Studies on screening and surveillance for colorectal cancer

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1 Introduction and outline of the thesis

EPIDEMIOLOGY OF COLORECTAL CANCER

Colorectal cancer (CRC) is a major public health problem in the Western world. The life-time risk for developing CRC is approximately five percent and increases with age. In The Netherlands, the incidence of CRC is 67.5 per 100 000 in men and 46.7 per 100 000 in women (European Standardized Rate), resulting in about 12 000 new cases each year. In Europe, CRC is the third most common cancer diagnosed (after prostate and lung carcinoma) in men and the second most common cancer diagnosed (after breast cancer) in women. In total, it accounts for 13% of all cancer cases in Europe (in both men and women).[1,2]

Across the world, the incidence of CRC varies in different regions. The CRC incidence is highest in Western countries, including Northern and Western Europe, North America and Australia. Developing countries have lower rates, particularly Africa and Asia.[3] These geographic differences appear to be attributable to environmental and dietary exposures, superimposed on genetically determined susceptibility. The incidence rates are gradually declining in North America due to CRC screening, remain stable in Northwest Europe, and increasing in East and Southern European countries due to lifestyle factors.[4,5]

In The Netherlands, each year, 4 500 deaths are CRC related. In Europe, CRC is the second most common cause of death from cancer after lung cancer. Five-year survival is 90% if the disease is diagnosed while still localized, 68% for a regional disease (i.e. disease with lymph node involvement), and only 10% if metastases are present. However, mortality rates are gradually declining in The Netherlands, which may be attributed to improvement of therapy, in particular adjuvant chemotherapy in colon carcinoma, and also improved staging, new surgical techniques, such as total mesorectal excision, and pre-operative radiotherapy for rectum tumours.[6-8] Furthermore, the earlier stage detection of CRC improves the survival rate for CRC. Further improvement of survival can be expected from the introduction of population-based screening for CRC. Primary prevention of CRC can, theoretically, also be accomplished by improvement of life-style associated risk factors.[9]

RISK AND PREVENTIVE FACTORS FOR SPORADIC COLORECTAL CANCER

The risk of developing CRC is influenced by genetic as well as environmental factors. The majority of CRC are sporadic and have a multifactorial aetiology. In 15 to 20% of all CRC, inherited genetic factors are expected to be a major underlying cause of the disease. The majority is classified as familial CRC and accounts for 10% of CRC. In familial CRC there is a clear family history of CRC, however a pathogenic mutation which causes the disease has not been found. Several genetic syndromes are known to cause CRC. Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC) is the most frequent diagnosed hereditary CRC

cancer syndrome, accounting for 2 to 5 %, followed by familial adenomatosis polyposis (FAP), accounting for less than 1% of CRC.[10]

Many risk factors are described for sporadic CRC. Age is known to be an important risk factor for CRC, as 90% of all CRC occur after the age of 50. At all ages the incidence of CRC is slightly higher in men than in women.[11] Several lifestyle factors are associated with an increased incidence of CRC. Among others, a daily alcohol consumption of more than 45 g/d (approximately ≥3 drinks/day) is associated with an increased risk of CRC (RR 1.4, CI 1.2-1.7).[12,13] Also smoking (RR 1.2, CI 1.1-1.3) and the long term consumption of red or processed meat is a reported risk factor.[13,14]

Furthermore, a relationship has been reported between CRC and obesity, with a relative risk of 1.2 to 1.6 in obese men and 1.1 to 1.2 in obese women, being more pronounced for cancer of the colon than the rectum.[15] The development of adenomatous polyps, as well as their progression to malignancy, has also been associated with increased body mass index.[16,17] The distribution of the adipose tissue, especially the waist circumference, seems to influence the risk. The systemic mechanisms supporting the association between obesity and (colorectal) cancer are pathways which include the insulin and the insulin-like-growth factor axis, sex steroids and adipocytokines.[15] Also, patients with diabetes and the metabolic syndrome are at an increased risk of developing CRC.[18,19]

Patients with inflammatory bowel disease are at substantially greater risk of developing CRC compared to the general population, with the extent and duration of the disease being the primary determinants.[20]

A number of factors has been reported to protect against CRC. Aspirin is reported to have an antineoplastic effect in the colon. The use of 300 mg or more of aspirin a day for about 5 years reduced the incidence of CRC after a latency of 10 years (HR 0.63, 95% CI 0.47-0.85).[21] Secondly, substantial observational data suggest that regular physical activity is associated with a preventive effect on the development of CRC in both men and women (RR 0.76, 95% CI 0.72-0.81).[22] The degree to which dietary fibre and a diet high in fruits and vegetables protects against the development of CRC is uncertain.[23,24] Also the use of folic acid or calcium plus vitamin D supplementation in the prevention of CRC remains unproven.[25,26]

PREVENTION OF COLORECTAL CANCER: SCREENING AND SURVEILLANCE

Screening for CRC

Most CRC are assumed to arise from premalignant precursors, adenomatous polyps, following the so-called adenoma-carcinoma sequence. The concept of the adenoma-carcinoma sequence has emerged as the dominant morphogenetic explanation of CRC.[27] A study into the natural history of colorectal adenomas reported that the cumulative risk of malignant transformation of adenomas with a diameter of at least 1 cm was 2.5%, 8% and 24% after

respectively 5, 10 and 20 years of follow-up.[28] The majority of polyps do not develop into an adenocarcinoma; only up to 5 to 10% of all adenomas turn malignant.[27,29] The likelihood that a polyp develops into cancer depends on the size and histopathology of the adenoma. Advanced adenomas, i.e. adenomas larger than 1 cm, with high-grade dysplasia or villous histology, have a higher risk of malignant degeneration.[30]

The adenoma-carcinoma sequence provides an unique opportunity to reduce the incidence and mortality of CRC by detection and removal of adenomas. In the early nineties, the National Polyp Study (NPS) showed a 70-90% lower than expected incidence of CRC in a group in which polypectomy and surveillance endoscopies were performed, compared with historical reference populations.[31] Several other studies have shown a reduction in incidence and mortality of distal CRC after sigmoidoscopy screening.[32,33]

As CRC is a major health problem with significant morbidity and mortality and fits the criteria of Wilson and Jungner, i.e. the disease has detectable and treatable precursors (adenomas), early detection improves the prognosis, and facilities for diagnosis and treatment are available, there has been considerable interest in CRC screening.[34] There are two goals in CRC screening, namely primary and secondary prevention. The goal of primary prevention is to reduce the incidence of CRC by improvement of life-style associated risk factors for CRC and by the removal of adenomas. Secondary prevention aims at the detection of CRC at an early stage, which does not lead to a lower incidence, however does improve the prognosis and mortality considerably.

Beginning in 1980, the American Cancer Society issued formal guidelines for CRC screening in average risk persons over the age of 50. Since then, several societies have issued recommendations for CRC screening and many studies have investigated the most optimal screening method. As several studies have shown that screening decreases both the incidence and mortality of CRC, it has become widely recommended and is increasingly practiced.[35-40]

There is a variety of screening tests for the average risk population, including non-invasive stool tests, such as the guaiac and immunochemical faecal occult blood tests (FOBT) and structural examinations, such as colonoscopy, sigmoidoscopy, double-contrast barium enema (DCBE) and computed tomographic colonography. The ideal screening test for CRC should combine a high sensitivity with a high specificity. However, acceptability of a screening test represents a critical determinant of the impact of an organised program. A more acceptable test, like FOBT, may pick up a higher proportion of prevalent lesions, even if the sensitivity is lower than other tests as more people would be likely to attend screening.[41]

The European Union Commission's cancer screening recommendations from 2003 advised their member states to launch comprehensive CRC screening programs on a national scale. However, in 2007 no more than about half of the member states have followed with this recommendation, either by introducing a national screening program or by conducting preliminary studies for its eventual launch.[42] Worldwide, screening programmes have been introduced at regional level, like in France, Spain, Italy and Sweden, or on an individual basis,

like in the USA, Japan, Poland and the Czech Republic.[43] In Finland, England, Scotland, Australia, Germany and Canada a nationwide call-recall screening program has been introduced. Several invasive and non-invasive tests are discussed below.

SCREENING METHODS

Non-invasive screening tests

Guaiac faecal occult blood testing

The guaiac-based faecal occult blood test (gFOBT) is the most extensively examined screening method. The test identifies haemoglobin in faeces by the presence of a peroxidase reaction of haem, which turns the guaiac-impregnated paper of the test card blue. For the purpose of screening, the tests are performed at home using two stool samples, collected from each of three consecutive bowel movements. A colonoscopy is recommended if any of the six cards are positive to rule out neoplasia as a cause of the faecal blood. Ideally, dietary prescriptions are recommended, to prevent false-positive peroxidase reactions (caused by red meat or cabbage) or false-negative reactions (Vitamin C).[44] However, when used for screening, it has been shown that the dietary restrictions caused a lower uptake and are therefore not recommended in the screening setting.[45]

The gFOBT is the first non-invasive test proven to be effective in reducing the mortality of CRC in randomized controlled trials. In 1993, the Minnesota FOBT trial showed a 18% reduction of mortality of CRC when using biennial gFOBT and performing colonoscopy for those with a positive screen.[35] Four large randomized controlled trials with annual gFOBT demonstrated a significant relative reduction in CRC mortality of 16% (OR 0.84, CI 0.78-0.90).[35-37,46,47] The high mortality reduction in the Minnesota trial might be attributed to the fact that many colonoscopies were performed in the work-up for positive gFOBTs, showing a cumulative colonoscopy rate of 38%, compared with 4% over 5 screening rounds in the Nottingham study.[36,38] The high colonoscopy rate is explained by the use of rehydrated gFOBT slides in the Minnesota trial, resulting in a high positivity rate.[47]

Although studies have shown that the gFOBT is safe, has a reasonable uptake, and reduces the mortality, many of the individual gFOBT tests have a limited sensitivity and specificity. Low positive predictive values have been reported for CRC, suggesting that at least 80% of the tests were false-positive.[35-37] Logically, the positive predictive values for all neoplasia together were higher (up to 47.1%).[36,37] In case of annual or biennial testing, the accumulated sensitivity results in a higher sensitivity, however, this requires stringent adherence of the population to the screening program. The attendance in the four trials varied from 60% to 78% in the first screening round, although decreasing attendance rates for following screen-

ing rounds were reported. The uptake of the consecutive colonoscopy after a positive test ranged from 90-96%.[37,46]

At this moment, in many countries FOBT tests are used for screening, as it is a non-invasive test shown to decrease the mortality of CRC. Because of the limitations of the gFOBT, in particular the low sensitivity, the interest in other tests, like the immunochemical FOBT, is growing.

Faecal Immunochemical Test

The faecal immunochemical test (FIT) uses antibodies specific for human (haemo)globin (Hb). The test is a rapid immunochromatographic assay for the qualitative detection of intact human haemoglobin in faecal specimens. Unlike the gFOBT, the FIT does not depend on peroxidase activity and is highly specific for detecting human blood. For this reason, no dietary or medication restrictions are necessary.

The analysis of the FIT can be performed quantitatively or non-quantitatively. In both tests, faeces is collected with a small stick and then placed in a collection tube and mixed with a sample buffer. In the non-quantitative test, the sample buffer is put on a test strip that contains anti-human Hb, which reacts with faecal Hb. The test is considered positive for occult blood if two lines appear in the reaction field. If one line appears, the test is considered negative. The test is invalid if no line appears or the whole reaction field colours. The disadvantages of this non-quantitative test are the error that is associated with human interpretation and the fact that the interpretation of the results is time consuming.

In the quantitative method, the buffer fluid is analysed automatically, offering values in nanograms haemoglobin per millilitre buffer fluid. The test is reproducible and less susceptible to inter-observer variability, compared to the non-quantitative test.[48] The major advantage of the quantitative results is that it allows determination of an optimal cut-off level for CRC screening, adapted to the endoscopy resources and the intended detection rate in a population.[49] For these reasons, the quantitative test is more suitable for population screening than the non-quantitative test.

The defined cut-off point predicts the sensitivity and the positive predictive value of the test, as the cut-off point determines the further work-up of a positive test, i.e. the performance of a colonoscopy. A low cut-off point provides a higher detection rate, however, it causes a high burden on the endoscopy capacity and more negative colonoscopies. A higher cut-off point is associated with a higher positive predictive value, although more adenomas and CRC will be missed. The optimal cut-off level is a value with an adequate positivity rate and an acceptable trade-off between the detection rate and number needed to scope to find a screenee with advanced neoplasia or CRC.

The gFOBT has shown to be effective in reducing mortality of CRC. The efficacy for FITs in decreasing CRC incidence and mortality has never been directly studied in randomized controlled trials. Many studies, however, compared the performance of gFOBT and FIT and

reported higher sensitivity and specificity for FIT compared to gFOBT. [49-57] A higher detection rate of advanced adenomas and CRC was reported for FIT than for gFOBT, depending on the cut-off level used in the FIT.[49,50,52] Furthermore, in comparison with gFOBT, immunochemical tests are more patient-friendly and higher attendance rates were seen when using the FIT for population screening.[49,50]

Faecal tumour markers

Several faecal tumour markers are under investigation for CRC screening. One test of interest is the determination of tumour pyruvate kinase isoenzyme type M2 in stool samples. This isoenzyme is expressed in proliferating cells and is present in a tetrameric form. In tumour cells, however, this isoenzyme is predominantly present in a dimeric form, due to interaction with certain oncogenes, which has therefore been termed tumour M2-PK (TuM2-PK). Studies showed that the level of TuM2-PK was up regulated in cancer tissue and is released by tumour cells of a wide range of different malignancies and can be detected in body fluids as well as in faeces. Stool sample for TuM2-PK are measured using a commercially available enzyme-linked immunosorbent assay (ELISA).

Several studies investigated the use of TuM2-PK as a screening tool for CRC. They reported a sensitivity ranging from 69% to 85% for CRC and 26% to 50% for adenomas.[58-66] The specificity ranged from 65% to 93% for CRC and 71% to 74% in adenomas. When compared to FIT, TuM2-PK performed inferiorly as a screening marker for CRC and adenomas.[63] However, TuM2-PK is thought to be more cancer-specific than faecal occult blood tests, which may be of additional value.

Invasive screening tests

Sigmoidoscopy

A sigmoidoscopy allows examination of the distal part of the colon, including the rectum, sigmoid and descending colon. Screening sigmoidoscopy is used to identify patients with distal colonic neoplasia, who will subsequently be referred for total colonoscopy based on the distal findings.

The advantage of sigmoidoscopy above colonoscopy is that it requires a less intense bowel preparation. A single self-administered enema is usually sufficient for adequate bowel preparation. Also, the duration of the examination is shorter and, in general, it is performed without sedation and therefore applicable to an office-based setting. For these reasons, the capacity for sigmoidoscopy screening is better to fulfill than colonoscopy screening. Furthermore, the complication rate is low in sigmoidoscopy screening trials. The most important complications are perforation and bleeding, which are reported to occur in 1-2 /1000 screening sigmoidoscopies.[67] One study showed that the risk of perforation was increased in association with higher age and the presence of two or more co-morbidities.[67] Important

limitations of sigmoidoscopy are the considerable variation in depth of insertion of the scope and the inability to detect right-sided neoplasia, which potentially impairs the yield of a sigmoidoscopy-based screening program.

In the early nineties of the previous century, three observational studies of sigmoidoscopy showed a 59-79% reduction in CRC related mortality in average-risk patients.[33,68,69] Based on these results, several randomized controlled trials were started in the US and Europe.[40,70-73] The Norwegian NORCCAP trial showed their interim results at 6 to 7 years follow-up. The intention-to-screen analysis showed no difference in cumulative CRC incidence at 7 years of follow-up between the screenees and the control group. Only a trend was reported towards reduced mortality from CRC for both total CRC mortality (27%) and rectosigmoidal cancer mortality (37%). The data, however, included prevalent cases and the period for developing CRC from a precursor lesion might be considerably longer than is commonly assumed. It may therefore take longer than these 7 years to determine the effectiveness of screening sigmoidoscopy. For those actually attending screening, a significant reduction in CRC related mortality was seen (HR 0.41, 95% CI 0.21-0.82).[40] Atkin et al. showed that after 11 years of follow-up after once-only sigmoidoscopy, CRC incidence was reduced by 33% and CRC mortality by 43% in those who underwent screening.[39] The results of two sigmoidoscopy screening trials in the United States and Italy are awaited in the near future.[70,72]

There are several issues that need consideration before implementing a sigmoidoscopy-based screening program. First of all, a total colonoscopy is performed in case of a positive sigmoidoscopy, i.e. detection of (advanced) adenomas in the distal colon. There is, however, still no consensus on which patients should be referred for colonoscopy based on the distal findings.

It is known that the risk of proximal advanced neoplasia is increased in persons with distal advanced neoplasia or those with three or more distal adenomas.[32,74,75] One study showed that patients with distal tubular adenomas, regardless of size, are not at increased risk of having synchronous proximal advanced neoplasia.[74] Furthermore, hyperplastic polyps are not associated with an increased risk of proximal advanced neoplasia and therefore a total colonoscopy is not indicated.[75-77] Referral rates for colonoscopy would be approximately 5% if referral was restricted to those patients with an advanced adenoma in the distal colon, increasing to 12.5% if all persons with at least one distal adenoma were to be referred for colonoscopy.[70,78,79] Most sigmoidoscopy screening trials performed a colonoscopy if 3 or more adenomas, an advanced adenoma or a CRC were detected during sigmoidoscopy.[39,51,70,73]

Consequently, the effectiveness of screening sigmoidoscopy to detect proximal advanced adenomas depends on the strength of the association between distal and proximal adenomas, as well as the proportion of patients who have advanced proximal adenomas without distal adenomas. Several studies reported the risk of proximal advanced neoplasia to be 2.5% to 5% in asymptomatic persons without distal adenomas.[74,75,77] For this reason, colonoscopy, instead of sigmoidoscopy, might be the preferred screening tool in certain populations.

It is reported that the distribution of CRC in the colon is age- and gender-dependent. Several studies reported an increased proportion of proximal (advanced) neoplasia or carcinoma with advancing age.[80-84] Besides this age-dependent increase in incidence, a left-right shift has been reported for CRCs over the last 20 years, particularly in women.[85-88] The detection of those proximal CRCs with sigmoidoscopy depends on the presence of distal marker lesions.

One colonoscopy study showed that if sigmoidoscopy were to have been performed, followed by colonoscopy if a distal adenoma of any size was found, 80% of all patients with advanced neoplasia in the distal and proximal colon would have been identified.[75] The detection rate of advanced adenomas seems to differ between men and woman: A detection rate of 66% was reported in a male population, in contrast to 35% in a female population.[77,89] These two studies also showed that increasing age is associated with a higher miss-rate of proximal advanced adenomas.[77,89] Therefore, sigmoidoscopy seems to be a less effective screening tool in women than in men, and also in elderly populations. In these populations colonoscopy might be considered as a primary screening tool.

Colonoscopy

Colonoscopy seems to be the most accurate method to detect neoplasia in the colon and is considered as the reference standard for the detection of neoplasia in the colon. It allows direct mucosal inspection of the entire colon and biopsies or polypectomies can be performed.

There are no prospective, randomized trials which have assessed the efficacy of colonoscopy screening in reducing CRC mortality. However, for several reasons, it is plausible that colonoscopy is effective as a primary screening test. Firstly, support for colonoscopy evolved as it has been used in the work-up for positive FOBTs and sigmoidoscopy. Colonoscopy is the means by which FOBT (and sigmoidoscopy) screening reduces mortality. Also, The National Polyp Study showed a 76% to 90% decrease in the incidence of CRC at 6 year after colonoscopic polypectomy, as compared to controls.[31,90] Furthermore, it can be assumed that if sigmoidoscopy is effective in reducing CRC mortality due to cancers in the left-sided colon, colonoscopy will have the same effect on cancers located in the proximal colon, assuming that the proximal colon biologically behaves in the same way as the distal colon. Despite these plausible arguments, randomized controlled trials are needed to confirm the effectiveness of colonoscopy screening.

Colonoscopy has been endorsed and has become popular in the US as the primary screening test. However, it may not be suitable for mass population screening because of several reasons.

Firstly, high endoscopy resources are required and colonoscopy is associated with higher costs. The colonoscopy capacity is limited. One US-study concluded that the capacity in the US was seriously limited and other screening strategies were needed to be able to screen the population at risk.[91] Secondly, the procedure is more demanding for individuals than other screening tests. The preparation for the colonoscopy is often experienced to be more bur-

dening than the procedure itself. Furthermore, it is an invasive test with a, albeit low, risk of perforation and bleeding. Colonoscopy screening in an average-risk population is associated with a low morbidity rate (0.1 to 0.3%) and low procedure-related mortality.[83] Compared to symptomatic patients, the complication rate in the asymptomatic population is lower, probably due to a lower frequency of therapeutic procedures. However, what should be kept in mind is that screening colonoscopy is performed in a healthy population and a cumulative risk of 0.1 to 0.3% morbidity rate may become quantitatively important when screening a large population. Thirdly, although colonoscopy allows total visualisation of the colon, miss rates have been reported in several studies. A review of studies on tandem colonoscopies (n = 465 patients) reported an increased miss rate with decreasing size of adenomas; a miss rate of 2 % for large adenomas (≥10 mm), 13% percent for small adenomas (5 to 10 mm), and even 25% for adenomas smaller than 5 mm. The overall miss rate for polyps of any size was 22%.[92] Furthermore, two recent studies reported that colonoscopy was less effective for right-sided CRC than for left-sided CRC, which might be the result of incomplete colonoscopies, inadequate bowel preparation or different growth pattern of right-sided CRC.[93,94]

SURVEILLANCE

Surveillance after polypectomy

Many countries developed guidelines for colonoscopic surveillance after polypectomy because of a high detection rate of adenomas at follow-up endoscopies (50-70%).[32,90] Colonoscopy is the examination of choice for surveillance. However, it is an invasive procedure, carries a risk for serious complications and requires many endoscopic facilities at high costs. Furthermore, as a result of CRC screening, there will be a dramatic increase in the number of surveillance endoscopies, which will cause a major burden on the endoscopy resources. For these reasons, examinations should be targeted at those who will benefit most.

The optimal surveillance strategy is unknown, concerning the surveillance interval and the predictive value of the size, number, villous histology and grade of dysplasia of the initial adenomas on the development of metachronous adenomas during follow-up. The main goal of surveillance is the prevention of CRC. In several studies, only small tubular adenomas were found during follow-up, of which most will not become malignant.[95] Therefore, advanced adenomas, which have a much higher malignant potential, are the main target in determining risk factors and surveillance intervals in many studies.[90,95-97] In a pooled analysis of 8 prospective studies, advanced neoplasia were diagnosed in 11.8% and CRC in 0.6% of the patients during a median of follow-up period of 47 months.[98] Risk factor pattern were similar for advanced neoplasia and invasive cancer.

Regarding the follow-up interval, several studies suggested that after polypectomy an interval of at least 3 years was safe. The NPS showed that surveillance endoscopy after removal

of adenomas performed after 3 years was as effective for detecting important adenomas as surveillance after both 1 and 3 years.[90]

Several factors were found to be an independent risk factor for the detection of (advanced) adenomas at follow-up. The strongest predictor was the number of baseline adenomas, although in some studies this was less evident for the prediction of development of advanced adenomas.[90,95-99] Also the size of the largest adenoma, the presence of villous histology and high-grade dysplasia were found to be predictors of adenomas in several studies, however, less convincing than the number of adenomas at baseline.[32,90,95-97] A pooled analysis of 8 prospective studies showed that the number (>5 adenomas) and size (>2 cm) of previous adenomas were most strongly associated with the risk of advanced adenomas during follow-up. In this analysis, the presence of high grade dysplasia was not an independent risk factor.[98]

Based on the previous findings, patients are often stratified either in a high-risk group, which includes having 3 or more adenomas, high-grade dysplasia, villous features or an adenoma larger than 1 cm, or in a low risk group. The low risk group includes patients with 1 or 2 small (< 1cm) tubular adenomas without high-grade dysplasia, which is associated with a very low risk of metachronous adenomas, probably similar to that of the average risk population.[32,95-97,100]

In the US, the interval of surveillance endoscopy is based on the low- and high risk stratification as mentioned above.[101] In the UK, patients are stratified in 3 risk groups, based on the number and size of the initial adenomas.[100] In these guidelines, the histology and the grade of dysplasia do not determine the surveillance interval, as there is uncertainty of the role of histology as a predictor of future adenomas. Also the histological sub-typing of adenomas is subjective and the reproducibility is poor.[100] Obviously, the multiplicity of adenomas depends on the efficacy of the endoscopist's clearing and polyp size is subject to endoscopist's interpretations. Furthermore, villous elements and high-grade dysplasia are subject to marked interobserver variation of pathologists.[102] In The Netherlands, the guidelines for surveillance after polypectomy are solely determined by the number of previous adenomas.[103]

Surveillance after colorectal cancer

It is known that patients diagnosed with CRC are at risk of having synchronous CRC. Reports on the frequency of synchronous colorectal lesions vary considerably. According to the literature, incidence figures range from 1-7%.[104,105] The presence of synchronous CRC stresses the importance of performing a total colon examination, preferably prior to surgery, and is recommended in several guidelines.[106,107] Besides the risk of a second primary CRC at the time of diagnosis, patients with a history of CRC have a lifelong risk of metachronous CRC. For this reason, several institutions developed guidelines for the optimal surveillance strategy, depending on the stage of the initial cancer. Different tests are used for surveillance: endoscopy, carcinoembryonic antigen (CEA) testing, computed tomography (CT) scan, abdominal ultrasound and X-rays.

In the US guidelines, follow-up after rectal cancer deviates from those after colon cancer, as higher recurrence rates are reported for rectal cancer. In addition to the recommended colonoscopy at a 1 and 3-year interval, a periodic examination of the rectum by sigmoidoscopy is recommended for the purpose of identifying local recurrence at 3 to 6-month intervals for the first 2 to 3 years.[106] In the Dutch recommendations, no distinction is made between endoscopic surveillance after resection of cancer in the colon or cancer in the rectum, because in The Netherlands total mesorectal excision (TME) in combination with radiotherapy is the prevailing therapy for rectal cancer and is accompanied with low recurrence rates. However, in patients treated for rectal cancer, a digital examination is recommended every 6 months.[107]

Several studies compared low-intensity and high-intensity CRC surveillance programmes. The ASCO guidelines are based on three meta-analyses, which reported a 20-33% reduction in risk of death from all causes for those individuals who received more intense follow-up programmes.[108,109] It was reported that individuals with more intensive surveillance had earlier documentation of recurrences and were more likely to undergo surgery for metastases or recurrent disease with curative intent. In the ASCO guidelines colonoscopy is recommended after 3 years. The Dutch guidelines also advise performing a colonoscopy after 2 to 3 years, when a total colonoscopy had been performed at the time of CRC diagnosis.

In contrast, the guidelines of the American Cancer Society and the US-multi society Task Force recommend a first colonoscopy after 1 year to look for metachronous lesions.[106] This recommendation is based on reports of high incidences of metachronous CRC in the first 2 years after the initial diagnosis. The guideline stresses the fact that the primary goal of surveillance endoscopies after CRC is the detection of metachronous CRC, since it does not have an established survival benefit for the purpose of the detection of local recurrences.

