General introduction

1.1 COLORECTAL CANCER

Disease burden

In 2018 a total of 1,800,977 new cases of colorectal cancer (CRC) were diagnosed worldwide; 1,006,019 in men and 794,958 in women. This makes it the third and second most common cancer in men and women, respectively.[1] Although an increasing incidence is observed in non-Western countries, the largest CRC burden is still present in developed countries. In Europe, 500,000 new cases were reported in 2018, although incidence varied between countries.[2] In the Netherlands, before the introduction of screening, yearly 13,000 individuals were newly diagnosed with CRC.[3] Worldwide, the incidence of CRC is increasing due to ageing of the population, change in dietary habits and rise in risk factors like smoking, obesity, and lack of physical activity.[4,5] It is expected that without interference the number of CRC cases in the Netherlands will increase from 13,000 to 17,000 persons per year by 2020.[6] Life-time risk of developing CRC is 5% for men and 4% for women in the Netherlands.[7] This is slightly lower than the observed life-time risk in the United Kingdom, estimating a life-time risk of 7% for men and 6% for women.[8]

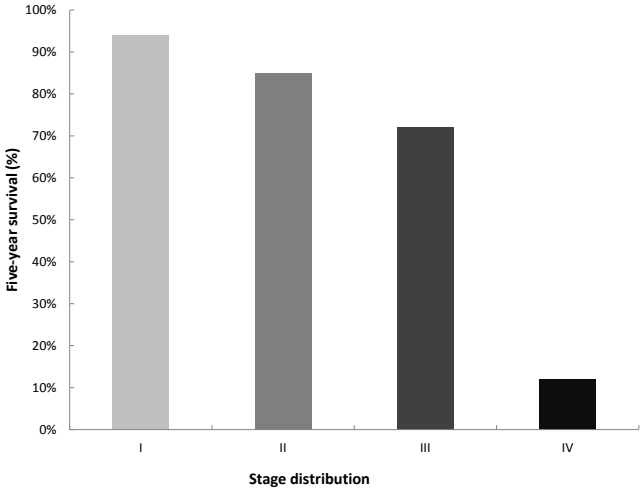
In 2018, worldwide 861,663 persons died of CRC; 474,606 men and 387,057 women. Therewith, it is the fourth and third cancer-related cause of death worldwide in men and women, respectively.[1] In Europe, 243,000 individuals died of CRC in 2018.[2] There is a wide variation in CRC-related mortality rates, with higher mortality rates in less developed countries. Consequently, 5-year survival varies from 35% in Poland to 58% in Finland and 60% in Sweden.[9,10] This variation is probably the result of different cancer treatment or stage distribution at diagnosis. Recent numbers from the Netherlands showed a 5-year relative survival of 61%.[7] The high incidence and mortality rates indicate that CRC is a major health problem.

Survival strongly depends on cancer stage at time of diagnosis.[11,12] Staging of CRCs is done according to the 7th edition of the TNM classification.[13] Stage 0 is considered carcinoma in situ. Stage I are tumours that were confined to the submucosa or had grown into the muscularis propria. Stage II are tumours that have invaded the serosa or penetrated to the peritoneal surface or other organs but without locoregional lymph node involvement. Stage III are tumours that also have metastasis in the locoregional lymph nodes. Stage IV are tumours that have distant metastases. In the Netherlands, 5-year survival is 94% for stage I compared to 12% for stage IV (Figure 1).[7] This strong association between survival and stage distribution emphasises the importance to detect CRCs as early as possible, as this will improve survival after CRC diagnosis.

Progression of colorectal cancer

Development from a small polyp into CRC is characterised by a multistep process involving series of histological, morphological, and genetic changes over time. Currently, two CRC

Figure 1: Five-year survival by stage distribution of individuals with colorectal cancers in the Netherlands



pathways have been identified. The first, so-called traditional pathway, gives rise to 70-85% of all CRC.[14] In this pathway, the normal colon epithelial cells change into aberrant crypt foci, and subsequently into small non-advanced adenomas (<1cm in size, with tubular histology). These adenomas can progress into advanced adenomas (AA) (adenomas with histology showing >=25% villous component or high-grade dysplasia or size >= 10 mm). From AA it can develop into early cancers and lastly advanced cancers with an accumulation of somatic mutations.[15,16] Besides this conventional adenoma pathway, there is an alternative pathway, the so-called serrated neoplasia pathway. This pathway has another precursor lesion, the serrated polyp. It is estimated that 15-30% of the CRCs results from this pathway.[17] Serrated lesions are divided in three subgroups: hyperplastic polyps, sessile serrated polyps and traditional serrated polyps. Of these subtypes, hyperplastic polyps are thought not to develop into CRCs.

