Colorectal cancer screening for average- and high-risk individuals: beyond one-size-fits-all

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Beyond one-size-fits-all

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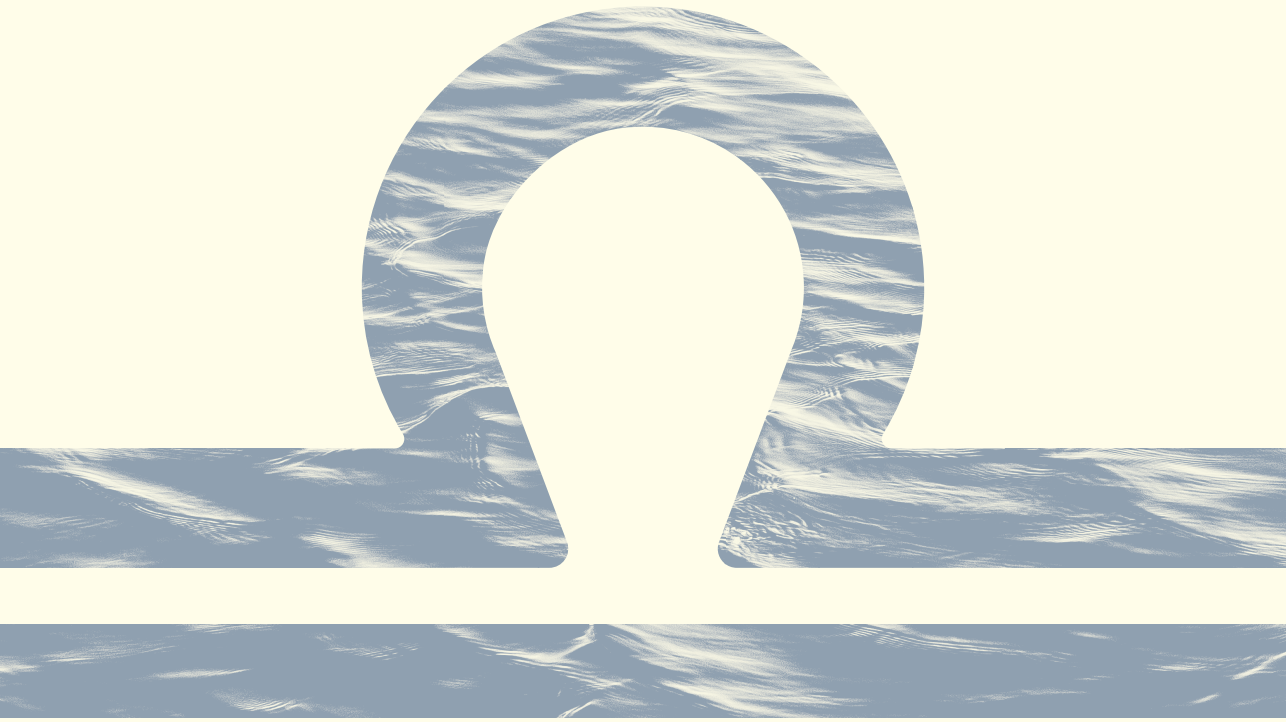

Chapter 1

Introduction

1.1 COLORECRAL CANCER AND SCREENING

Colorectal cancer (CRC), which includes cancer of the colon and rectum has a significant global health impact (1). With nearly two million new cases and one million deaths in 2020, CRC is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related deaths (2). The incidence of CRC has increased in recent decades and is predicted to continue to increase in the coming years (2,3). The CRC incidence is higher in countries with a high Human Development Index, particularly in Western nations (2). Roughly two pathways can be distinguished that comprise the precursors of CRC; i) the traditional adenoma-carcinoma pathway leading to development of advanced adenomas (AAs) into CRC, and ii) the serrated neoplasia pathway leading to the development of advanced serrated polyps (ASPs) into CRC. The adenoma-carcinoma pathway is responsible for ~70-90% of all CRCs, while the serrated neoplasia pathway is responsible for ~10-30% of all CRCs (4). Furthermore, precursor lesions are speculated to take at least 10-15 years before developing into CRC, making them excellent targets for prevention (1,5). Although progress has been made in understanding the pathophysiology and risk factors of this disease, it still poses significant challenges for prevention.

