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Review

Population screening for colorectal cancer: Faeces, endoscopes or X-rays?

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Abstract. Colorectal carcinoma (CRC) is a common cancer and the second most common cause of death. The therapeutic costs for this disease will continue to rise due to an increasing incidence and the introduction of new chemotherapeutic modalities. Colorectal carcinoma is preceded by precursor lesions, which can be used as a target for early detection and therapy. Biennial population screening with faecal occult blood tests (FOBT) lowers CRC mortality with 14–18%. Five year screening with flexible sigmoidoscopy is a cost-effective alternative, which yields a higher preventive effect when similar participation rates are achieved. Screening colonoscopy has the advantage of examination of the complete colon but disadvantages are the high participant burden and the higher demand for endoscopic personnel and endoscopy units. Future screening modalities like faecal DNA markers and CT colonography are promising but need further improvement. In Europe, faecal occult blood testing and flexible sigmoidoscopy are currently the most suitable screening modalities for colorectal cancer screening.

Keywords: Colorectal cancer screening, screening methods, faecal DNA analysis, participation

1. Introduction

Colorectal cancer (CRC) is a major health problem and the second most common cause of death from cancer in most Western countries. Screening can detect precursor lesions and early cancers, which reduces CRC incidence and mortality. For this reason, many European countries are developing colorectal cancer screening programmes. The most common screening methods being evaluated are faecal occult blood testing, flexible sigmoidoscopy and colonoscopy. The implementation of CRC screening programmes are being hampered by participation rates, costs, invasiveness of the screening method and the availability of health care resources. This paper will discuss the effectiveness, advantages and disadvantages of the available screening methods. Furthermore, the participation rate, costs and future perspectives of CRC screening programmes will be discussed.

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2. Colorectal carcinoma and screening

In Europe, colorectal cancer is the second most common form of cancer and a major cause of cancer mortality. In 2004 there were more than 375,000 new cases diagnosed and 203,000 deaths; corresponding figures for the Netherlands are 10,000 cases and 4300 deaths [12,69]. In the next years the incidence of CRC will keep rising, primarily due to an ageing population.

Detection of CRC at an early stage considerably improves prognosis. The 5 year survival rates of localised CRC (Dukes'stage A or B) are 82–93% while the 5 year survival rate of metastatic disease (Dukes'stage D) is less than ten percent [45]. Current combination schemes for adjuvant and palliative treatment of CRC result in an improvement of survival but are also associated with tremendous costs [52]. In the recent past, the therapeutic options for patients with metastatic dis-

ease due to CRC were very limited, and thus the average treatment costs for these patients were in the order of € 4000. Nowadays, there are more therapeutic options available. The mean survival of untreated patients with metastatic disease is approximately 6 months and combined chemotherapy with Fluoracil and Leucovorin can result in a prolonged mean survival of 10–12 months. The combination of Fluoracil with another chemotherapeutic agent like Irinotecan or Oxaliplatin prolongs the median survival to 14–16 months. Combining fluoracil with both Leucovorin and Irinotecan or Oxaliplatin results in an even more prolonged mean survival of 20 months or more. This survival rates has also been reported for the combination of Fluoracil with new target therapies like epidermal growth factor antagonists (Bevazicumab). However, treatment with new chemotherapeutic agents as well as surgical treatment of metastases can be associated with costs of € 150,000 or more [52].

The removal of adenomatous polyps, a non-malignant precursor of CRC, can prevent the disease and thus result in a lower incidence of CRC [59,70]. The high incidence and mortality, the ability to identify precursors, improved prognosis at early detection and the fact that removal of polyps lowers the incidence of CRC necessitate research into the feasibility and yield of CRC screening in the European Community. In the Netherlands, the importance of a CRC screening programme was long doubted [2,9,20,64]. Recently, a pilot study evaluating the participation rate of two different FOBT screening programmes has started as a combined initiative of the academic centers in Amsterdam and Nijmegen. Furthermore, a second feasibility and implementation study is being performed in the Rotterdam region, where 15,000 inhabitants in the age of 50–74 will be randomised for screening with either FOBT or flexible sigmoidoscopy. A third pilot study has started in the region of Maastricht. This study will evaluate the costs and results of screening with FOBT, colonoscopy and additional DNA and/or protein analysis of blood samples. Screening will be offered to a selected group of 3500 employees aged 50–65 years. These studies will form an important basis for the decision on implementation of CRC screening in the Netherlands.

Other European countries have already started a CRC screening programme, using different screening methods. In Germany colonoscopy and FOBT are used as screening method, while in Northern Italy screening is performed with flexible sigmoidoscopy [8,54]. In Finland, France and the United Kingdom, CRC screening is performed with guaiac FOBT [4]. In the United States, CRC screening is currently predominantly performed with colonoscopy, but CT-colonography has been introduced as an alternative and its use is rapidly increasing.

3. Screening methods

3.1. Faecal occult blood testing

Randomized trials have shown that biennial guaiac FOBT screening results in a 14–18% reduction of mortality due to CRC [25,28,33,40]. The guaiac FOBT detects the peroxidase activity of haemoglobin, indicating the presence of blood in the stool. Major advantages of the guaiac FOBT screening are the low costs, the simplicity and the possibility to perform the test at home at any time. The participant only needs to collect some faeces for further analysis.

However, screening with guaiac FOBT has important limitations. Firstly, the guaiac FOBT has a poor sensitivity of 24–50% for the detection of advanced neoplasia [7,38,65]. These lesions are defined as adenomas with a diameter of $\geqslant$10 mm, or with villous histology, high-grade dysplasia, or cancer.

The poor sensitivity of the guaiac FOBT is caused by its limitation of detecting only bleeding neoplasia, while non-bleeding lesions are missed. This means that most precursors of CRC will not be detected and FOBT screening is not expected to lead to a reduction of the incidence of CRC.