As there is no gold standard for surveillance after polypectomy or resection for CRC, surveillance strategies will differ without being 'right or wrong'. However, the effectiveness of these different surveillance strategies largely depends on the compliance in clinical practice, which is unknown for most of the guidelines.

AIM AND OUTLINE OF THE THESIS

The aim of this thesis was to get insight in the several aspects of colorectal adenomas and cancer, including the detection of adenomas and anatomical distribution of (multiple) sporadic colorectal cancers, and consequently the impact of the different detection modalities and the adherence to current surveillance guidelines.

In **Chapter 2 and 3** the incidence of synchronous and metachronous sporadic CRC is described with data obtained from the Rotterdam Cancer Registry in The Netherlands. Further-

more, we identified patient and tumour-related characteristics associated with the presence of synchronous and metachronous CRC.

Invasive screening tests, like colonoscopy and sigmoidoscopy, are performed as primary screening tests or for the work-up for positive primary (non-invasive) screening tests. Facing the introduction of a national screening program for CRC in the near future, we wanted to get insight in the current performance of colorectal examinations and evaluate the effect of these examinations on the development of CRC. A case-control study was performed in which the performance of colorectal examinations prior to a CRC diagnosis was investigated, using the Integrated Primary Care Information (IPCI) database (**Chapter 4**).

In **Chapter 5**, we evaluated the yield and miss-rate of CRC in men and women when using sigmoidoscopy for the purpose of CRC screening by using the Endobase endoscopic report system.

Non-invasive faecal tests for CRC screening are evaluated in **Chapter 6**. In this study the immunochemical FOBT was evaluated, compared to the Tumour M2-PK test.

For the prevention and detection of metachronous colorectal neoplasia, surveillance after polypectomy or CRC resection is of major importance. The introduction of CRC screening will cause a large increase in the amount of surveillance endoscopies. For this reason, a national inquiry among endoscopists in The Netherlands was performed to assess the adherence to the current Dutch post-polypectomy guidelines and to evaluate the follow-up policy after CRC resection in each endoscopy department in The Netherlands. In **Chapter 7** the results of this inquiry are described.

To evaluate the compliance with the surveillance guidelines in daily clinical practice, a database study was performed in which the surveillance endoscopies of patients treated for colorectal adenomas or CRC were evaluated and compared to the then prevailing guidelines (**Chapter 8**).

Chapter 9 gives an overview of the results of this thesis and recommendations for future research.

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II

Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study

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ABSTRACT

Background: A noticeable proportion of colorectal cancer (CRC) patients is diagnosed with synchronous CRC. Large population based studies on incidence, risk factors and prognosis of synchronous CRC are however scarce and are needed for better determination of risks of synchronous CRC in patients diagnosed with colonic neoplasia.

Methods: All newly diagnosed CRC between 1995-2006 were obtained from the Rotterdam Cancer Registry in The Netherlands, and studied for synchronous CRC.

Results: Of the 13 683 patients diagnosed with CRC, 534 patients (3.9%) were diagnosed with synchronous CRC. The risk of having synchronous CRC was significantly higher in men (OR 1.54, 95% CI 1.29-1.84) and in patients aged >70 years (OR 1.83, 95% CI 1.39-2.40). Synchronous CRC patients had a significantly higher risk of distant metastases (OR 1.69, 95% CI 1.27-2.26). In 34% (184/534) the two tumours were located in different surgical segments. Five-year relative survival of synchronous CRC was similar to patients with solitary CRC after multivariate adjustment for presence of distant metastases.

Conclusion: One out of 25 patients diagnosed with CRC presents with synchronous CRC. In the multivariate analysis, survival of patients with synchronous CRC was similar to patients with solitary CRC, when corrected for presence of distant metastases at first presentation. One-third of the synchronous CRC was located in different surgical segments, which stresses the importance of performing total colon examination preferably prior to surgery.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of death from malignant disease in the Western world.[1] The lifetime risk of CRC is around 5% in the general population.[2] Patients diagnosed with sporadic CRC are at risk of a synchronous CRC at the time of diagnosis as well as metachronous CRC during follow-up.[3] Early identification of synchronous CRC is essential because it may modify the extensiveness of the surgical procedure. Also, if not recognized, the lesions will progress, leading to more advanced cancer and thereby reducing the probability of cure at the time of detection.

Reports on the frequency and risk factors of synchronous colorectal lesions vary considerably. According to the literature, incidence figures range from 1-7%.[4,5] Part of this variation can be explained by differences in definitions, selection criteria, patient populations and time periods studied. Risk factors commonly reported are male gender [6-8], higher age [8,9] and the presence of synchronous adenomas.[5,8,10,11]

Data about the prognosis of patients with synchronous CRC are conflicting. Some studies suggest that patients with synchronous CRCs, when comparing the most advanced stage of the lesions, have the same prognosis as patients with solitary CRCs; others reported poorer survival.[6,8,9,11,12] Treatment guidelines do not yet mention synchronous CRC as a category requiring modified management, whether this is needed is not clear.

The aim of this study was to evaluate the prevalence of synchronous sporadic CRC in a large cohort of CRC patients and to identify patient and tumour-related characteristics associated with the presence of synchronous CRC. In this way we wanted to evaluate the possibility of constructing a prediction model for the presence of synchronous CRC based on patient of tumour-related characteristics. To evaluate whether patients diagnosed with synchronous CRC require a modified management, we investigated the occurrence of synchronous CRC in different colon segments and the survival of patients with synchronous CRC compared with survival of patients with solitary CRC.

METHODS

Study population

Electronic records for patients with CRC were derived from the Rotterdam Cancer Registry, covering the Southwestern part of The Netherlands, a region with 16 hospitals and approximately 2.4 million inhabitants.[13] Newly diagnosed cancer patients are notified to the registry through the records of the pathology departments and hospital discharge diagnoses. After notification, trained registration clerks collect medical information on patient characteristics, tumour type and site, extent of disease (TNM) and treatment. Follow-up information is retrieved through annual linkage with the Netherlands Municipal Administration Database.

Table 1 Exclusion criteria

Characteristics	Patients	
	n	(%)
Initial number of patients	17 146	
No resection	2 470	(14.4)
Known Lynch Syndrome or FAP	55	(0.3)
Carcinoma in situ	467	(2.7)
Aberrant morphology	*265*	(1.5)
Neuro-endocrine	*(206)*	
Squamous cell carcinoma	*(11)*	
Connective and soft tissue	*(16)*	
Others	*(32)*	
Location not specified	197	(1.2)
TNM stage not specified	9	(0.1)
Eligible patients	n=13 683	(79.8)

FAP, Familial adenomatosis poli

This process has been shown to have excellent coverage. Due to privacy restrictions in The Netherlands, the cancer registry does have information regarding time of death, but does not have access to cause of death information.

The study cohort comprised 17 146 patients, diagnosed with CRC in the period 1995-2006. For various reasons, 3 463 (20.2%) patients were excluded (Table 1). Patients who were not treated by resection (n=2 470) were excluded because exploration for concurrent tumours is likely to be incomplete. Patients known with predisposing conditions such as Lynch syndrome and familial adenomatous polyposis (FAP) at the time of diagnosis were excluded using a regional database of families with hereditary CRC syndromes. In total 55 patients (47 patients with single CRC and 8 patients with synchronous CRC) were excluded because of either Lynch syndrome or FAP.

Data classification

Synchronous CRC was defined according to the Warren and Gates criteria: i.e. i) proven adenocarcinoma, ii) proven to be distinct and iii) exclusion of probable metastatic lesions from the primary CRC.[14] By definition, the tumours were diagnosed at the same time or within six months after the initial CRC diagnosis.

Patients diagnosed with one CRC were classified as 'solitary' CRC. Patients with two or more invasive CRCs were classified as 'synchronous' CRC. When a second lesion only contained carcinoma in situ, the patient was also classified as solitary CRC. In patients with synchronous CRC, the most advanced lesion was considered as the index tumour in the analyses.

The location of the tumours, originally specified according to the International Classification of Diseases for Oncology (ICD-O) (cecum C18.0, appendix C18.1, ascending colon C18.2, hepatic flexure C18.3, transverse colon C18.4, splenic flexure C18.5, descending colon C18.6, sigmoid C 18.7, overlapping location C 18.8, location not specified C18.9, rectosigmoid C19.9,

rectum 20.9). The ICD-O was regrouped into right-sided (cecum to transverse colon) and left-sided (splenic flexure to (recto-)sigmoid) and the rectum. Furthermore, a second subdivision was made for the surgical segments; right-sided (cecum to hepatic flexure), transverse colon, descending colon (including splenic flexure), (recto-) sigmoid, and the rectum. Stage information had been gathered according to the TNM guidelines.

Statistical analyses

Prevalences were tabulated by category and analyzed with chi-square statistics. Differences between groups were tested by means of student T-test in case of continuous variables and by Pearson's chi-square test in case of categorical variables. Two-sided p-values <0.05 were considered to be statistically significant.

Multivariate analysis was performed using logistic regression. The categories of the variables were represented by indicator variables and their predictive value was assessed with the p-value of the log partial likelihood. Odds ratios (OR) were calculated with a 95% confidence interval (CI) and represented the relative risk against the reference category. Accuracy of the logistic regression model was measured by the area under the receiver operating characteristic curve (ROC). An area under the curve of 0.5 corresponds to pure chance classification, an area of 1 (or 0) to a perfect test.

Survival rates for patients with solitary or synchronous tumours were calculated using relative survival analysis.[15] In relative survival analysis, disease specific survival is approximated using the ratio of the observed mortality and the expected mortality for an age and gender matched series from the general population. It is preferred over an all cause mortality analysis if mortality due to non-related causes of death is substantial and the actual cause of death is unknown. Multivariate analysis of relative survival rates was performed using Poisson regression.[16] Statistical significance was assessed based on the p-values of the predictors in the univariate and multivariate Poisson regressions.

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 16.0. Survival analysis and Poisson regression were performed using STATA version 9.2.

RESULTS

Overall population

During the 12-year period, in total 13 683 patients were diagnosed with invasive CRC. The median age at diagnosis was 71 years (range 20-103) and 51.5% was male. The CRC was located proximal of the splenic flexure in 4 530 (33.1%) patients. Distant metastases were present in 12.4% of the patients at the time of diagnosis.

Presence of synchronous CRC

Overall, 3.9% (534/13 683) of the patients were diagnosed with a synchronous CRC (Table 2). Synchronous CRCs were significantly more often found in men than in women (OR 1.54, 95% CI 1.29-1.84), and in patients above 70 years of age compared to patients in younger age groups (OR 1.83, 95% CI 1.39-2.40). Furthermore, the risk of synchronous CRC was lower in patients with the most advanced tumour in the rectum compared to patients with cancer in the left sided colon (OR 1.64, 95% CI 1.25-2.15) or right sided colon (OR 1.67, 95% CI 1.29-2.16) (Table 2).

The grade of differentiation of the index tumour was not associated with the presence of synchronous CRC. Significantly more patients with a synchronous CRC did present with distant metastases at the time of diagnosis compared to patients with a solitary CRC (OR 1.69, 95% CI 1.27-2.26).

Table 2 Patient characteristics and determinants of the prevalance of synchronous CRC

	Total	**Solitary CRC**		**Synchronous CRC**		**% N_{tot}** [a]	**Multivariate OR**
	n_{tot}	*n*	*(%)*	*n*	*(%)*	*%*	*(95% CI)*
Total	13 683	13 149		534		3.9	
Sex							
Female	6 637	6 426	(48.9)	211	(39.5)	3.2	1
Male	7 046	6 723	(51.1)	323	(60.5)	4.6	1.54 (1.29-1.84)
Age groups							
<60	2 765	2 693	(20.5)	72	(13.5)	2.6	1
60-69	3 515	3 391	(25.8)	124	(23.2)	3.5	1.35 (1.00-1.81)
70-79	4 662	4 445	(33.8)	217	(40.6)	4.7	1.83 (1.39-2.40)*
80+	2 741	2 620	(19.9)	121	(22.7)	4.4	1.82 (1.35-2.46)*
Localisation (most advanced in sCRC)							
Rectum	3 168	3 088	(23.5)	80	(15.0)	2.5	1
Left colon[b]	5 985	5 724	(43.5)	261	(48.9)	4.4	1.64 (1.25-2.15)*
Right colon	4 530	4 337	(33.0)	193	(36.1)	4.3	1.67 (1.29-2.16)*
Grade of differentiation							
Good	808	773	(5.9)	35	(6.6)	4.3	1
Intermediate	9 332	8 983	(68.3)	349	(65.4)	3.7	0.84 (0.59-1.20)
Poorly	2 179	2 093	(15.9)	86	(16.1)	3.9	0.85 (0.56-1.29)
Not specified	1 364	1 300	(9.9)	64	(12.0)	4.7	-
Stage of most advanced tumour (TNM)							
I	3 226	3 114	(23.7)	112	(21.0)	3.5	1
II	4 944	4 763	(36.2)	181	(33.9)	3.7	1.00 (0.78-1.29)
III	3 823	3 680	(28.0)	143	(26.8)	3.7	1.09 (0.84-1.41)
IV	1 690	1 594	(12.1)	98	(18.4)	5.8	1.69 (1.27-2.26)*

sCRC, synchronous CRC.

[a] Row percentage: Number of synchronous CRC devided by n_{tot}

[b] Left colon: including splenic flexure, descending colon, sigmoid and recto-sigmoid.

* p< 0.001

Multivariate analysis confirmed an independent predictive value of gender, age, localisation and presence of distant metastases for the presence of synchronous CRC. However, the final logistic model had limited accuracy (ROC=0.6) suggesting that the prediction model for the presence of synchronous CRC will be of limited use in clinical practice.

Anatomical distribution of first and second CRC

Table 3 shows the distribution of synchronous CRCs in the colon and rectum. In more than half (54.3%) of the patients with synchronous CRCs, both tumours were localised in the left colon or rectum. In one fourth (24.5%) of the patients both tumours were localised in the right colon, i.e. proximal of the splenic flexure. In the remaining 20.2% the tumours were located in both subsides. In 5 cases (1.0%) the location of the second lesion was not specified.

Table 3 Anatomical distribution of first and second synchronous CRC in 534* patients with multiple synchronous lesions.

	Second CRC		
	Right colon	**Left colon**	**Rectum**
First CRC			
Right colon	131 (25) [a]	46 (9)	13 (2)
Left colon [b]	34 (6)	202 (38)	24 (4)
Rectum	15 (3)	16 (3)	48 (9)

[a] (%): proportion of 534.
[b] Left colon: including splenic flexure, descending colon, sigmoid and recto-sigmoid.
*In 5 cases (0.9%) the location of the second lesion was not specified.

Surgical consequences

Using a surgery classification, 34% (184/534) of the synchronous CRC patients had both tumours located in different surgical segments (Table 4). In these patients, the presence of synchronous CRC required a modification of the extent of the surgical procedure. In 65% (345/534) of patients with synchronous CRCs, the tumours were located in the same surgical segment: 20% patients had both tumours located in the right colon, 2% in the transverse

Table 4 Surgical anatomical distribution of first and second synchronous CRC in 534* patients with synchronous CRC.

	Localisation of second CRC				
	Right sided colon	**Transverse colon**	**Descending colon**	**Sigmoid**	**Rectum**
Localisation of first CRC					
Right sided colon	105	6	9	26	11
Transverse colon	7	13	1	10	2
Descending colon	6	4	24	12	4
Sigmoid	23	1	11	155	20
Rectum	11	4	3	13	48

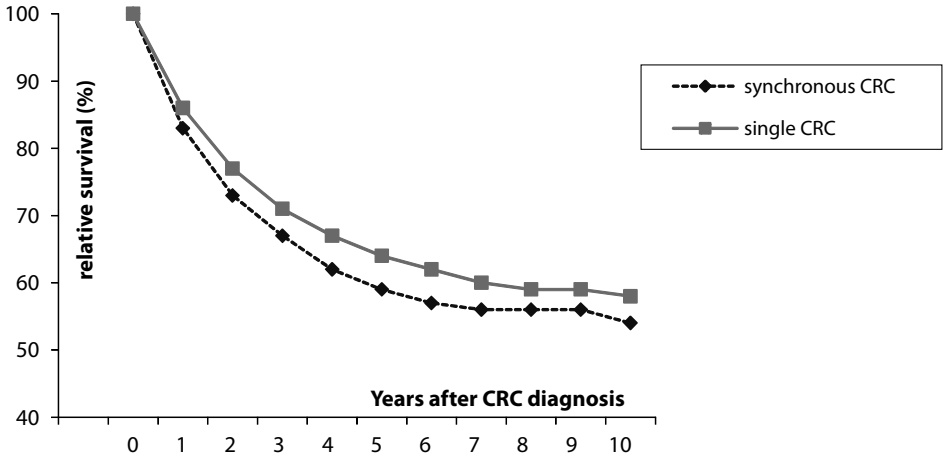
*In 5 cases the location of the second lesion was not specified

colon, 5% in the descending colon, 29% in the sigmoid and 9% in the rectum. In 5 (1%) cases the location of the second lesion was not specified.

Survival analysis

In the univariate relative survival analysis, the five-year and ten-year survival rates were significantly better for patients diagnosed with solitary CRCs compared to those with synchronous CRCs, 64% versus 58% after 5 year and 58% versus 54% after 10 year (hazard ratio (HR) 1.22, 95% CI 1.03-1.43) (Figure 1).

Figure 1 Univariate relative survival analysis



However, multivariate analysis revealed that this effect disappeared after adjustment for age, gender, presence of distant metastases and tumour localisation (HR 1.01; 95% CI 0.86-1.19).

In the relative survival analysis, the dominant predictor was the presence of distant metastases (HR 9.60, 95% CI 8.93-10.31) (Table 5). Other factors associated with a poorer survival were right-sided localisation of the CRC and higher age at the time of diagnosis. Gender did not have impact on the survival.

DISCUSSION

This population based study shows a 3.9% prevalence of synchronous CRC in a large Dutch cohort. This risk is in line with previous published data, reporting an percentage between 1.1 and 7% (Table 6). However, most of these studies were single centre and of older date, representing a time period in which colonoscopy was not widely available (Table 6). The strength of our study is that it was performed in a time period where total colonoscopy was routinely available and the standard in the work-up of patients diagnosed with CRC. Furthermore, our

Table 5 Multivariate relative survival analysis of potential prognostic factors

	Hazard Ratio	p-value
Synchronous CRC		
Solitary	1	
Synchronous	1.02 (0.86-1.20)	n.s.
Gender		
Male	1	
Female	0.99 (0.93-1.07)	n.s.
Age		
<59	1	
60-69	1.18 (1.07-1.29)	<0.001
70-79	1.33 (1.21-1.47)	<0.001
>80	1.86 (1.66-2.09)	<0.001
Location		
Rectum	1	
Left colon [a]	1.02 (0.94-1.11)	n.s.
Right colon	1.19 (1.09-1.29)	<0.001
Presence of distant metastases		
No	1	
Yes	9.60 (8.93-10.31)	<0.001

n.s. , not significant

[a] Left colon: including splenic flexure, descending colon, sigmoid and recto-sigmoid.

results were based on data from a long-term prospective cancer registry with full coverage of a large population, which included information from all newly diagnosed patients with (colorectal) cancer. For these reasons we are able to provide accurate data about the risk, risk factors, and prognosis of patients diagnosed with synchronous CRCs.

The occurrence of synchronous CRCs should be recognized as it has important consequences in clinical practice. In comparison to other types of cancer, synchronous lesions are quite common in the large bowel due to the inherent similarity in predisposition and exposure.

Sources of variation in reported risk

Although definitions of synchronous CRC tend to differ in the literature, synchronous CRC is generally defined as two or more distinct colorectal tumours diagnosed within six months after the initial diagnosis (Table 6). This period has been introduced to account for the fact that not all patients can be accurately examined by colonoscopy before surgery and full colon evaluation has to be postponed. Proper evaluation may even be abandoned if the patient has incurable disease or is inoperable due to co-morbidity. For this reason we decided to exclude all patients not treated by resection, a decision that might underestimate the prevalence. Most studies also included operated patients (Table 6).

Other causes of the variation in occurrence rates are the limited population sizes in many studies and differences in population characteristics. In contrast, our study comprised more than 17 000 CRC patients who were registered in a large region using standardized registration guidelines. Most studies were performed in a single centre with small study populations (Table 6).[10,17-19] Differences in patient characteristics were caused by a diversity of exclusion criteria. In many studies patients known with FAP were excluded. In contrast, patients with Lynch syndrome, which is also known to be a predisposing condition for synchronous CRC, were not excluded in most of the studies.[4-7,9-11,17]

Discrepancy may also be caused by differences in time periods studied.[8,9,17] Over the last decades various modalities were used to examine the colon, for example sigmoidoscopy and barium enemas. Only in the early nineties colonoscopy became the gold standard for examining the colon. These changes in diagnostic modalities may cause a variation in tumour detection and the reported incidence of synchronous CRCs. This was also suggested by Latournerie et al., who showed an increased use of colonoscopy and an increased incidence of synchronous CRC in the period 1976 up to 2004.[8] For this reason we studied a time period in which total colonoscopy was standard in the work-up, making the detection and the occurrence of synchronous tumours more reliable.

Finally, many cancer registries define synchronous CRC only when both tumours are found within *different* segments of the large bowel.[20] This definition causes a lower incidence rate of synchronous CRC since our study showed that synchronous tumours were often found within the same segment. A study performed in a regional cancer registry in France did not report about this fact and their registration of synchronous CRCs in the same colon segment is unknown.[8]

Risk factors

In our study, higher age (above 70 years) was an important risk factor for the occurrence of synchronous CRC. This finding is confirmed by other studies.[8,9] As incidence of sporadic CRC increases with age, it is rational that multiple sporadic tumours are more often discovered in the elderly.

Furthermore, synchronous CRC were more often diagnosed in men (OR 1.5). Two other studies confirmed this, although several studies did not show a difference between men and women (Table 6). We found a significantly higher risk for having synchronous CRCs in patients diagnosed with an index tumour in the colon, compared to those located in the rectum. Pinol et al. showed that a proximal localisation of the primary CRC was a risk factor for synchronous colorectal neoplasms, although this also included synchronous adenomas.[7] Passman et al. showed that synchronous CRCs (index and second CRC) were more often localised in the right colon, compared to single CRCs, however, the statistics were univariate analyses.[9]

Although several risk factors proved to be independently associated with synchronous CRC in multivariate analysis, the predictive value of the final regression model was too low (area under the ROC-curve of 0.6) to predict the occurrence of synchronous CRC in clinical practice.

Surgical consequences

An important finding of our study was the fact that in 34% of the patients the synchronous tumours were located in different surgical segments. Similar percentages were reported in other studies, however these studies were performed before the introduction of routine endoscopy.[5,21] This distribution throughout the colon illustrates the importance of preoperative diagnosis of synchronous lesions, as these patients require extended surgery or (sub)total colectomy. Since the early nineties several guidelines, like those of the American Society of Clinical Oncology (ASCO), recommend a full colonoscopy to ensure a cancer-free and polyp-free colon in the preoperative or perioperative setting in all CRC patients.[22]

Survival

Five-year survival for patients with synchronous CRC (58%) was slightly worse than for patients with a solitary tumour (64%), however this difference disappeared in multivariate analysis after adjustment for age, location and presence of distant metastases.

Our findings are in line with other studies which also did not show a difference in survival between patients with solitary or synchronous CRC (Table 6). Passman et al. also reported a similar prognosis for synchronous and solitary CRCs when the most advanced stage of CRC was used for comparison.[9] Latournerie et al. reported that, apart from stage at diagnosis and age, the presence of synchronous adenomas was an independent predictor of the prognosis.[8]

Conclusion

This large population-based study showed that synchronous tumours can be found in nearly 4% of patients with CRC. Synchronous CRCs were more common in males, patients aged over 70 years and cancer localised in the colon. Distant metastases were more common in synchronous CRC and explained the poorer survival. One third of the synchronous lesions were located in different surgical segments, requiring extended resection, which stresses the importance of performing total colon examination preferably prior to surgery.

Table 6 Synchronous CRC Studies

Author	Country and year	Definition [a]	Population	Exclusion	Time period	No pts	% sCRC	Risk factors for sCRC	Survival
Lasser [21]	USA 1978	Before or after surgery	Operated patients, single centre	FAP, UC. CIS	1967-1976	1,002	6.2%	- 62% of sCRC in same surgical segment	-
Langevin [17]	USA 1984	0-6 mo	Operated patients and colonoscopy	FAP, UC, incomplete colonoscopy	1978-1983	166	4.8%	- Male gender (n.s.) and presence of synchronous adenomas (n.s.)	-
Evers [5]	USA 1988	0-6 mo	Operated patients, veterans administration hospital	FAP, IBD, CIS	1977-1985	320	7%	- Synchronous adenomas - Trend for younger patients - 38% of sCRC in different colon segments	-
Passman [9]	USA 1996	0-6 mo	Operated patients, multi-institutional database	FAP, UC	1976-1993	4,878	3.3%	- Higher age - Right sided colon	Same survival rate
Takeuchi [10]	Japan 1997	0-6 mo	Operated patients, single centre	FAP, IBD. CIS not excluded	1990-1993	225	4%	- Synchronous adenomas	-
Chen [11]	China 2000	0-12 mo	Operated patients, single centre	FAP, IBD, non-epithelial cancers	1987-1993	1,780	3%	- Presence of synchronous adenoma - Better histologic grade of sCRC - No difference in age and gender - More proximal location of second sCRC	Same survival rate
Oya [6]	Japan 2003	0-12 mo	Operated patients, single centre	FAP, UC, CIS	1984-1999	876	4.8%	- Male gender and presence of distant metastases - No difference in age, size, location and differentiation	Same survival rate
Wang [4]	China 2004	0-6 mo	Operated patients, surgery dept	FAP, UC	1974-1998	1348	1.1%	- No difference in age and gender between synchronous and metachronous CRC	-
Nikoloudis [18]	Greece 2004	-	Operated patients, single centre	No exclusion Second CRC also CIS	1990-2003	283	2.1%	- Better histologic grade and more synchronous adenomas (n.s.)	Same survival rate

Table 6 (continued)

Author	Country and year	Definition [a]	Population	Exclusion	Time period	No pts	% sCRC	Risk factors for sCRC	Survival
Pinol [7]	Spain 2004	Before or after surgery	Operated patients, 25 centres	FAP, IBD, incomplete bowel examination, incomplete family history	2000-2001	1,522	6.2%	- Male gender, history of adenoma, proximal location, TNM IV, mucinous CRC [b]	-
Kim [19]	Korea 2007	Pre- and preoperative diagnosed CRC	Operated curative patients, single centre	Total colonoscopy after surgery	2001-2006	316	5.4%	- In 23.8% of patients the extend of surgery had to be modified because of synchronous adenomas or carcinomas.	-
Latournerie [8]	France 2008	0-6 mo	Population based cancer registry	FAP, Lynch, UC, non-epithelial cancers	1976-2004	15.562	3.8%	- Male gender - Age >75 yr - Adenoma and adenomatous remnants	Same survival rate

sCRC, synchronous CRC; mo, months; FAP, Familial adenomatosis poli; IBD, Inflammatory Bowel Disease; UC, ulcerative colitis; CIS, carcinoma in situ.

