U/ml for those with colorectal cancer, 8 U/ml for those with adenomas, and 2 U/ml for those with normal colonoscopy. Our only colorectal cancer with a negative faecal tumour M2-PK test had a rectal cancer.

In a recent study of 60 patients with colorectal cancer and 144 control patients the presence of tumour M2-PK in the faeces revealed a sensitivity of 73% and a specificity of 78% for colorectal cancer. In addition there was a strong correlation between the stage of the tumour and faecal tumour M2-PK, with sensitivities of 59% for Dukes stage A, and 90% for Dukes stage D respectively [187]. We did not find a similar progression of sensitivities with the stage of colorectal cancer. As a result we found a much higher overall sensitivity at 97% with a specificity of 98% for colorectal cancer.

The reasons for this discrepancy in faecal tumour M2-PK results are not clear. It is known that tumour M2-PK both in plasma and faeces is increased in inflammatory bowel disease however all our patients underwent colonoscopy and had no evidence of inflammatory bowel disease [185 206]. Plasma levels of tumour M2-PK levels are increased with both acute inflammatory reactions and in chronic diseases such as congestive cardiac failure, diabetes mellitus, and in the spondylarthritis including rheumatoid arthritis, seronegative arthritis, and systemic lupus erythematosus [207-210].

There are currently no studies of faecal tumour M2-PK for acute inflammatory or chronic medical conditions, and such studies may help clarify the issue. Our patients with colorectal cancer were a heterogeneous group ranging in age from 52 to 85 years with some having co-existing medical conditions. However our patients without colorectal cancer also had a wide age range from 23 to 70 years with some having co-existing medical conditions, yet they did not have an elevated faecal tumour M2-PK. Similarly our specificity at 98% is reassuring that the false positive rate was low. It is possible that our high level of faecal tumour M2-PK in all stages of colorectal cancer represents an acute inflammatory reaction to the cancer as well as the cancer itself. Or the higher sensitivity and specificity we found may simple be due to chance, further studies will help to clarity the situation.

The once-off guaiac-based faecal occult blood test has a sensitivity of 25-50% for colorectal cancer and 9-36% for adenomas [151]. Our study reveals similar sensitivities of 20% for colorectal cancer and 7% for adenomas using the guaiac-based faecal occult

blood test with a specificity of 93%. Although the specificity is satisfactory the low sensitivity rate is a cause of concern. However with repeated faecal occult blood testing at one to two yearly intervals the programme sensitivity reaches as high as 90%, justifying its use for mass screening [142]. Repeated faecal occult blood testing has an impact on compliance and in this study we have shown that a once-off faecal tumour M2-PK has comparable sensitivity and specificity. How frequently faecal tumour M2-PK should be repeated needs to be the subject of further studies.

Chapter Six

Conclusion and future research

Colorectal cancer is a major public health problem. According to a recent report from the United European Gastroenterology Federation colorectal cancer is the leading cause of morbidity and death from cancer in Europe, and its incidence is steadily increasing in both males and females.[198] Screening programmes can be an effective method of reducing morbidity and mortality from disease by detecting it before symptoms occur and colorectal cancer fits the criteria widely used for screening suitability suggested by Wilson and Jungner:[211]

- Colorectal cancer is prevalent and sufficiently serious and 1730 patients with colorectal cancer are diagnosed each year in Ireland, with 925 deaths occurring.[191]
- The biology of colorectal cancer is well-defined, developing as a result of a stepwise accumulation of genetic mutations. The transformation from normal mucosa to adenoma and ultimately to carcinoma appears to occur slowly over about 10-20 years.
- Colorectal cancer is undiagnosed in many cases and this late presentation leads to a poor survival outcome.[2]
- There is evidence of a benefit from screening for colorectal cancer with several studies suggesting that earlier detection leads to a reduction in mortality.[8 141 142]
- The ideal screening tool for colorectal cancer should be non-invasive with a good sensitivity and specificity and a reasonable positive predictive value in the population to be screened.

FOBT is non-invasive with a programme sensitivity of 47-90% and specificity of 86-97%, and as such is currently regarded as an ideal screening tool for colorectal cancer in average individuals.[9 151] However FOBT is not the ideal tool for all individuals, and for those at high risk due to a family history of colorectal cancer colonoscopy rather than FOBT is currently recommended. Moreover work is ongoing into non-invasive screening tools that may have a higher specificity and sensitivity than FOBT. These newer tools, such as faecal M2-PK may eventually replace FOBT.