In an average elderly Western population, a positive guaiac FOBT is encountered in 2–5% of the participants in a screening programme (Table 1) [28,33,71]. When these subjects are subsequently investigated by colonoscopy, advanced neoplasia is detected in 50% of them. In the remaining subjects no lesions are detected, and the guaiac FOBT is considered false positive. Contrariwise, 4.5–8.5% of subjects in the age of 50–79 years with a negative family history for CRC and a negative guaiac FOBT nevertheless have advanced colonic neoplasia [50].

Despite these considerable rates of false-positives and -negatives, guaiac FOBT screening is in most European countries considered as the mainstay for CRC screening because of its proven efficacy for mortality reduction where similar results of screening with other methods is still awaited. However, the low sensitivity of the guaiac FOBT and the resulting limited effect on CRC incidence and mortality request for a more sensi-

Table 1
Test characteristics of a FOBT & flexible sigmoidoscopy CRC screening programme

	Guaiac (Haemoccult II)	Immunochemical (OC Hemodia Latex)	Flexible sigmoidoscopy
Screening interval	biennial	biennial	once-only*
Positive test result	2%	5%	5–8%
PPV	50%	40%	72%§
Diagnostic yield**	1%	2%	6%
Participation	25–70%	25–70%†	28%
Proven effectiveness	yes	yes	yes
Evidence	RCT	extrapolation Guaiac FOBT	case control studies
Mortality reduction	14–18%	?§§	?

PPV = positive predictive value, RCT = randomised controlled trial.
* Based on data of the running randomised clinical trials with flexible sigmoidoscopy [3,55].
§ Based on data of Segnan et al. [54] and Lieberman et al. [38].
** Proportion of the screened population in which an advanced neoplasia is detected.
† Estimated participation, based on the data of the randomised controlled trials with guaiac FOBT.
§§ Data concerning the mortality reduction of an immunochemical FOBT are lacking. Given the higher diagnostic yield in comparison with the guaiac FOBT it is expected that the mortality reduction will be higher than 14–18%.

tive and specific test, with a sufficient level of acceptability and cost effectiveness.

One alternative is screening by means of an immunochemical FOBT test. Immunochemical FOBT tests use antibodies specific for human haemoglobin and therefore do not require any dietary restrictions. Studies comparing guaiac based and immunochemical FOBT tests estimated a higher sensitivity (68–82%) and specificity (97%) for immunochemical test for the detection of colorectal neoplasia [7,65,71].

A limitation of these studies was that not all patients with a positive test result underwent colonoscopy. In a recent Japanese study the sensitivity and specificity of one time immunochemical FOBT tests for colorectal neoplasia was evaluated more accurately, since every subject underwent colonoscopy regardless of the test result [41]. The sensitivity for one time immunochemical FOBT testing was 65.8% and the sensitivity was better for the detection of Dukes' stages C–D (78.3%) compared with Dukes' A (52%) or B (70%) and large adenoma (20%).

The specificity of the immunochemical FOBT was 95% for advanced neoplasia.

Another Japanese study evaluated one, two and three day immunochemical FOBT testing [43]. The sensitivity reported in this study was 56% for one day testing, which increased with 2-day (83%) and 3-day (89%) testing. The specificity was 97% for the one day testing method and decreased to 94% for the three-day testing method.

Many CRC screening programmes are using guaiac based FOBT, because the impact of faecal immunochemical testing on CRC incidence and mortality has not been evaluated in prospective randomized controlled trials. Another factor that is limiting the replacement of guaiac FOBT is the higher cost of immunochemical FOBT. However, based on the available literature, faecal immunochemical testing appears an appropriate and acceptable alternative to guaiac based FOBT.

3.2. Endoscopic screening

The sensitivity of endoscopic screening for the detection of advanced neoplasia is higher compared to FOBT. Endoscopic screening also enables the detection and removal of adenomatous polyps, resulting in the additional benefit of providing a tissue diagnosis and offering therapy by means of polypectomy. It is expected that screening with colonoscopy or flexible sigmoidoscopy will lead to a greater reduction in the incidence and mortality of CRC compared to screening with FOBT. However, the specificity of endoscopic screening in terms of cancer prevention is low, since only a minority of the detected adenomatous polyps will eventually progress to colorectal cancer [59].

Furthermore, a potential drawback of endoscopic screening is the possibility of missing flat adenomas or depressed tumours, since these lesions are not always visible by endoscopy [67]. The further development of new endoscopic techniques such as high magnification endoscopy, autofluorescence endoscopy and narrow band imaging should reduce this problem.

3.2.1. Flexible sigmoidoscopy

Almost two thirds of CRC occur in the distal colon and are therefore detectable with flexible sigmoidoscopy. Lesions proximal to the splenic flexure are missed with sigmoidoscopy, unless these are associated with the presence of advanced distal adenomas, as these lesions are considered an indication for further colonoscopy.

Performing flexible sigmoidoscopy in the above mentioned strategy allows detection of 75–85% of CRC cases in men and 45–55% in women [10,37,50].

A few studies have reported a preventive effect of flexible sigmoidoscopy screening [42,44,56]. In a retrospective case control study 261 case subjects with CRC were compared with 868 age and sex matched control subjects [56]. Patients diagnosed with distal CRC were much less likely to have undergone a sigmoidoscopy in the prior ten years compared to matched controls. The investigators estimated that a screening programme using flexible sigmoidoscopy could lead to a reduction of at least 30% in total mortality from colorectal cancer. This effect is likely based on the larger amount and earlier stage of lesions detected with sigmoidoscopy in comparison with FOBT. A recent Italian study reported a three times higher detection rate for advanced neoplasia following screening by flexible sigmoidoscopy than by immunochemical FOBT (Table 1) [54].

The effectiveness of flexible sigmoidoscopy screening on the mortality reduction of CRC has never been demonstrated in randomized controlled trials. However, two large prospective trials are ongoing in Italy and the United Kingdom. The preliminary results of these studies demonstrate that flexible sigmoidoscopy screening is feasible, safe and has a high diagnostic yield. The first results on mortality are due to be published in 2007.