[a] Definition of synchronous CRC: interval after the initial diagnosis (in months).

[b] Risk factors for synchronous CRC *and* adenomas

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III

The incidence and risk factors of metachronous colorectal cancer: a Dutch population-based study

Submitted

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ABSTRACT

Background: Patients with colorectal cancer (CRC) are at risk of developing metachronous CRC. The purpose of post-treatment surveillance is to detect and remove premalignant lesions in order to prevent metachronous CRC. In this study we investigated the incidence of and predictive factors for metachronous CRC in newly diagnosed CRC patients.

Methods: All newly diagnosed CRC patients between 1995-2006 were obtained from the Rotterdam Cancer Registry in The Netherlands, and studied for metachronous CRC. The annual incidence rate and the standardized incidence ratios (SIRs) were calculated.

Results: During a 12-year period, 10 283 patients were diagnosed with an invasive CRC, including 39 974 person-years follow-up. The mean annual incidence rate of metachronous CRC was 314 / 100 000 person-years at risk during 10 years of follow-up, corresponding with a mean annual incidence of 0.3% and a cumulative incidence of 1.1% at 3 years, 2.0% at 6 years and 3.1% at 10 years. The incidence of metachronous CRC after resection of a first CRC is significantly higher than the incidence of CRC in an age- and gender matched general population (SIR 1.3, 95% CI 1.1-1.5). This difference is especially seen during the first 3 years after first CRC diagnosis (SIR 1.4, 95% CI 1.1-1.8). In multivariate analysis, presence of synchronous CRC at first CRC diagnosis was the only significant risk factor for developing metachronous CRC (RR 13.9, 95% CI 4.7-41.0).

Conclusion: Despite the availability of colonoscopy, metachronous CRC are still seen during follow-up of CRC patients, with the highest risk during the first 3 years after initial diagnosis. For this reason, a follow-up colonoscopy is useful at short term interval after CRC diagnosis. The presence of synchronous CRC at the time of first CRC diagnosis is the only predictive risk factor for developing metachronous CRC. A tailored surveillance program may be considered in patients diagnosed with synchronous tumours.

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the Western world. The lifetime incidence of CRC in persons at average risk is about five percent.[1] Patients with a history of CRC are at increased risk of developing a second primary CRC. The risk of developing metachronous CRC varies widely in the literature, ranging from 0.6-9%.[2-6] This wide variation is caused among others by differences in patient populations, selection criteria and variation in length of follow-up after the index CRC.

Risk factors reported to be associated with the occurrence of metachronous CRC are proximally located primary CRC, presence of mucinous histology, younger age at time of primary tumour, and the presence of synchronous adenomas or CRC at the first diagnosis.[3,6-13] Identifying patients at risk for developing a second primary CRC has important clinical implications. A tailored surveillance program for patients at risk may prevent the development of metachronous CRC.

The aim of this study was to assess the incidence of metachronous CRC in a large cohort of sporadic CRC patients, and to identify patient and tumour-related characteristics associated with the development of metachronous CRC in order to select high risk patients who might benefit from a tailored surveillance program.

PATIENT AND METHODS

Study population

Electronic records for patients with CRC were derived from the Rotterdam Cancer Registry, covering the Southwestern part of The Netherlands, a region with 16 hospitals and approximately 2.4 million inhabitants.[14] Newly diagnosed cancer patients are notified to the registry through the records of the pathology departments and hospital discharge diagnoses. After notification, trained registration clerks collect medical information on patient characteristics, tumour type and site, extent of disease (TNM) and treatment. Due to privacy restrictions in The Netherlands, the cancer registry does have information regarding time of death, but does not have access to cause of death information. Follow-up information is retrieved through annual linkage with The Netherlands Municipal Administration Database. This process has been shown to have excellent coverage.

The study cohort comprised 17 146 patients, diagnosed with an initial CRC in the period 1995-2006. For various reasons, 6 863 patients were excluded (Table 1). Patients who were not treated by resection for their first CRC (n=2 470) were excluded as exploration for concurrent tumours was likely to be incomplete. Furthermore, patients who underwent a total colectomy for their primary CRC (n=273) were excluded. Patients with less than 6 months of follow-up, due to death or those diagnosed after June 2006, were excluded from the

Table 1 Exclusion criteria

Characteristics	Patients	
	n	(%)
Initial number of patients	17 146	
No surgery	2 470	(14.4)
Lynch or FAP	55	(0.3)
Non-invasive CRC	467	(2.7)
Aberrant morphology	265	(1.5)
Neuro-endocrine	*206*	
Squamous cell carcinoma	*11*	
Connective and soft tissue	*16*	
Others	*32*	
Location not specified	197	(1.2)
TNM stage not specified	9	(0.1)
Died within 6 mo	1 376	(8.0)
Less than 6 mo follow-up	549	(3.2)
Total colectomy at index CRC	273	(1.6)
Distant metastases	1 202	(7.0)
Eligible patients	n=10 283	(60.0)

FAP, Familial adenomatosis poli

analyses (n=1 925). Patients known with predisposing conditions, such as Lynch syndrome and familial adenomatous polyposis (FAP) were excluded using a regional database with the outcome of molecular and germline mutation analyses. In total, 55 patients (47 patients with single CRC and 8 patients with synchronous CRC) were excluded, because of either Lynch syndrome or FAP.

Data classification

Metachronous CRC was defined according to the criteria previously defined by Moertel et al. as 1) a pathologically proven adenocarcinoma; 2) distinctly separated from the previous line of anastomosis, and 3) diagnosed at a minimal interval of 6 months after the initial carcinoma.[15] Tumours diagnosed within 6 months after the initial diagnosis were considered as synchronous CRC. The location of the tumours, originally specified according to the International Classification of Diseases for Oncology (ICD-O), was regrouped into right-sided (coecum to transverse colon, C18.0-C18.4), left-sided (splenic flexure to (recto-) sigmoid, C18.5-C19.9), and rectum (C20).[16] Stage information was gathered according to the TNM guidelines.

The annual and cumulative incidences were calculated for the total follow-up period. In order to compare the characteristics of 'early' versus 'late' metachronous CRC, patients with metachronous CRC were classified as those diagnosed with metachronous CRC within 3 years or after 3 years of first CRC diagnosis.

Statistical analyses

Differences between groups were tested by means of Student's *t*-test in case of continuous variables and by Pearson's χ^2 test in case of categorical variables. Two-sided p-values of $p<0.05$ were considered to be statistically significant.

A logistic regression analysis was performed to calculate the probability of developing a metachronous CRC according to the characteristics of the first CRCs in patients with solitary and metachronous CRC, including gender, age, tumour location, grade of differentiation and TNM stage.

Person-years at risk were calculated from 6 months after the date of diagnosis of the first CRC until the censored date of metachronous CRC, date of death or end of follow-up (December 2006), whichever occurred first. The expected number of metachronous CRC is obtained by multiplying the person-years at risk with corresponding gender- and age-specific incidence rates for the Dutch population, derived from The Netherlands Cancer Registry. The observed / expected annual incidence rate was calculated by dividing the observed / expected number of metachronous CRC patients by the annual person-years at risk per 100 000 person-years. Cumulative incidence was calculated using actuarial methods, censoring for end of follow-up or death.

The risk of metachronous CRC was expressed as standardized incidence ratios (SIR), calculated as the ratio of the observed rate of metachronous CRC among patients with CRC to the expected rate of first CRCs among individuals from the general population matched by sex and age. Differences in excess incidence, observed minus expected, was analysed using log-rank tests (univariate) and poisson regression (multivariate). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 and STATA version 9.2.

RESULTS

Characteristics of the total CRC population

During the 12-year period, in total 10 283 patients were diagnosed with an invasive colorectal adenocarcinoma, and included in the further analysis (Table 1). The median age at the time of the initial CRC was 70.0 years (interquartile: 62 to 77 years) and 50.6% was male. The initial CRC was located in the right-sided colon in 31.5% of the patients (Table 2). The total follow-up time was 39 974 person-years (mean 3.9 year, M/F 19 985 / 19 989 person years).

Table 2 shows the characteristics of patients diagnosed with solitary and metachronous CRC. In total, 135 patients (1.3%) developed a metachronous CRC during follow-up. There was no difference in the occurrence of metachronous CRC between men and women (1.4% versus 1.2%, respectively) or among the different age groups.

Table 2 Characteristics of patients with solitary versus metachronous CRC

	Total	Initial CRC without m-CRC group		Initial CRC with m-CRC group		% n_{tot} [a]	Multivariate OR [b]
	n_{tot}	n	(%)	n	(%)		
	10 283	10 148		135		1.3	
Sex							
Male	5 199	5 124	(50.5)	75	(55.6)	1.4	1
Female	5 084	5 024	(49.5)	60	(44.4)	1.2	0.8 (0.6-1.2)
Age at initial CRC							
<60	2 110	2 091	(20.6)	19	(14.1)	0.9	1
60-69	2 731	2 696	(26.4)	35	(25.9)	1.3	1.3 (0.7-2.2)
70-79	3 549	3 489	(34.4)	60	(44.4)	1.7	1.6 (0.9-2.7)
80+	1 893	1 872	(18.4)	21	(15.6)	1.1	1.1 (0.6-2.0)
Localisation of initial CRC							
Proximal colon	3 242	3 200	(31.5)	42	(31.1)	1.3	1
Distal colon [c]	4 438	4 354	(42.9)	84	(62.2)	1.9	1.4 (0.96-2.1)
Rectum	2 603	2 594	(25.6)	9	(6.7)	0.3	0.3 (0.1-0.6)*
Grade of differentiation							
Good	658	646	(6.4)	12	(8.9)	1.8	1
Intermediate	7 152	7 057	(69.5)	95	(70.4)	1.3	0.8 (0.4-1.5)
Poor	1 473	1 459	(14.4)	14	(10.4)	1.0	0.7 (0.3-1.5)
NOS	1 000	986	(9.7)	14	(10.4)	1.4	0.8 (0.4-1.8)
TNM stage							
I	2 869	2 829	(27.9)	40	(29.6)	1.4	1
II	4 180	4 111	(40.5)	69	(51.1)	1.7	1.1 (0.7-1.6)
III	3 234	3 208	(31.6)	26	(19.3)	0.8	0.6 (0.3-0.9) *
IV	-	-			-		
Presence of synchronous CRC							
No	9 949	9 829	(96.9)	120	(88.9)	1.2	1
Yes	334	319	(3.1)	15	(11.1)	4.5	3.4 (1.9-5.9)**

m-CRC, metachronous colorectal cancer; NOS, not otherwise specified

[a] Row percentage: Number of metachronous CRCs divided by $n_{tot.}$

[b] Logistic regression analysis.

[c] Distal: splenic flexure, descending colon and (recto-) sigmoid colon.

* p=0.02. **p<0.001.

The initial CRC of patients diagnosed with metachronous CRC was less often localised in the rectum compared to patients with solitary CRC (6.7% versus 25.6%, p<0.05). Furthermore, patients diagnosed with a metachronous CRC had more been often diagnosed with a synchronous CRC at the time of the initial CRC compared to patients with a solitary CRC (11.1% versus 3.1% respectively, p<0.001).

Standardized Incidence Ratio

The risk of developing of a second primary CRC after resection of an initial CRC is significantly increased (SIR 1.3, 95% CI 1.1-1.5) compared to the incidence of CRC in an age- and gender matched general population (Table 3).

In the univariate analysis, the excess risk was most pronounced in patients younger than 60 years of age at the time of first CRC diagnosis (SIR 2.3, 95% CI 1.2-3.5), gradually decreasing with increasing age (SIR 1.3 at 60-69 years and SIR 1.2 at 70-79 years). There was no excess risk among patients with a primary CRC above 80 years of age (SIR 0.9).

The SIR was increased during the first 3 years of follow-up (SIR 1.4, 95% CI 1.1-1.8), however, after > 3-6 and > 6 years of follow-up the risk was comparable to the risk in the general population (SIR 1.1 and 0.9, respectively). Excess risk was most pronounced in patients who

Table 3 Standardized Incidence Ratio: Observed and expected incidence of metachronous colorectal cancer

	Person years at risk	Observed m-CRC	Expected m-CRC	SIR	95% CI	Rate ratio [a] (95% CI)
Total	39 974	135	107	1.3	(1.1-1.5)	
Sex						
Male	19 985	75	62	1.2	(0.9-1.5)	1
Female	19 989	60	45	1.3	(1.0-1.7)	2.2 (0.7-7.2)
Age at first CRC						
<60	9 244	19	8.1	2.3	(1.2-3.5)	1
60-69	11 414	35	27.2	1.3	(0.9-1.7)	0.5 (0.1-2.1)
70-79	13 432	60	49.4	1.2	(0.9-1.5)	0.6 (0.2-1.9)
80+	5 884	21	22.5	0.9	(0.6-1.3)	0
Interval between first to m-CRC						
0 yr - 3 yr [b]	22 641	83	57.9	1.4	(1.1-1.8)	1
> 3 yr - 6 yrs	11 363	36	31.4	1.1	(0.8-1.5)	1.0 (0.3-3.3)
> 6 yrs - 11 yrs	5 932	16	17.8	0.9	(0.5-1.4)	0.7 (0.2-3.3)
Characteristics of first CRC						
TNM stage						
I	13 084	40	35.5	1.1	(0.8-1.5)	1
II	16 598	69	46.1	1.5	(1.2-1.8)	2.9 (0.7-12.3)
III	10 292	26	25.5	1.0	(0.6-1.4)	0.4 (0.1-6.2)
IV	NA					
Presence of Synchronous CRC						
No	38 648	120	103	1.2	(1.0-1.4)	1
Yes	1 327	15	3.6	4.2	(2.2-6.5)	13.9 (4.7-41.0)

m-CRC, metachronous colorectal cancer; NA, not applicable.

[a] Multivariate analysis (Poisson regression).

[b] Counted from the first day at risk (6 months after the initial CRC diagnosis).

presented with a synchronous tumour at the time of first CRC diagnosis (SIR 4.2, 95% CI 2.2-6.5), compared to patients with a solitary CRC at first diagnosis (SIR 1.2, 95% CI 1.0-1.4).

Of the studied risk factors, the presence of synchronous CRC at the first CRC diagnosis was the only significant predictor for developing metachronous CRC (RR 13.9, 95% CI 4.7-41.0) in the multivariate analysis. Age, gender and TNM stage were not associated with the occurrence of metachronous CRC.

Incidence of metachronous CRC

The metachronous CRCs were diagnosed ≤ 3 year at risk in 83/135 (61%) patients, in 36 (27%) patients >3 to 6 years, and in 16 (12%) patients > 6 years after the initial CRC (Table 3).

Table 4 shows the observed and expected annual incidence rates. The mean observed annual incidence rate of metachronous CRC was 314 / 100 000 py at risk during 10 years of follow-up. The observed and expected annual incidence rates are shown in Figure 1; the curve shows that the observed incidence rate of metachronous CRC is highly variable during follow-up because of small numbers, however the expected incidence (mean 280/100 000 py) is lower than the mean observed annual incidence rate (Table 4). The cumulative incidence of metachronous CRC is 1.1% at 3 years, 2.0% at 6 years and 3.1% at 10 years of follow-up (Table 4).

Table 4 Annual and cumulative incidence rates of metachronous CRC

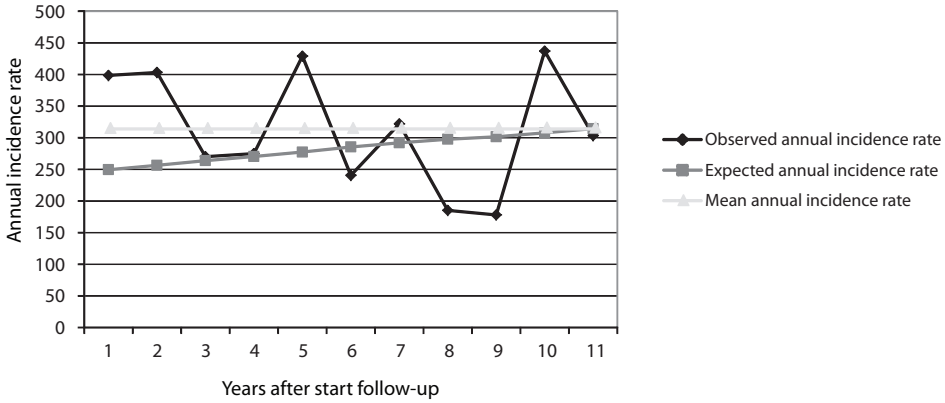
	Py at risk	No of m-CRC	No of exp m-CRC	Obs. annual inc rate [b]	Exp. annual inc rate [c]	Cum inc [d] (%)
0-<1[a] yr	9 281	36	23.2	398.6	249.6	0.4
≥ 1-2 yr	7 439	31	19.1	403.3	256.5	0.8
≥ 2-3 yr	5 921	16	15.6	270.2	263.9	1.1
≥ 3-4 yr	4 725	13	12.8	275.1	270.4	1.3
≥ 4-5 yr	3 729	16	10.3	429.1	277.5	1.8
≥ 5-6 yr	2 909	7	8.3	240.6	285.5	2.0
≥ 6-7 yr	2 174	7	6.3	322.0	292.1	2.3
≥ 7-8 yr	1 619	3	4.8	185.3	297.7	2.5
≥ 8-9 yr	1 123	2	3.4	178.1	301.6	2.7
≥ 9-10 yr	687	3	2.1	437.0	307.8	3.1
≥ 10-11 yr	329	1	1.0	303.5	314.5	3.4

Py, patient years; m-CRC, metachronous CRC; obs, observed; exp, expected; cum, cumulative; inc, incidence.
[a] Counted from the first day at risk (6 months after the initial CRC diagnosis).
[b] Observed Incidence rate: Number of observed m-CRC divided by the annual py at risk x 100.000 py
[c] Expected Incidence rate: Number of expected m-CRC divided by the annual py at risk x 100.000 py.
[d] Cum inc: cumulative incidence: calculated using actuarial methods, censoring for the end of follow-up or death.

'Early' versus 'late' metachronous CRC

Table 5 shows the characteristics of metachronous CRC detected during the first 3 years of follow-up ('early' metachronous CRC, n= 83) compared to those detected after > 3 years of follow-up ('late' metachronous CRC, n=52).

Figure 1: Observed and expected annual incidence rate



Number of patients developing a metachronous CRC divided by the annual patient-years at risk per 100.000 py.

A multivariate logistic regression analysis showed that women were more often diagnosed with late metachronous CRC compared to men (OR 3.1, 95% CI 1.3-7.7). Furthermore, late metachronous CRCs were more often diagnosed in the proximal colon compared to the distal colon (OR 0.2, 95% CI 0.1-0.6). Finally, early metachronous CRC were significantly more often poorly differentiated CRCs compared to late metachronous CRCs (Table 5). The TNM stage did not differ between early and late metachronous CRCs.

DISCUSSION

Patients with a history of CRC are at increased risk of developing metachronous CRC. This population-based study showed a mean annual incidence rate of 314/100 000 person years at risk, corresponding with a mean annual incidence of 0.3% and a cumulative incidence of 1.1% at 3 years, 2.0% at 6 yrs and 3.1% at 10 years. Data were derived from a long-term prospective cancer registry with full coverage of a large population, which included information from all patients with newly diagnosed CRC. Striking is the fact that despite easy access to endoscopy surveillance, metachronous CRC was still frequently seen during follow-up.

Comparison of our data with the available literature is hampered by several factors. First, the wide variation in reported incidences is partly caused by the inconsistency of the definition used for metachronous CRC. In this study, the distinction between synchronous and metachronous lesions was set at 6 months according to the definition of Moertel et al.[15] The time interval between the initial and second primary CRC, chosen to distinguish between synchronous and metachronous CRC, varies in the literature between 0.6 and 3 years (Table 6). Some studies used longer time intervals, for the reason that metachronous CRC appearing within 3 years might be considered as missed synchronous CRC that had been present at the time of the initial CRC.[17,18]

Table 5 Characteristics of metachronous CRC diagnosed during ≤ 3 and > 3 years of follow-up

	Total	m-CRC ≤ 3 years FU		m-CRC > 3 years FU		Multivariate OR
		n= 83		n= 52		
		n	%	n	%	
Sex						
Male	75	50	60	25	48	1
Female	60	33	40	27	52	3.1 (1.3-7.7)*
Age at initial CRC						
<60	19	10	12	9	17	1
60-69	35	18	22	17	33	1.3 (0.3-5.3)
70-79	60	43	52	17	33	0.4 (0.1-1.6)
80+	21	12	14	9	17	0.9 (0.2-3.9)
Localisation of m-CRC						
Proximal colon	64	33	39.8	31	59.6	1
Distal colon [a]	40	31	37.3	9	17.3	0.2 (0.1-0.6)**
Rectum	26	16	19.3	10	19.2	0.6 (0.2-1.9)
NNO	5	3	0.1	2	0.1	-
Grade of differentiation m-CRC						
Good	6	2	2.4	4	7.7	1
Intermediate	80	45	54.2	35	67.3	0.3 (0.1-2.6)
Poor	18	14	16.9	4	7.7	0.1 (0.1-0.8)***
NOS	31	22	26.5	9	17.3	-
TNM stage m-CRC						
CIS	10	6	7.2	4	7.7	1
I	36	26	30.1	10	19.2	0.4 (0.1-2.8)
II	51	30	36.1	21	40.4	1.1 (0.2-7.0)
III	29	15	18.1	14	26.9	1.4 (0.2-10.8)
IV	9	6	7.2	3	5.8	1.1 (0.1-11.8)
Presence of synchronous CRC						
No	120	77	92.8	43	82.7	1
Yes	15	6	7.2	9	17.3	0.3 (0.1-1.2)

m-CRC, metachronous colorectal cancer

[a] Distal: splenic flexure, descending colon and (recto-) sigmoid colon. *p =0.01; ** p = 0.005; *** p=0.03

Furthermore, the duration of follow-up is an important determinant of the incidence of metachronous CRC and varies widely in different studies. Some studies do not even mention the total follow-up time, making it difficult to interpret the results.[8,19] Another factor is the variation in study populations. Several studies included operated patients in a single centre, whereas others were based on cancer databases in which all CRC patients were included. Finally, many studies were performed during a time frame in which colonoscopy was not standard in the work-up for CRC or for the surveillance afterwards, causing an underestimation of metachronous CRC (Table 6). Only in the early nineties colonoscopy became the gold standard for examining the colon. The introduction period of routine colonoscopy examina-

tions may have caused an overestimation as synchronous CRC might become apparent as metachronous CRC.

Risk of metachronous CRC

We showed that the risk of a (second) primary CRC is higher in a population with a previous history of CRC than in the general population (SIR 1.3). A comparable SIR is reported in several older studies performed in a period before the introduction of colonoscopy surveillance programs.[10,11,20]

In the multivariate analysis, the presence of synchronous CRC at the time of the initial CRC was the only significant risk factor for developing metachronous CRC (RR 13.9). Several studies showed that the presence of synchronous CRC, but also synchronous adenomas, increases the risk of development of metachronous CRC, however, most of these studies only performed univariate analyses or included a small number of patients.[9,11,13,21]

In our study, gender, age, TNM stage and grade of differentiation of the initial CRC were not associated with the development of metachronous CRC. Several studies reported an inverse relation between age and the risk of metachronous CRC.[9,10,20] These studies, however, performed univariate analyses or included patients known with Lynch syndrome and FAP, which may have caused an overrepresentation of young patients with multiple primary CRCs. Furthermore, studies reported that metachronous CRC arise in patients with a more favourable Dukes stage and histological grade of the initial CRC than in patients diagnosed with a solitary CRC.[4,19] This, however, may be a reflection of mortality bias.[21,22]

In this study, the SIR was not calculated for the tumour localisation since the metachronous CRC arise in a partially resected colon. This can not be compared with the number of expected CRCs in the general population, in which the whole colon is in situ, and the CRC can arise in any location in the colon.

Besides the presence of synchronous CRC, no other patient or tumour-related characteristic could be used as a predictor for the development of metachronous CRC. For this reason, a prediction model to identify patients at (high) risk for the development of metachronous CRC can not be constructed based on these patient or tumour-characteristics. Further research is needed to elucidate risk factors and be able to identify patients at risk. As the presence of synchronous CRC is the only predictor, patients diagnosed with synchronous CRC should receive a tailored surveillance program. Considering the fact that many metachronous CRC are detected in the first 3 years after the initial CRC, it should be generally recommended to perform the first surveillance endoscopy at 1 year.

A remarkable finding in our study was the observation that the risk of developing a metachronous CRC was highest during the first 3 years of follow-up and gradually declined thereafter. During the years after the initial CRC, several factors will influence the SIR in opposite ways. On one hand, it is to be expected that the number of metachronous CRC is lower in the first years after diagnosis compared to a corresponding general population as the colon is

disposed of neoplasms at the time of the first CRC, assuming that all patients underwent total colonoscopy at the time of diagnosis. Second, after the initial CRC, surveillance endoscopies will have been performed in order to prevent the development of a metachronous CRC by detection and removal of adenomas. Furthermore, at the time of the initial CRC (a part) of the colon was resected. This (partial) resection results in a smaller SIR as these patients will be at lower risk of developing CRC than the general population, in which the whole colon is in situ.[23] In contrast, a higher SIR is to be expected as CRC patients have proven to be prone to develop CRC and have a higher risk of developing a second neoplasm compared to the general population.

Regarding those factors which influence the SIR in opposite ways, it is likely that the number of metachronous CRC will initially be lower compared to the general population and will rise several years after the initial CRC. However, in our study the excess risk of metachronous CRCs was highest during the first three years after the initial diagnosis and gradually decreased during 10 years of follow-up to a risk comparable to the general population.

An explanation for the early presentation of metachronous CRC may be that these early metachronous CRCs may have developed in a short period of time, suggesting an alternative pathway to CRC than the adenoma-carcinoma pathway. Another explanation may be that colon examinations at the time of the initial CRC were not, or not adequately, performed and that the metachronous CRC detected during the first years of follow-up can be considered as missed synchronous lesions. In this way, the incidence of metachronous CRC may be overestimated, as synchronous CRC become apparent as metachronous CRC. Although colonoscopy is considered as the gold standard for detection of adenomas, in the literature increased miss-rates are reported with decreasing size of adenomas, with an overall miss-rate of polyps of any size of 22%.[24] Furthermore, two studies reported that colonoscopy was less effective for right-sided CRC than for left-sided CRC, which among others may be caused by inadequate bowel preparation or incomplete colonoscopies.[25,26]

To investigate the possibility of synchronous CRC presenting as metachronous CRC in our study, the grade of differentiation and TNM stage of 'early' and 'late' metachronous CRC were compared. The TNM stage did not differ between 'early' and 'late' metachronous CRCs, however, the proportion of poorly differentiated CRC was significantly higher in the group of early metachronous CRCs, compared to those diagnosed after 3 years. This finding might suggest that those 'early' metachronous tumours grow more aggressively and are true metachronous CRC, instead of missed synchronous CRC.