The focus of this thesis is mainly on (secondary) prevention of CRC through CRC screening. The primary goal of CRC screening programs is to reduce (late-stage) CRC incidence and CRC-related mortality. This can be accomplished through a two-pronged approach; i) detection and resection of precursor lesions and ii) detection and treatment of CRCs at an earlier stage. With the first strategy, resection of these precursor lesions (AAs and ASPs) during endoscopy can prevent the development of CRC. With the second strategy, CRC screening is intended to detect CRC at an earlier stage, thereby decreasing CRC-related morbidity and mortality. Detecting early-stage (stage I and II) CRC leads to lower morbidity for CRC patients and reduces costs associated with intensive CRC treatment for late-stage (stage III and IV) CRC. In addition, the survival rates for early-stage CRC are much more favorable than those for late-stage CRC (6).

CRC screening can be tailored to meet the needs of a country and its specific target populations (7). Several guidelines on CRC screening in Europe were established for quality assurance and measuring short- and long-term outcomes (8,9). When selecting an optimal strategy for CRC screening, several elements should be taken into account: the choice of screening modality, local circumstances, availability of resources, and organizational frameworks associated with screening

programs. As a result, CRC screening strategies can widely vary in the organization of screening (organized vs. opportunistic), invitation interval, age range, and primary screening modality (10,11). After introduction and implementation of a CRC screening program, the effectiveness and cost-effectiveness should be carefully assessed to ensure that the intended short- and long-term outcomes are met. By evaluating these short- and long-term outcomes, potential areas for improvement can be identified (9).

This thesis focuses on the evaluation of short-and long-term outcomes of CRC screening for average- and high-risk populations and explores pathways to optimize (personalized) screening strategies for these populations.

1.2 COLORECTAL SCREENING FOR AVERAGE-RISK INDIVIDUALS

For average-risk individuals, population-based CRC screening programs have been widely implemented over the past three decades (10). Several screening modalities are available for CRC screening. In theory, colonoscopy would be the best way to prevent CRC, as it has the highest sensitivity and specificity for both CRC and advanced neoplasia (AN) (defined as AAs, ASPs, and CRC). However, colonoscopy is costly, carries risk of adverse events, and can be burdensome. As a result, individuals can be less willing to undergo screening. This has led to the evaluation of other, less invasive tests, including flexible sigmoidoscopy, computed tomography colonography, capsule endoscopy and fecal occult blood testing (FOBT) (12–14). One of these FOBTs is the fecal immunochemical test (FIT) for human hemoglobin (Hb), which is currently the most widely used test in Europe and has been shown to be effective and potentially cost-saving (12). In Europe, colonoscopy and FIT are the two most commonly used primary screening methods, and the age range of the target population is typically 50 to 74 years, as recommended by the European guidelines for CRC screening (11,15).

In the Netherlands, several pilot studies were initiated in 2006 to compare various CRC screening modalities. These pilot studies showed that the FIT had high sensitivity for AN and relatively high participation rates, resulting in a higher detection rate (DR) of AN compared to other screening modalities (16–20). These findings led to the adoption of FIT as the preferred screening method for the Dutch CRC screening program, which was then introduced in early 2014, with FIT at a cutoff of 15 µg hemoglobin (Hb)/gram (g) feces. Six months into the program, the observed positivity rates were higher and the positive predictive value (PPV) was lower than

expected (21). This led to more false-positive test results and unnecessary colonoscopies. Therefore, the cut-off was adjusted to 47 µg Hb/g feces. The program was gradually rolled out by birth cohort, until in 2019 the program was fully implemented. The program invites all individuals between the ages of 55 and 75 years to undergo FIT once every two years. In cases where the FIT results exceed the cutoff, participants are invited for an intake for colonoscopy. In 2014-2018, approximately 14,000 CRCs and 76,000 AAs were detected (22). While these detection rates are promising, it is now important to evaluate the extent to which this affects short- and long-term outcomes (i.e., (early- and late-stage) CRC incidence, stage distribution, and CRC-related mortality at the population level). **Part I** of this thesis encompasses the evaluation of short- and long-term outcomes of the CRC screening program in the Netherlands after the implementation phase of the program from 2014-2019.