High-risk individuals

The majority of "familial" colorectal cancer is seen in first-degree relatives of patients with colorectal cancer. In the present study of 405 individuals at moderate risk of developing colorectal cancer due to their family history colonoscopy revealed adenomatous polyps in 74 (18.3%), high-grade dysplasia in 8 (2%), multiple polyps in 9 (2.2%), and cancer in 6 (1.5%). Data from the National Cancer Registry of Ireland reveals an annual incidence of just fewer than 2,000 for colorectal cancer with a European age-standardised rate of 40.09.[191] The age-standardised rate of colorectal cancer in our moderate risk population is 420.

Guillem et al, found adenomatous polyps in 14.4% of the family group and 8.4% of the control group, a relative risk of 3.49. The exact relationship of the index case had a significant effect; 24% with a sibling affected had an adenoma compared with 9% of those with a parent affected. Likewise we found that cancer or adenomatous polyps

occurred more often when the affected relative was a sibling compared with a parent. In line with our findings no significant difference was found between having one first-degree relative with colorectal cancer and having two or more first-degree relatives with colorectal cancer.[66] Our yield of adenomatous polyps is considerably lower than that of Bazzoli et al, who found adenomatous polyps in 69% of asymptomatic individuals with one first-degree relative with colorectal cancer. However they also found a high proportion of adenomatous polyps among their asymptomatic patients without a family history at 36%.[71] Pariente et al in a larger study of 185 first-degree relatives of patients with colorectal cancer and 370 patients without a family history corroborated our findings with adenomas in 23.2% of the family history group and 17.3% of the controls.[72]

A meta-analysis of 20 published case-control and 7 cohort studies reveals a pooled relative risk of 2.25 for developing colorectal cancer among individuals with a first degree relative with colorectal cancer and 4.25 for those having more than one affected first-degree relative. The relative risk was greatest for those relatives of cases diagnosed young, with pooled relative risk of colorectal cancer of 3.87 in relatives of cases diagnosed < 45 years and 1.82 in those > 59 years.[81]

Our study however found no increased risk for those with more than one affected first-degree relative compared with those with one affected relative, and no increased risk associated with the age of index patient < 45 years compared with > 45 years. It is possible that HNPCC families may have contributed to the increased risk for multiple family members and those diagnosed at a younger age in the meta-analysis: of the 6

studies which showed an increased risk with more than one affected first-degree relative five were case-control studies with only one excluding cases with HNPCC, one was a cohort study by Fuchs et al which prospectively analysed data from two ongoing studies, the Nurses' Health Study and the Health Professionals Follow-up Study, however no attempt was made to verify the cancer cases.[79 212-216] Of the 7 studies which showed that the index patient's age influenced the risk four were case-control studies with only one excluding cases of HNPCC, three were case control studies with no attempt to exclude HNPCC.[64 79 213 215-218] Since this meta-analysis a large prospective colonoscopy study of 249 first-degree relatives has failed to show a difference in the incidence of neoplasia according to the number of affected first-degree relatives.[75]

The presence of lesions in those over 60 years might be attributable to environmental factors rather than genetic factors. However both Guillem et al, and Pariente et al found the risk of neoplastic lesions in first-degree relatives of those with colorectal cancer increased with increasing age of the individual when compared with a control population.[66 72] Similarly Dove-Edwin et al found a statistically significant increase of finding and adenoma or cancer with increasing age in their family cancer clinic: of the 1124 individuals with moderate family risk, cancer or high risk adenomas were present in 2.2% of those aged under 65 years compared with 12.5% of those aged over 65 years. Our data shows a significantly increased yield from screening colonoscopy as the age of the individual increased. We therefore do not believe there should be an upper age-limit for screening colonoscopy in those with a first-degree relative with colorectal cancer. However increasing the age at which individuals had their screening colonoscopy to 40

years would have eliminated the need for 87 colonoscopies, and the loss of detecting two tubular adenomatous polyps.

Average-risk individuals

The FOBT study yielded disappointing compliance with less than one-third of those individuals who agreed to do FOBT complying. In randomised controlled trials the highest compliance occurred in Minnesota with 90% completing at least one screening round and all the screening rounds completed by 46.2% of the annual group and 59.7% of the biennial group.[142] In the Nottingham trial 59.6% completed at least one screening round and 38.2% completed all the screening rounds.[8] In the Funen trial 67% completed one screen and 46% completed all screening rounds.[141] These clinical trials represent the idealized situation and in clinical practice compliance is often much lower.

Participation in FOBT screening can be separated into two distinct components, agreement to participate and then compliance with the screening test. Different factors appear related to each component and a critical review of six FOBT studies attempted to identify these factors. Those with higher levels of perceived susceptibly to cancer are more likely than others to agree to participate in screening, but not more likely to comply with screening. Interest in health has a positive influence on agreement but no influence on compliance. In contrast a concern about health seems to have no influence on agreement but does have a negative influence on compliance. Perceived benefits regarding the efficacy of treatment for colon cancer appears to be related to participation.