As described above, CRC disease is characterised by a long pre-malignant stage. The dwell time is the time from the development of adenomas to symptom-detected CRCs in the absence of screening, which is estimated with microsimulations models to be 17-25 years.[18] The pre-cancerous stage polyps, either early adenomas or sessile serrated lesions, are asymptomatic. With advancing lesions, symptoms may become present but are often a-specific: abdominal pain, change in bowel habits, rectal blood loss, or weight loss.[19] By the time the signs of CRC become evident, the disease has often already developed in an advanced stage with poor associated survival rates.

Aetiology

Table 1 shows an overview of several risk factors and their impact on the development of CRC.[20] These factors can be divided in two subgroups, modifiable and non-modifiable risk factors:

Table 1: Overview of risk and preventive factors of colorectal cancer
Adapted from Brenner et al.[20] with permission.

	Risk
Sociodemographic factors	
Older age	↑↑↑
Male sex	↑↑
Medical factors	
Family history	↑↑
Inflammatory bowel disease	↑↑
Diabetes	↑
Helicobacter pylori infection	(↑)
Other infections	(↑)
Colonoscopy	↓↓
Hormone replacement therapy	↓
Aspirin	↓
Statins	(↓)
Lifestyle factors	
Smoking	↑
Excessive alcohol consumption	↑
Obesity	↑
Physical activity	↓
Diet factors	
High consumption of red and processed meat	↑
Fruit and vegetables	(↓)
Cereal fibre and whole grain	(↓)
Fish	(↓)
Dairy products	(↓)

↑↑↑=very strong risk increase. ↑↑=strong risk increase.↑=moderate risk increase.
↓↓=strong risk reduction. ↓=moderate risk reduction.
Parentheses show probable but not fully established associations.

Modifiable risk factors

Different modifiable factors can lead to an increased risk for CRC. First, choice of diet can impact your risk for CRC. It has been shown that intake of processed meat or red meat increases the risk for CRC up to 17-18%.[21] Note, large amounts of red meat have to be consumed (100 g/day). Second, obesity, low levels of physical activity, alcohol consumption

and cigarette smoking are also be related with an increased risk for CRC.[22,23] In contrast, intake of calcium, whole grains, fibre, and fruit and vegetables might decrease the risk for CRC up to 50%.[24,25] It was estimated that 45% of all CRCs were attributable to an unhealthy lifestyle, irrespectively of a person's genetic risk.[26] Therefore, a healthy lifestyle with physical activity and healthy diet might lower the risk of CRC.

Non-modifiable risk factors

There are various non-modifiable factors that increase individuals CRC risk. Well-known non-modifiable risk factors are sex and age.[1,27] Besides these two important risk factors, several diseases can lead to an increased CRC risk. Some examples are inflammatory bowel disease, type II diabetes and cystic fibrosis.[28-31] Lastly, DNA plays an important role in the development of CRC. Genetic contribution to CRCs can be divided in a few subgroups: family history with nonhereditary CRC, hereditary CRC syndrome (such as Lynch syndrome and familial adenomatous polyposis (FAP)), and other genetic variation (known as single-nucleotide polymorphisms (SNPs)).[27,32,33]

Modifiable and non-modifiable risk factors should be considered together to determine the overall risk for CRC. The combination of family history, environmental factors and genetics on top of age and gender will give the best prediction for an individual's CRC risk.[27] It is unknown whether the impact of the above-mentioned risk factors is similar for the two precursors of CRC: conventional adenomas and serrated polyps. A recent study suggests that both precursors share most common risk factors, but the magnitude of the association might differ.[34] Cigarette smoking, BMI, and alcohol consumption were more strongly associated with serrated polyps, whereas physical activity and dietary factors like folate, calcium, and Vitamin D had a stronger inverse association with conventional adenomas.