In conclusion, our study shows that patients diagnosed with CRC are at increased risk of developing metachronous CRC compared to the general population, especially during the first 3 years after the initial CRC. For this reason, follow-up colonoscopies are useful at a short term interval after CRC diagnosis. The presence of synchronous CRC at the time of first CRC diagnosis is the only predictive risk factor for developing metachronous CRC. A tailored surveillance program may be considered in patients diagnosed with synchronous tumours

with a first surveillance endoscopy at one year. Further research is needed to identify patient or tumour-related characteristics associated with the development of metachronous CRC to identify patients at risk.

Table 6 Metachronous incidence studies

Author	Country Year	Definition m-CRC	Study Population	Exclusion criteria	Time period	No. pts	M-CRC	Incidence rate	Risk factors for M-CRC
Bulow [27]	1990 Denmark	-	Curatively operated patients, < 40 yrs	> 40 yr, not curatively	1943-1967	501	9% (FU up to 41 yrs)	CI: 30% (FU up to 41 yrs)	
Cali [2]	1993 USA	>2 yr	Cancer registry	FAP, CU and CIS	1965-1985	5476	-	CI: 0.35% / yr 6.3% / 18 yr	
Rennert [22]	1995 Israel	6 mo	SEER Database USA	Only white patients included	1973-1986	141,945	1.1%	230 / 100000 py	- Left sided colon tumours
Yamazaki [13]	1997 Japan	> 6 mo	Resection of CRC, single hospital	FAP, UC	1981-1994	284	1.8% (CIS in 8.8%)	1.8% at mean FU time of 53 mo (total 1254 yr)	- Presence of synchronous CRC or adenomas at first CRC - Age, gender, tumor stage, location or grade n.s.
Leggett [6]	1999 Australia	> 6 mo	Operated patients, single center	FAP, Lynch. No colonoscopy within 6 mo.	1980-1994	433	2.3%	Annual incidence 0.61%	- Proximal located CRC, mucinous pathology
Chen [7]	2000 China	>1 to 3 yr after first CRC	Operated patients, single center	FAP, IBD, non-epithelial tumours	1978-1993	1780	0.7%	-	- Significantly more often proximal located, less often in rectum - No difference in age, gender, stage and grade of differentiation
Togashi [12]	2000 Japan	CRC detected at surveillance	Curatively resected CRC, single hospital	- <3 yr FU and <2 colonoscopies - no total colon examination at index CRC - IBD and FAP	1992-1995	341	5.7%	CI: 4.3% / 5 yr	- Presence of synchronous adenomas at first CRC - Synchronous CRC, CRC in family (n.s.)
Shureiqi [10]	2001 USA	> 2 mo	SEER Database	-	1979-1996	217,705	1.9%	SIR 1.9 (95% CI 1.8-1.9)	- Inverse association between age and risk of metachronous CRC - Sex, location and stage not correlated
Evans [23]	2002 UK	-	Thames Cancer registry database	Non malignant tumours	1961-1995	127,281	0.4% (max mean FU time 5 yrs)	SIR: Male <60 yr: colon 2.33, rectum 1,40 Male > 60 yr: colon 0.58, rectum 0.36 Female < 65 yr: colon 1.28, rectum 1.04 † Female > 65 yr: colon 0.60, rectum 0.49	

Table 6 (continued)

Author	Country Year	Definition m-CRC	Study Population	Exclusion criteria	Time period	No. pts	M-CRC	Incidence rate	Risk factors for M-CRC
Fukutomi [28]	2002 Japan	First colonoscopy 6 mo	Resected CRC	FAP, Lynch	1985-1999	107	5.6% (median FU 39 months)	-	- Risk factors reported for metachronous adenomas and CRC
Papadopoulos [19]	2004 Greece	> 6 mo	Operated patients, single center	FAP, IBD, non-epithelial tumours	1970-1999	1160	2.1%	-	- Localisation in rectum, better stage (Dukes A) - Age and gender not significant
Gervaz [8]	2005 Switzerland	>6 mo	Geneva Cancer Registry	FAP, Lynch, non-epithelial tumours, CIS	1970-1999	5,006	2.4%	-	-Proximal localization of first CRC
Lan [17]	2005 China	>12 mo	Curatively resected CRC, single hospital	Family known with FAP or Lynch. CIS, loss of follow-up <1 yr	1981-2001	3846	1.1%	Annual incidence 0.18%	- No significant predicting factors (age, sex, location, presence of synchronous CRC/adenomas)
Park [9]	2006 Korea	> 6 mo	Operated patients, single center	FAP, Lynch, patients without colonoscopy in first year	1989-2004	5447	0.7%	Mean FU 39 mo	- Synchronous adenomas or CRC and age < 40 yr - Histological grade, location and gender were not significant
Balleste [3]	2007 Spain	Colonoscopy in 2nd year of follow-up	All CRC patients in 1 yr in 10 centers	IBD and FAP	2000-2001	353	2% / 2yr		- Presence of synchronous adenomas - Gender, grade of differentiation not significantly associated
Bouvier [11]	2007 France	> 6 mo	Cancer Registry	FAP, Lynch, IBD, < 6 mo FU	1976-2002	10,801 (61,879 py)	CI*: 1.8% at 5 yr 3.4% at 10 yr 7.2% at 20 yr	SIR 1-5yr: 1.9 (1.6-2.3)	- History of CRC and synchronous CRC - No personal or CRC related risk factors
Ringland [20]	2010 Australia	> 2 mo	Cancer registry New South Wales	Patients < 30 yrs, No exclusion of FAP or Lynch	1987-2004	29.471	660 (2.1%) Median FU: 5.1 yrs CI : 2.1% / 5 yrs 5.5% / 18 yrs	SIR 1.5 (95% CI 1.4-1.6)	- Inversely related to the age at first diagnosis. - Female 50-69 yr, compared to men in this age group - Right-sided primaries

m-CRC, metachronous CRC; CI, cumulative incidence; CIS, carcinoma in situ ; FAP, Familial adenomatosis poli; IBD, inflammatory bowel disease; FU, Follow up. † not significant.

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IV

Exposure to colorectal examinations before a colorectal cancer diagnosis: a case-control study

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ABSTRACT

Background: To assess the prior exposure to colorectal examinations between colorectal cancer (CRC) patients and matched control participants to estimate the effect of these examinations on the development of CRC and to obtain insight into the background incidence of colorectal examinations.

Methods: A population-based case-control study was conducted within the Dutch Integrated Primary Care Information database over the period 1996-2005. All incident CRC cases were matched with up to 18 controls (n=7 790) for age, gender, index date (date of CRC diagnosis) and follow-up before diagnosis. All colorectal examinations performed in symptomatic participants in the period 0.5-5 years before index date were considered in the analyses.

Results: Within the source population of 457 024 persons, we identified 594 incident cases of CRC. In the period 0.5-5 years before index date 2.9% (17 of 594) of the CRC cases had undergone colorectal examinations, compared with 4.4% (346 of 7 790) in the control population (odds ratio (OR_{adj}) 0.56, 95% confidence interval (CI) 0.33-0.94). For left-sided CRC, significantly more controls than cases had undergone a colorectal examination (4.7% versus 2.0% respectively, OR_{adj} 0.36, 95% CI 0.17-0.76), which was not seen for right-sided CRCs (3.3% versus 3.9% respectively, OR_{adj} 0.98, 95% CI 0.42-2.25).

Conclusion: Patients diagnosed with CRC were less likely than controls to have had a colorectal examination in previous years, being more pronounced in patients diagnosed with left-sided CRCs. If diagnostic examinations have a similar protective effect as screening examinations, this finding supports the concept that colorectal examinations can have a major impact on the reduction of CRC risk.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in the Western world and is the second most common cause of cancer mortality.[1] The lifetime risk of CRC in the general population is approximately 5%. In The Netherlands, approximately 10 000 new cases are diagnosed each year and about half of them die within 5 years.[2]

The majority of CRCs arise in benign adenomatous polyps that slowly progress over at least 5 to 20 years to invasive cancer.[3-7] This slow evolution from adenoma to cancer provides an unique opportunity for early CRC detection and cancer prevention by polypectomy.

Organized population screening for CRC is with increasing frequency organized at both regional and national levels; however, it is still being offered to far less than half of the European community.[8] This is among others because of the fact that the efficacy, preferred organization, and uptake of different screening methods, like sigmoidoscopy and colonoscopy, are much debated within the European Union.[9]

The extent to which colorectal examinations are being performed in the target population at present is unknown. It is important to identify this proportion as it informs us first of the required additional efforts needed for a population-wide screening program, and second of the potential impact, which such an organized program may have. For these reasons, we evaluated the exposure to colorectal examinations (colonoscopy, sigmoidoscopy and barium enema) in a large primary care population in The Netherlands. To estimate the effect of colorectal examinations on CRC risk we compared exposure to these examinations between CRC patients and matched control participants.

METHODS

Data sources

We performed a population-based case-control study using the Integrated Primary Care Information (IPCI) database. This longitudinal observational database is a general practitioner (GP) research database, containing over 800 000 computer-based patient records, obtained from a group of more than 150 GPs throughout The Netherlands. This database was established in 1992 by the Department of Medical Informatics of the Erasmus University Medical Center Rotterdam in The Netherlands, with the specific purpose to conduct epidemiological and pharmaco-economic studies. Since then the database has expanded. The database is representative of the Dutch population regarding age and sex.[10]

In The Netherlands, the GP plays a central role in the health care system and acts as a gatekeeper by referring patients to other medical disciplines for outpatient or inpatient care and as a central receiver of information from secondary or tertiary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information

about that person. Each inhabitant of The Netherlands is registered at a GP, independently of whether they visit their GP or not. For this reason, patients who do not visit their GP are also registered in the IPCI database.

The electronic records of the IPCI database contain anonymous demographic information (date of birth, sex) as well as information about symptoms and diagnoses (coded according to the International Classification for Primary Care (ICPC)[11] and free text), drug prescriptions with ICPC-coded indications, referrals to secondary care and hospitalizations. Summaries of hospital discharge letters or information from specialists are included as free text and copies can be provided upon request. To ensure completeness of the data, participating GPs are not allowed to use additional paper-based medical records. Furthermore, improvement in registration might occur soon after the date that GPs participate, they are asked for a coded indication. For this reason it is required that all persons in the study shall have a 1 year valid database history.

Anonymized data from the GP computer system are downloaded on a monthly basis and sent to the IPCI gatekeeper who removes all GP contact information before further access is provided. The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[10]

Source population

The source population comprised all patients contributing data to the database between January 1996 and June 2005, with at least 1 year of database history. One year of database history was required to be able to assess medical history at baseline. All patients with a history of CRC at the start of follow-up were excluded as well as patients with a diagnosis of hereditary CRC. Follow-up started on 1 January 1996 or on the first date at which 1 year of valid history was available, whichever was latest. All patients were followed until a diagnosis of CRC, transferring out of the GP practice, last data obtained from the GP, death of the patient, or 31 June 2005, whichever occurred first.

Case and control definition

Cases were patients with a specialist diagnosis of CRC in the electronic medical record of the GP. All potential cases of CRC were identified using an electronic search for ICPC code D75.1 (malignant neoplasm colon/sigmoid), and for related free text occurrences. Malignancies of the rectum were searched for in free text occurrences and in fixed text associated with coded information (using the word 'Rect'). The medical records of all potential cases were reviewed manually by two medically trained reviewers. They confirmed the diagnosis of CRC, and established the date of diagnosis and the tumour location (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, or unknown). The index date was defined as the date of diagnosis of CRC. Case validation was performed for the purpose of another study

and case reviewers were unaware of the exposure of interest of this study.[12] For each case, up to 18 controls were randomly drawn from the source population matched on age (year of birth), gender, calendar time and duration of follow-up before to the date of diagnosis (index date). More controls were selected than were needed to reach significance, as we were also interested in the uptake of the colorectal examinations in the general population.

Exposure definition

Exposure to colorectal examinations (colonoscopy, sigmoidoscopy and barium enema) in the case and control population was assessed by manually review of the records for up to a maximum of 5 years until 6 months prior to CRC diagnosis (index date).

Examinations occurring within 6 months before the diagnosis were considered as being part of the diagnostic procedure leading to CRC, and were excluded from the analyses. As this 6-month window is arbitrarily chosen, we evaluated the presence of protopathic bias by performing a sensitivity analysis with varying exclusion windows ranging from 3 to 12 months prior to the index date. Previous studies have also used a 6-month window of exclusion.[13,14]

The indication for the examination and the clinical findings were collected. Multiple colorectal examinations within a period of 3 months were counted as one and classified according to the most informative type of examination that was performed (i.e. colonoscopy first, then sigmoidoscopy). Colorectal examinations that were recorded as having been 'unsuccessful', because of faecal contamination, patient's discomfort or other reasons were not considered in the analyses. Most of these patients with an unsuccessful examination underwent a second examination shortly thereafter. Ascertainment of exposure was done blinded for case or control status. The Netherlands does not have an organized CRC screening program and faecal occult blood tests are very rarely used for this purpose. The use of faecal occult blood tests was not separately assessed in this population.

Covariates

Information on potential confounders was retrieved from the medical records by electronic searches and manual validation. As potential confounders we considered the following items: obesity (defined by ICPC code T82.0 [adiposity] or body mass index [BMI] >30), smoking, diabetes mellitus, inflammatory bowel disease, co-morbidity in the 365 days before the index date (aggregated in the Chronic Disease Score, which is based on the use of specific drugs as a proxy for long-term diseases [15]), low socioeconomic status (as living in a deprived area based on the zip-code), and alcohol (defined by ICPC code P15 [chronic alcohol abuse] or D97.1 [alcoholic liver cirrhosis]). As comedication we evaluated the use of aspirin, NSAIDs and statins for more than 365 days before the index date.

Statistical analyses

Descriptive statistics were used to analyze and report the data. Differences between groups were tested by means of Student's *t*-test in case of continuous variables after checking for normal distribution and by χ^2 test in case of categorical variables. Two-side P values less than 0.05 were considered to be statistically significant.

The incidence of CRC was calculated by dividing the total number of incident cases of CRC by the total number of person years at risk accumulated by the study population. Ninety-five percent confidence intervals (95% CI) were calculated based on the Poisson distribution.

The risk of developing CRC was estimated by calculation of odds ratios (OR) with 95% CI using conditional logistic regression analysis. All covariates were entered in the univariate model one by one, and were kept in the final multivariate model if the risk estimate changed more than 5%. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, Illinois, USA) for Windows Version 16.0 (Microsoft Corporation, USA).

RESULTS

Within the source population of 457 024 persons, we identified 595 incident cases of CRC. The overall incidence rate of CRC was 34.6 per 100 000 person years (95% CI: 31.9-37.4), 35.2 per 100 000 person years (95% CI: 31.4-39.4) among males and 33.9 per 100 000 person years (95% CI: 30.2-38.0) among females. The mean age at diagnosis was significantly lower in men than in women (67.5 versus 69.5 years; p=0.03).

Out of 595 CRC cases, 178 (30%) tumours were located in the right hemicolon (75 in cecum, 69 in the ascending and 34 in the transverse colon) and 392 (66%) in the left hemicolon (33 in descending colon, 189 in sigmoid colon and 170 in the rectum). In 25 (4%) cases, no location of the tumour was recorded.

To one case, no controls could be matched due to high age. To the remaining 594 cases, we matched 7 790 controls (median: 14 controls per case, interquartile range: 9-18 controls). Median follow-up of the cases before a CRC diagnosis was 1 031 days (interquartile range: 442-1825 days). Controls were matched to cases on duration of follow-up before the index date.

Table 1 shows the characteristics of the cases and controls and the univariate associations between these characteristics and the risk of CRC. The presence of inflammatory bowel disease (OR 2.40, 95% CI 1.12-5.13) was significantly associated with an increased risk of CRC (Table 1).

Table 1 Characteristics of the case-control population and univariate associations

	Cases (n= 594)		Controls (n=7790)		$OR_{matched}$ [a] (95%CI)
	n	(%)	n	(%)	
Mean age in years ± SD	69.5 ± 11.9		69.3 ± 11.9		-
Male gender	301	(50.7)	4 037	(51.8)	
Obesity	39	(6.6)	458	(5.9)	1.03 (0.73-1.46)
Smoking	105	(17.7)	1 386	(17.8)	0.99 (0.79-1.23)
Alcohol abuse	4	(0.7)	83	(1.1)	0.58 (0.21-1.59)
Aspirin >365 days	56	(9.4)	621	(8.0)	1.17 (0.87-1.59)
Statin > 365 days	23	(3.9)	306	(3.9)	1.02 (0.66-1.59)
NSAID >365 days	8	(1.3)	171	(2.2)	0.57 (0.28-1.18)
Diabetes mellitus	72	(12.1)	793	(10.2)	1.20 (0.92-1.56)
Inflammatory bowel disease	8	(1.3)	46	(0.6)	2.40 (1.12-5.13)
Comorbidity (CDS) 1-4	168	(28.3)	2 306	(29.6)	1.10 (0.89-1.36)
>4	187	(31.5)	1 945	(25.0)	1.47 (1.19-1.82)
Low socioeconomic status	34	(5.7)	356	(4.6)	1.17 (0.81-1.69)

CDS, Chronic Disease Score; CI, confidence interval; OR, odds ratio; SD, standard deviation.
[a] Matched on age, gender, calendar time and duration of follow-up prior to the index date.

Colorectal examinations

The details of the colorectal examinations are shown in Table 2. Change of bowel habits was the main indication for the colorectal examinations in the control group (22%), whereas abdominal complaints was the most important indication among the cases (40%). In the control population, 36% of the examinations did not show any abnormalities in contrast to 10% in the case population.

In the period of 0.5 to 5 years before the index date, 4.3% of the total study population underwent one or more colorectal examinations (363 of 8 384). Of the cases, 2.9% (17 of 594) had undergone a diagnostic colorectal procedure, compared to 4.4% (346 of 7 790) of the control population (OR_{adj} 0.56, 95% CI 0.33 to 0.94) (Table 3).

The difference between cases and controls with respect to prior exposure to colorectal examinations was significantly more pronounced in the female population (2.4% versus 4.8%, respectively, OR_{adj} 0.40, 95% CI 0.18-0.90, p=0.02) than in the male population (3.3% versus 4.1%, respectively, OR_{adj} 0.75, 95% CI 0.38-1.48, n.s.) (Table 3).

Significantly more controls than cases had undergone at least one colonoscopy (2.2% versus 1.2%, OR_{adj} 0.45, 95% CI 0.20-0.98). A sigmoidoscopy had been performed in 1.2% of the controls and in 0.5% of the cases, and a barium enema in 1.6% versus 1.3%, respectively (Table 4).

In the population aged 50 to 75 years, the eligible population for CRC screening in many screening programs, 3.7% (195 of 5 211) had undergone a colorectal examination (Table 3). This included 2.1% (8 of 372) of the cases compared with 3.9% (187/4839) of the control population (OR_{adj} 0.41, 95% CI 0.19-0.89). In addition, in this age group, in the female popula-

Table 2 Number, indication and diagnosis of previous colorectal examination in the case and control population 0.5 - 5 years before index date

Previous examinations	Case population n (%)	Control population n (%)
Number of subjects	594	7 790
0 examinations	577 (97.1)	7 444 (95.5)
1	14 (2.4)	317 (4.1)
≥2	3 (0.5)	29 (0.4)
	No. of examinations	
Total number of colorectal examinations	20	375
Indication for the examination		
Changed bowel habits	4 (20)	81 (22)
Abdominal complaints	8 (40)	62 (17)
Blood loss	4 (20)	62 (17)
Polyp surveillance	1 (5)	23 (6)
Anemia	2 (10)	20 (5)
Unknown		99 (26)
Other	1 (5)	28 (7)
Diagnosis		
No abnormalities	2 (10)	136 (36)
Polyps	6 (30)	75 (20)
Colitis/IBD	2 (10)	30 (8)
Diverticulosis/-itis	10 (50)	95 (25)
Others	-	39 (11)

IBD, inflammatory bowel disease.

tion the difference in performance of colorectal examinations prior to diagnosis was more pronounced between cases and controls (1.7% versus 4.3%, respectively, OR_{adj} 0.28, 95% CI 0.08-0.99) than in the male population (2.6% versus 3.5%, respectively, OR_{adj} 0.56, 95% CI 0.21-1.50) (Table 3).

In the stratum of left-sided CRC, significantly more controls than cases had undergone a colorectal examination (2.0% of cases versus 4.7% of controls, OR_{adj} 0.36, 95% CI 0.17-0.76) (Table 3). In the stratum of right-sided CRC, there was no significant difference in the frequency of colonoscopy or barium enema examinations between cases and controls (3.9% of cases versus 3.3% of controls, OR_{adj} 0.98, 95% CI 0.42-2.25).

Analysis of the 6 month-window of exclusion

To validate the 6 month-window of exclusion of examinations in the analysis, we performed a sensitivity analysis with variable windows of exclusion, ranging from 3 to 12 months prior to the index date. The difference in previous colorectal examinations between cases and controls remained significant at a 3 and 12-month window (OR_{adj} 0.59, 95% CI 0.36-0.97, respectively OR_{adj} 0.53, 95% CI 0.30-0.93, p=0.03).

Table 3 Number of persons who underwent at least one colorectal examination 0.5 - 5 years before index date

	Cases n (%)	Controls n (%)	$OR_{matched}$ (95% CI) [a]	OR_{adj} (95% CI) [b]
Number of previous examinations				
Total population				
Total	17/594 (2.9)	346/7790 (4.4)	0.63 (0.38-1.04)	0.56 (0.33-0.94)*
Among men	10/301 (3.3)	166/4037 (4.1)	0.79 (0.41-1.53)	0.75 (0.38-1.48)
Among women	7/293 (2.4)	180/3753 (4.8)	0.49 (0.23-1.06)	0.40 (0.18-0.90)*
Population aged 50-75 year				
Total	8/372 (2.1)	187/4839 (3.9)	0.52 (0.25-1.08)	0.41 (0.19-0.89)*
Among men	5/194 (2.6)	92/2608 (3.5)	0.68 (0.27-1.71)	0.56 (0.21-1.50)
Among women	3/178 (1.7)	95/2231 (4.3)	0.38 (0.12-1.22)	0.28 (0.08-0.99)**
Performance of previous examination by location of CRC [c]				
Right hemicolon[d]	7/178 (3.9)	76/2283 (3.3)	1.13 (0.50-2.53)	0.98 (0.42-2.25)
Left hemicolon	8/392 (2.0)	247/5234 (4.7)	0.41 (0.20-0.85)	0.36 (0.17-0.76) ***

[a] Matched on age, gender, calendar time and duration of follow-up prior to the index date.
[b] Adjusted for IBD.
[c] Right hemicolon includes cecum, ascending and transverse colon. Left hemicolon includes descending colon, sigmoid colon and rectum. Twenty-four CRC are of unknown location, including one CRC with previous endoscopy.
[d] Only colonoscopies and barium enemas are included, single sigmoidoscopy were excluded for the right hemicolon.
* p=0.02. **p=0.05. *** p= 0.008

Table 4 Total number of different colorectal examinations performed 0.5 - 5 years before index date in cases versus controls

	Cases n (%)	Controls n (%)	$OR_{matched}$ (95% CI) [a]	OR_{adj} (95% CI) [b]
Performance of at least one examination				
Colonoscopy	7/594 (1.2)	175/7790 (2.2)	0.53 (0.25-1.13)	0.45 (0.20-0.98)*
Sigmoidoscopy	3/594 (0.5)	90/7790 (1.2)	0.45 (0.14-1.42)	0.41 (0.13-1.31)
Barium enema	8/594 (1.3)	123/7790 (1.6)	0.85 (0.41-1.75)	0.84 (0.41-1.73)

CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.
[a] Matched on age, gender, calendar time and duration of follow-up before the index date
[b] Adjusted for IBD.
* p <0.05.

DISCUSSION

This population-based study compared CRC patients and matched controls for prior exposure with diagnostic colorectal procedures. The purpose for this comparison was, first to estimate the preventive effect of these examinations on the development of CRC and second to obtain insight into the proportion of participants of the general population that is currently seen for colonic investigation by any method.

With respect to our first aim, we showed that patients with CRC were 44% less likely than controls to have had a colorectal examination in the years before being diagnosed with CRC

(Table 3). Our results are consistent with previous studies reporting on the effect of screening endoscopy. Several studies investigated the effect of a single screening sigmoidoscopy, in combination with secondary colonoscopy screening in positive cases, and showed that such a policy led to a reduction in mortality and incidence of CRC in the years after colon examination.[16-24] Further prospective studies from Italy, UK, and Norway into the effect of sigmoidoscopy screening are awaited.[25-27]

There are no randomized controlled trials which assessed the efficacy of screening colonoscopy alone in reducing CRC mortality, although a few retrospective studies showed a reduction in incidence and mortality after colonoscopy screening, in particular for left-sided CRC.[13,18,28] Furthermore, in our study, there was a significant difference in the frequency of colorectal examinations between cases and controls only for the left-sided CRC.

In this study, we found a higher rate of prior examinations in patients with right-sided CRC compared with patients with left-sided lesions (3.9% versus 2.0%, Table 3), after excluding sigmoidoscopies for the right-sided CRCs. This might suggest that more right-sided CRCs were 'missed' compared with left-sided CRCs. Several studies provided evidence that colonoscopy is less effective for right-sided CRC than for left-sided CRC, which might be caused by incomplete colonoscopies and poor bowel preparation in the right-sided colon.[13,14,29] Another reason might be that left-sided and right-sided CRCs differ biologically, leading to rapid tumour progression in right-sided CRC.[30] It is important to investigate the risk factors for false-negative examinations to minimize the miss-rate and to enlarge the preventive effect of colorectal examinations on the incidence of CRC.

With regard to our second aim, 4.3% of our study population (cases and controls together) and 3.7% in the study population between 50 and 75 years of age underwent a colorectal examination during a mean follow-up period of almost 3 years. Overall, the uptake of colorectal examinations in The Netherlands is relatively low due to a restrictive policy towards non-organized screening and a shortage of endoscopy capacity. Despite these circumstances, close to 5% of the total study population had received colon screening by different modalities within a time frame of 3 years.

As this is an observational study, we have to consider the influence of bias and confounding on our results. Selection bias was avoided by employing a population-based design in a large population with existing registries and blinded assessment of both case and exposure status. In our study the incidence of CRC is slightly lower than reported by the Dutch National Cancer Registry.[2] This can partly be explained by the fact that in our study patients with a genetic or family history of CRC were excluded, as well as those with a recurrent CRC. However, underreporting of CRC will not interfere with the results as the case selection was performed independently of the exposure to colorectal examinations. By using complete electronic patient records we did not have to rely on self-reporting of patients and were able to avoid recall bias. The influence of confounding was limited by performing multivariate logistic regression. The fact that some known risk factors did not yield statistically significant

associations with CRC could point at a power problem. The presence of protopathic bias was made less likely by showing that the difference in colorectal examinations between cases and controls remained significant after varying the window of exclusion from 3 to 12 months.