Flexible sigmoidoscopy is potentially limited by the inability to detect right-sided neoplasia. In an American study 23 of the 1564 (1.5%) asymptomatic patients had advanced proximal neoplasia without the presence of distal lesions [31]. Screening in an asymptomatic veteran population (Veterans Affair (VA) Cooperative Study 380) showed that 2.7% of asymptomatic patients had advanced proximal neoplasia without pathology in the distal colon [37]. Fifty-two to 62% of patients with advanced proximal neoplasia in these two studies would not have been referred for colonoscopy if screening sigmoidoscopy was performed. In females CRC are relatively more often located in the right side of the colon compared to males. This could result in less detected CRC by flexible sigmoidoscopy in females. A recent trial suggested that colonoscopy is therefore the preferred method of screening women [50]. This trial examined the yield of screening colonoscopy in 1463 women. The investigators reported that if flexible sigmoidoscopy alone had been performed, advanced neoplasia would have been detected in 1.7% of women (25 of 1463) and missed in 3.2% (47 of 1463). A possible explanation for this finding is that women tend to have more advanced proximal neoplasia and fewer distal lesions indicating colonoscopy. Colorectal cancer is more frequent in men than in women, which means that the number of missed cancers per 100 screened males and females will likely be fairly similar [12].

The referral rate for colonoscopy in a flexible sigmoidoscopy screening programme is determined by the strategy and by the age distribution of the screened population. The most common strategy is referral for colonoscopy of subjects with advanced neoplasia, or with three or more adenomas [3,55]. However, there is no consensus about who to send for colonoscopy based on the flexible sigmoidoscopy findings. The presence of advanced distal neoplasia is clearly associated with a higher risk of advanced neoplasia in the proximal colon. The presence of one or two small distal tubular adenoma (<1 cm) is associated with at most a slighter increased risk of proximal lesions, because in previous studies such an increase has not been found [35,49,51].

Referral rates for colonoscopy would be approximately five percent if referral is restricted to those with three of more adenomas or advanced neoplasia and increases to 12.5% if all persons with at least one adenoma are referred for colonoscopy [26,31,55].

In order to obtain the most optimal strategy further validation of referral criteria is needed.

Endoscopic screening is an invasive investigation and carries the risk of complications. However, the complication rate of flexible sigmoidoscopy is low (0.002–0.009%) [3,34,55].

3.2.2. Colonoscopy

In a few countries, in particular the United States and Germany, CRC screening is performed with colonoscopy. The major advantage of colonoscopy is that it allows examination of the complete colon, thus ensuring a maximum detection rate of advanced lesions.

A few studies have demonstrated that colonoscopy is superior to a screening programme consisting of flexible sigmoidoscopy, for the detection of proximal neoplasia [10,37,50]. It has been suggested that screening with colonoscopy would result in 76–90% reduction in

cancer incidence [70]. Colonoscopy however is more demanding for individuals undergoing the procedure, requires more endoscopic facilities and costs and carries a risk of serious complications.

The complication rate of screening colonoscopy was evaluated in a cohort of 3196 asymptomatic patients from 13 US Veterans Affairs Medical Centers [37]. Major complications (in particular lower gastrointestinal bleeding, myocardial infarction, cerebrovascular accident or thrombophlebitis) occurred in 0.3% of all procedures. No perforations were reported. One death was observed two days following a colonoscopy, but this was considered unrelated to the procedure.

Both colonoscopy and flexible sigmoidoscopy can be employed for endoscopic screening programmes. However, colonoscopy has a lower additional value than flexible sigmoidoscopy in terms of costs and time benefits, assuming that the procedure of flexible sigmoidoscopy requires half the time and far less day-care admissions than colonoscopy, and that in particular in men the majority of the advanced lesions are located in the distal colon.

Flexible sigmoidoscopy is at present judged more suitable for population screening than colonoscopy, because it is safer, quicker, and more convenient.

4. Future developments

4.1. Faecal DNA markers

In recent years much advances have been made in understanding the molecular pathology involved in the development of CRC. These advances have led to the development of screening techniques based on detection of colonocyte DNA in faeces. DNA of sheded cells can be detected in faeces and can be amplified with the use of PCR technology for further analysis. Current technical challenges for DNA tests are the degradation of DNA in stool and the potential presence of PCR inhibitors, such as bile and food components.

The DNA changes found are mostly tumour-derived mutations in suppressor genes and oncogenes like KRAS, APC and tP53 genes. Mutations in these genes can be used as markers for faecal DNA analysis [18]. KRAS mutations can be identified in the stool of patients with curable CRC [57]. A previous study reported the presence of the ras mutation in 8 of 9 patients with curable CRC. An American study evaluated the use of multiple genetic targets (tp53, BAT26 and K-RAS) to detect CRC in stool [23]. Analysis was performed on stool samples of 51 patients with CRC, including 39 patients whose tumour had a mutation at any of the three target genes. The use of multiple genetic targets detected stool DNA mutations in 36 patients (71%) and all these DNA mutations were detected in the 39 patients with a known gene alteration. Another American study evaluated the feasibility of detecting APC mutations in faecal DNA [62]. Stool samples of 28 patients with non-metastatic CRC, 18 patients with adenomas sized $\geqslant$1 cm and 28 controls without neoplastic lesions were evaluated. APC mutations were detected in 17 patients with CRC and 9 patients with an adenoma, while no mutations were identified in the 28 control patients. The results of this study suggested that APC mutations are detectable in faecal DNA from patients with non-metastatic CRC.