The perceived barriers that FOBT screening would be embarrassing, distasteful, worrisome, or painful effect agreement to participate in screening. Only beliefs that doing the test would be embarrassing or worrisome were related to compliance, and this is attributed to the fact that individuals had an opportunity to examine the FOB slides and consider the steps necessary to participate.[193] Our study shows that the discrepancy between individuals' intention to perform certain behaviour and their actual performance of that behaviour is important; the relationship between the two is quite strong, but by no means perfect.

Similar results with poor compliance have been demonstrated in other FOBT screening studies of workers. Of 5547 employees in a chemical company contacted via mail 13% agreed to participate in FOBT screening and of these only 226 or 31% complied with FOBT screening. Just 4% of eligible employees completed the FOBT suggesting that mailing invitations in an FOBT screening campaign is not only inadequate but a waste of resources.[219] A more aggressive informational campaign resulted in 20.2% of 1909 employees completing FOBTs. A forty minute information lecture on colorectal cancer was arranged at several times over a two-month period and employees were given time off to attend this, FOBTs were then mailed out to employees.[220] An important aspect therefore of FOBT screening is to incorporate a public awareness campaign.

Our study in AMNCH revolved around a "Bowel Awareness Week", with repeating lectures, information leaflets, and posters yielding 29.6% compliance. Our study with the CWHT, due to the disparity of sites involved an awareness day only for the CWHT

nurses. Thereafter the CWHT nurses discussed colorectal cancer screening with the construction workers and offered information leaflets and FOBT kits. This yielded a lower compliance of 20.5%. Thus our study supports the notion that compliance can be improved through increasing public awareness. A national screening programme would involve a more intensive public awareness campaign and so improve compliance further.

Reasons for non-participation in a colorectal cancer screening programme were sought in a pharmaceutical company when only 16% of an eligible 26,366 employees participated. Variables significantly associated with having had an FOBT were recommendations by their own doctor and perceived barriers. Of the 63.7% who reported that their doctor had not recommended a FOBT to them, 51.1% had complied. In comparison among those whose doctor had advised FOBT compliance was 71.6%. Of the 50.5% who reported high barriers 36.2% had not had a FOBT.[221]

Doctors obviously play a key role in encouraging participation in FOBT screening and this was highlighted in the FOBT screening of 91,000 individuals in Burgundy. The FOBT kits were initially supplied by GPs, with a compliance of 81.4%. If individuals had not visited their GP within four months the FOBT kits were mailed to them with a compliance of 33.8%.[101]

A random sample of this population, 27,421, were surveyed to identify the barriers to screening. Among non-compliers the most common reason listed for not responding were:

- "I do not wish to know more about my health" 34.3%;
- "It does not really concern me because I am healthy" 29.1%;
- "It is embarrassing to touch fecal material" 29.1%;
- "The test appears too complicated" 21.9%.

These suggest that a lack of knowledge of colorectal cancer is the main barrier to screening, something that could easily be addressed in a public awareness campaign.[202]

A telephone-administered questionnaire of 61,068 individuals aged over 50 years of age identified other important influences on colorectal cancer compliance. In multivariate analyses significant predictors of screening included older age, black race, high household income, high educational attainment, having a routine doctor's visit, being retired, poor self-reported general health, presence of health care coverage, vitamin use, and the use of exercise or low fat diet to reduce heart disease. The most important modifiable predictor of current colorectal cancer screening was a routine doctor's visit in the last year, odds ratio 3.5. These findings may be useful in designing interventions aimed at improving participation in colorectal cancer screening.[195]

Interventions designed to increase screening uptake have focused on education and risk perception strategies but also on the minimization of barriers. Individualized invitation appointments, reminder letters, telephone calls, telephone counseling, videos in physicians' offices, and removal of financial barriers have all been demonstrated to increase screening uptake.[194 222 223]

Cost-effective studies have failed to show a difference between the recommended screening methods FOBT, sigmoidoscopy, or colonoscopy.[92] However cost-effective studies are quite clear that the single most important determinant of effectiveness for any of the screening methods is compliance.[224] Compliance in FOBT screening needs to be above 60%, not under one-third as found in this study. Lessons need to be learned from studies abroad and from our colleagues in Breast Check. A public awareness campaign in the national media, re-enforced by GPs is necessary for the success of a FOBT screening programme.