The validity of the database used in this study was shown in a benchmarking validity analysis.[10] Second, several studies conducted within the IPCI database have been published that confirmed incidence rates or associations known from studies performed with other data sources, giving an indication of the external validity of the IPCI database.[31-34]

An important limitation of our study, however, resides in the limited period of observation. We compared the exposure to colorectal examinations during a follow-up period up to a maximum of 5 years. It would have been preferable to have a longer follow-up time as endoscopy is thought to have a protective effect for a longer period in patients with no high-risk adenomas.[16,35] A screening interval of 10 years after a 'normal' colonoscopy has been adopted in the US in average risk adults above the age of 50 years, although the appropriate interval remains uncertain because lack of long-term follow-up data.[36]

Second, we compared the performance of colorectal procedures in a symptomatic population. In symptomatic persons, both the incidence and spectrum of disease is likely to differ from an asymptomatic, screening population. The yield of colorectal examinations will be enlarged in a symptomatic population owing to the higher likelihood of having (more advanced) colorectal neoplasm compared to an asymptomatic screening population.[37-39] In contrast, in an asymptomatic population, the effect of colorectal examinations on the incidence and mortality of CRC will be larger because of the early identification of polyps and asymptomatic CRC, and thereby increasing the probability of cure at the time of detection.

Furthermore, the interpretation of the performance of colorectal examinations in a symptomatic case-control population is difficult. The performance of colorectal examinations might exert its effect in two ways: first, the incidence of CRC will be reduced by colorectal examinations because of the performance of polypectomies. In this way the examination will be protective in the control population. Second, in patients who had already developed CRC, an examination will not be preventive and will only determine the timing of diagnosis and thereby the prognosis. Early detection of the cancer will lower the mortality owing to the more favourable stage of disease.

In conclusion, the protective effect of diagnostic colorectal examinations was estimated at 44%, being more pronounced in patients diagnosed with left-sided CRCs. This supports the hypothesis that colorectal examinations exert a preventive effect on the development of CRC.

This study shows a 4.3% exposure to colorectal examinations during a period up to 5 years before the diagnosis in the overall study population and 3.8% in the population between 50 and 75 years of age. This study enables determination of the additional efforts that are needed to obtain a population-wide coverage of a CRC screening program.

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V

Risk analyses for screening sigmoidoscopy based on a colorectal cancer population. An indication for CRC screening

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ABSTRACT

Background: Although colonoscopy can be effective in the prevention of colorectal cancer (CRC), it requires many endoscopic facilities, has a high patient burden and risk of complications, and is expensive. The aim of this study was to determine the risk for proximal CRC and to identify subgroups in which screening sigmoidoscopy can be effective.

Methods: A database search was carried out on all patients who underwent endoscopy of the lower gastrointestinal tract between 1997 and 2005. All patients diagnosed with CRC were included. Variables including age, gender and the presence of distal colonic neoplasia were used for risk analyses.

Results: In total, 783 patients were diagnosed with CRC. The tumour was located in the proximal colon in 68/255 (27%) of the patients <65 years. Of the patients <65 years, 22% (57/255) had a proximal CRC without synchronous distal lesions and would thus have been missed by sigmoidoscopy screening. Among patients >65 years, 41% (216/528) were diagnosed with a proximal CRC, significantly more often in women than in men ($p<0.001$). In 35% of the patients (185/528) a proximal CRC without distal colonic neoplasia was found, significantly more than in patients under 65 yrs of age ($p<0.001$).

Conclusion: Significantly more proximal localized CRC would have been missed by screening sigmoidoscopy in elderly patients, especially in women. In subjects <65 years of age, sigmoidoscopy screening allows detection of almost 80% of CRC and might suffice as a screening method.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality and is a major public health issue in all Western countries. Screening for CRC can reduce the mortality of this disease in an asymptomatic, average-risk population. In the United States, screening for CRC is recommended in men and women over 50 years of age, because more than 90% of cases are diagnosed in individuals aged 50 years or older.[1,2]

A difference is reported in the distribution of CRC between men and women; an age-dependent shift to the right side of the colon is described for both sexes; however, this shift is more pronounced in women.[3-8]

In several European countries emphasis is placed on screening with the faeces occult blood test (FOBT) and/or sigmoidoscopy. In the UK, Norway, Finland and also in The Netherlands, screening strategies using a FOBT and/or sigmoidoscopy were recently introduced, or are currently evaluated for implementation in population-based screening programs.

The optimal CRC screening method is still under debate. FOBT is non-invasive, easy to perform, but has a low diagnostic yield. Screening with sigmoidoscopy detects three times more neoplastic lesions compared to FOBT screening, but is more invasive.[9] Colonoscopy is the most complete endoscopic procedure available for CRC screening and is more effective for CRC prevention than sigmoidoscopy. Therefore, colonoscopy is often considered the most complete method for CRC screening. However, in many countries this method is considered unsuitable for mass population screening because of the higher demand of endoscopic capacity, the higher patient burden, the risk of complications and the higher costs.[10,11]

For these reasons, in many populations sigmoidoscopy screening may be the more optimal strategy for screening than colonoscopy screening. We therefore investigated the prevalence of distal and proximal CRC in both male and female patients and calculated the diagnostic yield of sigmoidoscopy screening using retrospective data from colonoscopies performed in a large teaching hospital.

METHODS

Patient selection

The study was carried out in a large teaching hospital in The Netherlands with a large gastroenterology practice providing care to both urban and rural regions in the South West of the country. Data of all patients who were diagnosed with CRC between January 1997 to December 2005 were retrospectively collected. CRC patients were identified by a database search of the endoscopic report system Endobase®.[12] Endoscopic reports in this system are coded with the GET-C coding system, an extension of the ICD-10 coding system.[13] All endoscopy reports in the centre have been stored in the Endobase® database and can be used for

analyses. During the study period, 16 249 endoscopies of the lower GI tract were performed in 11 136 patients. All endoscopies were performed in symptomatic patients. In total, 798 CRC patients were identified by using the following identifiers: polyp, adenoma and colorectal cancer. Patients known with familial adenomatous polyposis, hereditary non-polyposis CRC, inflammatory bowel disease (IBD), or a prior history of CRC were excluded, leaving 783 patients for analysis. Separate analyses were performed for men and for women, as well as for patients over 65 years of age and patients younger than 65 years of age.

Data collection

Data regarding demographic information (date of birth, gender, patient identification), date of endoscopy, diagnosis at endoscopy including number and site of neoplastic lesions, therapy and TNM classification at time of diagnosis or follow up were collected.

For analysis, the colon was subdivided into two regions; the proximal and distal colon, assuming that the distal colon was examined during sigmoidoscopy. The distal colon was defined as rectum and sigmoid. Furthermore, as in the majority of patients the descending colon can be viewed, there was a second analysis for the miss-rate for sigmoidoscopy, defining the distal colon as the rectum, sigmoid and descending colon.[14]

Histological results, i.e. type of tumour and grade of dysplasia or differentiation, were obtained from the PALGA database. This database is a nation-wide archive containing the abstracts and diagnostic codes of all histopathology and cytopathology reports in The Netherlands since 1991.[15] Polypoid lesions were classified as adenomatous or non-adenomatous polyps. Non-adenomatous polyps included hyperplastic polyps, hamartomas, lymphoid aggregates and inflammatory polyps. Adenomatous polyps were classified according to the World Health Organization as tubular, tubulovillous and villous, depending on the presence and volume of villous tissue.[16] The grade of dysplasia was classified as low or high grade. Patients with intra-mucosal carcinoma or carcinoma *in situ* were classified as having an adenoma with high-grade dysplasia. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosa.[6,16]

Calculated miss-rates

In this study the miss-rate for sigmoidoscopy was calculated, i.e. the proportion of colon cancers that would be missed when sigmoidoscopy was used as a screening method. This miss-rate was calculated as the number of patients diagnosed with proximal CRC without the simultaneous presence of distal adenomas, divided by the total number of CRC patients. In a sigmoidoscopy screening program, the decision to perform a colonoscopy after sigmoidoscopy screening would be based on the distal findings (i.e. adenomatous lesions of any size and any grade of dysplasia). Proximal colon cancers without simultaneous distal marker lesions will not be diagnosed when sigmoidoscopy is used for screening and therefore these lesions were considered as 'missed lesions'.

Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences for Windows version 12.0. Descriptive statistics were used to analyse and report the data. Differences in outcome between groups of patients were calculated by means of Student's t-test or the χ^2 / Fisher exact test, when appropriate.

RESULTS

During the period January 1997 to December 2005, 798 patients were diagnosed with CRC. Fifteen patients were excluded from further analysis, because of locally recurrent or metachronous CRC (13 patients), or IBD-associated CRC (2 patients).

The characteristics of patients diagnosed with CRC are presented in Table 1. Male patients were significantly younger at time of diagnosis than female patients ($p<0.001$). CRC was localized in the proximal colon in 284 of the 783 (36%) patients; a proximal location was significantly more common in women than in men (43% versus 31%, respectively, $p<0.001$) (Table 1).

Table 1 Characteristics of patients diagnosed with colorectal cancer (n=783) in the period 1997-2005

Characteristics	CRC	
	Male	Female
Gender	414/783 (53%)	369/783 (47%)
Age (years)		
Median (range)	69 (27-95) *	73 (27-94) *
Median per location (range)		
Distal colon [a]	69 (32-95)	72 (27-94)
Proximal colon	70 (27-88)	76 (42-91)
Localization		
Proximal colon	127/414 (31%) **	157/369 (43%)**
Proximal-distal ratio	0.44 (127/287)	0.74 (157/212)

[a] Distal colon defined as rectum and sigmoid.

* Significantly higher median age of CRC diagnosis in women compared to men ($p<0.001$, Student's t-test).

** Significantly higher percentage proximal CRC in women compared to men ($p< 0.001$, χ^2)

Calculated miss rate in patients < 65 years

The distribution of CRC in men and women per age-group is summarized in Table 2.

A total of 255 patients (148 M, 107 F) were younger than 65 years at the time of diagnosis of CRC. In 68/255 (27%) of them, the CRC was localized in the proximal colon; this prevalence did not differ between men and women (Table 2). Synchronous distal adenomas were found in 11 (16%) of the 68 patients with a proximal CRC. The remaining 57 of the 68 patients had a proximal CRC without the simultaneous presence of distal neoplasia, and therefore would

Table 2 Distribution of colorectal cancer in men and women

	< 65 years		> 65 years	
	n=255 (%)		n=528 (%)	
Distal [a]	187/255 (73)		312/528 (59)	
Proximal	68/255 (27) *		216/528 (41) *	
	Male	**Female**	**Male**	**Female**
	n=148 (%)	n=107 (%)	n=266 (%)	n=262 (%)
Distal	111/148 (75)	76/107 (71)	176/266 (66)	136/262 (52)
Proximal	37/148 (25)	31/107 (29) **	90/266 (34)	126/262 (48) **

[a] Distal colon defined as rectum and sigmoid.
* Significantly higher percentage of proximal CRC in the overall population > 65 years compared to < 65 years of age ($p<0.01$, χ^2).
** Significantly higher percentage of proximal CRC in women > 65 years compared to < 65 years of age ($p<0.001$, χ^2).

Table 3 Miss-rate for sigmoidoscopy screening in patients under and over 65 years of age; distal colon compared to extended distal colon

	< 65 years of age		> 65 years of age	
	% missed CRC	Yield of sigmoidoscopy (%)	% missed CRC	Yield of sigmoidoscopy (%)
Distal colon (Rectum and sigmoid)				
Overall	22 (57/255)	78*	35 (185/528)	65*
Women	23 (25/107)	77***	42 (110/262) **	58***
Men	22 (32/148)	78	28 (75/266) **	72
Extended distal colon (Rectum, sigmoid and descending colon)				
Overall	18 (46/255)	82	31 (163/528)	69
Women	19 (20/107)	81	40 (104/262)	60
Men	18 (26/148)	82	22 (59/266)	78

* Significantly higher yield of sigmoidoscopy compared to the group above 65 years ($p<0.001$, χ^2).
** Significantly higher miss-rate in women > 65 years than in men > 65 years ($p<0.001$, χ^2).
*** Significantly higher yield of sigmoidoscopy in women < 65 years compared to > 65 years ($p<0.001$, χ^2).

have been missed by sigmoidoscopy screening. Overall, 22% (57/255) of all CRCs in patients < 65 years of age, would have been missed by sigmoidoscopy screening. The overall detection rate of CRC using sigmoidoscopy in the group <65 years of age would thus be 78% (198/255) (Table 3). There was no significant difference between men and women regarding the prevalence of proximal CRC without simultaneous presence of distal neoplasia, 22% (32/148) versus 23% (25/107), respectively (Table 3).

Calculated miss rate in patients > 65 years

A total of 528 patients (266 M, 262 F) were over 65 years of age at the time of diagnosis of CRC. In 216 (41%) of them, the CRC was localized in the proximal colon (Table 2). The prevalence of proximal CRC was significantly higher in the over 65 years age group compared to the group below 65 years (41% versus 27%) ($p<0.01$) (Table 2).

The proportion of proximal CRC was significantly higher in women >65 years than in women <65 years (48% (126/262) versus 29% (31/107), p<0.001), in men this difference was smaller and non-significant (34% (90/266) versus 25% (37/148); Table 2).

In patients >65 years, 185/528 (35%) had a proximal CRC without synchronous distal neoplasia; the calculated miss-rate for sigmoidoscopy screening in the female population was significantly higher than in the male population (42% (110/262) versus 28% (75/266) respectively, p< 0.001; Table 3).

The overall proportion of CRCs that would have been diagnosed by sigmoidoscopy, followed by colonoscopy in case of the presence of synchronous neoplasia in the distal colon, was significantly lower in the older age group compared with the younger group (65% (343/528) versus 78% (198/255), p<0.001). The yield of sigmoidoscopy in the female population significantly decreased from 77% (82/107) in the <65 years age group to 58% (152/262) in the >65 years age group (p<0.001). In the male population, this reduction was not significant (Table 3).

When the distal colon was defined as the rectum, sigmoid and descending colon, the calculated yield of sigmoidoscopy increased by 2-6% in both men and women in the younger and older age groups, compared to the limited sigmoidoscopy (i.e. rectum and sigmoid) (Table 3). This increase in yield was most pronounced, but not significant, in the older male population (72% to 78%).

DISCUSSION

This study shows the characteristics of a large population of CRC patients. Based on demographic data and clinical characteristics including tumour location and presence or absence of distal synchronous neoplasia, the potential detection rate of a sigmoidoscopy screening program was determined in relation to age and gender.

In many countries in Western Europe, the health authorities and clinicians are involved in decisions concerning CRC screening. Most of these countries consider FOBT as the primary screening tool, with endoscopy as the primary alternative. Both colonoscopy and flexible sigmoidoscopy can be implemented for endoscopic screening programs. Flexible sigmoidoscopy screening is feasible and safe. However, the yield of a sigmoidoscopy-based screening program is potentially impaired by the inability to detect right-sided neoplasia. There is no consensus on which patients should be referred for colonoscopy based on the sigmoidoscopy findings. Referral rates for colonoscopy would be approximately 5% if referral was restricted to those patients with three of more adenomas or those with an advanced neoplasia in the distal colon, increasing to 12.5% if all persons with at least one distal adenoma are to be referred for colonoscopy.[17-19]

The advantage of colonoscopy is that it allows examination of the complete colon, thus ensuring a maximal neoplasia detection rate. The procedure is, however, more demanding for individuals, carries a risk of serious complications, requires more endoscopic facilities and is associated with higher costs, assuming that the procedure of flexible sigmoidoscopy requires half the time and fewer day-care admissions than colonoscopy.

For these reasons, in most countries it is not feasible to use colonoscopy as a first-choice endoscopic screening method. In addition, in some populations, e.g. in Germany, the population uptake of colonoscopy screening is very low, a phenomenon that strongly impairs the yield of a screening program using colonoscopy. In several European countries, flexible sigmoidoscopy is at present judged more suitable for population screening in the average risk population.[20,21]

There are several issues that need consideration before implementing a screening program. Based on the results of this study, it may be necessary to assign high-risk groups in which colonoscopy should be performed because of the higher miss-rate for sigmoidoscopy screening.

Firstly, the distribution of CRC is age- and gender-dependent. In our study population, the proportion of proximal CRC increased with advancing age, especially in women. Several studies confirmed the increasing proportion of proximal (advanced) neoplasia or carcinoma with advancing age.[3-5,22] Our data show that this increase is more prominent in women than in men; a similar observation has been made by others.[3,23] A US study reported that age was significantly associated with the risk of having proximal advanced neoplasia, with a relative risk of 1.3 for every 5-year interval between the ages of 50 and 80 years. Other studies confirmed this left-right shift for neoplasia, even independently of age.[24-26]

Second, there is a strong association between the presence of distal adenoma and synchronous advanced proximal adenomas (pooled odds ratio of 2.80).[6,24,27] Several factors including older age, male gender, a positive family history of CRC, larger size and villous histology of the distal adenomas increase the risk for advanced proximal neoplasia.[24,28] Three studies reported a 2-5% prevalence of isolated advanced neoplasia in the proximal colon in asymptomatic persons.[6,19,27] However, about half of the advanced proximal neoplasia (splenic flexure to caecum) is not associated with synchronous distal adenomas, and will remain undetected with sigmoidoscopy.[6,24]

In our study, the calculated yield of sigmoidoscopy significantly decreased above 65 years in the female population. Two studies reported an overall yield of sigmoidoscopy for advanced neoplasia of 68-70%.[6,24] In contrast, Schoenfeld et al. reported that 65% of advanced neoplasia in women would have been missed if they had undergone sigmoidoscopy alone; this miss-rate is much higher than in our study.[7] However, these studies did not take into account the differences between age groups.

The results of our study differ from the other studies on several points. The studies of Lieberman et al. and Schoenfeld et al. were screening studies in an asymptomatic healthy

population, whereas we used a symptomatic clinical population.[6,7] More advanced CRC may be accompanied by a higher rate of (distal) adenomas. Furthermore, our study reported lower miss-rates than those in the American screening studies, especially in the female population (37% versus 65%).[7] The difference in miss-rates may partly be due to the fact that, in both other studies, persons with a family history of CRC were overrepresented. A positive family history of CRC is associated with a higher risk of proximal neoplasia.

A possible limitation of our study is its retrospective design. Using retrospective data carries an inevitable risk of missing data or of incomplete endoscopy reports. However, the endoscopic data, all medical records and the pathology reports are fully computerized, which to a certain extent prevents incomplete or incorrect data.

In conclusion, our study shows that the proportion of proximal CRC increases with age, and usually occurs without synchronous distal marker neoplasia. Below the age of 65 years, almost 80% of CRCs would be diagnosed by sigmoidoscopy for primary screening; in this age group, sigmoidoscopy might suffice as a screening tool in both men and women. Above 65 years of age, especially in women, screening with sigmoidoscopy result in a higher miss-rate and is therefore less effective for screening. In persons above 65 years of age colonoscopy should be considered.

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VI

Tumour pyruvate kinase isoenzyme M2 and immunochemical faecal occult blood test: performance in screening for colorectal cancer

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ABSTRACT

Background: Immunochemical faecal occult blood test (FOBT) and determination of tumour pyruvate kinase isoenzyme type M2 (TuM2-PK) in stool samples may be valuable new screening tools for colorectal cancer (CRC). The aim of this study was to compare the accuracy of faecal TuM2-PK testing with immunochemical FOBT in patients with CRC or adenomas.

Methods: A total of 52 patients with CRC were analyzed, 47 with colorectal adenomas and 63 matched controls with a normal colonoscopy. Nineteen additional patients with inflammatory bowel disease (IBD) were tested to determine influence of inflammation on the test results. Stool samples were analyzed with two immunochemical FOBTs, Immo-care and OC-Light, and with a commercial enzyme-linked immunosorbent assay for TuM2-PK.

Results: In patients with CRC, the sensitivity of TuM2-PK, Immo-care and OC-Light was respectively 85%, 92% and 94%. In patients with adenomas, the sensitivity was respectively 28%, 40% and 34%. Specificity for these tests was 90% for TuM2PK and 97% for both immunochemical FOBTs. All tests showed a high positivity rate in IBD patients (79% for TuM2-PK and Immo-care, and 89% for OC Light).

Conclusion: Both immunochemical FOBTs appear valuable and sensitive tests for CRC screening. TuM2-PK does not have supplemental value for screening for CRC because of a lower sensitivity and specificity. IBD patients should be excluded from CRC screening when using immunochemical FOBT or TuM2-PK.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer death in the Western world. Screening for CRC reduces morbidity and mortality from this very common disease.[1]

The ideal test for CRC screening should combine a high sensitivity with an acceptable specificity. In this respect, colonoscopy is an ideal screening method: this test is, however, invasive and limited by patient compliance and endoscopy capacity.[2] Evaluation of non-invasive screening tests is therefore of great interest.

One test of interest is the determination of tumour pyruvate kinase isoenzyme type M2 (TuM2-PK) in stool samples. This isoenzyme is expressed in proliferating cells and present in tetrameric form. In tumour cells, this isoenzyme is predominantly present in a dimeric form, which has therefore been termed tumour M2-PK.[3,4] It is released by tumour cells of a wide range of different malignancies and can be detected in body fluids as well as in faeces. The latter is of interest for CRC screening.

A few studies evaluated the accuracy of TuM2-PK as a screening tool for CRC.[5,6] One study evaluated the TuM2-PK test in 60 CRC patients, compared with the biochemical (guaiac) faecal occult blood test (FOBT), and concluded that the TuM2-PK test was a sensitive and promising screening tool for CRC.[5] This study, however, only evaluated TuM2-PK in CRC patients, whereas the detection of colorectal adenomas is interesting in a screening setting as adenomas are the non-malignant precursors of CRC. Furthermore, the accuracy of TuM2-PK was compared with the biochemical FOBT. Although this is the only non-invasive test proven to be effective in reducing CRC mortality, it is known to have a low sensitivity.[7] Several studies have shown a higher sensitivity for the immunochemical than the biochemical FOBT.[8] Therefore, it would be more interesting to compare the performance of TuM2-PK with an immunochemical FOBT.

The aim of this study is to determine the accuracy of the faecal TuM2-PK test in patients with CRC or adenomas compared with two different immunological FOBTs, using colonoscopy as reference value.

METHODS

Study protocol

This study took place in four medical centres in The Netherlands. Approval of the study protocol was obtained by the institutional review board of participating centres. Each patient gave written informed consent before inclusion into the study.

All out-clinic patients above 18 years of age, who had an appointment for colonoscopy were asked to provide a stool sample for measuring faecal TuM2-PK and immunochemical FOBT. For collecting the faeces sample, a plastic container (100 ml), latex gloves and a plastic

spoon were provided. A small faeces sample (tablespoon-size) was requested for performing the tests.

In total, 392 patients provided a stool sample: 117 patients were excluded from the study because of other active neoplastic disease (e.g. pancreatic cancer, N=3) or previous colon-carcinoma (N=8), an incomplete colonoscopy (N=19), multiple diagnoses (e.g. colorectal neoplasms and inflammatory bowel disease, N= 27), other diagnoses in the colon and rectum (e.g. arteriovenous malformation, diverticulitis, N=36), or patients without a histological evaluation of the neoplasm (N=24).

Of the remaining 275 persons a group of 118 patients was analyzed, including 52 patients diagnosed with invasive CRC, 47 with colorectal adenomas, and 19 patients diagnosed with active inflammatory bowel disease (IBD). The IBD patients were included to investigate the influence of inflammation of the colon on the test results. From the 157 patients without abnormalities on colonoscopy, 63 were randomly selected for the control group.

Faecal samples were collected before bowel preparation for the endoscopic procedure. In 14 patients diagnosed with CRC, the faecal samples were also collected after colonoscopy; at least two weeks after the procedure, in order to minimize the possible effect of biopsies on the test results. Stool samples were stored at 4°C immediately after collection at home and transferred within 24 h to a hospital freezer set at -20°C. The faecal samples could savely be stored at -20°C according to the manufacture.

The colonoscopies were carried out for various indications. Histology was obtained in those patients in whom abnormalities were found. The location of the most advanced lesion was noted. Data about age, gender, location of the CRC, size and histology were recorded. Dukes' stage and TNM stage were determined. The adenomas were classified as non-advanced, or advanced (i.e. an adenoma with significant villous features (>25%), a diameter of one cm or more, high-grade dysplasia, or containing early invasive cancer).[9] The different tests were all performed by a chemical analyst who was blinded for the results of the colonoscopy.

TuM2-PK test

The stool samples were stored at –20°C until the TuM2-PK test was performed. For the test 100 mg of each faeces sample was required. TuM2-PK levels were measured with a commercially available enzyme-linked immunosorbent assay (ScheBo® Biotech AG, Germany) and performed according to the manufacturer's protocol. The results were expressed in units TuM2-PK/ml. The test kit allowed the quantification of TuM2-PK within the range of 1 to 30 U/ml, values out of range were specified as < 1 U/ml or > 30 U/ml respectively. The cut-off level of 4 U/ml was used according to the manufacture's instructions and according to the cut-off level used in other studies.[5,6] Above this level patients were classified as positive for TuM2-PK.

Immunochemical faecal occult blood testing

Immo-care-C (CARE Diagnostica, Möllersdorf, Austria) and OC-Light (Eiken Chemical Co Ltd, Tokyo, Japan) were used for the detection of faecal occult blood. Both tests are rapid immunochromatographic assays for the qualitative detection of intact human hemoglobin in faecal specimens. The immunochemical FOBTs were performed according to the manufacturer's protocol; a little stick was put into the faeces on three different spots and then put in the collection tube and mixed with the sample buffer. Fluid from the collection tube was put on the test strips and the test result was read out after 10 minutes. The test was considered positive for occult blood if two lines appeared in the reaction field. If one line appeared, the test was considered negative. The test was considered invalid if no line appeared or the whole reaction field turned purple.

Statistical analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. Descriptive statistics were used to analyze and report the data. Specificity and sensitivity were calculated using the colonoscopy results and histology as reference value. Differences in outcome between groups of patients were calculated by means of Student's t-test or Chi-square / Fisher exact test, when appropriate.

RESULTS

A total of 181 patients were analyzed, including 52 with invasive CRC, 47 with adenomas, and 63 matched controls with a normal colonoscopy. Finally, 19 patients with IBD were analyzed to determine the influence of inflammation on test results (Table 1).

Table 1 Group characteristics

	CRC n=52	Adenoma n=47	Controls n=63	IBD n=19
Median age in yrs (range)	67 (42-91)	61 (44-78)	56 (23-81)	48 (27-76)
Male/Female	33/19	24/23	27/36	9/10
Location lesion				
Proximal [a]	18/52	13/47		
Distal [b]	34/52	34/47		

IBD, inflammatory bowel disease

[a] Proximal: Caecum, ascending and transverse colon. [b] Distal: Descending colon, sigmoid and rectum

Table 2 Number of positive and negative results of TuM2-PK and two Immunochemical FOBTs

	n	TuM2-PK		Immo-Care-C		OC-Light	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Controls	63	6	57	2	61	2	61
CRC	52	44	8	48	4	49	3
Adenoma	47	13	34	19	28	16	31
IBD	19	15	4	17	2	15	4

FOBT, faecal occult blood test; IBD, inflammatory bowel disease; TuM2-PK, tumour pyruvate kinase isoenzyme type M2; Pos, positive test result; Neg, negative test result.