1.3 PERSONALIZED CRC SCREENING FOR AVERAGE-RISK INDIVIDUALS

Evaluating the harms and benefits of (CRC) screening programs, is of great importance (23). Benefits of CRC screening include the prevention of CRC (by removal of precancerous lesions) and early detection of CRC, ultimately leading to a reduction in CRC-related morbidity as well as CRC-related mortality. Harms include false-positive test results, leading to unnecessary follow-up testing and increased healthcare costs, complications of follow-up tests such as colonoscopy (a relatively invasive and uncomfortable procedure, with the risk of bleeding or perforation (24)), and overdiagnosis. The Health Council recently concluded that there is a favorable balance between benefits and harms in the Dutch CRC screening program (25). Notwithstanding this positive assessment, it is important and a continuous responsibility to try to further improve the balance between benefits and harms of CRC screening programs. Risk stratification is one way forward to improve this balance. This can be done by identifying those at high(er) risk, offering more intensive screening and thereby increasing benefits, while reducing harms for those at low(er) risk by offering less intensive screening. This personalized screening approach has been debated for more than three decades (26). However, until now, it has not become a reality. Seeking a better balance between benefits and harms of CRC screening through a personalized approach namely also comes with challenges: it may involve a range of screening modalities, differing screening invitation intervals, incorporation of individuals' risk factors (i.e., sex, age, familial history, environmental,

genetic and lifestyle factors), cut-off for FIT positivity, and so on (27). While the concept of personalized CRC screening is promising, research is needed to fully evaluate its benefits and limitations (27). Challenges remain in determining the most suitable risk factors for personalized CRC screening and in developing cost-effective screening algorithms. Additionally, population-level implementation is challenging in terms of organization, execution, and acceptance of the target population. **Part II** of this thesis elaborates on risk stratification of CRC screening based on fecal Hb (f-Hb) concentrations after negative FIT and information preferences of the target population for personalized CRC screening strategies.

1.4 CRC SCREENING AND SURVEILLANCE FOR HIGH-RISK INDIVIDUALS

While population-based CRC screening may be (cost-)effective for average-risk individuals, high-risk populations have at least twice the risk of developing CRC during their lifetime, highlighting the importance of potential intensified CRC screening and surveillance for these individuals (28–32). High-risk individuals include those with familial CRC risk, Lynch syndrome, familial adenomatous polyposis, other genetic syndromes, and inflammatory bowel disease (28–30,32,33). Currently, colonoscopy surveillance is recommended for these high-risk populations and has been shown to be cost-effective (33–35). These individuals are offered colonoscopy from a younger age than average-risk individuals. CRC surveillance for high-risk individuals is repeated at a preset surveillance interval, depending on the estimated risk and the guidelines in the respective countries (33,36–38). Another group of high-risk individuals is childhood cancer survivors (CCS), who are at increased risk of developing a wide range of second malignant neoplasms (SMNs), including gastrointestinal (GI) SMNs, raising the importance of surveillance guidelines for CCS (39,40). The risk of developing GI SMNs seems to be associated with both radiation therapy and systemic treatment of the primary cancer in CCS. As such, the risk of GI SMNs increases with the duration of treatment, the treatment dose, and the number of years since treatment (41).