National Screening Programme

Our questionnaire on colorectal cancer knowledge had promising results. Family history, the most important predisposing risk factor was recognized by 78% of respondents as such. The effects of lifestyle and age were known to 60% and 71% respectively. The knowledge that males were more at risk than females was poorly appreciated at 39%, worryingly suggesting that those most at risk do not realize it. Encouragingly after the education campaign this had increased to 44% overall and to 54% among men.

Survival from colorectal cancer is closely linked to the stage of colorectal cancer at presentation. Although 69% recognized warning symptoms of colorectal cancer almost all individuals, 96%, stated that they would delay attending a doctor due to embarrassment over symptoms. Following our "Bowel Cancer Awareness Week" the recognition of warning symptoms increased up to 75%, however there was only a slight

decrease to 93% in the number of individuals who felt too embarrassed to talk to their doctor.

Across Europe there is a variation in the willingness of the public to talk to their doctor about bowel symptoms. This is a serious barrier in countries like Finland, UK, and Ireland. However in Belgium, the Netherlands, Spain, Italy and Iceland patients are happier to discuss their bowel problems with their doctor.[201] Colorectal cancer screening programmes help to remove this barrier with the surrounding publicity and information bombardment from medical personnel, celebrity endorsements, and media campaigns.

Colorectal cancer screening programmes are associated with an increased diagnosis of symptomatic cancers along with the anticipated asymptomatic cancers detected on screening, the implication being increased public awareness and willingness to discuss bowel problems.[102]

Our week-long "Bowel Cancer Awareness Week", while it did not cause a significant reduction in the numbers wary of discussing their symptoms, did manage to improve willingness to talk to their doctor. A more sustained campaign as would be anticipated in a national screening programme would no doubt help further.

There are several psychological models which attempt to explain what motivates health behaviour and one of the most popular is the health belief model. Under this model to engage in screening an individual must perceive a disease as serious, must perceive

themselves at increased risk for developing the disease, and the perceived benefits of the action must outweigh the perceived barriers to taking the action.[225]

In a literature review of colorectal cancer screening participation the perceived risk of colorectal cancer was only modestly associated with objective measures of risk such as hereditary factors or environmental factors.[226] Indeed most individuals tend to underestimate their risk of colorectal cancer. In addition a lack of knowledge about colorectal cancer and the advantages of early diagnosis with beliefs such as "I feel fine, so I don't need a test", or fatalistic attitudes such as "I don't want to know if I have cancer, since there is nothing I can do" impact on screening compliance.[227]

With this in mind it is reassuring from our questionnaire that 82% believe colorectal cancer can be treated easily if diagnosed early. Our respondents were less willing to accept that colorectal cancer took many years to develop and was therefore one of the most successfully treated cancers, that a simple screening tool existed, or that screening reduced colorectal cancer mortality. Following the education campaign almost two-thirds felt that colorectal cancer was one of the most successfully treated cancers and three-quarters were aware there was a simple screening tool.

Our questionnaire could be biased as it was directed towards staff working in a hospital. As would be expected separating the respondents into clinical and non-clinical staff resulted in a significant difference in perceived risk, with clinical staff more correctly identifying perceived risk based on hereditary and environmental factors. However there

was no significant difference with respect to knowledge of colorectal cancer screening, or those who felt too embarrassed to discuss their symptoms with a doctor.

The majority of GPs in Ireland see a need for colorectal cancer screening in Ireland, and more importantly, given their key role in educating patients about the disease and influencing compliance with screening, would participate in a colorectal cancer screening programme. With physicians often failing to practice what they preach the fact that over 90% of respondents would themselves avail of colorectal cancer screening is reassuring.

Colonoscopy is the preferred screening tool of 35.4% of GPs, although the myriad of screening options chosen in table 2 conforms with the consensus of various international task forces that the advantages and disadvantages of each often results in a failure to recommend one single screening option, and that the best screening tool is that which gets done.[198] A sensitivity of 75-100% and mortality reduction of 50-75% were correctly attributed to colonoscopy screening by over 70% and 50% of the respondents respectively. Furthermore the high mortality reduction attributed to colonoscopy screening had a significant effect on its choice as screening tool.

The EU has recommended FOBT for colorectal cancer screening as the best evidence supports FOBT with three large randomised controlled trials of 330,000 individuals and cohort series of over two million individuals to date.[24 101 102 150 152 153 228-230] In the European trials between 4-8% of individuals screened with FOBT required follow-up with a colonoscopy, a figure that could readily be accommodated. In our survey 18.1%

of GPs felt FOBT should be the screening tool of choice. However the sensitivity of FOBT in colorectal cancer screening was under-estimated at less than 50% by over three quarters of the respondents. This perceived low sensitivity had a significant effect on the choice of screening tool.