Microsatellite instability (MSI) and hypermethylated DNA markers are also useful in faecal DNA analysis. The term microsatellite instability refers to the expansion and contraction of short repeated DNA sequences that are caused by insertion of deletion of repeated units. MSI can be detected in 15% of sporadic CRC where MSI is typically due to methylation of the promotor region of the MLH1 gene, an epigenetic mechanism of gene silencing. The most frequently used marker of MSI is BAT 26. An American study evaluate the use of a BAT26 faecal test in stool samples of 46 patients with proximal CRC, 19 patients with proximal adenomas and 69 patients without neoplasia [63]. The BAT 26 faecal test identified 17 of 46 patients with CRC as positive, corresponding with a sensitivity of 37%. The specificity of the BAT 26 faecal test was 100%.

An important early defect in oncogenesis is an imbalance in cytosine methylation, with hypermethylation of CpG islands and genome hypomethylation [32]. Promotor hypermethylation of multiple genes has been reported to occur early in colorectal carcinogenesis [22,39]. Detection of hypermethylated DNA markers in stool can be helpful for the identification of patients with CRC. A simple but effective laboratory test exists to detect promotor hypermethylation in multiple types of specimens, including stool derived DNA [21].

Another approach to faecal DNA analysis is the detection of long DNA. Colorectal neoplasms (CRC and adenomas) exfoliate non-apoptotic colonocytes while normal colonic mucosa exfoliate apoptotic colonocytes [11]. The non-apoptotic colonocytes will contain long, intact strands of DNA while apoptotic colonocytes will contain fragmented DNA. The presence of long DNA in faeces may allow the identification of pa-

tients with CRC. In a recent American study the presence of long DNA was identified in 15 of 27 (56%) patients with CRC, compared to 2 of 77 (3%) controls [13].

Several small studies have assessed the sensitivity and specificity of DNA stool markers. A pilot study evaluating 33 tumours reported a sensitivity of 91% and a specificity of 93% for CRC. The reported sensitivity for advanced adenomas was 82% [6]. However, other subsequent prospective studies have reported a lower sensitivity ranging from 52 to 63% and a specificity ranging from 94 to 97% for CRC [15,30, 61].

The major advantage of faecal DNA marker tests is, similar to FOBT, the simplicity and the possibility to sample material for the test at home at any time. However, the impact of faecal DNA markers on CRC incidence and mortality has yet to be proven. Furthermore, faecal DNA markers have a few limitations which yet prevent their widespread use for primary screening.

The genetic heterogeneity of CRC has until now made it impossible to identify one single mutation that is expressed uniformly across all colorectal neoplasia. Faecal DNA markers therefore need to target multiple DNA mutations in a range of genes. The use of such a panel is essential for the improvement of detection rates and reduction of the number of false positives. Another limitation of faecal DNA markers is that DNA analyses from faeces is labour-intensive and costly, DNA has to be extracted from faeces and must be amplified for mutation analysis. The current DNA assays costs between $500–$800, while the guaiac and immunochemical FOBT costs between $5 and $30. The high costs relate to the multiple assays that are required in each test and the need to isolate DNA from faeces.

At this moment, faecal DNA markers are not suitable for CRC screening because of the low sensitivity, the lack of a uniform DNA mutation panel and the high costs. However, lowering costs by the use of one or two markers instead of a whole panel could make this technique suitable for the future if this would not strongly impair sensitivity of the test in the general population.

4.2. Proteomics

Proteomics focuses on the characterization of a large spectrum of proteins in body fluids, cells or tumours. Currently, two tests based on protein analysis in blood are available, namely carcinoembryonic antigen (CEA) and the gastrointestinal cancer related antigen (CA19-9). These tests are used in clinical practice to monitor therapy, however these markers are not useful for CRC screening because of their low test specificity.

Developments in the mass spectrometry have made it possible to simultaneously measure a large number of proteins with high accuracy and to identify every single protein. This enables the differentiation between different tumour types, normal and malignant cells and different tumour stages. Proteomics have already been used to define protein profiles for other tumour types such as ovary, prostate and breast cancer [5,36,46]. For CRC, proteomics could be used to identify protein profiles in both blood and faecal samples. Faecal samples contain large amounts of colorectal cancer cells but also other proteins. Thus it will be necessary to purificate faecal samples before proteomics testing is performed. Until now, few protein profiling studies on the detection of CRC have been performed in small study populations [19,24]. In these studies protein profiling was performed on serum samples of CRC patients with mainly metastatic disease. The reported sensitivity for CRC ranged from 65–95% and the specificity ranged from 70–90%. The use of proteomics for CRC screening is still in its infancy and more research is needed before this method can be used for the detection of (pre)cancerous lesions.

4.3. CT colonography

CT colonography is a quick, non-invasive method in which CT images of the colon are obtained after inflating the colon with air or carbon dioxide [60]. Assessment of the CT images can be done in a two-dimensional view or in a three-dimensional view, in the latter a moving picture is created and this can be assessed like a colonoscopy.

A study evaluating the performance of CT colonography in an asymptomatic population reported a sensitivity of 92% (95% confidence interval: 81.1–97.8%) and a specificity of 88% (95% confidence interval 76.1–95.6%) for the detection of adenomas $\geqslant$10 mm in size [47]. Another study evaluating an asymptomatic population reported a sensitivity of 89% for adenomas $\geqslant$10 mm [60].

However, the sensitivity and specificity for small adenomatous polyps ($<$5 mm) is very low and CT colonography does not ensure adequate detection of flat adenomas.

Just as for colonoscopy, the currently used protocols for CT colonography require bowel preparation, which is a burden for participants and can influence participation rates. Methods of faecal tagging are being studied,

this would make a bowel preparation unnecessary [16]. Faecal tagging is the per oral ingestion of contrast material (barium and/or iodinated contrast) prior to CT colonography to label or tag faecal residue remaining in the colon after preparation. As a consequence polyps are recognized as they are not labelled or appear as negative filling defects in tagged fluid. Another disadvantage of CT colonography is the exposure of participants to radiation, which in conventional protocols amounts to significant levels. Studies into the use of low-dose radiation colonography are being performed and suggest that reduction of the radiation dose for the detection of polyps $\geqslant$5 mm dose reduction is feasible [66]. The risk that a 50 year old person develops a fatal malignancy due to CT colonography with current methods has been calculated to be one in 5000 [1, 58].