In the United States, colonoscopy is recommended for CCS starting at the age of 45 and repeated at a five-year interval, like individuals with familial CRC risk (42). European guidelines are more diverse (43–46). Recently, in the Netherlands, it was suggested that Hodgkin lymphoma survivors treated with infradiaphragmatic radiotherapy and/or procarbazine-containing chemotherapy should start colonoscopy screening no later than the age of 40 at five-year intervals in case of a

negative colonoscopy (47). This was based on a cohort study that showed a higher prevalence of AN in these survivors compared to a general population cohort (25% vs. 12%, p<0.001), especially ASPs (12% vs. 4%, p<0.001) (47). Several retrospective cohort studies have also demonstrated that testicular cancer survivors (TCS) are at increased risk of developing SMNs, including CRC, especially when treated with platinum-based chemotherapy (48–51). The diagnostic yield of colonoscopy surveillance in TCS treated with platinum-based chemotherapy is unknown. **Part III** of this thesis examines the prevalence and carcinogenesis of colorectal neoplasia and CRC in TCS and assessed the yield of colonoscopy in these TCS.

1.5 OUTLINE OF THIS THESIS

General outline

This thesis evaluated the outcomes of CRC screening, with a focus on the evaluation of and pathway to (personalized) CRC screening programs for average- and high-risk populations. As outlined above, this thesis consists of three parts. Part I addresses the evaluation of short- and long-term outcomes of the Dutch population-based CRC screening program. Part II focuses on personalization of the CRC screening program in the Netherlands based on prior f-Hb concentrations after negative FIT. Part III focuses on CRC screening and the carcinogenesis of CRC in high-risk individuals (CCS), in this case TCS.

Outline per part and chapter

Part I comprises Chapters 2-5. **Chapter 2** discusses important outcomes of CRC screening (i.e., overall, early- and late-stage CRC incidence, CRC-related mortality, and characteristics and treatment of screen-detected vs. clinically detected CRC). **Chapter 3** further elaborates on changes in trends of late-stage CRC incidence based on the timing of invitation in the Dutch CRC screening program, as the program was gradually implemented by birth cohort beginning in 2014. **Chapter 4** concerns the differences in treatment of stage I CRCs detected within and outside the CRC screening program, further elaborating on findings presented in Chapter 2. The last chapter of Part I, **Chapter 5**, involves the DR and PPV of the CRC screening program including ASPs alongside AAs and CRC.

Part II consists of Chapters 6-8. **Chapter 6** presents the results that were the foundation for personalized CRC screening strategies and elaborates on the sensitivity of the FIT, and the risk of CRC after a negative FIT before the next screening

invitation, based on the prior f-Hb concentration after negative FIT. **Chapter 7** involves the study protocol of a mixed-methods study on personalized CRC screening based on prior screening history, including a randomized controlled trial, focus group studies, and a cost-effectiveness study. **Chapter 8** presents the results of the first focus group study on the information need on personalized CRC screening of individuals in the target population.

Part III comprises Chapters 9-11. **Chapter 9** encompasses the mutational signature of secondary CRC detected in non-seminoma TCS. **Chapter 10** presents the results of a study on the yield of a first colonoscopy in TCS treated with platinum-based chemotherapy. **Chapter 11** describes the retention of platinum plasma, urine, and normal colonic mucosa of TCS treated with platinum-based chemotherapy.

Finally, **Chapter 12** includes the general discussion and future perspectives of these lines of research.