As Ireland currently has no national colorectal cancer screening programme it comes as no surprise that the preponderance of patients with whom colorectal cancer screening was discussed and offered to were those deemed to be at a high risk of developing colorectal cancer. What therefore becomes important is how these high-risk individuals are identified.

The majority identified as high-risk individuals those with a family history consistent with HNPCC, those with a first degree relative with colorectal cancer at aged 45 years, and those with a long history of ulcerative colitis. Although questionnaires often reveal an idealized view of practice with physicians tending to overestimate their provision of certain medical services clinical scenarios have been shown to reflect clinical practice. [231] [232] Thus in the absence of a formal colorectal cancer screening programme it appears that in clinical practice opportunistic screening is being offered to those at highest risk of developing colorectal cancer.

A national screening programme for colorectal cancer was supported by 88% of GPs. The main barrier to a screening programme was felt to be a lack of resources and just over 70% of GPs stated that additional staff and incentives to participate would be

required. The lack of resources pertained not only to the screening programme itself but also to a concern that there may be further delays in the management of symptomatic patients. This is a valid concern given the increased presentation of symptomatic patients to the health care services that is associated with the introduction of colorectal cancer screening.[102] This is thought to be due to an increased awareness about bowel cancer and its symptoms among the public. The Irish public have a poor awareness of colorectal cancer and 80% of GPs recommended a public information campaign as part of a screening programme.

Faecal tumour M2-PK

Newer screening tools for colorectal cancer are under evaluation and may take their place in future guidelines, or even supercede current screening options. We have shown in this study that faecal tumour M2-PK has a high sensitivity of 97% for colorectal cancer and a specificity of 98%. For adenomatous polyps the sensitivity of faecal tumour M2-PK was 76%.

Our numbers were too small to determine if there was a statistically significant difference in faecal tumour M2-PK positivity with the type or size of polyps detected, or the colorectal cancer stage. One of our patients with colorectal cancer had a negative faecal tumour M2-PK, and this patient had Dukes A rectal adenocarcinoma. Of our patients with adenomatous polyps 7 had a negative faecal tumour M2-PK: four of these had tubular adenomas, two in the caecum, one in the descending colon, and one in the rectum; and three had a tubulovillous adenoma all in the rectum, all seven were less than 1cm in

size. None-the-less our results are encouraging for faecal tumour M2-PK in comparison with other tests and investigations in current colorectal screening guidelines.

In a recent study of patients with colorectal cancer the presence of tumour M2-PK in the faeces revealed a sensitivity of 73% and a specificity of 78% for colorectal cancer. In addition the stage of the tumour, both by Dukes' classification and TNM revealed a strong correlation between the amount of faecal tumour M2-PK and staging, with sensitivities of 57% for T1 and 59% for Dukes' A, and 78% for T4 and 90% for Dukes' D respectively.[187]

Faecal tumour M2-PK has a high sensitivity and specificity for colorectal cancer and adenomatous polyps. As an ELISA test it can be automated for mass screening and is a viable option for colorectal cancer screening.

Cost-effectiveness of colorectal cancer screening

Cost-effective implies producing additional benefits that are worth the additional cost, compared with an alternative practice. So for colorectal cancer, screening with FOBT is cost-effective compared with no screening if the additional benefit obtained from screening in terms of cancers and cancer deaths avoided is worth the additional cost of screening. Cost-effectiveness analysis aims to quantitatively compare the expected outcomes of the competing management strategies, FOBT, sigmoidoscopy, colonoscopy, and newer screening tools, in environments with limited economic resources. Costs are

accurately measured and strategies of each screening tool have established clinical effectiveness from published trials.

A sensitivity analysis determines if uncertainties in assumptions alter the conclusions, for example the sensitivity of FOBT would range from 40%-90% and both extremes would be utilized in the analysis. The results should include the incremental cost-effectiveness ratio, which quantifies the resources required to achieve greater benefit with one strategy compared to another. This is calculated as the change in cost divided by the change in life expectancy for one strategy compared with another, and is measured as a ratio of euro per life-year gained. Final interpretation of a cost-effectiveness analysis relies on whether costs and outcomes in the study can be realised in one's own health care environment.