Colorectal cancer

The CRC group included 52 patients. The tumour was located in the proximal colon in 35% of patients (Table 1). The number of positive and negative results obtained with each diagnostic test is given in Table 2. The median TuM2-PK level in the CRC group was 18 U/ml (range <1 - >30). The test showed a sensitivity of 85% and a specificity of 90% (Table 3). The immunochemical FOBTs showed higher sensitivities than the TuM2-PK test, 92% and 94% for the Immo-care and OC Light respectively.

The sensitivity of TuM2-PK was significantly higher in T3/T4 tumours compared to T1/T2 tumours, 89% versus 67% ($p<0.05$). No significant difference in the performance of the immunochemical FOBTs was observed in the different TNM-tumour stages.

Although not significant, the sensitivity of both immunochemical tests was higher for distal tumours (94% and 97% for Immo-Care and OC-Light respectively), than for tumours in the proximal colon (89% in both tests). This difference could not be shown in the TuM2-PK test.

Adenoma

The adenoma group consisted of 47 patients (Table 1). In 72% (34/47) of the patients, the most advanced adenoma was located in the right-sided colon.

The overall sensitivity of the TuM2-PK test was 28% (median level of 2.1 U/ml [range <1 - >30]) (Table 3), whereas the Immo-care and the OC-Light had a sensitivity of 40% and 34% respectively.

Twenty-two patients (47%) were diagnosed with an advanced adenoma. Both immunochemical FOBTs showed significantly higher sensitivities for detection of advanced adenomas compared to nonadvanced adenomas ($p<0.01$), this difference was not seen in the TuM2-PK test.

Inflammatory bowel disease

The group diagnosed with inflammatory bowel disease consisted of 19 patients (Table 1). The TuM2-PK test showed positive results in 79% of the patients diagnosed with colitis (median 17 U/ml, range <1 - >30) (Table 2). The Immo-care was positive in 89% of the patients and the OC-Light in 79%.

Table 3 Accuracy of the three tests expressed in sensitivity and specificity

		TuM2-PK	Immunochemical FOBT	
			Immo-Care	OC-Light
CRC (n=52) [a]	Overall sensitivity	85% (44/52)	92% (48/52)	94% (49/52)
	Extension			
	T1-T2 [b]	67% (6/9)*	100% (9/9)	100% (9/9)
	T3-T4	89% (34/38)*	89% (34/38)	92% (35/38)
Adenoma (n=47)	Overall sensitivity	28% (13/47)	40% (19/47)	34% (16/47)
	Classification			
	Advanced	27% (6/22)	64% (14/22)**	55% (12/22)***
	Non-adv.	29% (7/24)	20% (5/25)**	16% (4/25)***
Specificity		90% (57/63)	97% (61/63)	97% (61/63)

FOBT, faecal occult blood test; TuM2-PK, tumour pyruvate kinase isoenzyme type M2

[a] 5 patients did not undergo colorectal resection. In those cases the tumour invasion could not be determined.

[b] T1: Tumour invasion limited to submucosal layer, T2: Tumour invasion limited to m. propria T3: Tumour invasion through m.propria, T4: Tumour invasion into other organs or through the visceral peritoneum

* $p < 0.05$ χ^2 . ** $p < 0.01$ χ^2. *** $p < 0.01$ χ^2

DISCUSSION

Adequate non-invasive detection of colon neoplasia is of major importance for screening for CRC, thereby lowering the incidence of CRC. In our study we evaluated the TuM2-PK test and two immunochemical FOBTs, non-invasive tests which might be useful for CRC screening. In recent years several studies were performed to evaluate the accuracy of TuM2-PK as a screening tool for CRC. It was shown that the detection of TuM2-PK in faeces was more accurate for screening for CRC than in serum and plasma.[3-5,10]

Other studies, also performed in symptomatic patients, showed a lower sensitivity (73-77%) and specificity (72-78%) for CRC compared to our results.[5,6] Even with an overall sensitivity of 85% and specificity of 90% as reported in our study, CRC will be missed in 15% and 10% of persons will have a false positive result.

Both immunochemical tests performed better and showed higher sensitivities and specificities for detecting CRC than the TuM2-PK test, however, not significantly higher. No difference was observed in performance of both immunochemical tests used in this study.

In a recent Japanese study, an immunochemical FOBT was performed in 21 805 asymptomatic persons and showed an overall sensitivity of 66% for CRC, increasing to 78% in Dukes D disease.[8] The reason for this difference in sensitivities might be that, in contrast to our population, the Japanese study was performed in a large and asymptomatic population.

We observed a low sensitivity for the detection of adenomas corresponding to other studies on TuM2-PK. Furthermore, both immunochemical FOBTs showed low sensitivities for the detection of adenomas, but performed slightly better for advanced adenomas. This is an

important advantage of the immunochemical FOBT, as these lesions are the nonmalignant precursor lesions of CRC and the incidence of CRC can be reduced by detecting and removing these lesions. The sensitivity for adenomas, however, should be evaluated in a larger sample size.

From our data we cannot determine the sensitivity for early-stage CRC as our study was performed in a symptomatic population. It would be useful to evaluate the sensitivity of screening tests in asymptomatic persons with a different background risk than in our study. It is important to detect patients with early-stage CRC. The high 5-year survival rate is far better for early stage CRC than for disseminated CRC.

It should be emphasized that these sensitivities are based on single test results. When used for program screening, the tests will be performed every 1-2 years and will show a cumulative sensitivity, which will be higher than the single screening sensitivity as is shown in our study.

A recent study suggested that inflammatory reactions in the bowel could cause an elevation in the faecal TuM2-PK level.[11] Our study confirmed this result showing a positive test 79% of IBD patients. The cancer specificity of the faecal TuM2-PK test is thus limited, especially in patients with intestinal inflammation, and should, therefore, not be used for CRC screening in patients known to have IBD. The immunochemical FOBTs also showed high positivity rates in IBD patients. Other studies did not report about positive immunochemical FOBTs in IBD patients and only investigated the sensitivity and specificity of the tests for detecting colorectal neoplasms in asymptomatic persons.[8,12-14] Our results are, however, not surprising as positive results were to be expected in patients with active colitis with blood loss, as this test detects hemoglobin and is not cancer-specific. Our data show that the distinguishing characteristic of the TuM2-PK test, i.e. the cancer-specificity, that sets it apart from the immunochemical FOBTs, is limited and the benefit of using the TuM2-PK test is restricted.

In conclusion, the immunochemical FOBTs showed high overall sensitivities with acceptable specificities and performed better than the TuM2-PK test in patients diagnosed with CRC. It was expected that TuM2-PK would be highly cancer specific, compared to the immunochemical FOBT. The specificity is, however, much too low for the purpose of population screening as there was a high positivity rate in the population diagnosed with IBD.

In our opinion, the TuM2-PK test does not have additional value beside the immunochemical FOBT for non-invasive CRC screening. Both immunochemical FOBTs seem to be a useful and appropriate tool for screening for CRC. Furthermore, although the sensitivity of immunochemical FOBT was relatively low for advanced adenomas, repeated testing may result in an acceptable cumulative sensitivity and in an accurate screening tool.

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VII

A nationwide survey evaluating adherence to guidelines for follow-up after polypectomy or treatment for colorectal cancer

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ABSTRACT

Background: Endoscopic follow-up in patients treated for colorectal adenomas or cancer (CRC) is intended to reduce the incidence of CRC. In the Dutch postpolypectomy guidelines, the follow-up interval is solely determined by the number of previous adenomas, whereas in other countries size and histology are also taken into account. Whether this difference in policy is also reflected in clinical practice is unknown. Furthermore, follow-up guidelines after CRC are not standardized in The Netherlands, even though national recommendations are available. The aim of this study is to assess the adherence to the current Dutch postpolypectomy guidelines and to evaluate the follow-up policy after CRC resection.

Methods: A survey was sent to all Gastrointestinal Departments in The Netherlands. The survey consisted of questions on logistic organisation of follow-up, postpolypectomy follow-up intervals and follow-up after CRC.

Results: The response rate was 85%. In contrast to the national guidelines, size and histology of the adenomas were often taken into account, leading to shortening of the follow-up interval. With respect to the CRC cases, 52% of the respondents advised shorter follow-up intervals than advised by the national recommendations.

Conclusions: Despite recent Dutch postpolypectomy guidelines, clinicians incorporate histology and size into their clinical strategy. Either further education on the guidelines is needed, or the guidelines need to be reconsidered. Furthermore, evidence-based guidelines for follow-up after CRC should be formulated.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of death from malignant disease in the Western world. Several studies have shown that repeated endoscopic screening with removal of adenomas reduces the incidence of CRC.[1-3] The rationale behind colonoscopic surveillance after removal of adenomas is based on the 30 to 50% detection rate of recurrent adenomas at follow-up.[4]

For the surveillance of colorectal adenomas after polypectomy and after treatment for CRC, evidence-based guidelines are mandatory. In the United States, postpolypectomy surveillance consumes considerable endoscopic capacity. Several surveys have shown that a large proportion of endoscopists are conducting surveillance at shorter intervals than recommended by their guidelines.[5-9]

Adherence to these guidelines is crucial; on the one hand, to remove recurrent adenomas and detect CRC in an early stage and, on the other hand, to limit endoscopic burden for patients and optimize the use of endoscopic capacity.

In The Netherlands, the adherence to postpolypectomy guidelines is unknown. The Dutch postpolypectomy guidelines deviate from the guidelines of several other countries. In the Dutch guidelines the number of adenomas is the only determinant for the follow-up interval.[10] The guidelines were formulated with available evidence up to 2000. Several newer guidelines such as those in the US and the United Kingdom, also take the size and/or the grade of dysplasia of adenomas into account.[11,12]

It is unknown whether this difference in policy is also reflected in clinical practice in determining the follow-up interval after polypectomy in The Netherlands.

Furthermore, with regard to surveillance after treatment for CRC, there are no unambiguous, evidence-based guidelines in The Netherlands. The Dutch oncology recommendations for follow-up after treatment for CRC were formulated in 2001 and are available on the internet (www.oncoline.nl). A surveillance colonoscopy was recommended 3 to 5 years after colorectal resection and carcinoembryonic antigen (CEA) testing once every 3 months for 3 years.[13] However, it is not known to which extent these recommendations are adhered to.

The aim of this study was to assess the adherence to the current Dutch postpolypectomy guidelines and the recommendations for follow-up after treatment for CRC by the Dutch gastroenterologists.

METHODS

A survey was sent to all 75 Gastroenterology Departments in The Netherlands. Each gastrointestinal (GI) unit received 1 survey and was asked to answer the questions according to the policy of the GI-unit. The answers were supposed to represent the practice of all gastroenter-

ologists in the department. The survey consisted of 2 questions on the logistic organization of follow-up (Figure 1). Six fictitious cases focused on postpolypectomy follow-up intervals, including cases with different numbers, sizes and grade of dysplasia of the adenomas. The fictitious patients differed in age from 45 to 75 yrs, had had their first colonoscopy and did not have a family history of CRC. Adenomas were stated to have been radically removed.

An additional four cases focused on follow-up after curative resection for CRC; the interval advised for endoscopic follow-up, liver ultrasound after colorectal resection and the interval of CEA testing (Figure 1).

Figure 1 Survey for evaluating adherence to the guideline for follow-up after polypectomy and the recommendations for follow-up after treatment for CRC.

Logistic organisation of follow-up

1. How do you inform patients about follow-up colonoscopy after polypectomy?
   - [ ] An advice for follow-up interval is given to the patients after endoscopy. The patients themselves are responsible for making an appointment for follow-up.
   - [ ] The follow-up interval is mentioned in the endoscopy report to the general practitioner. He/she has to remind the patient at the time of the next follow-up endoscopy.
   - [ ] Patients receive a recall letter at the time of follow-up endoscopy.
   - [ ] Other, ……
2. How are the follow-up-appointments documented?
   - [ ] In a database system.
   - [ ] In the medical record.
   - [ ] The appointments are not documented.
   - [ ] Other, ……

Follow-up after polypectomy

A colonoscopy is performed in the following persons. It is their first colonoscopy and the adenomas are completely removed. There is no family history of colorectal neoplasia or CRC.
At what interval do you recommend follow-up?

1. A 45-yr-old man, diagnosed with 1 tubular adenoma, LGD
2. A 45-yr-old man, diagnosed with 1 villous adenoma, HGD
3. A 75-yr-old man, diagnosed with 1 villous adenoma, HGD
4. A 45-yr-old man diagnosed with 2 adenomas of 10 mm each, both LGD
5. A 50-yr-old man, diagnosed with 2 adenomas of 20 mm each
6. A 65-yr-old man, diagnosed with 5 adenomas, 10-20 mm

Follow-up after treatment for CRC

A 50-yr-old man, diagnosed with CRC, stage T3-N0-M0, TNM 2 classification, underwent a complete colonoscopy prior to segmental resection of the colon. Which examinations do you recommend for follow-up after curative surgery and at what interval?

1.	Follow-up endoscopy	[ ] … yrs	[ ] no follow-up
2.	CEA testing	[ ] … yrs	[ ] no follow-up
3.	Ultrasound abdomen	[ ] … yrs	[ ] no follow-up
4.	If no abnormalities are found during follow-up, after how many years will this patient be discharged from follow-up?	[ ] … yrs	[ ] not

LGD, low-grade dysplasia; HGD, high-grade dysplasia.

Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. Descriptive statistics were used to analyse and report the data. Differences in outcome between groups of patients were calculated by means of Student's *t*-test or χ^2 / Fisher exact test, where appropriate.

RESULTS

In total, the response rate was 85% (64/75), including 7/8 academic hospitals and 57/67 general hospitals.

Thirty-one percent (20/64) of the units kept record of the follow-up schedules of their patients by means of a database, 28% in the medical record and in 16% all scheduled follow-up dates were recorded in an appointment book. In 25% (16/64) there was no documentation of follow-up appointments at all.

Following colonoscopy with removal of adenomas, 58% (37/64) of the GI-units applied a passive surveillance policy; they provided advice for the follow-up interval to the patient and/or the general practitioner (GP) after index endoscopy; the follow-up is solely the responsibility of the patients and/or their GP. In the remaining 42% of the units, invitation letters for follow-up endoscopy were sent to the patient towards the end of the follow-up interval.

Surveillance after polypectomy

For the first query-case, the respondents were asked to state the follow-up interval, as used in their clinic, for a fictitious 45-year-old patient diagnosed with one tubular adenoma with low-grade dysplasia, completely removed at colonoscopy (Figure 1). Seventy-three percent of the respondents advised follow-up endoscopy after 6 years, which is in agreement with the guideline (Table 1). Seventeen percent however underwent advised follow-up already within 3 years.

In contrast, only 22% of the respondents adhered to the recommended follow-up interval of 6 years in case of a 45-year-old patient with a villous adenoma with high-grade dysplasia (HGD). The majority (51%) of respondents even advised follow-up within 1 year.

In the third query-case, a 75-year-old man diagnosed with a villous adenoma with HGD, 39% (16/64) of the respondents advised follow-up within 1 year, even at older age. Twenty-five percent did not advise any follow-up. Most of the respondents noted that they would consider the general condition of the patient in their follow-up advice.

The two further query-cases concerned patients who each had two large adenomas of, respectively, 10 mm and 20 mm in diameter. In these cases, a 6-year interval was recommended in 63% respectively 55% of the respondents, as advised in the guidelines. Almost one-fourth of the respondents (25% and 22% respectively) nevertheless advised follow-up after 3 years.

Table 1 Follow-up intervals after polypectomy with complete removal of the adenoma

Query Case Response 64/75	No FU (%)	≤1 yr (%)	2 yr (%)	3 yr (%)	4-5 yr (%)	6 yr (%)
# Case 1 (45 yr, 1 adenoma, LGD)	1	1	3	13	8	73*
# Case 2 (45 yr, 1 villous adenoma, HGD)	-	51	8	17	2	22*
# Case 3 (75 yr, 1 villous adenoma, HGD)	25*	39	6	17	-	13
# Case 4 (45 yr, 2 adenomas, 10 mm, LGD)	-	1	1	25	9	63*
# Case 5 (50 yr, 2 adenomas, 20 mm)	-	9	11	22	3	55*
# Case 6 (65 yr, 5 adenomas 10-20 mm, LGD)	-	13	5	80*	1	1

* The recommended interval according to the Dutch guidelines for follow-up after polypectomy.
LGD, low-grade dysplasia; HGD, high-grade dysplasia; FU, follow-up

For the query case with five adenomas, 80% of the respondents advised follow-up after 3 years, which is according to the guidelines. Eighteen percent advised follow-up at a shorter interval (Table 1).

Surveillance after colorectal resection

Four respondents indicated that the follow-up in CRC patients in their hospital was taken over by the surgical department. One of these respondents did not answer the remaining questions and was excluded from further analysis, leaving 63/64 of the respondents for further analysis.

Most respondents indicated that endoscopic follow-up would only be performed if the patient's health allowed endoscopy and the examination could have consequences for the individual's treatment. Forty-four percent (28/63) advised patients with curatively resected CRC to undergo endoscopic surveillance with an interval of 3 to 5 years, which is in accordance with national recommendations; 51% advised follow-up at a shorter interval (Table 2).

Sixty percent of the GI-units continued follow-up after colorectal resection, also after repetitive negative colonoscopies. In contrast, 19% of the respondents discharged patients after 5 years when no abnormalities had been found during follow-up. The national oncol-

Table 2 Follow-up after treatment for CRC.

	No FU (%)	≤ 1 yr (%)	2 yr (%)	3-5 yr (%)	6 yr (%)
Endoscopic follow-up	2	37	14	44*	3
	Not discharged (%)	**3 yr (%)**	**5 yr (%)**	**6-7 yr (%)**	**≥10 yr (%)**
Discharged of follow-up	60	2	19	8	11

FU, follow-up.
* According to recommendations on internet (www.oncoline.nl).

ogy recommendations recommend a switch to the postpolypectomy guidelines when no metachronous CRC is found at first follow-up endoscopy.

CEA testing is common practice in 82% of the GI-units, only 26% determines a CEA level within 3 months after colorectal resection. Although repeated liver ultrasounds are not recommended as routine surveillance, it is routinely performed within 1 year by 61% of the respondents.

DISCUSSION

This study focused on the organizational aspects of follow-up after treatment for colorectal neoplasia in Dutch clinical practice. A wide variation in organizational aspects of follow-up was seen with regard to the documentation and invitation strategy of follow-up. First of all, it was remarkable to note that only 42% of the GI units used an active invitation policy, reminding patients and their GPs of the need for surveillance endoscopy at the end of the scheduled follow-up interval. All these units recorded the appointments in an electronic or handwritten database.

In the units without registration of surveillance endoscopies and without active follow-up policy, the attendance at follow-up endoscopy is expected to be lower, as patients may not attend their follow-up appointment after 3 to 6 year intervals. We recently observed that in a unit with a passive invitation policy the patient uptake of follow-up endoscopy was low. Only 27% of the patients underwent follow-up at the advised interval, 38% underwent delayed follow-up and 35% did not undergo any follow-up.[14]

Follow-up after polypectomy

This survey shows that despite clear and unambiguous guidelines for follow-up after polypectomy, the adherence to these guidelines by gastroenterologists varies widely. In cases for which the guidelines recommend a six-year follow-up interval, 27% to 78% of the respondents advised follow-up at a shorter interval, depending on parameters such as the number and histologic characteristics of the adenomas at baseline endoscopy.

The performance of surveillance endoscopies at shorter intervals than recommended in the guidelines as shown in this study has also been reported in other studies. Surveys in the US and Australia showed that a large proportion of endoscopists perform surveillance endoscopies at inappropriate shorter intervals than recommended in national guidelines.[5-9] Factors which influenced adherence to the guidelines included reimbursement policies, liability issues, community influence, and insufficient knowledge of practice guidelines.[5]

Our study shows that in The Netherlands the performance of surveillance endoscopy at shorter intervals than recommended is due to the fact that gastroenterologists tend to take the histologic characteristics of the removed adenoma into consideration, especially in the

Table 3 Variance in guidelines for follow-up after polypectomy in several countries.

	Interval based on:	**Follow-up interval**		
		≤ 1 yr	**3 yrs**	**6 yrs**
Dutch guidelines (2001) [10]	- Number	Earlier colonoscopy in case of incomplete colonoscopy Incomplete resection of adenomas	≥ 3 adenomas	1 or 2 adenomas
		≤ 1 yr	**3 yrs**	**5-10 yrs**
AGA guidelines US (2003) [11,33,34]	- Size - Number - Histology	After resection of large sessile adenoma If uncertain about removing all adenomas	≥ 3 adenomas Adenoma ≥ 1 cm Villous histology, HGD or invasive CRC	1 or 2 small (< 1 cm) tubular adenomas
		≤ 3 mo	**3 yrs**	**4-6 yrs**
Australia (NHMRC) (1999) [9,35]	Number Size Histology	After resection of: - Large sessile adenoma - Malignant adenoma - Incomplete resection of adenomas ≤ 1 yr: - If uncertain about removing all adenomas	≥ 3 adenomas Adenoma ≥ 1 cm Villous histology or HGD	1 or 2 small tubular adenoma (< 1 cm)
		1 yr	**3 yrs**	**5 yrs**
United Kingdom (2002) [28]	Number Size	≥ 5 adenomas or ≥ 3 adenomas and one of at least ≥ 1 cm Earlier colonoscopy in case of incomplete colonoscopy	3 to 4 adenomas or at least one ≥ 1 cm	1 or 2 small tubular adenoma (< 1 cm) (or no follow-up depending on patient)

NHMRC: National Health and Medical Research Council.

presence of HGD. Furthermore, the follow-up interval was also influenced by the size of the removed adenoma.

The results of this study can be interpreted in two ways. On the one hand, there may be unfamiliarity with the guidelines. It is widely recognized that physicians' adherence to evidence-based guidelines may often be poor.[15,16] Guidelines should therefore be compatible with existing values and not be too controversial.[17] Furthermore, guidelines should be easily accessible to clinicians; if possible preferably with a summary, often presented as an algorithm. In the case of this study, Dutch adenoma surveillance guidelines are widely available via the internet and the Dutch Gastroenterology Association. They have been distributed to all members of this society, including a summarized pocket card. Furthermore, the guidelines have been widely presented at different meetings and should thus be familiar to all endoscopists in our country. For these reasons, we hypothesize that lack of accessibility is not the main explanation for insufficient physician adherence. Therefore, it seems that compatibility with clinical values might be a more relevant explanation. The rationale behind the Dutch

guidelines to only include the number of adenomas in the determination of the follow-up interval came from the US National Polyp Study which showed that the initial number of adenomas was the sole significant predictor for adenoma recurrence after 3 years of surveillance.[2] In the case of the Dutch postpolypectomy guidelines, it must be emphasized that this guideline was thoroughly and repeatedly discussed before acceptance with the professional societies involved in this field and recommendations were made with the available literature at that time.

However, more recent studies showed that adenoma size and multiplicity were also found to be predictors of recurrence of advanced adenoma.[2,18-22] These results may to some extent have played a role in the consideration of many clinicians in our country to include size and grade of dysplasia in the determination of surveillance intervals.

The American Gastroenterological Association (AGA) and the Australian guidelines are based on histology (presence or absence of a villous component, and grade of dysplasia), size, and number of adenomas.[11,18,23] In the recent consensus update for surveillance after polypectomy in the US, patients diagnosed with adenoma >1 cm, containing HGD or villous histology are classified in the high-risk group, undergoing surveillance at a 3-year interval.[24] The low-risk group consists of patients diagnosed with no more than 2 small (<1 cm) tubular adenomas without HGD or a villous component, undergoing follow-up at a 5 to 10-year intervals.

The difficulty of including histologic characteristics in the guidelines is that histology is a particularly difficult predictor to evaluate because of the subjective nature of classifying tubular, tubulovillous, and villous adenomas. In several studies a considerable interobserver variation was reported for the interpretations of the histologic type and the degree of dysplasia.[25-27]

The British Society of Gastroenterology bypassed this problem and based their guidelines on number and size of adenomas; they did not include histologic characteristics, as it was argued that size and histology of adenomas correlate.[28]

Guidelines for follow-up intervals after treatment for CRC

The intervals for the endoscopic follow-up after CRC resection were also shorter than recommended. Over 50% of the respondents advised shorter follow-up intervals than recommended.

For the follow-up after colorectal resection there is general agreement about the usefulness of postoperative surveillance; however, with respect to the most effective strategy, so far no consensus has been reached in The Netherlands.

Follow-up schedules are highly heterogeneous regarding both the choice and the frequency of diagnostic procedures.[29,30] Recently, the American Cancer Society and the US Multi-Society Task Force published guidelines for colonoscopy after intended curative resection for colon cancer. Their guidelines advise to perform surveillance colonoscopy at

1 year, after clearing for synchronous lesions at the time of diagnosis.[31] They underline the usefulness of endoscopic surveillance after colon cancer because of the high detection rate of metachronous colon cancer. However, endoscopic follow-up for the purpose of detecting local recurrence does not have an established survival benefit in patients diagnosed with colon cancer.

As higher recurrence rates are reported for rectal cancer, the follow-up after rectal cancer deviates from follow-up after colon cancer in the new US guidelines. A periodic examination of the rectum is recommended for the purpose of identifying local recurrence at 3 to 6-month intervals for the first 2 to 3 years.[32]

In the Dutch recommendations, no distinction is made between surveillance after resection of cancer in the colon or cancer in the rectum. Reason for this is that total mesorectal excision is the prevailing therapy for rectal cancer in the Netherlands and is accompanied with low recurrence rates.

In conclusion, our results show that adherence to guidelines for the surveillance of colorectal adenomas after polypectomy and treatment after CRC is low in The Netherlands, leading to shorter surveillance intervals than recommended in the guidelines.

With regard to follow-up after polypectomy of adenomas, revision of the Dutch guidelines seems appropriate as new evidence to change the guidelines is now available and it might be considered to include size and histology.

Furthermore, it is necessary to give greater publicity to the existing recommendations for follow-up after treatment for CRC in order to create uniformity in follow-up policy. Compliance with the guidelines is important, since inappropriate surveillance can result in enormous costs regarding time, resources, and patient inconvenience or risk.

In The Netherlands, introduction of population-based CRC screening is expected to cause a major increase in the amount of endoscopic procedures, which stresses again the need to limit the amount of unnecessary procedures for the purpose of postpolypectomy surveillance.

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VIII

Attendance at surveillance endoscopy of patients with adenoma or colorectal cancer

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ABSTRACT

Background: Surveillance of patients treated for adenoma or colorectal cancer (CRC) is intended to reduce the incidence of CRC. Responsibility for the adherence to surveillance advice is often left to the patients and family physician. It is not known whether this type of passive policy affects the efficacy of surveillance. The aim of this study was to determine the yield of surveillance without active invitation to follow-up endoscopy.

Methods: This study comprised a cohort follow-up of patients under 75 years of age with adenomas or CRC at index endoscopy in the period 1997-99. Adherence and intervals of follow-up endoscopy were determined up to December 2004.