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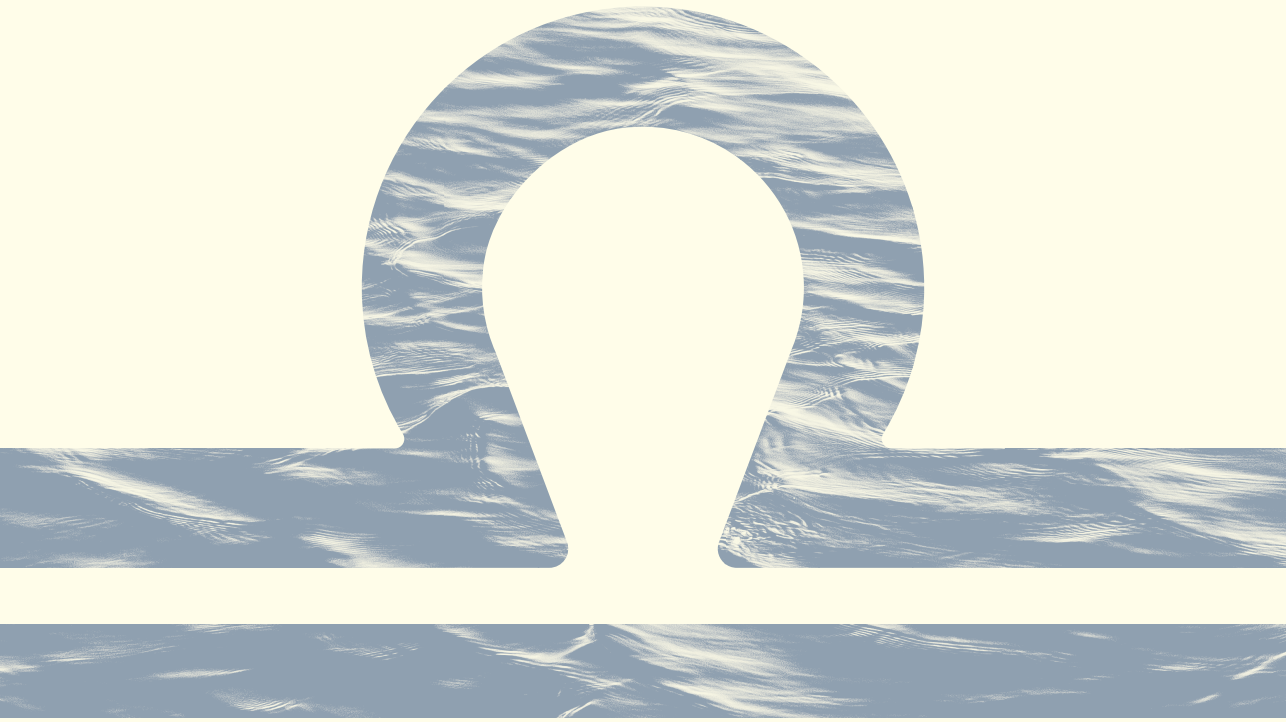
Part I

Evaluation of the Dutch colorectal cancer screening program



Chapter 2

Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study

ECH Breekveldt, I Lansdorp-Vogelaar, E Toes-Zoutendijk, MCW Spaander, AJ van Vuuren, FJ van Kemenade, CRB Ramakers, E Dekker, ID Nagtegaal, MF Krul, NFM Kok, KFD Kuhlmann, GR Vink, ME van Leerdam, MAG Elferink, on behalf of the DutchNational Colorectal Cancer Screening Working Group

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ABSTRACT

Background

In 2014, a population-based colorectal cancer (CRC) screening programme was stepwise implemented in the Netherlands comprising faecal immunochemical testing once every 2 years, with a cutoff value for positivity of 47 µg haemoglobin per g faeces. We aimed to assess CRC incidence, mortality, tumour characteristics, and treatment before and after introduction of this screening programme.

Methods

We did a retrospective, observational, population-based study in the Netherlands and gathered CRC incidence data from the Netherlands Cancer Registry from Jan 1, 2010, to Dec 31, 2019, in people aged 55 years or older. Patients with a CRC diagnosis between Jan 1, 2014, and Dec 31, 2018, in the Netherlands Cancer Registry were linked with the nationwide registry of histopathology and cytopathology (PALGA) to identify mode of detection (i.e., screening-detected vs. clinically detected). We calculated age-standardised CRC incidence rates and used data from Statistics Netherlands to calculate CRC-related mortality in 2010–19. We compared localisation, stage distribution, and treatment of screening-detected CRCs with clinically detected CRCs diagnosed in 2014–18 in patients aged 55–75 years.