Other disadvantages of CT colonography are the fact that the method is subject to considerable inter-observer bias and the fact that CT colonography allows detection of extracolonic lesions. Furthermore, CT colonography is in contrast to colonoscopy a diagnostic tool only, which means that when a colonic lesion is detected persons still have to undergo a colonoscopy to remove the lesion.

Further improvement of the sensitivity, a reduction of the radiation doses and scanning without cathartic preparation are needed to make CT colonography a suitable screening method.

5. Cost effectiveness

The costs of a CRC screening programme are related to the screening method, the frequency of screening (once-only or repeated screening), the screening location (screening center or hospital), the background of the screening personnel (GI specialist or nurse endoscopist) and the selection criteria for referral.

In the last 5–10 years, several models including Markov and micro-simulation models have been used to evaluate the effectiveness and cost effectiveness of different screening modalities for CRC screening. A systematic review of these different models reported that colonoscopy screening every 10 years or the combination of FOBT annually and flexible sigmoidoscopy every 5 years was found to be the most effective [48].

The efficacy of annual FOBT alone and flexible sigmoidoscopy every 5 years alone appeared to be similar. The costs of these screening strategies were between the $10,000 to $25,000 per year of life saved. This systematic review also reported that not a single testing method proved to be superior to the others in terms of cost effectiveness. This finding suggests that all current FOBT and endoscopic methods of CRC screening are effective compared to no screening at all.

6. Participation

The success of a screening programme depends on the participation rate of the asymptomatic population. Higher participation rates will increase the cost effectiveness of a screening programme. Several European studies have reported different participation rates of guaiac based FOBT screening programmes. The European randomized controlled trials that evaluated the effect of guaiac FOBT screening reported participation rates ranging from 52% (France) to 67% (Denmark) [25,28,33]. A British study assessing the feasibility of a guaiac FOBT screening programme reported a participation rate of 57%.

In an Italian feasibility study of CRC screening by immunochemical FOBT 2961 subjects were invited and 1631 subjects (55%) participated [17]. However, the first round results of the immunochemical FOBT screening programme in the region of Tuscan showed lower participation rates of 41% [27].

The participation rate of flexible sigmoidoscopy screening programmes also show various results. In the UK flexible sigmoidoscopy screening trial, subjects were asked about their interest in participating in a CRC screening programme and 55% responded positive. Thereafter, eligible subjects were randomised to undergo either flexible sigmoidoscopy or no screening. Seventy-one percent of those randomized for flexible sigmoidoscopy actually participated leading to an overall participation rate of 39% [3].

In the Italian flexible sigmoidoscopy trial 26% of eligible subjects attended flexible sigmoidoscopy [55]. In a Norwegian population of 799 subjects between 50–59 years of age, 80% participated in a flexible sigmoidoscopy program [29].

European studies comparing participation rates of both FOBT and flexible sigmoidoscopy screening also show different results. In a Swedish population of 6376 persons between 55–56 years of age 59% participated in FOBT-screening compared to 49% to flexible sigmoidoscopy screening [14]. In a British study in 3744 subjects between 50–75 years, 47% participated in flexible sigmoidoscopy screening compared to 32% in FOBT-screening and 30% in the combined screen-

ing with flexible sigmoidoscopy screening and FOBT. Telephone reminders increased the participation rate in the flexible sigmoidoscopy group to 62% [68].

Randomised studies in Northern-Italy have shown no difference in participation rates to flexible sigmoidoscopy screening (28%) and an immunochemical FOBT screening (28%) [54].

The available European data suggest that participation in a colonoscopy screening programme may be lower than in FOBT or sigmoidoscopy screening. In an Italian study the participation rate in a colonoscopy screening programme was 22%, while in Germany the participation rate is 2% [8,53].

7. Conclusions

Colorectal carcinoma is a serious health problem in all European countries. New chemotherapeutic and surgical developments have led to an improved prognosis of patients with CRC, but the developments are accompanied with high therapeutic costs. Screening can offer a major health benefit for asymptomatic individuals. Current acceptable screening modalities include faecal occult blood testing, flexible sigmoidoscopy and colonoscopy. Participation rates of European CRC screening programmes are moderate, however screening appears to be more cost effective than no screening at all.

References

[1] 1990 Recommendations of the International Commission on Radiological Protection, *Ann. ICRP* **21** (1991), 1–201.

[2] Health Council of the Netherlands, Population screening for colorectal cancer, The Hague (2001), publication no. 2001-01. 2001.

[3] Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial, *Lancet* **359** (2002), 1291–1300.

[4] UK Colorectal Cancer Screening Pilot Group, Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom, *BMJ* **329** (2004), 133.

[5] B.L. Adam, Y. Qu, J.W. Davis, M.D. Ward, M.A. Clements, L.H. Cazares, O.J. Semmes, P.F. Schellhammer, Y. Yasui, Z. Feng and G.L. Wright Jr., Serum protein fingerprinting coupled with a pattern-matching algorithm distinguishes prostate cancer from benign prostate hyperplasia and healthy men, *Cancer Res.* **62** (2002), 3609–3614.

[6] D.A. Ahlquist, J.E. Skoletsky, K.A. Boynton, J.J. Harrington, D.W. Mahoney, W.E. Pierceall, S.N. Thibodeau and A.P. Shuber, Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel, *Gastroenterology* **119** (2000), 1219–1227.

[7] J.E. Allison, I.S. Tekawa, L.J. Ransom and A.L. Adrain, A comparison of fecal occult-blood tests for colorectal-cancer screening, *N. Engl. J. Med.* **334** (1996), 155–159.