1.2 COLORECTAL CANCER PREVENTION

Reducing the burden of CRC could be established in three ways: primary prevention, secondary prevention and tertiary prevention. As the focus of the thesis is on screening, secondary prevention will be explained in more detail.

Primary prevention

It was estimated that almost half of all CRCs are attributable to an unhealthy lifestyle, such as smoking, alcohol consumption, diet, limited physical activity and body fatness.[26] Therefore, it is of great importance that primary prevention will be focussed on these risk factors. Additional benefit of reducing these risk factors is the positive side effects on many other diseases such as diabetes and cardiovascular diseases.

Besides a healthy lifestyle there is some evidence for a preventive effect of certain drugs (chemoprevention) on CRC. Best-known chemoprevention agents are aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[35] Although aspirin and NSAIDs have the potential to lower the CRC risk, they may also cause negative side effects, such as haemorrhagic strokes and gastrointestinal complications such as peptic ulcers and bleeding. Maybe it should only be considered for specific high-risk groups.[20,36] However, there is no guideline yet on the usage of chemoprevention agent.

Secondary prevention

With screening, asymptomatic individuals are systematically tested to identify the disease or risk factors for the disease. Screening can prevent the disease or detect the disease in an earlier stage. CRC is a good candidate for screening as it is a slow growing cancer, characterised by a long pre-malignant disease stage. Premalignant lesions can be removed before they become cancer or otherwise CRCs can be detected in an early stage.[11,12] Adenomas with histology showing >=25% villous component or high-grade dysplasia (both considered as AA), are in generally larger in size and are more likely to conceal cancer cells. Also, the risk for adenomas to develop into CRC increases as the size of the polyp increases (>10mm, also considered as AA).[37] Accordingly, AA is also considered as relevant finding of CRC screening. Both CRC and AA are therefore considered as true positives in CRC screening.

There are many different screening methods available for CRC screening. The most commonly used screening methods in Europe are stool-based occult blood test and endoscopy methods. Two types of stool-based occult blood test are used, the guaiac Faecal Occult Blood (gFOBT) and the faecal immunochemical test (FIT). Most important difference between those two tests is that FIT is a quantitative test, enabling to choose the preferred cut-off (µg Hb/g faeces) for referral for follow-op colonoscopy. This is important when considering a desired balance between true and false positive test results or encountering colonoscopy capacity problems. Two endoscopy methods are carried out, sigmoidoscopy and colonoscopy.[38,39] Stool-based test and sigmoidoscopy also have to be followed by a colonoscopy for diagnosis and removal of lesions. Computed tomography colonography (CTC), so-called virtual colonoscopy, is another CRC screening method. This screening method is hardly offered within an organised programme. Newer screening methods are also available, like multitarget-stool DNA testing, SEPT9 biomarker assay or video capsule endoscopy.[40-42] These newer screening methods are currently not offered in population-based screening programmes in Europe.

There is robust evidence that both repeated gFOBT and once-only flexible sigmoidoscopy screening can reduce CRC-related mortality.[43-49] No evidence is available from randomised controlled trials of the FIT on mortality reduction. gFOBT and FIT are similar tests, both stool-based tests; however performance of FIT is superior to gFOBT. Therefore, it is expected that the mortality reduction with FIT could even be larger than gFOBT. Additionally, there is

evidence on mortality reduction from observational studies.[50-54] Therefore, it is assumed that FIT screening will also result in a reduction of CRC-related mortality. Currently randomised controlled trials of colonoscopy screening are executed. Estimates of long-term effect of colonoscopy screening on CRC-related mortality will soon be available.[55-56] Colonoscopy is similar to sigmoidoscopy, but inspects the entire colon whereas sigmoidoscopy only inspects the lower part of the colon. As colonoscopy screening has a better test performance than sigmoidoscopy screening, combined with the evidence from observational studies, reduction of CRC-related mortality is also expected.[57] Note, to observe a mortality reduction within the population, it is crucial that not only a proper screening test is used, but also that the screenings test is accepted within the population.