Cost-utility analysis is a subtype of cost effectiveness analysis and accounts for patient preferences for differing health states so that time spent in less desirable states such as cancer or chemotherapy is valued less than time spent in perfect health. Cost-utility analysis is particularly useful when alternative treatments produce outcomes of different types, or if increased survival is associated with a reduction in the quality of life. The outcome of a cost-utility analysis is a ratio of costs to quality-adjusted life-years (QALYS).[233]

Unfortunately there are no published data from randomized controlled trials on the cost-effectiveness of colorectal cancer screening, and information is provided by health

economic models. A review of 17 papers published from 1994 to 2003 which assessed yearly FOB, sigmoidoscopy every 5 years, and colonoscopy every 10 years, starting at 50 years of age, was carried out. Twelve papers were from the USA, three from Europe, and one from Australia and Japan. Overall the results do not help to distinguish between the three strategies with the median incremental cost-effectiveness ratios being €9950/life-year saved, €13,200/life-year saved, and €10,000/life-year saved, for FOBT, sigmoidoscopy, and colonoscopy respectively compared with no screening. Interestingly nine of the papers came to different conclusions. The main reason is the lack of quality data on the efficacy of sigmoidoscopy and colonoscopy screening in prevention of colorectal cancer, and the failure to compensate for this using sensitivity analysis.[92] Studies have shown that $50,000 per life-year saved is an amount society has shown a willingness to pay, and colorectal cancer screening is certainly well within this limit.[93]

The assumption is that colorectal cancer screening will lead to a reduction in costs by resulting in the detection and treatment of earlier stage disease. Certainly the stage of diagnosis of colorectal cancer has a considerable impact on costs as observed from a Group Health Cooperative. The cost of initial care increased with stage at diagnosis from $9041 with carcinoma in situ to $17,223 with metastasis. Total costs of continuing care increased with stage from $820 with carcinoma in situ to $4632 with metastasis.[234] Looking specifically at screening detected versus symptomatic colorectal cancer, the diagnosis and staging of screening-detected colorectal cancer is €4,400 less than the diagnosis and staging of symptomatic colorectal cancer: The on-going treatment over a 12-month period is €7,102 less for screen-detected colorectal cancer than for

symptomatic colorectal cancer.[235] This difference is due to the more advanced stage of presentation of colorectal cancer without screening.

These costs do not take account of the indirect costs to society with loss of work days on behalf of the person diagnosed with colorectal cancer and their next-of-kin who may be obliged to take time off work to bring their relative to hospital for clinic visits, radiology visits, chemotherapy visits, radiotherapy visits, etc; cost of traveling to and fro to the hospital; increased cost of eating out in the hospital café rather than at home; etc.

Screening allows us to detect colorectal cancer at an earlier stage. Screening colorectal cancers are potentially curable, and the need for chemoradiotherapy can be reduced with almost three-quarters presenting with Stages A and B.[102] Without chemoradiotherapy the median survival for advanced colorectal cancer was 8 months. Recent years have seen a great improvement in survival to 21 months with newer chemotherapy agents. This comes with a significant cost - $161,000 per person.[236] To put this in perspective, based on the number of colorectal cancer cases per year in Ireland and their stage of presentation it is estimated that we will face a drug bill of over €160million per year for colorectal cancer chemotherapy alone.[237]

Conclusion

Recently performed trials indicate that screening targeted at particular age-groups significantly reduces colorectal cancer mortality. The European Union has made recommendations to set up "fecal occult blood screening for colorectal cancer in men and women aged 50-74", and this is already underway in several European countries.

Such studies, however, are not in progress in Ireland. This proposal defines the start of an endeavor that will initiate significant information about many aspects of a screening programme for CRC in the Ireland. Such a screening programme is cost-effective and will save lives.

Chapter seven

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Appendices

After the test

• When you have completed the three kits, place the kits in the envelope supplied.

•Return the envelopes in the post.

•The results of your test kit will be sent to you.

•If no blood is found, your test is negative.

•A negative test does not mean you will never develop bowel cancer. You will need to repeat the test in two years.

•If blood is found, your test is positive.

•A positive test **DOES NOT** mean you have bowel cancer.

•Blood can appear for many reasons in the bowel.

Further testing

•If you have a positive test you will need further testing to see why there is blood present.

•A colonoscopy, or camera test on the bowel, will be arranged for you.

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Early detection is the best protection

Bowel cancer screening

This leaflet explains how to use the kit.

Please read carefully

In your kit you will find:
✓ Return envelope
✓3 wooden sticks
✓Red and white cardboard test kits

Your kit will last for many months unopened.
BUT must be completed and returned for testing within **14 days** of the first sample being taken.

Before doing the test

•Do not open the side marked "**DO NOT OPEN**" as this will affect your result.

•There are 3 parts in this kit for 3 separate bowel motions.

•Only use one kit at a time.

•Write the date that you use each kit under the number on the back of the kit.

•Get one kit and one stick ready to use before sitting on the toilet.