[8] L. Altenhofen, J. Knoepnadel, W. Schmiegel, G. Brenner and M. Classen, Acceptance and findings of the first nationwide screening colonoscopy round in Germany, *Gastroenterology* **128** (2005), A96.

[9] KWF kankerbestrijding (Signaleringscommissie Kanker): *Vroege opsporing van dikkedarmkanker; minder sterfte door bevolkingsonderzoek (Early detection of colorectal cancer; reduction in mortality by population based screening)*. Amsterdam, The Dutch Cancer Society (Signalling Committee Cancer), 2004. ISBN: 90-71229-12-2.

[10] W.S. Atkin, J. Cuzick, J.M. Northover and D.K. Whynes, Prevention of colorectal cancer by once-only sigmoidoscopy, *Lancet* **341** (1993), 736–740.

[11] A. Bedi, P.J. Pasricha, A.J. Akhtar, J.P. Barber, G.C. Bedi, F.M. Giardiello, B.A. Zehnbauer, S.R. Hamilton and R.J. Jones, Inhibition of apoptosis during development of colorectal cancer, *Cancer Res.* **55** (1995), 1811–1816.

[12] P. Boyle and J. Ferlay, Cancer incidence and mortality in Europe, 2004, *Ann. Oncol.* **16** (2005), 481–488.

[13] K.A. Boynton, I.C. Summerhayes, D.A. Ahlquist and A.P. Shuber, DNA integrity as a potential marker for stool-based detection of colorectal cancer, *Clin. Chem.* **49** (2003), 1058–1065.

[14] H. Brevinge, E. Lindholm, S. Buntzen and J. Kewenter, Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55–56 years' old population, *Int. J. Colorectal Dis.* **12** (1997), 291–295.

[15] D. Calistri, C. Rengucci, R. Bocchini, L. Saragoni, W. Zoli and D. Amadori, Fecal multiple molecular tests to detect colorectal cancer in stool, *Clin. Gastroenterol. Hepatol.* **1** (2003), 377–383.

[16] M.R. Callstrom, C.D. Johnson, J.G. Fletcher, J.E. Reed, D.A. Ahlquist, W.S. Harmsen, K. Tait, L.A. Wilson and K.E. Corcoran, CT colonography without cathartic preparation: feasibility study, *Radiology* **219** (2001), 693–698.

[17] S. Crotta, G. Castiglione, G. Grazzini, F. Valle, S. Mosconi and R. Rosset, Feasibility study of colorectal cancer screening by immunochemical faecal occult blood testing: results in a northern Italian community, *Eur. J. Gastroenterol. Hepatol.* **16** (2004), 33–37.

[18] R.J. Davies, R. Miller and N. Coleman, Colorectal cancer screening: prospects for molecular stool analysis, *Nat. Rev. Cancer* **5** (2005), 199–209.

[19] M.E. de Noo, B.J. Mertens, A. Ozalp, M.R. Bladergroen, M.P. van der Werff, d.van, V, A.M. Deelder and R.A. Tollenaar, Detection of colorectal cancer using MALDI-TOF serum protein profiling, *Eur. J. Cancer* **42** (2006), 1068–1076.

[20] M. de Visser, M. van Ballegooijen, S.M. Bloemers, S.J. van Deventer, J.B. Jansen, J. Jespersen, C. Kluft, G.A. Meijer, J. Stoker, G.A. de Valk, M.F. Verweij and F.A. Vlems, Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT, *Cell. Oncol.* **27** (2005), 17–29.

[21] S. Derks, M.H. Lentjes, D.M. Hellebrekers, A.P. de Bruine, J.G. Herman and M. van Engeland, Methylation-specific PCR unraveled, *Cell. Oncol.* **26** (2004), 291–299.

[22] S. Derks, C. Postma, P.T.M. Moerkerk, S.M. van den Bosch, B. Carvalho, M.A.J.A. Hermsen, W. Giaretti, J.G. Herman, M.P. Weijenber, A.P. de Bruine, G.A. Meijer and M. van Engeland, Promoter methylation precedes chromosomal alterations in colorectal cancer development, *Cell. Oncol.* **5/6** (2006) (in press).

[23] S.M. Dong, G. Traverso, C. Johnson, L. Geng, R. Favis, K. Boynton, K. Hibi, S.N. Goodman, M.D'Allessio, P. Paty, S.R. Hamilton, D. Sidransky, F. Barany, B. Levin, A. Shuber, K.W. Kinzler, B. Vogelstein and J. Jen, Detecting colorectal cancer in stool with the use of multiple genetic targets, *J. Natl. Cancer Inst.* **93** (2001), 858–865.

[24] J.Y. Engwegen, H.H. Helgason, A. Cats, N. Harris, J.M. Bonfrer, J.H. Schellens and J.H. Beijnen, Identification of serum proteins discriminating colorectal cancer patients and healthy controls using surface-enhanced laser desorption ionisation-time of flight mass spectrometry, *World J. Gastroenterol.* **12** (2006), 1536–1544.

[25] J. Faivre, V. Dancourt, C. Lejeune, M.A. Tazi, J. Lamour, D. Gerard, F. Dassonville and C. Bonithon-Kopp, Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study, *Gastroenterology* **126** (2004), 1674–1680.

[26] G. Gondal, T. Grotmol, B. Hofstad, M. Bretthauer, T.J. Eide and G. Hoff, Grading of distal colorectal adenomas as predictors for proximal colonic neoplasia and choice of endoscope in population screening: experience from the Norwegian Colorectal Cancer Prevention study (NORCCAP), *Gut* **52** (2003), 398–403.

[27] G. Grazzini, G. Castiglione, C. Ciabattoni, F. Franceschini, D. Giorgi, S. Gozzi, P. Mantellini, P. Lopane, M. Perco, T. Rubeca, P. Salvadori, C.B. Visioli and M. Zappa, Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results, *Eur. J. Cancer Prev.* **13** (2004), 19–26.