Another important aspect that should be considered before implementing CRC screening is the harm-benefit ratio. Benefits of screening have been discussed above, the potential of various screening methods to reduce CRC-related mortality. However, there are more noteworthy benefits like reduction in advanced disease stage and reduction of the CRC incidence. The harms of screening differ substantially between screening methods. Harms of stool-based test could be psychological distress after receiving a positive test result and fear of CRC diagnosis.[58,59] The aversion of individuals to perform a stool test may also be considered as harm.[60] An important harm is the number of false-positives undergoing an unnecessary follow-up with colonoscopy. Fear of receiving a positive test result and CRC diagnosis also apply for endoscopy screening. However, endoscopy screening can have more substantial harms than FOBT screening, namely endoscopy-related complications. Estimated risk for a major bleeding was estimated to be 8 per 10,000 colonoscopies and for a perforation 4 to 7 per 10,000 colonoscopies.[59,61] Fatal complications after colonoscopy are very rare. Meta-analyses estimated the mortality rate ranging from 3 to 7 deaths per 100,000 colonoscopies.[62] Note, this rate includes fatal complications of colonoscopy with all indications and therefore not directly applicable on endoscopy screening. Another harm associated with screening, regardless of the screening method, is overdiagnosis. Overdiagnosis in CRC screening concerns detection of polyps or CRCs that, without screening, would not have been diagnosed in an individual's lifetime. It is unknown which polyp's progress or deteriorates. Therefore, it is uncertain which polyps would never develop into CRC and therefore will be removed unnecessarily. Thus, it is uncertain to what extent overdiagnosis is present in CRC screening. But inviting older individuals or individuals with comorbidities to participate in FIT screening, will most likely lead to overdiagnosis.[63] However, quantification of the magnitude of overdiagnosis in CRC screening is currently lacking. It is very complicated to come up with a good estimation, as by the removal of precancerous polyps CRCs will also be prevented. To sum up, CRC screening is associated with harms, however serious harms like death as a result of endoscopy rarely occur. In generally, it is considered that the benefits of CRC screening outweigh the harms.[52]

Tertiary prevention

Treatment of individuals with a CRC diagnosis to prevent further complications is considered as tertiary prevention, so-called survivorship. Tertiary prevention aims to prevent further health impact and improve quality of life after a diagnosis with CRC. Treatment of CRC is continuously changing with new innovations. A recent Dutch study presented an overview of the last 25 years of CRC treatment.[64] This study showed an increase in the use of postoperative chemotherapy for individuals diagnosed with stage III colon cancer and an increase in preoperative radiotherapy for rectal cancer. Another increase was the more intensified care of stage IV CRC, resulting in improved outcomes.[64] Other preventive strategies besides CRC treatment are similar to primary CRC prevention. But the target is on treatment-related side-effects or CRC-related morbidity. Strategies for tertiary prevention besides treatment options are an understudied topic. Known examples of strategies are; physical activity, healthy diet containing vitamin D, fibre, coffee, marine omega-3 fatty acid. Those strategies might improve survival and quality of life.[25,65]

1.3 MONITORING AND EVALUATION OF SCREENING PROGRAMMES

Screening programmes

Worldwide, many countries have implemented a CRC screening programme.[38] Programmes are predominantly introduced in high income countries. Screening can be designed as opportunistic or organised programmes. In an organised screening programme, like in the Netherlands, the entire target population receives an invitation to participate. In an opportunistic screening programme, like in the US and Germany, screening is recommended and reimbursed but depends on individuals' decision. They have to request the screening test themselves at the doctor or pharmacy.

Choosing the best screening strategy for the population is a complex process. When deciding on which test to use several aspects should be taken into account: test sensitivity, specificity, population preference, adherence, harms, capacity and costs. Colonoscopy has the highest sensitivity of all CRC screening methods; however it has downsides like severe complications, high costs, lack of adherence and straining colonoscopy capacity.[66,67] All these downsides need also to be considered when offering screening to the total population. There is a growing recognition that an optimal screening method heavily depends on population preference and availability of resources.[68,69] Besides the choice for the best test, starting age, stopping age and screening interval should be explored to design most effective screening programme for a population.