•Peel back the flap on the kit, when you are ready to use it.

•When the kit is opened, there are 2 small circles, on which you will put your sample.

Doing the test

•If the sample you use on the kit has been in the toilet bowl this will affect the result.

•To stop this happening you need to catch your bowel motion. You can do this with folded pieces of toilet paper, a small plastic bag, or a clear disposable container.

•Use the stick to take a small sample of your bowel motion, and spread it thinly over the first circle on the kit.

•Use the stick to take a second sample and spread it thinly over the second circle on the kit.

•When you have done this, close the flap on your kit and tuck it under the red tab to keep closed

BOWEL CANCER AWARENESS

Please fill in the following details about yourself:

Age: > 30 years ○ 30-40 years ○ 40-50 years ○ > 50 years ○

Sex: Male ○ Female ○

What area do you work in: Admin/Clerical ○

Allied Health ○

Clinical ○

Services ○

Please fill in the following details about bowel cancer:

What is the most common form of cancer in Europe: Lung ○

Bowel ○

Breast ○

Unsure ○

Does your lifestyle affect your change of getting bowel cancer?

Yes ☐ No ☐ Unsure ☐

You are at greater risk of developing bowel cancer if someone else in your family has had it?

Yes ☐ No ☐ Unsure ☐

Does the risk of bowel cancer increase with age? Yes ☐ No ☐ Unsure ☐
Bowel cancer affects women more than men? Yes ☐ No ☐ Unsure ☐
Changes in bowel habit, for example loose stool, going more frequently, or constipation are associated with bowel cancer? Yes ☐ No ☐ Unsure ☐
Blood in your bowel motion or unexpected weight loss can be associated with bowel cancer? Yes ☐ No ☐ Unsure ☐
Diets that are rich in fruit and vegetables reduce the risk of bowel cancer? Yes ☐ No ☐ Unsure ☐
Can lack of exercise increase your risk of bowel cancer? Yes ☐ No ☐ Unsure ☐
Bowel cancer can be easily treated if diagnosed early? Yes ☐ No ☐ Unsure ☐
Bowel cancer is one of the most successfully treated cancers because it develops slowly over many years? Yes ☐ No ☐ Unsure ☐

There is a simple screening test which helps identify the early stages of bowel cancer before any symptoms develop?

Yes ☐ No ☐ Unsure ☐

Routine screening can half the numbers who die from bowel cancer?

Yes ☐ No ☐ Unsure ☐

People feel embarrassed by bowel problems to such an extent that they delay seeing their doctor to discuss their symptoms?

Yes ☐ No ☐ Unsure ☐

Would you be interested in a simple screening test that you can use at home?

Yes ☐ No ☐ Unsure ☐

We would like to thank you for taking the time to complete this questionnaire.

Please fill in the following details about yourself:

Age:_____ Sex:_____

Number of years in general practice:_____

Please fill in the following details about your practice:

Is your practice: urban:_____ Rural_____

Number of doctors in practice: 1_____ 2-4_____ 5-6_____ >6_____

Ancillary staff: Receptionist _____
Secretary _____
Nursing staff _____
Physiotherapist ____

Is your practice computerised: _____

How sensitive do you think the following tests are in detecting colorectal cancer ?

	0-25%	25-50%	50-75%	75-100%
Faecal occult blood testing	☐	☐	☐	☐
Sigmoidoscopy	☐	☐	☐	☐
Colonoscopy	☐	☐	☐	☐
Barium enema	☐	☐	☐	☐
Virtual colonoscopy	☐	☐	☐	☐

By how much do the following tests reduce colorectal cancer mortality ?

	0-25%	25-50%	50-75%	75-100%
Faecal occult blood testing	☐	☐	☐	☐
Sigmoidoscopy	☐	☐	☐	☐
Colonoscopy	☐	☐	☐	☐
Barium enema	☐	☐	☐	☐
Virtual colonoscopy	☐	☐	☐	☐

Would you place the following asymptomatic people at low, average, or high risk for developing colorectal cancer ?

	Low	Average	High
Patient aged 45 years	☐	☐	☐
Patient aged 65 years	☐	☐	☐
Patient whose brother had colorectal cancer at 45 years	☐	☐	☐
Patient whose brother had colorectal cancer at 65 years	☐	☐	☐
Patient whose brother had colorectal cancer at 60 years, whose father had colorectal cancer at 55 years, and whose uncle had colorectal cancer at 45 years	☐	☐	☐
Patient with ulcerative colitis for 5 years	☐	☐	☐
Patient with ulcerative colitis for 15 years	☐	☐	☐

Do you discuss colorectal cancer screening with your patients ?