Results: During the inclusion period 2 946 patients underwent lower endoscopy. In total, 393 patients were newly diagnosed with colorectal polyps (n=280) or CRC (n=113). Polyps were classified as adenomas in 167/280 (61%) patients. Forty-five (27%) of the adenoma patients underwent surveillance endoscopy within the guideline interval, 63 (38%) underwent a delayed endoscopy, and 59 (35%) did not have any follow-up at all. CRC was diagnosed in 113 patients. Thirty-six patients who died during the first year or were diagnosed with metastases were excluded from the analysis. Twenty-three (30%) of the remaining 77 patients underwent endoscopic surveillance according to guidelines, 40 (52%) had delayed surveillance endoscopy, and 14/77 (18%) did not undergo surveillance endoscopy at all.

Conclusion: In surveillance for colorectal neoplasia, active follow-up invitation is important. Given the low follow-up rate in our series, passive follow-up policies may lead to underperformance of surveillance programs. An active and controlled follow-up is advisable.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of death from malignant disease in the Western world. The disease is the result from a multi-step adenoma-carcinoma sequence.[1-4] In a study of the natural history of colorectal adenomas it is reported that the cumulative risk of malignant transformation of adenomas with a diameter of at least 1 cm was 2.5%, 8% and 24%, respectively, after 5, 10 and 20 years of follow-up.[5]

Several studies have shown that repeated endoscopic screening with removal of adenomas reduces the incidence of CRC.[6-8] The rationale for colonoscopic surveillance is based on the 30 to 50% detection rate of recurrent adenomas at follow-up.[2] Consequently, a well-planned and evidence-based scheme for follow-up is mandatory in order to detect advanced colorectal neoplasia in an early stage, and to prevent the development of CRC.

Until 2001 the Dutch guidelines recommended a first surveillance endoscopy one year after removal of an adenoma, followed by further colonoscopy at 5-year intervals when none or one adenoma was encountered and at 3-year intervals when two or more adenomas were found at follow-up.[9]

During the time frame of this study, there was no clear consensus on guidelines regarding endoscopic follow-up after colorectal resection in patients diagnosed with CRC. As a result, follow-up programs for CRC used in Dutch hospitals varied considerably.[10] One workgroup recommended that the entire colon should be visualized by colonoscopy before or shortly after CRC resection, followed by surveillance colonoscopy one year after resection, to detect metachronous carcinoma. Further surveillance endoscopies should be performed at 3- to 5-year intervals when no new neoplasia were encountered.[11] Our local guidelines recommended colonoscopic surveillance one year after colorectal surgery for CRC.

In most Dutch clinical practices, removal of adenomas or CRC is followed by a documented advice to both patient and general practitioner (GP) for surveillance endoscopy, but does not include active invitation when the screening interval has passed. The GP thus serves as the central manager of care, as is common in many countries. To what extent this policy showing a passive role of the hospital affects the efficacy of surveillance is unknown.

The aim of this study was to assess the yield of surveillance without an active hospital-initiated invitation for follow-up endoscopy.

METHODS

Patient selection

In a prospective study we evaluated the follow-up of all patients under 75 years of age who were diagnosed between January 1997 until December 1999 with CRC or adenomas during colonoscopy or sigmoidoscopy. The study was performed in a single general hospital in The

Netherlands with a large gastroenterology practice covering both urban and rural regions of the South West of The Netherlands. Patients were identified by a database search of the endoscopic report system Endobase®. This report system is used in 40% of the Dutch hospitals. The reports are based on textblocks, which are coded with the GET-C coding system, an extension of the ICD-10 coding system. All endoscopy reports are stored in the Endobase® database and can be used for analyses.[12,13]

The following identifiers were used: polyp, adenoma and colorectal cancer. Patients known to have familial adenomatous polyposis, hereditary non-polyposis CRC, inflammatory bowel disease or with a prior history of CRC or adenomas were excluded.

Data collection

The interval of follow-up endoscopy was determined from index endoscopy in the period 1997-99, until December 2004. Endoscopies performed in subjects who had no previous records of CRC or adenomas were labeled as index endoscopy. There were various reasons for colonoscopy, ranging from abdominal pain and diarrhea to rectal blood loss and changed bowel habit. On the day before colonoscopy patients received 4 l polyethylene glycole-based electrolyte solution for bowel preparation, in accordance with the instructions for use. Midazolam was administered intravenously before the endoscopic procedure. When a colonoscopy was performed within 3 months of the prior endoscopy, this was reported as one procedure when the repeated endoscopy was performed in order to complete the previous endoscopic procedure.

After the initial procedure patients were advised about the interval for follow up endoscopy. GPs were informed about the recommended follow-up interval through the endoscopic report. For accurate follow-up data, it was verified whether patients had been alive and eligible for surveillance at the time of the intended follow-up visit by checking their records or contacting their GP. Furthermore, endoscopies which were performed because of abdominal complaints were not counted as surveillance endoscopies.

The following data were collected: demographic information (date of birth, gender, patient identification), date of index endoscopy, diagnosis at index endoscopy including number and site of the neoplastic lesions, surveillance endoscopies until December 2004, time of interval between the subsequent endoscopies, therapy, double contrast barium enema and metastases at time of diagnosis or follow up.

The histology results, i.e. type of polyp or tumour and grade of dysplasia or differentiation, were obtained from the PALGA database. This database is a national archive containing the abstracts and diagnostic codes of all histopathology and cytopathology reports in The Netherlands since 1991.[14] Patients were classified on the basis of their most advanced lesion in order to determine the prevalence of pathological features. Patients with intramucosal carcinoma or carcinoma *in situ* were classified as having an adenoma with high-grade dysplasia. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosa.[15,16]

Only patients diagnosed with adenocarcinoma were included in the CRC-group. Patients with other lesions, such as carcinoid, lymfomas, sarcoma, leiomyoma, lymphangioma and hemangioma, were excluded because of the different follow-up approaches used compared with that for adenocarcinoma.[15]

Polypoid lesions were classified as adenomatous and non-adenomatous polyps. Non-adenomatous polyps included hyperplastic polyps, hamartomas, lymphoid aggregates and inflammatory polyps. Adenomatous polyps were classified according to the World Health Organization as tubular, tubulovillous and villous, depending on the presence and volume of villous tissue.[16] The grade of dysplasia was classified as low, intermediate or high-grade.

Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. Descriptive statistics were used to analyse and report the data. Differences in outcome between groups of patients were calculated by means of Student's *t*-test or Chi-square/Fisher exact test, when appropriate.

RESULTS

From January 1997 to December 1999, a total of 2 946 patients under 75 years of age underwent colonoscopy (n=1 932) or sigmoidoscopy (n=1 014), 46% of them were men (M/F 1355/1591). During the study period, polyps were newly diagnosed in 280 (10%) patients and CRC in 113 (4%). For these patients the endoscopy was defined as index endoscopy.

Among all patients who underwent colonoscopy, significantly more male patients had neoplastic lesions in comparison with female patients (230/1 355 versus 163/1 591, $p<0.01$). Table 1 shows the characteristics of patients diagnosed with polyps or CRC. The median age of the patients diagnosed with CRC was significantly higher than the age of patients with polyps, 65 versus 60 years of age ($p<0.001$).

Polypoid lesions

In total, 280 patients were diagnosed with polypoid lesions and classified according to their most advanced lesion. Adenomas were present in 167/280 (60%) patients and only hyperplastic polyps in 26/280 (9%). No histological evaluation was performed in 77 (28%) patients (Table 2). Six patients diagnosed with inflammatory polyps, as well as four patients diagnosed with hamartomas and lipomas, were excluded from further analysis.

Table 1 Characteristics of patients diagnosed with polyps or colorectal cancer in the period 1997-99

Characteristics	All Polyps n (%)	Adenomatous polyps n (%)	CRC n (%)
Gender			
Male	165/280 (59)	99/167 (59)	65/113 (58)
Female	115/280 (41)	68/167 (41)	48/113 (42)
Age group (years)			
<40	14/280 (5)	6/167 (4)	3/113 (3)
40-49	29/280 (11)	19/167 (11)	4/113 (4)
50-59	85/280 (30)	50/167 (30)	24/113 (21)
60-69	106/280 (38)	61/167 (36)	42/113 (37)
70-75	46/280 (16)	31/167 (195)	40/113 (35)
Age (years)			
Median (range)	60 (22-75)	61 (22-75)	65 (26-75)

Adenomatous polyps at index endoscopy

The histological examination of the adenomas showed tubular adenomas in 70/167 (42%) patients, tubulovillous in 20/167 (12%), villous in 18/167 (11%) and adenomas without further specification in 59/167 (35%) patients.

During follow-up at least one surveillance endoscopy was performed in 65% (108/167) of the patients (Table 2). This was performed within one year in 27% (45/167), in accordance with the then prevailing guidelines. Sixty-three (38%) adenoma patients underwent a delayed surveillance endoscopy, and 59 (35%) did not have any follow-up at all. At first surveillance endoscopy, CRC was diagnosed in 1/108 patients (interval 3 years) and adenomas in 7/108 (6%) patients. Of the 59 patients who did not undergo surveillance, 4 (7%) died within one year after index endoscopy as a result of other illnesses.

Other polypoid lesions

Even though the guidelines advised against surveillance endoscopy in patients diagnosed with hyperplastic polyps only, 8 (31%) of the 26 patients in this category underwent a surveillance endoscopy. Among those 8 patients, 1 patient was diagnosed with a single adenoma. A second endoscopy was performed in 4 of the 26 patients for reasons other than surveillance.

Of the 77 patients in the group in whom polypoid lesions were removed without further histological evaluation, 21 (27%) received surveillance endoscopy. In this group, one patient was diagnosed with CRC at surveillance endoscopy after an interval of one year. Single adenomas were diagnosed in 3 patients, while no histologic evaluation was performed in 6 patients.

Table 2 Number of patients undergoing surveillance endoscopy in relation to baseline histology, interval at first endoscopy and findings at surveillance endoscopy

	POLYPS			
	No histology n=77	**Hyperplastic** n=26	**Adenomatous** n=167	**CRC** n=113
No of pts with SE (% of cases, 95% CI)	21/77 (27%, 17-37)	8/26 (31%, 13-49)	108/167 (65%, 57-72)	63/77 [a] (82%, 73-90)
Interval of first SE				
0-1 yr (% of cases)	9/77 (12%)	2/26 (8%)	45/167 (27%)	23/77 (30%)
Findings				
Polyp [b]	3		9	
Adenoma	2	1	3	3
CRC	1			
>1-3 yr (% of cases)	10/77 (13%)	5/26 (19%)	50/167 (30%)	31/77 (40%)
Findings				
Polyp	3	1	16	
Adenoma			4	5
CRC			1	1
>3-6 yr (% of cases)	2/77 (2%)	1/26 (4%)	13/167 (8%)	9/77 (12%)
Findings		No neoplasia		No neoplasia
Polyp			2	
Adenoma	1			
CRC				

SE, Surveillance endoscopy.

[a] 113 patients minus patients who died during the first year after diagnosis and those who were known with metastases.

[b] Polyp: hyperplastic polyp and polyp without histological evaluation.

CRC

At index endoscopy, CRC was diagnosed in 113/2 946 (4%) of the patients. At the time of diagnosis metastases were found in 11 (10%) patients. In total, 102 (90%) underwent resection. In this group, metastases were diagnosed in 15/102 patients during the first year after diagnosis. Fifteen of the 113 patients died within one year after they were diagnosed with CRC, of whom 6 were known with metastases and 9 died from complications of surgery or from co-morbidity.

Those patients who died during the first year after diagnosis or were known with metastases were excluded from further follow-up analysis. Furthermore, one patient moved to an other city during time of follow-up and was also excluded from follow-up analysis.

The attendance rate at surveillance endoscopy was thus analysed for 77 curatively treated patients. Sixty-three (82%) of them underwent surveillance endoscopy, 30% within one year according to the guidelines (Table 2). No surveillance was performed in 14 (18%) of the 77 patients with at least twelve months' survival.

At first surveillance endoscopy, 1/63 patient was diagnosed with recurrent CRC at an interval of 1.5 years and 8/63 (13%) patients were diagnosed with adenomas during surveillance endoscopy. A double contrast barium enema for surveillance was performed after 6 months in one of the 15 patients who did not undergo any surveillance endoscopy.

DISCUSSION

Colorectal neoplasia is a common disorder with a high tendency for metachronous recurrence. National and international guidelines therefore advise surveillance after endoscopic or surgical removal of colorectal adenomas and/or cancer. The organization and quality control of surveillance differ between regions. In many countries it is common practice to rely on the patient and GP for adherence to follow-up and scheduling of surveillance endoscopy. Such a policy is also common practice in The Netherlands. The adherence to surveillance guidelines under such policies is, however, unknown.

Therefore, as the impact of surveillance protocols largely depends on adherence, the aim of this study was to provide data on the attendance rates for surveillance endoscopy. We show that despite unambiguous guidelines in a region with a well-organized health care system with unrestricted access for all and full insurance coverage of costs, the majority of patients tend not to undergo adequate surveillance. Only 27% of the adenoma patients underwent a surveillance endoscopy within the recommended period, one-third underwent delayed surveillance, and 35% did not undergo surveillance endoscopy at all. Of the CRC patients, only 30% of the eligible patients had surveillance within the advised 1-year interval. In addition to this undertreatment, overtreatment was also observed as 31% of patients with solitary or a limited number of hyperplastic polyps and 27% of patients in whom polypoid lesions had been removed without further histological evaluation, nevertheless underwent surveillance endoscopy.

Several factors may be responsible for the low attendance rate in eligible patients. First of all, the general follow-up policy in most clinical practices in The Netherlands is that after the removal of adenomas or CRC both patient and GP are advised to comply with follow-up endoscopy. This advise is not accompanied by a specific appointment, nor are reminders sent to either patient or GP by the end of the intended interval. Most hospitals do not keep track of their adenoma patients, and are thus also unable to send reminders when the surveillance interval has passed without control endoscopy. In The Netherlands only a few hospitals use an active invitation strategy, which may be an efficient way of improving guideline adherence. In the hospital in which this study was performed, an automatic recall system was developed in the beginning of 2005, using the Endobase® report system for flexible endoscopies.[17]

The poor adherence to follow-up guidelines may to some extent also be related to patients' lack of compliance. This may be due to the burden of bowel preparation or the endoscopy

procedure itself, which is uncomfortable and inconvenient, and associated with a, albeit low, risk for complications.[18,19] Furthermore, lack of compliance may be caused by fear for recurrent pathology, as well as by ignorance and insufficient information about reasons for surveillance endoscopy.[20] This suggests that adherence to follow-up schedules might be improved by providing better information to patients.

Little is known about attendance at surveillance endoscopy in other countries. A survey study conducted by the National Cancer Institute in the United States among gastroenterologists and surgeons about their perceived need for the frequency of surveillance after polypectomy suggests considerable over-performance of surveillance colonoscopy, particularly for hyperplastic polyps and small adenoma, when compared with the published guidelines.[21] However, this study was based on physicians' self-reported practice patterns and not on actual data of individual patients, which means that the results may not truly reflect the clinical practice of surveillance endoscopy.

During the time this study was performed, there was no consensus regarding the follow-up of patients with CRC in The Netherlands.[10] In our practice and that of most other gastroenterologists, patients were advised to undergo surveillance within one year after surgery, depending on their clinical condition. Only 30% of the eligible CRC patients underwent a surveillance endoscopy within one year.

Recent Dutch oncology guidelines recommend a surveillance colonoscopy 3 to 5 years after colorectal resection.[22] However, in clinical practice there is still wide variation in CRC follow-up programs used in the different hospitals in The Netherlands, among other things induced by differences in regional cancer-center guidelines.[23] In other countries there is also considerable controversy about how often patients should be seen and what tests should be performed for surveillance after treatment for CRC. It is nevertheless general practice to follow patients with CRC for several years after their surgery, resulting in an overall survival benefit.[24] Different studies claim that the most crucial phase of follow-up is the first two to three years after primary tumor resection, since during this time the vast majority of recurrences will become apparent.[25,26] We demonstrate in this study that 18% of the colon cancer patients with curative surgery did not undergo any surveillance endoscopy.

Our results are in line with data from an American database study, which reported that 17% of 52 283 patients did not undergo surveillance endoscopy after curative resection of CRC.[27]

The results of this study were derived from one hospital covering both a city and rural area of the South West of The Netherlands. There are no data available about the application of the guidelines in other hospitals. However, approximately 60% of the endoscopy units in The Netherlands apply the same passive follow-up policy, i.e. not sending invitation letters, as in the hospital of this study, so the current findings are likely to be representative of the situation in those gastroenterology practices, given the fact of the mixed catchment area.[28] Furthermore there is a long-standing excellent contact with the referring family physicians,

and the gastroenterology practice has long been in the forefront of the development of endoscopy database applications.

In conclusion, in this study the majority of adenoma and CRC patients do not receive adequate surveillance endoscopy despite guidelines and documented written and oral follow-up advice to patient and GPs. It is important to take note of this low adherence to surveillance which shows that passive follow-up policies may lead to underperformance of surveillance programs. In view of the growing interest for colorectal screening, it is necessary to evaluate the efficacy of existing national surveillance programs. Implementing an active approach policy is important and should encourage physicians and patients to adhere to a surveillance protocol as well as improving attendance at surveillance endoscopy. The efficacy of such an alternative approach needs to be proven. We should invest in a regional or even national surveillance strategy including active invitation by means of combined endoscopy and histology database systems, as well as by increasing patients' awareness.

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IX

General discussion and conclusions

MULTIPLE PRIMARY COLORECTAL CANCERS

Patients diagnosed with sporadic colorectal cancer (CRC) are at risk of synchronous CRC at the time of diagnosis as well as metachronous CRC during follow-up. The reported incidences of synchronous and metachronous CRC vary considerably, partly caused by differences in time periods studied, definitions, selection criteria, and patient populations. Identification of patients at risk for developing a second primary CRC requires tailored surveillance.

To evaluate the incidence of synchronous and metachronous sporadic CRC and identify patient and tumour-related characteristics associated with the presence of synchronous and metachronous CRC, we studied data from the Rotterdam Cancer Registry in The Netherlands (**Chapter 2**). In this study focusing on 13 683 patients diagnosed with sporadic CRC in the period 1995 to 2006, almost 4% of the patients presented with synchronous CRC. Multivariate analysis revealed several risk factors for synchronous CRC, in particular male gender, age above 70 years, and localization in the colon. However, the predictive value of a regression model based on these risk factors was too low (area under the ROC-curve of 0.6) for adequate prediction of the occurrence of synchronous CRC in clinical practice. An important finding was that one third of the synchronous CRCs were localized in different surgical segments than the primary tumour. This fact stresses the importance of performing a total colonoscopy at the time of diagnosis, preferably prior to surgery, as the patients with synchronous CRC require extended surgery or (sub)total colectomy.

The cumulative incidence of metachronous CRC was 1.1% at 3 years, 2.0% at 6 years and 3.1% at 10 years (**Chapter 3**). We showed that patients diagnosed with CRC had a higher risk of developing a second primary CRC compared to the risk of developing CRC in the general population (SIR 1.3). The presence of synchronous CRC at the time of the initial CRC was the only significant predictor for the higher incidence of metachronous CRC in the multivariate analysis. This finding was confirmed in other studies.[1-4]

Furthermore, a remarkable finding was that the increased risk was highest during the first 3 years of follow-up after the initial CRC. The risk of developing metachronous CRC persists during follow-up, however, the risk after 6 to 10 years follow-up is similar to the risk of developing primary CRC in the general population. The fact that many metachronous CRC were detected during the first 3 years of follow-up suggests that those tumours developing in a short period of time, may behave more aggressively, and may follow an alternative pathway to CRC than the adenoma-carcinoma pathway. Another explanation might be that colon examinations at the time of the initial CRC were not, or not adequately performed and that the metachronous CRC detected during the first years of follow-up can be considered as missed synchronous lesions.

Although colonoscopy has become accepted as the most effective method of visualizing the colon, colonoscopy and polypectomy are complex technical procedures that require training and experience in order to maximize accuracy and safety. In the literature, miss-rates

have been reported to increase with decreasing size of adenomas, with an overall miss-rate of polyps of any size of 22%.[5] Furthermore, it was reported that colonoscopy was less effective for right-sided CRC than for left-sided CRC.[6,7] In an attempt to guarantee the effectiveness of colonoscopy, Rex et al. postulated quality indicators for colonoscopy.[8,9] Amongst others, the following quality indicators have been proposed: (1) cecal intubation rates of 90% of all cases and in 95% of cases when the indication is screening; (2) adenoma detection rate of ≥25% in average risk men and in ≥15% in average risk women over 50 years of age at the first colonoscopy; (3) mean withdrawal time of ≥6 minutes in colonoscopies with normal results and intact colons; (4) the use of the recommended post-polypectomy and post-CRC surveillance guidelines; (5) documentation of the quality of bowel preparation; (6) documentation of the incidence of perforation by procedure type (symptomatic versus screening), which should be observed in less than 0.5% and 0.1% respectively, and the incidence of post-polypectomy bleeding, which should be less than 1%.[9]

A recent study confirmed that the adenoma detection rate to be an independent predictor of the risk of interval CRC after screening endoscopy, however, the cecal intubation rate was not significantly associated with this risk.[10] Another study reported that patients who had their colonoscopy performed by a gastroenterologist were less likely to develop a CRC, compared to those who had their colonoscopy performed by another specialist.[11] Factors for incomplete colonoscopy were mentioned in the literature, among others obstruction because of a distally located tumour, increasing age and female sex.

Conclusions and recommendations

Our study shows that in patients diagnosed with synchronous CRC, one third of the synchronous CRC is located in different surgical segments. This finding stresses the importance of total colon examination, preferably prior to surgery, as extended surgery or a (sub)total colectomy is required for synchronous CRC. Given the fact that the presence of synchronous CRC at the initial CRC diagnosis is the most important risk factor for detecting metachronous CRC during follow-up, a tailored surveillance program might be considered in patients diagnosed with synchronous tumours at baseline. Furthermore, as many of the metachronous CRCs are detected during the first 3 years of follow-up, a part of the metachronous CRC presenting during the first years of follow-up might be considered as missed synchronous lesions.

For the future, in order to get insight in the origin of the early metachronous CRC, the performance of total colonoscopies at the time of the initial CRC diagnosis should be investigated together with determination of a more aggressive growth pattern (for example microsatellite instability of the primary tumour). The quality indicators of those colonoscopies should also be evaluated, like the quality of bowel preparation, cecal intubation rate, adenoma detection rate, draw-back time etc.

Furthermore, emphasis should be placed on improving the quality of colorectal examinations. Endoscopists should be aware of the shortcomings of colonoscopy and should pay

attention to the quality indicators of colonoscopy. Methods to investigate the causes of the miss-rates are currently under investigation, like video assisted colonoscopy training.[12] Several techniques to improve polyp detection are available or under investigation, among others chromoendoscopy, which improves the detection of adenomas and facilitates the detection of mucosal lesions. However, this technique is time consuming and not widely available.[13,14] Also techniques like narrow-band imaging, autofluorescence colonoscopy and immunoscopy are currently in the experimental phase.[5,15]

TESTS FOR COLORECTAL CANCER SCREENING

There is a variety of screening tests for the average risk population, including the structural examinations, like colonoscopy and sigmoidoscopy, and non-invasive stool tests, like the guaiac faecal occult blood tests (gFOBT) and the faecal immunochemical test (FIT). We investigated the efficacy of several invasive and non-invasive screening methods.

Invasive screening tests, like colonoscopy and sigmoidoscopy, are being performed as primary screening tests or for the work-up of positive primary (non-invasive) screening tests. As the endoscopy resources are limited, it will not be feasible to offer an invasive endoscopy to all eligible screenees. The extent to which colorectal examinations are currently being performed in the target population for screening in The Netherlands is unknown. It is important to identify this proportion as it informs us of the required additional efforts needed for a population-wide screening program. Furthermore, the potential impact which such an organized program may have is unknown.

For these reasons, we evaluated the exposure to colorectal examinations (colonoscopy, sigmoidoscopy and barium enema) in a large primary care population in The Netherlands (**Chapter 4**). To estimate the effect of colorectal examinations on the CRC risk, we compared exposure to these examinations in 594 CRC patients and 7790 matched control participants in a period up to 5 years before diagnosis.

We showed that 4.3% of the total population and 3.7% in the study population between 50 and 75 years of age underwent a colorectal examination during a mean follow-up period of almost 3 years. In total, 2.9% of the CRC patients had undergone a diagnostic colorectal procedure up to 5 years before CRC diagnosis, compared to 4.4% of the control population. This fact supports the hypothesis that colorectal examinations exert a preventive effect on the development of CRC. Remarkably, only in the stratum of left-sided CRC significantly more controls than cases had undergone a colorectal examination. This difference was not seen for right-sided CRCs, suggesting a larger impact of colorectal examinations on left-sided CRC compared to right-sided CRC.

Several other studies also reported that colonoscopy was less effective for right-sided CRC than for left-sided CRC.[6,7,16] This may have several reasons. Firstly, some 'complete' colonos-

copies do not evaluate the entire colon and right-sided neoplasia can be missed. Secondly, bowel preparation may be poor, which preferentially affects the proximal colon. Finally, right and left-sided neoplasia may differ biologically.[17] Right-sided neoplasia are more often non-polypoid and serrated lesions, which makes them harder to identify and remove.[7,18]

Because of the restricted capacity of endoscopy, the burden of colonoscopy and the inevitable risk of complications in healthy screenees, it may be useful to select persons in whom colonoscopy as a primary screening test would be benificial and in whom sigmoidoscopy screening would suffice. In the literature, a higher detection rate for sigmoidoscopy was reported in a male population compared to a female population (66% versus 35% respectively). Also increasing age is reported to be associated with a higher miss-rate of proximal advanced adenomas.[19,20]

For this reason, we determined the risk for proximal CRC and identified subgroups in which sigmoidoscopy might be a sufficient screening method instead of colonoscopy, based on their risk profile for (proximal) advanced lesions (**Chapter 5**). Using the Endobase database, all patients diagnosed with CRC during the period 1997-2005 were selected. We showed that the proportion of proximal CRC increases with age (27% < 65 years of age versus 41% > 65 years of age) , and more often occur without synchronous distal adenomas. Below the age of 65 years, 78% of all CRCs could be diagnosed by sigmoidoscopy, followed by colonoscopy in case of distal adenomas, compared to only 65% in the population above 65 years of age. In this older population, the calculated miss-rate for sigmoidoscopy was significantly higher in women than in men (42% versus 28% respectively), a difference that was not seen in the populations below 65 years of age.

The gFOBT is the only non-invasive test with a proven mortality reduction.[21-23] The FIT has shown to have superior participation rates and detection rates than the gFOBT.[23] Besides the faecal occult blood tests, several faecal tumour markers are under investigation for CRC screening. In our study, we were interested in the performance of the faecal tumour pyruvate kinase isoenzyme type M2 test (TuM2-PK). This isoenzyme, which is released by tumour cells of a wide range of different malignancies predominantly in dimeric form, can be detected in the faeces. This test might be of additional value as a non-invasive screening test as it is expected to be more cancer specific than faecal occult blood tests.