[28] J.D. Hardcastle, J.O. Chamberlain, M.H. Robinson, S.M. Moss, S.S. Amar, T.W. Balfour, P.D. James and C.M. Mangham, Randomised controlled trial of faecal-occult-blood screening for colorectal cancer, *Lancet* **348** (1996), 1472–1477.

[29] G. Hoff, J. Sauar, M.H. Vatn, S. Larsen, F. Langmark, I.E. Moen, A. Foerster and E. Thiis-Evensen, Polypectomy of adenomas in the prevention of colorectal cancer: 10 years' follow-up of the Telemark Polyp Study I. A prospective, controlled population study, *Scand. J. Gastroenterol.* **31** (1996), 1006–1010.

[30] T.F. Imperiale, D.F. Ransohoff, S.H. Itzkowitz, B.A. Turnbull and M.E. Ross, Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population, *N. Engl. J. Med.* **351** (2004), 2704–2714.

[31] T.F. Imperiale, D.R. Wagner, C.Y. Lin, G.N. Larkin, J.D. Rogge and D.F. Ransohoff, Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings, *N. Engl. J. Med.* **343** (2000), 169–174.

[32] J.P. Issa, CpG island methylator phenotype in cancer, *Nat. Rev. Cancer* **4** (2004), 988–993.

[33] O. Kronborg, C. Fenger, J. Olsen, O.D. Jorgensen and O. Sondergaard, Randomised study of screening for colorectal cancer with faecal-occult-blood test, *Lancet* **348** (1996), 1467–1471.

[34] T.R. Levin, C. Conell, J.A. Shapiro, S.G. Chazan, M.R. Nadel and J.V. Selby, Complications of screening flexible sigmoidoscopy, *Gastroenterology* **123** (2002), 1786–1792.

[35] T.R. Levin, A. Palitz, S. Grossman, C. Conell, L. Finkler, L. Ackerson, G. Rumore and J.V. Selby, Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy, *JAMA* **281** (1999), 1611–1617.

[36] J. Li, Z. Zhang, J. Rosenzweig, Y.Y. Wang and D.W. Chan, Proteomics and bioinformatics approaches for identification of serum biomarkers to detect breast cancer, *Clin. Chem.* **48** (2002), 1296–1304.

[37] D.A. Lieberman, D.G. Weiss, J.H. Bond, D.J. Ahnen, H. Garewal and G. Chejfec, Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380, *N. Engl. J. Med.* **343** (2000), 162–168.

[38] D.A. Lieberman and D.G. Weiss, One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon, *N. Engl. J. Med.* **345** (2001), 555–560.

[39] G.E. Lind, K.K. Kleivi, G.I. Meling, M.R. Teixeira, E. Thiis-Evensen, T.O.L.R.A. Rognum, ADAMTS1, CRABP1, and NR3C1 identified as epigenetically deregulated genes in colorectal tumorigenesis, *Cell. Oncol.* **5/6** (2006) (in press).

[40] J.S. Mandel, T.R. Church, F. Ederer and J.H. Bond, Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood, *J. Natl. Cancer Inst.* **91** (1999), 434–437.

[41] T. Morikawa, J. Kato, Y. Yamaji, R. Wada, T. Mitsushima and Y. Shiratori, A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population, *Gastroenterology* **129** (2005), 422–428.

[42] A.D. Muller and A. Sonnenberg, Protection by endoscopy against death from colorectal cancer. A case-control study among veterans, *Arch. Intern. Med.* **155** (1995), 1741–1748.

[43] H. Nakama, M. Yamamoto, N. Kamijo, T. Li, N. Wei, A.S. Fattah and B. Zhang, Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia, *Hepatogastroenterology* **46** (1999), 228–231.

[44] P.A. Newcomb, R.G. Norfleet, B.E. Storer, T.S. Surawicz and P.M. Marcus, Screening sigmoidoscopy and colorectal cancer mortality, *J. Natl. Cancer Inst.* **84** (1992), 1572–1575.

[45] S.L. Parker, T. Tong, S. Bolden and P.A. Wingo, Cancer statistics, 1997, *CA Cancer J. Clin.* **47** (1997), 5–27.

[46] E.F. Petricoin, A.M. Ardekani, B.A. Hitt, P.J. Levine, V.A. Fusaro, S.M. Steinberg, G.B. Mills, C. Simone, D.A. Fishman, E.C. Kohn and L.A. Liotta, Use of proteomic patterns in serum to identify ovarian cancer, *Lancet* **359** (2002), 572–577.

[47] P.J. Pickhardt, J.R. Choi, I. Hwang, J.A. Butler, M.L. Puckett, H.A. Hildebrandt, R.K. Wong, P.A. Nugent, P.A. Mysliwiec and W.R. Schindler, Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults, *N. Engl. J. Med.* **349** (2003), 2191–2200.

[48] M. Pignone, S. Saha, T. Hoerger and J. Mandelblatt, Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force, *Ann. Intern. Med.* **137** (2002), 96–104.

[49] P.F. Pinsky, R.E. Schoen, J.L. Weissfeld, R.S. Bresalier, R.B. Hayes and J.K. Gohagan, Predictors of advanced proximal neoplasia in persons with abnormal screening flexible sigmoidoscopy, *Clin. Gastroenterol. Hepatol.* **1** (2003), 103–110.

[50] P. Schoenfeld, B. Cash, A. Flood, R. Dobhan, J. Eastone, W. Coyle, J.W. Kikendall, H.M. Kim, D.G. Weiss, T. Emory, A. Schatzkin and D. Lieberman, Colonoscopic screening of average-risk women for colorectal neoplasia, *N. Engl. J. Med.* **352** (2005), 2061–2068.