Yes:_____ No:_____

If yes :-

With all your patients: ☐

With those at high risk: ☐

Only those that ask: ☐

Do you offer colorectal cancer screening to your patients ?

Yes:_____ No:_____

If yes do you:-

Offer screening to all your patients: ☐

Offer screening to those at high risk: ☐

Offer screening to those that ask: ☐

Do you think there is a need for a national colorectal cancer screening program ?

Yes:_____ No:_____

If yes which method would you favour :-

Faecal occult blood testing ☐

Sigmoidoscopy ☐

Colonoscopy ☐

Barium enema ☐

Virtual colonoscopy ☐

What do you feel are the barriers to a national colorectal screening program ?

	Strongly Disagree	Disagree	Agree	Strongly Agree
Lack of national guidelines	☐	☐	☐	☐
Lack of evidence to support screening	☐	☐	☐	☐
Current screening tools are inadequate	☐	☐	☐	☐
Worry regarding false negative tests	☐	☐	☐	☐
Worry regarding false positive tests	☐	☐	☐	☐
Lack of resources	☐	☐	☐	☐
Lack of time	☐	☐	☐	☐
Worry that symptomatic patients may face longer delays	☐	☐	☐	☐

Would you participate in a national colorectal screening program ?

Yes:_____ No:_____

What is needed to facilitate participation in a colorectal screening program ?

- National guidelines ☐
- Educational information regarding tests ☐
- Incentives for participation ☐
- Additional staff ☐
- Awareness campaign for public ☐

Would you personally avail of colorectal cancer screening ? Yes ___ No ____

What Is Bowel Cancer?

Bowel cancer is a malignant growth which begins in the colon or rectum, and sometimes it is called colorectal cancer.

Most cancers of the bowel develop from tiny growths in the bowel called polyps. It takes many years for a polyp to grow and become a cancer in the bowel.

How Common Is Bowel Cancer?

Bowel cancer is the most common cancer in Europe, and in Ireland 1,700 people are diagnosed every year.

But the good news is that it is one of the most curable cancers you can get if it is discovered early

Who Is at Risk?

Both men and women are affected.

The risk of bowel cancer increases with age.

Lifestyle factors such as lack of exercise, a poor diet, alcohol, and cigarettes all increase the risk.

Those with a family history of bowel cancer may be at a higher risk.

What Will Reduce the Risk of Bowel Cancer?

•Regular exercise

•A diet high in fibre with four pieces of fruit or vegetables a day

•Stop smoking

•Alcohol within moderation

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•Those with a family history of bowel cancer should discuss screening options with their doctor.

What Are the Symptoms?

•Recent change of bowel habit
•Blood appearing in the stool
•Pain in the stomach
•Frequent gas or bloating
•Weight loss

Most people with these symptoms do not have cancer. But the only way to be certain is to discuss them with your doctor.

Screening for Bowel Cancer.

Bowel cancer can be prevented by taking part in screening programmes.

Early detection is the best protection

It is important not to wait until symptoms develop as detecting the cancer, if it is present, at the earliest stage is best.

Men and women over 50 years of age should have a simple screening test done, every two years, called a FOBT, or faecal occult blood test.

This is a simple test to look for the presence of blood in a stool sample. A small sample of stool is put on the kit and then this is sent to the laboratory where it is analysed.

If this is positive, it does not mean you have bowel cancer, but further testing is needed.

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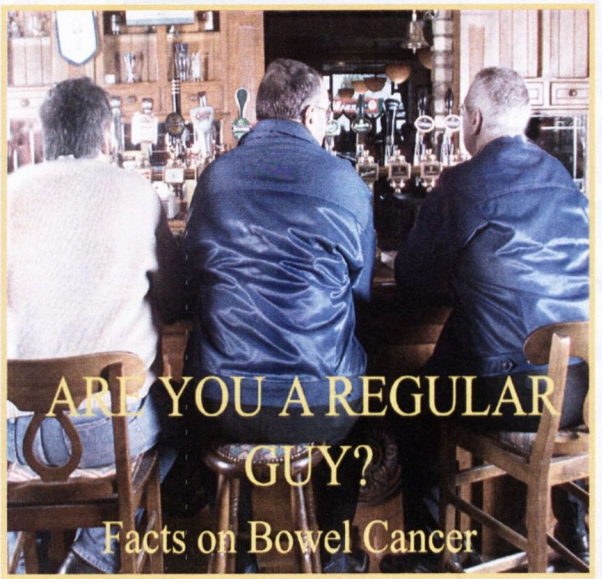
Are You a Regular Guy?



Know the Facts on Bowel Cancer.

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