The Dutch colorectal cancer screening programme

The Netherlands may serve as an excellent example weighing all these various aspect of screening in the decision for the optimal screening method for the Dutch population. In the Netherlands an extensive preparatory process has taken place before the implementation of the national population-based CRC screening programme.[70] This process started with a report from the Dutch Health council in 2001 indicating the need for a national screening programme.

Pilot studies

In 2006 pilot studies were initiated to study the potential of a national CRC screening programme in the Netherlands.[51,71-74] The aim of these Dutch pilot studies was to evaluate most important aspects (i.e. participation, diagnostic yield and cost-effectiveness) of most relevant screening methods: gFOBT, FIT (with FIT cut-offs ranging from 10-40 µg Hb/g faeces), colonoscopy, sigmoidoscopy and CTC. These trials were conducted in Rotterdam, Amsterdam and Nijmegen. FIT screening showed the highest participation rate up to 60-62% in the first round, compared to 47-50% for gFOBT, 32% for sigmoidoscopy, 34% for CTC and 22% for colonoscopy. FIT also showed the highest diagnostic yield, with the highest detection of CRC per 1,000 invitees over two screening rounds.[75] Because of these favourable outcomes of FIT screening, the next step was to determine the optimal FIT cut-off. Outcomes of the pilot studies and subsequent modelling were used to inform policy makers to decide on the most optimal or feasible cut-off for referral to colonoscopy follow-up.[70]

Modelling studies

Microsimulation Screening Analysis (MISCAN)-Colon, a decision model that can be used to predict the benefits, harms and associated costs of different CRC screening strategies, was used to determine the optimal FIT cut-off. This model showed that a FIT cut-off of 10 µg Hb/g faeces will result in highest sensitivity and will be most effective.[76] With unlimited colonoscopy the optimal screening strategy for the Dutch population would be an annual FIT, with a cut-off of 10 µg Hb/g faeces for individuals aged 45-80 years.[77] But in practice, colonoscopy capacity is not unlimited. The model demonstrated that with restricted colonoscopy capacity, the most effective strategy would be annual screening with a FIT cut-off of 40 µg Hb/g faeces and smaller age range of individuals aged 50-75 years.[77]

Health Council

The Health Council plays an important role in designing and implementing a national screening programme in the Netherlands, advising the Minister of Health. They strongly advised on biennial screening with a FIT cut-off of 15 µg Hb/g faeces for individuals aged 55-75 years old.[78] This advice was based on the outcomes of the pilot studies and subsequent

modelling, but also on expert opinion and literature review. The final screening strategy in terms of FIT cut-off, interval and age range was based on the several considerations.

A FIT cut-off of 15 µg Hb/g faeces was advised by the Health council because it has a more favourable balance between true-positives and false-positives (higher positive predictive value (PPV)) and it results in a lower colonoscopy demand. Increasing the FIT cut-off from 10 to 15 µg Hb/g faeces will have a minor impact on CRC detection, but more AA and non-advanced adenoma will be missed.[71]

Annual gFOBT did show a higher CRC-related mortality reduction compared to biennial gFOBT screening (33% versus 20%).[47] However, additional benefit of annual screening over biennial screening is debated.[79] The Health Council concluded that the disadvantage of screening every year, as opposed to every second year, is that screening cost will almost be twice as high, while the desirable effects increase by smaller amounts. Therefore, biennial screening was considered as a more attractive option. The Health council therefore advised that the extra costs involved in annual screening do not outweigh the potential extra benefits.

The target age group was narrowed to individuals aged 55-75 years. This higher starting age was chosen because of the lower incidence of CRC in younger individuals at that time.[78] The lower stopping age was decided to avoid the higher risk of colonoscopy-related complications in older individuals. This recommendation was based on the results of the modelling studies of our research group.

Design Dutch organised CRC screening programme

In accordance with the advice of the Health council, the minister of Health decided on May 25, 2011 to gradually implement a national population-based screening programme with biennial FIT with a cut-off of 15 µg Hb/g faeces for men and women aged 55 to 75 years. The Dutch CRC screening programme was gradually implemented by age groups from 2014 onwards. This phased implementation of five years allowed a timely increase of the colonoscopy capacity. Ultimately, in 2019 all individuals between 55-75 years old should have been invited at least once.