[51] P. Schoenfeld, J. Shad, E. Ormseth, W. Coyle, B. Cash, J. Butler, W. Schindler, W.J. Kikendall, C. Furlong, L.H. Sobin, C.M. Hobbs, D. Cruess and D. Rex, Predictive value of diminutive colonic adenoma trial: the PREDICT trial, *Clin. Gastroenterol. Hepatol.* **1** (2003), 195–201.

[52] D. Schrag, The price tag on progress – chemotherapy for colorectal cancer, *N. Engl. J. Med.* **351** (2004), 317–319.

[53] N. Segnan, B. Andreoni, L. Bisanti, G. Castiglione, A. Ederle, A. Ferrari, S. Gasperoni, G. Malfitana, A. Pera, S. Recchia, M. Rizzetto, C. Senore and P. Turco, Colonoscopy screening for colorectal cancer: a comparative study in Italy, *Gastroenterology* **126** (2004), A198.

[54] N. Segnan, C. Senore, B. Andreoni, A. Arrigoni, L. Bisanti, A. Cardelli, G. Castiglione, C. Crosta, R. DiPlacido, A. Ferrari, R. Ferraris, F. Ferrero, M. Fracchia, S. Gasperoni, G. Malfitana, S. Recchia, M. Risio, M. Rizzetto, G. Saracco, M. Spandre, D. Turco, P. Turco and M. Zappa, Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates, *J. Natl. Cancer Inst.* **97** (2005), 347–357.

[55] N. Segnan, C. Senore, B. Andreoni, H. Aste, L. Bonelli, C. Crosta, R. Ferraris, S. Gasperoni, A. Penna, M. Risio, F.P. Rossini, S. Sciallero, M. Zappa and W.S. Atkin, Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy" – SCORE, *J. Natl. Cancer Inst.* **94** (2002), 1763–1772.

[56] J.V. Selby, G.D. Friedman, C.P. Quesenberry Jr. and N.S. Weiss, A case-control study of screening sigmoidoscopy and mortality from colorectal cancer, *N. Engl. J. Med.* **326** (1992), 653–657.

[57] D. Sidransky, T. Tokino, S.R. Hamilton, K.W. Kinzler, B. Levin, P. Frost and B. Vogelstein, Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors, *Science* **256** (1992), 102–105.

[58] J. Stoker, H.W. Venema, Radiation in screening: an overview, in: *Proceedings Third International Symposium Virtual Colonoscopy*, 2002.

[59] S.J. Stryker, B.G. Wolff, C.E. Culp, S.D. Libbe, D.M. Ilstrup and R.L. MacCarty, Natural history of untreated colonic polyps, *Gastroenterology* **93** (1987), 1009–1013.

[60] R.M. Summers, J. Yao, P.J. Pickhardt, M. Franaszek, I. Bitter, D. Brickman, V. Krishna and J.R. Choi, Computed tomographic virtual colonoscopy computer-aided polyp detection in a screening population, *Gastroenterology* **129** (2005), 1832–1844.

[61] K.S. Tagore, M.J. Lawson, J.A. Yucaitis, R. Gage, T. Orr, A.P. Shuber and M.E. Ross, Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia, *Clin. Colorectal Cancer* **3** (2003), 47–53.

[62] G. Traverso, A. Shuber, B. Levin, C. Johnson, L. Olsson, D.J. Schoetz, Jr., S.R. Hamilton, K. Boynton, K.W. Kinzler and B. Vogelstein, Detection of APC mutations in fecal DNA from patients with colorectal tumors, *N. Engl. J. Med.* **346** (2002), 311–320.

[63] G. Traverso, A. Shuber, L. Olsson, B. Levin, C. Johnson, S.R. Hamilton, K. Boynton, K.W. Kinzler and B. Vogelstein, Detection of proximal colorectal cancers through analysis of faecal DNA, *Lancet* **359** (2002), 403–404.

[64] M. van Ballegooijen, *Screening op colorectaal kanker in Nederland: tijd om te starten. ('Cocast-report')*, Instituut Maatschappelijke Gezondheidszorg, Erasmus MC, Augustus 2003. ISBN: 90-77283-04-8.

[65] M. van Ballegooijen, J.D.F. Habbema, R. Boer, A.G. Zauber and M.L. Brown, A comparison of the cost-effectiveness of faecal occult blood tests with different test characteristics in the context of annual screening in the population, Instituut Maatschappelijke Gezondheidszorg, Erasmus MC, 2003.

[66] R.E. van Gelder, H.W. Venema, J. Florie, C.Y. Nio, I.W. Serlie, M.P. Schutter, J.C. van Rijn, F.M. Vos, A.S. Glas, P.M. Bossuyt, J.F. Bartelsman, J.S. Lameris and J. Stoker, CT colonography: feasibility of substantial dose reduction – comparison of medium to very low doses in identical patients, *Radiology* **232** (2004), 611–620.

[67] J.C. van Rijn, J.B. Reitsma, J. Stoker, P.M. Bossuyt, S.J. van Deventer and E. Dekker, Polyp miss rate determined by tandem colonoscopy: a systematic review, *Am. J. Gastroenterol.* **101** (2006), 343–350.

[68] J.E. Verne, R. Aubrey, S.B. Love, I.C. Talbot and J.M. Northover, Population based randomized study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing, *BMJ* **317** (1998), 182–185.

[69] O. Visser and K.J. van Noord, Feiten + Fabels over kanker in Nederland '05. Vereniging van Integrale Kankercentra, 2006. ISBN: 90-72175-35-2.

[70] S.J. Winawer, A.G. Zauber, M.N. Ho, M.J. O'Brien, L.S. Gottlieb, S.S. Sternberg, J.D. Waye, M. Schapiro, J.H. Bond and J.F. Panish, Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup, *N. Engl. J. Med.* **329** (1993), 1977–1981.

[71] M. Zappa, G. Castiglione, E. Paci, G. Grazzini, T. Rubeca, P. Turco, E. Crocetti and S. Ciatto, Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience, *Int. J. Cancer* **92** (2001), 151–154.