In **Chapter 6** the accuracy of the faecal TuM2-PK test was compared with two types of immunochemical faecal occult blood tests (FIT) (Immo-care and OC-Light) in patients diagnosed with CRC or adenomas. In total, 52 patients with CRC were analyzed, 47 with colorectal adenomas, and 63 matched controls with a normal colonoscopy. In addition, 19 patients with inflammatory bowel disease (IBD) were tested to determine the influence of inflammation in the bowel on the test results of TuM2-PK.

In our population, the FITs showed high overall sensitivities (92% and 94%) with acceptable specificities (97%) in patients diagnosed with CRC and performed better than the TuM2-PK test. Also the sensitivity for advanced adenomas was higher for both FITs (55% and 64%)

compared to the TuM2-PK test (27%). It was expected that the TuM2-PK test would be highly cancer specific, however, almost 80% of the patients with IBD tested positive for TuM2PK. An elevation of faecal TuM2-PK in patients with inflammatory bowel reactions was also reported in another study.[24] Low sensitivities (73-77%) and specificities (72-78%) for TuM2-PK in CRC patients were also reported in other studies.[25,26] Based on this study, we concluded that the TuM2-PK test did not have supplemental value to the FIT for the detection of CRC and advanced adenomas.

Conclusions and recommendations

We show that patients with CRC are 44% less likely than controls to have had a colorectal examination in the years before being diagnosed with CRC, a fact that supports the hypothesis that colorectal examinations exert a preventive effect on the development of CRC. This effect is more pronounced for left-sided neoplasia compared to right-sided neoplasia, which is also seen in other studies. For the future, it is important to investigate the risk factors for false-negative examinations of right-sided neoplasia to minimize the miss-rate and to enlarge the preventive effect of colorectal examinations on the incidence of both left *and* right-sided CRC.

Furthermore, we conclude that sigmoidoscopy may suffice as a screening tool in both men and women younger than 65 years of age, as almost 80% of CRC would be detected by sigmoidoscopy, followed by colonoscopy in the case of distal adenomas. However, screening with sigmoidoscopy results in a higher miss-rate in the population above 65 years of age, especially in women. In this age group, colonoscopy should be considered as a primary screening tool.

Finally, we conclude that the FIT performs better than the TuM2-PK test in detecting CRC and adenomas. The TuM2-PK test does not have an additional value to the FIT for non-invasive CRC screening as the expected additional value of the TuM2-PK test, i.e. the cancer specificity, could not be shown. Further research should be performed to determine the optimal screening strategy using FIT.

SURVEILLANCE AND ADHERENCE TO THE GUIDELINES

Clinical practice guidelines for surveillance after polypectomy have been developed by different professional societies worldwide on the basis of scientific evidence. Nevertheless, the optimal surveillance strategy is unknown, as the predictive value of the reported risk factors of metachronous adenomas during follow-up, like size, number, villous histology and grade of dysplasia of the baseline adenomas, is controversial.[27-32]

On the one hand, composing guidelines for surveillance based on available evidence is difficult. On the other hand, the guidelines must also be applicable in clinical practice, as

the impact of surveillance largely depends on adherence. Adherence to these guidelines is crucial; both to remove recurrent adenomas and detect CRC in an early stage, as well as to limit the endoscopic burden for patients and optimize the use of endoscopic capacity.

To evaluate the adherence to the current Dutch guidelines for surveillance after polypectomy, a survey among Dutch gastroenterologists was performed (**Chapter 7**). We showed that Dutch gastroenterologists often take size and histology of the baseline adenomas, especially the presence of high-grade dysplasia, into consideration when determining the surveillance interval. This fact often causes shortening of the follow-up intervals.[33] In cases for which the guidelines recommend a six-year follow-up interval, 27% to 78% of the respondents advised follow-up at a shorter interval.

Explanation for this non-compliance may be unfamiliarity with the current guidelines. However, much publicity has been given to the guidelines on the internet and during symposia, so the lack of accessibility is unlikely to be the main explanation for insufficient physician compliance. It seems that compatibility with clinical values might be a more relevant explanation. Several guidelines from international societies incorporated the histology and size of the baseline polyps.[34,35] These results may to some extent have played a role in the consideration of many clinicians in The Netherlands to include size and grade of dysplasia in the determination of surveillance intervals.

It is known that physicians' compliance with evidence-based guidelines is often poor.[36,37] A survey study conducted in the United States among gastroenterologists and surgeons about their perceived need for the frequency of surveillance after polypectomy showed a lack of compliance with surveillance guidelines, with repeated examinations being recommended at shorter intervals than the guidelines indicate.[38] They stated that this non-compliance might be due to lack of knowledge of the guidelines, medical liability concerns, financial incentives, and differing recommendations by professional societies.

In **Chapter 8** the results of a database study were shown, in which the actual attendance at surveillance endoscopies was evaluated in clinical practice. We showed that the majority of patients did not undergo adequate surveillance endoscopies according to the guidelines. Only 27% of adenoma patients underwent a surveillance endoscopy within the recommended period, one third underwent delayed surveillance and 35% did not undergo surveillance endoscopy at all. Overtreatment was also observed, as 31% of the patients with solitary or a limited number of hyperplastic polyps underwent surveillance endoscopy.

Several factors contribute to this low attendance rate at surveillance endoscopy. First of all, most of the hospitals advise their patients and the general practitioner (GP) about the interval of surveillance endoscopy. This recommendation is not accompanied by a specific appointment, nor are reminders sent to either patient or GP by the end of the intended interval. Actually, most hospitals do not keep track of their adenoma patients, and are thus also unable to send reminders when the surveillance interval has passed without control endoscopy. Only a few hospitals use an active, call-recall invitation strategy, which might

improve the attendance at surveillance endoscopies.[33] In the hospital in which this study was performed, an automated recall system was introduced early in 2005, using the Endobase® endoscopy report system to track patients and improve attendance at surveillance.[39]

Furthermore, the low attendance rate may also be related to the patients' lack of compliance. This may be due to the burden of bowel preparation or the endoscopy procedure itself, and, albeit low, the risk for complications.[40,41]. Also, lack of compliance may be caused by fear for recurrent pathology, as well as by ignorance and insufficient information about reasons for surveillance endoscopy.[42] Providing better information to patients about the reasons for surveillance endoscopies may thus improve the attendance.

Conclusions and recommendations

The main conclusions of chapter 7 and 8 are that despite unambiguous guidelines in a region with a well-organized health care system with unrestricted access for all and full insurance coverage of costs, the majority of patients tend not to undergo adequate surveillance after polypectomy. On one hand, Dutch gastroenterologists often tend to shorten follow-up intervals despite clear guidelines and endoscopy waiting lists. On the other hand, more than half of the patients undergo delayed surveillance or no surveillance at all due to a variety of reasons.

As the impact of surveillance protocols largely depends on adherence, gastroenterologists should become aware of the insufficient surveillance policy. Firstly, the rationale and evidence behind the national guidelines should be emphasized in order to improve physician adherence to guidelines. Secondly, implementing an active call-recall policy is important and should encourage physicians and patients to adhere to a surveillance protocol as well as improving attendance at surveillance endoscopy. We should invest in a regional or even national surveillance strategy including active invitation by means of combined endoscopy and histology database systems, as well as by increasing patients' awareness.

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Summary
Samenvatting

SUMMARY

Colorectal cancer (CRC) is a major health problem in the Western world. The life-time risk for developing CRC is approximately five percent. The fact that most CRC arise from premalignant precursors, adenomatous polyps, provides an unique opportunity to reduce the incidence and mortality of CRC by detection and removal of the adenomas. Furthermore, detection of CRC at an early stage improves the prognosis and CRC related mortality considerably. For these reasons, there has been considerable interest for CRC screening during the last decades. This thesis focusses on several aspects of screening and surveillance for CRC and adenomas.

Chapter 1 gives an overview of the epidemiology and risk factors of CRC. Furthermore, several invasive and non-invasive screening methods for CRC and guidelines for surveillance after polypectomy and CRC resection are discussed. At the end of the chapter, the general aims and outline of the thesis are described.

Patients diagnosed with sporadic CRC are at risk of developing multiple primary CRCs. Identification of patients at risk requires a tailored surveillance to prevent the development of metachronous CRCs. In **Chapter 2** the prevalence and risk factors of synchronous CRC are evaluated based on data from the Rotterdam Cancer Registry in The Netherlands. In this study focusing on 13 683 patients diagnosed with sporadic CRC in the period 1995 to 2006, nearly 4% of the patients presented with synchronous CRC. Multivariate analysis revealed several risk factors for synchronous CRC, in particular male gender, age above 70 years and localization in the colon. However, no prediction model could be constructed based on these risk factors. An important finding was that one third of the synchronous CRCs were localized in another surgical segments than the primary tumour, underlining the importance of performing a total colonoscopy at the time of diagnosis, preferably prior to surgery, as these patients with synchronous CRC require extended surgery or (sub)total colectomy.

Also the incidence and risk factors of metachronous CRC were analysed (**Chapter 3**). The cumulative incidence of metachronous CRC was 1.1% at 3 years, 2.0% at 6 years and 3.1% at 10 years. Patients diagnosed with CRC had a higher risk of developing a (second) primary CRC compared to the risk of developing CRC in the general population (SIR 1.3). The presence of synchronous CRC at the time of the initial CRC was the only significant predictor for the higher incidence of metachronous CRC.

This study shows that patients diagnosed with CRC are at increased risk of developing metachronous CRC, mainly during the first 3 years of follow-up, thereafter decreasing to the average risk of CRC compared to the general population. Development of metachronous CRC during the first 3 years of follow-up may be caused by aggressive, fast growing CRCs or due to inadequately performed colonoscopies at the time of the initial CRC. As a consequence, a part of the metachronous CRC detected during the first years of follow-up may thus be considered as missed, synchronous lesions. Further explanation for the occurrence of these early metachronous CRCs should be investigated.

Several invasive and non-invasive screening methods were evaluated. To evaluate the background incidence of colorectal examinations (colonoscopy, sigmoidoscopy and barium enema) in a population in which CRC screening has not yet been introduced, we performed a study in a large primary care population in The Netherlands using the IPCI database (**Chapter 4**). We showed that 4.3% of the total population and 3.7% in the study population between 50 and 75 years of age underwent a colorectal examination during a mean follow-up period of almost 3 years. To estimate the effect of those colorectal examinations on the CRC risk, we compared the exposure to these examinations in 594 CRC patients and 7790 matched control participants in a period up to 5 years before diagnosis. In total, 2.9% of the CRC patients had undergone a diagnostic colorectal procedure up to 5 years before CRC diagnosis, compared to 4.4% of the control population, supporting the hypothesis that colorectal examinations exert a preventive effect on the development of CRC. This preventive effect was only seen in patients diagnosed with left-sided CRC and not in patients diagnosed with right-sided CRCs, suggesting a larger impact of colorectal examinations on left-sided CRC compared to right-sided CRC. Why the effect of the examinations on right-sided CRC differs from left-sided CRC should be further investigated.

We furthermore determined the risk for proximal CRC and identified subgroups in which sigmoidoscopy might be a sufficient screening method instead of colonoscopy, based on their risk profile for (proximal) advanced lesions (**Chapter 5**). Using the Endobase database, all patients diagnosed with CRC (n=783) during the period 1997-2005 were selected. We showed that the proportion of proximal CRC increases with age (27% < 65 years of age versus 41% > 65 years of age), and more often occur without synchronous distal adenomas. Below the age of 65 years, 78% of all CRCs could be diagnosed by sigmoidoscopy, followed by colonoscopy in case of distal adenomas, compared to only 65% in the population above 65 years of age. In this older population, the calculated miss-rate for sigmoidoscopy was significantly higher in women than in men (42% versus 28% respectively), a difference that was not seen in the population below 65 years of age.

We conclude that sigmoidoscopy might suffice as a screening tool in both men and women younger than 65 years of age. However, as screening with sigmoidoscopy results in a higher miss-rate in the population above 65 years of age, especially in women, colonoscopy should be considered as a primary screening tool in persons above 65 years of age.

In **Chapter 6** the accuracy of the faecal tumour pyruvate kinase isoenzyme type M2 (TuM2-PK) test was compared with two types of immunochemical faecal occult blood tests (FIT) (Immo-care and OC-Light) in patients diagnosed with CRC (n=52) or adenomas (n=47). Also patients diagnosed with inflammatory bowel disease were tested to investigate the cancer-specificity of the TuM2-PK test. The FITs showed a higher sensitivity and specificity in patients diagnosed with CRC and advanced adenomas than the TuM2-PK test. It was expected that the TuM2-PK test would be highly cancer-specific, however, almost 80% of the patients with IBD tested positive for TuM2-PK. We conclude that the TuM2-PK test does not have supplemental value to the FIT for the detection of CRC and (advanced) adenomas.

As the efficacy of surveillance largely depends on the adherence, a national survey was performed among Dutch gastroenterologists to evaluate the adherence to the current Dutch guidelines for surveillance after polypectomy (**Chapter 7**). We showed that Dutch gastroenterologists often take size and histology of the baseline adenomas into consideration when determining the surveillance interval, leading to shortening of the follow-up intervals. In patient cases for which the guidelines recommend a six-year follow-up interval, 27% to 78% of the respondents advised follow-up at a shorter interval. This study concludes that gastroenterologists should become aware of the insufficient compliance with the guidelines, as the impact of surveillance largely depends on compliance. Furthermore, as the number of surveillance endoscopies will increase as a result of CRC screening, inadequate surveillance strategies will enlarge the number of surveillance endoscopies and will cause a major burden of the, already restricted, endoscopy resources.

In **Chapter 8** the attendance at surveillance endoscopies is evaluated in clinical practice, based on the endoscopy database Endobase. We showed that the majority of patients did not undergo surveillance endoscopies at intervals recommended in the guidelines. Only 27% of the adenoma patients underwent a surveillance endoscopy within the recommended period, one third underwent delayed surveillance, and 35% did not undergo a surveillance endoscopy at all. Overtreatment was also observed as 31% of the patients with solitary or a limited number of hyperplastic polyps underwent a surveillance endoscopy. Causes of this inadequate adherence to the guidelines may be caused by passive follow-up policies by most hospitals or related to the patients' lack of compliance. Our conclusion is that we should invest in a regional or even national surveillance strategy, including active invitation policy by the hospitals at the end of the follow-up interval, as well as by increasing patients' awareness.

Chapter 9 provides an overview of the main findings and conclusions. Furthermore, suggestions for future research are made.

SAMENVATTING

Het colorectaal carcinoom (CRC) is een belangrijk gezondheidsprobleem in de Westerse wereld. Het risico op het ontwikkelen van CRC gedurende het leven is ongeveer vijf procent. Het feit dat de meeste CRC voortvloeien uit premaligne voorlopers, de adenomateuze poliepen, biedt een unieke mogelijkheid om de incidentie en sterfte van CRC te verminderen door detectie en resectie van adenomen. Verder, de detectie van CRC in een vroeg stadium kan de prognose en de darmkanker gerelateerde mortaliteit aanzienlijk verbeteren. Om deze redenen is er de laatste decennia veel belangstelling voor darmkanker screening. Dit proefschrift richt zich op verschillende aspecten van screening en follow-up van CRC en adenomen.

Hoofdstuk 1 geeft een overzicht van de epidemiologie en de risicofactoren van CRC. Verder wordt een aantal invasieve en niet-invasieve screeningsmethoden voor CRC en de richtlijnen voor follow-up na poliepectomie en resectie van CRC besproken. Aan het eind van het hoofdstuk worden de doelstellingen en de achtergrond van het proefschrift beschreven.

Patiënten met een sporadisch CRC hebben een risico op het ontwikkelen van multipele primaire CRCs. Het identificeren van patiënten met een verhoogd risico heeft belangrijke klinische implicaties, zoals een aangepast surveillance programma om metachrone CRC te voorkomen. In **hoofdstuk 2** worden de prevalentie en risicofactoren van synchrone CRC bestudeerd op basis van gegevens uit het Integraal Kanker Centrum in Rotterdam. In deze studie onder 13 683 patiënten met sporadisch CRC in de periode 1995 tot 2006, presenteerde bijna 4% van de patiënten zich met een synchroon CRC. De multivariate analyse toonde een aantal risicofactoren voor het optreden van synchrone CRC, zoals het mannelijk geslacht, leeftijd boven de 70 jaar en lokalisatie in het colon. Er kon echter geen voorspellend model worden geconstrueerd op basis van deze risicofactoren. Een belangrijke bevinding was dat een derde van de synchrone CRCs gelokaliseerd waren in verschillende chirurgische darmsegmenten. Deze bevinding onderstreept het belang van het verrichten van een colonoscopie ten tijde van de diagnose, bij voorkeur voorafgaand aan een operatie, aangezien deze patiënten een uitgebreidere chirurgische ingreep of een (sub-)totale colectomie zullen moeten ondergaan.

In **hoofdstuk 3** beschrijven we de incidentie en risicofactoren van metachrone CRC. De cumulatieve incidentie van metachrone CRC was 1,1% na 3 jaar, 2,0% na 6 jaar en 3,1% na 10 jaar. Patiënten met een sporadisch CRC hadden een verhoogd risico op het ontwikkelen van een (tweede) primair CRC, vergeleken met het risico op het ontwikkelen van een CRC in de algemene bevolking (SIR 1,3). De aanwezigheid van een synchroon CRC bij eerste presentatie was de enige significante voorspeller voor dit toegenomen risico op een metachroon CRC.

Deze studie toont aan dat patiënten met een CRC een verhoogd risico hebben op het ontwikkelen van een metachroon CRC, vooral tijdens de eerste 3 jaar van follow-up, daarna afnemend tot het gemiddelde risico op CRC in vergelijking met de algemene bevolking. Metachrone CRCs gediagnosticeerd tijdens de eerste 3 jaar van de follow-up kunnen worden veroorzaakt door een agressief, snel groeiend CRC of doordat de colonoscopie ten tijde van

het eerste CRC niet adequaat is uitgevoerd. Dientengevolge kan mogelijk een deel van de metachrone CRCs die gedurende de eerste 3 jaar van follow-up optreden worden beschouwd als een gemiste, synchrone laesies. Verdere verklaring voor het vroeg optreden van deze metachrone CRCs moet worden onderzocht.

Een aantal invasieve en niet-invasieve screening methoden zijn beschreven. Om de huidige incidentie van colorectale onderzoeken (colonoscopie, sigmoïdoscopie en coloninloopfoto) te onderzoeken in een populatie waarin screening op darmkanker nog niet is ingevoerd, hebben we een studie verricht in een grote eerstelijns-populatie in Nederland met behulp van de IPCI database (**hoofdstuk 4**). We lieten zien dat 4,3% van de totale populatie en 3,7% van de populatie tussen 50 en 75 jaar een darmonderzoek had ondergaan in een gemiddelde follow-up periode van bijna 3 jaar.

Om het effect van de darmonderzoeken op het CRC risico in te kunnen schatten, vergeleken we de blootstelling aan deze onderzoeken in een populatie van 594 CRC patiënten en een gematchte controle groep van 7790 personen in een periode van maximaal 5 jaar voorafgaand aan de diagnose. In totaal had 2,9% van de patiënten met CRC een darmonderzoek ondergaan in de 5 jaar voorafgaand aan de CRC diagnose, vergeleken met 4,4% in de controle groep, hetgeen de hypothese ondersteunt dat darmonderzoeken een preventief effect hebben op het ontwikkelen van CRC. Dit preventieve effect werd alleen gezien bij patiënten gediagnosticeerd met een linkszijdig CRC en niet bij patiënten met een rechtszijdig CRC, hetgeen een grotere impact van darmonderzoeken op de linkszijdig CRCs suggereert vergeleken met rechtszijdig CRCs. Waarom het effect van darmonderzoeken verschilt tussen links- en rechtszijdige CRCs zal verder moeten worden onderzocht.

In **hoofdstuk 5** brengen we het risico op het hebben van een proximaal CRC in kaart en zijn subgroepen geïdentificeerd waarin sigmoïdoscopie een goede screening methode zou kunnen zijn in plaats van colonoscopie, gebaseerd op het risico profiel voor (proximale) hoogrisico neoplasieën. In de Endobase database werden alle patiënten geselecteerd die gediagnosticeerd waren met CRC (n=783) tijdens de periode 1997-2005. Deze studie liet zien dat het aantal proximale CRCs toenam met de leeftijd (27% <65 jaar versus 41%> 65 jaar) en vaker optrad zonder synchrone distale adenomen. Beneden de 65 jaar zou 78% van alle CRC kunnen worden gediagnosticeerd middels een sigmoïdoscopie, gevolgd door een colonoscopie bij aanwezigheid van het distale adenomen, in vergelijking met slechts 65% in de populatie boven de 65 jaar. In deze oudere populatie werden significant meer CRCs gemist bij vrouwen dan bij mannen bij het gebruik van een sigmoidoscopie (42% versus 28% respectievelijk), dit verschil tussen mannen en vrouwen werd niet gezien in de populatie beneden de 65 jaar.

In **hoofdstuk 6** wordt de accuratesse van de faeces tumor pyruvaat kinase iso-enzym type M2 (TuM2-PK) test vergeleken met twee soorten van immunochemische faeces occult bloed testen (FIT) (Immo-care en OC-Light) bij patiënten gediagnosticeerd met CRC (n=52) of adenomen (n=47). Ook patiënten met inflammatoire darmziekten (IBD) werden getest om de

kanker-specificiteit van de TuM2-PK test te evalueren. De FITs lieten een hogere sensitiviteit en specificiteit zien bij patiënten met CRC en hoogrisico adenomen dan de TuM2-PK-test. Verwacht werd dat de TuM2-PK-test sterk kanker-specifiek zou zijn, echter bij bijna 80% van de patiënten met IBD was de TuM2-PK test positief. We concluderen dat de TuM2-PK-test geen aanvullende waarde heeft ten opzichte van de FIT voor de detectie van CRC en adenomen.

Omdat de effectiviteit van follow-up na poliepectomie grotendeels afhangt van de naleving van de richtlijnen, werd een nationale enquête uitgevoerd onder de Nederlandse MDL-artsen (**hoofdstuk 7**). Uit de enquête bleek dat de Nederlandse MDL-artsen, in tegenstelling tot hetgeen wordt geadviseerd in de richtlijnen, vaak de grootte en histologie van de initiële adenomen meenemen bij het bepalen van het follow-up interval, hetgeen geregeld leidt tot een verkorting van de follow-up intervallen. In patiënt casus waarin de richtlijnen een interval van zes jaar aanbevolen, adviseerde 27% tot 78% van de respondenten een korter follow-up interval. Deze studie concludeert dat MDL-artsen zich bewust moeten zijn van het feit dat de richtlijnen niet afdoende worden nageleefd, aangezien de impact van follow-up grotendeels afhangt van de naleving hiervan. Bovendien, het aantal surveillance endoscopieën zal toenemen ten gevolge van de screening op darmkanker, hetgeen nog meer zal toenemen door een inadequaat follow-up beleid en een zware druk zal geven op de reeds beperkte endoscopie capaciteit.

In **hoofdstuk 8** wordt de opkomst van patiënten bij surveillance endoscopieën geëvalueerd in de praktijk, gebaseerd op gegevens van de endoscopie database van Endobase. We lieten zien dat de meerderheid van de patiënten de follow-up endoscopieën niet volgens de richtlijnen onderging. Slechts 27% van de patiënten gediagnosticeerd met adenomen onderging een follow-up endoscopie binnen de aanbevolen periode, een derde onderging follow-up na een langer interval en 35% onderging helemaal geen follow-up. Overbehandeling werd ook waargenomen, aangezien 31% van de patiënten met een enkele of een klein aantal hyperplastische poliepen een surveillance endoscopie onderging. Oorzaken van deze gebrekkige naleving van de richtlijnen zou kunnen worden veroorzaakt door passief follow-up beleid door de meeste ziekenhuizen of door nalatigheid van patiënten zelf. De conclusie van deze studie is dat we moeten investeren in een regionaal of zelfs nationaal follow-up beleid, bijvoorbeeld een actief uitnodigingsbeleid door het ziekenhuis ten tijde van het verstrijken van het follow-up interval, alsmede door betere voorlichting aan patiënten.

Hoofdstuk 9 geeft een overzicht van de belangrijkste bevindingen en conclusies van alle hoofdstukken, alsmede suggesties voor toekomstig onderzoek.

DANKWOORD

En dan, het dankwoord. Het laatst geschreven en het meest gelezen. Aangezien dit proefschrift met behulp van vele mensen op directe of indirecte wijze tot stand is gekomen, wil ik graag van de gelegenheid gebruik maken om een aantal mensen te bedanken.

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Een belangrijke rol in het tot stand komen van dit proefschift heeft Endobase gespeeld. Om te beginnen waren de Endobase werkzaamheden initieel de belangrijkste dagelijkse bezigheid, ook zijn enkele artikelen gebaseerd op de endoscopie database. Mijn twee voorgangers hebben me wegwijs gemaakt in Endobase. Beste Ram, bedankt voor je hulp bij de inwijding van de ins en outs van de 'computer' en Endobase: Er ging een wereld voor me open! Ik moest me in het begin even aanpassen aan je Surinaamse kwartiertje en relaxedheid, maar de samenwerking liep altijd soepel. Beste Marcel, jij ook bedankt voor je de gezellige uurtjes achter de computer in het kleine kamertje! Ook Gerard van der Hoorn en de andere 'Olympus

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CURRICULUM VITAE

Sanna Mulder werd op 13 mei 1977 geboren in Lijdenburg, Zuid-Afrika. In 1995 behaalde zij cum laude het eindexamen Gymnasium aan Het Drachtster Lyceum in Drachten. In hetzelfde jaar ging zij geneeskunde studeren aan de Rijksuniversiteit in Groningen. In 1999 vertrok zij voor een uitgebreide wetenschappelijk stage naar Zuid Afrika, waar ze onderzoek deed naar Schistosomiasis en de ernst van leverziekten en voedingsstatus (prof. C.H. Gips en prof. van der Merwe, GISH-T).

De co-schappen heeft zij gelopen in het Martini Ziekenhuis te Groningen. Na het behalen van het arts-examen werkte zij van mei 2002 tot december 2003 als poortarts op de spoedeisende hulp van 'Nij Smellinghe' te Drachten.

In januari 2004 startte zij in het Ikazia Ziekenhuis te Rotterdam als fellow van de Trans-IT werkgroep bij dr. R.J.Th. Ouwendijk. Hiernaast startte ze met het promotie onderzoek onder begeleiding van haar promotor prof. dr. E.J. Kuipers en haar co-promotoren dr. R.J.Th. Ouwendijk en dr. M.E. van Leerdam.

Van december 2006 tot september 2008 deed zij haar vooropleiding Interne Geneeskunde (opleider: Dr. A. Dees) in het Ikazia Ziekenhuis te Rotterdam. Vanaf september 2008 tot heden vervolgt zij haar opleiding tot maag-, darm-, en leverarts in het Erasmus Medisch Centrum te Rotterdam (opleider: Dr R.A. de Man en afdelingshoofd: Prof. dr. E.J. Kuipers).