Relevance of monitoring and evaluation

The European guidelines for quality assurance in CRC screening state the relevance of monitoring and evaluation as follows: evaluation and interpretation of screening outcomes are essential to recognise whether a CRC screening programme is achieving the goals for which it has been established.[80] Twenty important recommendations on CRC screening are given in this extensive guideline. Examples of relevant recommendations are: database with individual's records, annual monitoring reports by age and gender, minimal FIT participation of 45%, minimal participation to follow-up colonoscopy of 90%, more favourable stage distribution for screen-detected CRCs than symptom-detected CRCs, and evaluation of

interval CRCs. If the above-mentioned recommendations are followed, it is expected that CRC screening will be effective in reducing CRC-related mortality.

In the Netherlands, as described above, an extensive preparatory process was followed before the implementation of a national CRC screening programme. Next, during a planning phase public tenders for test, laboratories and packaging were set out. In addition, quality assurance and accreditation programmes were set up for endoscopy, pathology and laboratories. Also, a large IT infrastructure was developed. This information system automatically structures the total screening process, integrates information from different sources and is continuously updated. This national information system (ScreenIT) enables real-time monitoring of the national CRC screening programme. Monitoring of a screening programme is crucial. Although the design of the Dutch CRC screening programme is evidence-based and well-planned, it is unknown if the performance on a national level will be in line with expectations. The Netherlands is indeed a good example that expectations and reality are not in line. In the first year in 2014 weekly monitoring was carried out to evaluate the performance of the national CRC screening programme. These weekly reports showed high positivity rates, low PPV and an increase in waiting period for colonoscopy. Consequently, the programme was adjusted after 6 months that will be described in more detail in Chapter 2.

1.4 AIM AND RESEARCH QUESTION

The general aim of this thesis is to evaluate the implementation phase of the national CRC screening programme in the Netherlands. After many years of extensive preparations, expectations on programme performance were high. To ensure that these expectations are met on a national level, monitoring and evaluation of the national screening programme in real setting c.q. national level is important. This led to the following research question of this thesis:

Is the performance of the Dutch colorectal cancer screening programme during the implementation phase satisfying and according to expectations?

The performance of the Dutch CRC screening programme was evaluated separately per performance indicator; participation FIT, FIT positivity, participation to follow-up colonoscopy, CRC and AA detection, stage distribution, location, interval cancers, socioeconomic differences and consistency of FIT performance. The outcomes of important performance indicators were also compared with surrounding countries using FIT screening.

1.5 OUTLINE OF THIS THESIS

Chapter 2 to 7 addresses the Dutch national population-based CRC screening programme. In **Chapter 2** the first year of the Dutch national population-based CRC screening programme was evaluated. It describes the relevance of real-time monitoring to optimise programme performance. We evaluated the participation rate, positivity rate, PPV and detection rates before and after needed adjustment of the FIT cut-off. **Chapter 3** we compared the stage distribution of screen-detected and symptom-detected CRCs. In **Chapter 4** the programme performance of the second screening round was evaluated. We also estimated the impact of the adjusted FIT cut-off on positivity rate, PPV and detection rates. In In **Chapter 5** we estimated the interval CRC incidence and FIT sensitivity after the first screening round and the impact of the adjusted FIT cut-off. In **Chapter 6** we evaluated social economic status (SES) differences in participation and yield of FIT screening. We used area SES and compared the performance indicators participation rate, positivity rate, PPV and detection rate. In **Chapter 7** we evaluated the consistency of FIT in testing positive or detecting CRC or AA for different batches of specimen collection devices, lot reagents and laboratories. **Chapter 8** compared important screening programme indicators of four organised CRC screening programmes using FIT; Basque country (Spain), France, Flanders (Belgium) and the Netherlands. In the general discussion in **Chapter 9**, the research question will be answered and discussed per element. Subsequently the methodological considerations of the analyses in this thesis will be explained and future perspectives will be touched on briefly. Lastly, overall conclusions will be drawn and recommendations will be given.

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