Results

Between Jan 1, 2010, and Dec 31, 2019, 125215 CRCs were diagnosed in individuals aged 55 years or older and were included in the analyses for CRC incidence. Before the introduction of the screening programme, the age-standardised CRC incidence rate was 214.3 per 100,000 population in 2013 in people aged 55 years or older. After the introduction of the screening programme, this rate initially increased to 259.2 per 100,000 population in 2015, and subsequently decreased to 181.5 per 100,000 population in 2019. Age-standardised incidence rates for advanced CRCs (stage III and IV) were 117.0 per 100,000 population in 2013 and increased to 122.8 per 100,000 population in 2015; this rate then decreased to 94.7 per 100,000 population in 2018. Age-standardised CRC mortality decreased from 87.5 deaths per 100,000 population in 2010 to 64.8 per 100,000 population in 2019. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be located in the left side of the colon (48.6% vs. 35.2%) and to be detected at an early stage (I or II; 66.7% vs. 46.2%). Screening-detected CRCs were more likely to be treated by local excision compared with clinically detected CRCs, and this finding persisted when stage I CRCs were analysed separately.

Conclusions

After introduction of this national screening programme, a decrease in overall and advanced-stage CRC incidence was observed. In view of this observation, together with the observed shift to detection at earlier stages and more screening-detected CRCs being treated by local excision, we might cautiously conclude that, in the long-term, faecal immunochemical testing-based screening could ultimately lead to a decrease in CRC-related morbidity and mortality.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the Netherlands and the third most common type in cancer incidence for both men and women (1). CRC incidence is affected by risk factors, such as diet and lifestyle characteristics (ie, smoking, obesity, and physical inactivity) (2,3). CRC screening programmes have been shown to be effective in reducing CRC incidence and mortality in the long-term, resulting in the implementation of various screening programmes worldwide (4–8). After an extensive pilot phase, a population-based CRC screening programme has been stepwise implemented in the Netherlands from 2014 onwards, using faecal immunochemical testing (FIT) to detect and quantify human haemoglobin level in faeces once every 2 years. As of 2019, the complete target population is being invited, with consistently high participation rates (around 72%) and satisfactory detection rates of advanced neoplasia over each of the screening rounds (9). Monitoring of CRC screening programmes is important to evaluate their efficacy and optimise screening strategies. The main objective of these programmes is to reduce CRC-related mortality. This reduction can be achieved by a decrease in CRC incidence rate as well as by detecting CRCs at earlier stages. It was hypothesised that after initiation of the Dutch national CRC screening programme, CRC incidence rates would initially increase due to detection of prevalent—yet asymptomatic—cancers, and would subsequently decrease over time due to the removal of (advanced) adenomas. In the Netherlands, it has been shown that the stage distribution of screening-detected CRCs was more favourable than clinically detected CRCs (ie, a greater proportion of screening-detected CRCs were early stage) (10). However, these results should be interpreted with caution, because a shift in stage distribution does not necessarily mean that the number of advanced-stage CRCs detected on a population level decreases. The shift could simply be the result of detecting more indolent CRCs, while the number of advanced-stage CRCs diagnosed remains equal. However, if the incidence of advanced-stage CRCs at a population level would decrease after initiation of the screening programme, we could conclude that screening leads to early detection of CRCs and will probably result in reduced CRC-related mortality in the long-term. Few data are available on the effect of implementation of FIT-based screening programmes on CRC incidence and mortality rates. We aimed to evaluate CRC incidence and mortality rates before and after introduction of the Dutch national CRC screening programme and analyse trends in incidence rates of early-stage and advanced-stage CRCs. Our secondary objective was to assess the effect of a national FIT-based CRC screening programme on tumour characteristics (localisation and stage distribution) and type of treatment of screening-detected CRCs versus clinically detected CRCs.

METHODS

Study design and participants

We did a retrospective, observational, population-based study in the Netherlands and gathered CRC incidence data from Jan 1, 2010, to Dec 31, 2019, in people aged 55 years or older. The Dutch national CRC screening programme was launched in 2014 with a stepwise introduction by age cohorts, until all eligible age cohorts were invited in 2019. Men and women aged 55–75 years were invited once every 2 years to send in stool samples for FIT (FOB-Gold; Sentinel Diagnostics, Milan, Italy). The (invitation) coverage of the target population increased from around 40% in 2014 to 100% in 2018. Initially, in 2014, a cutoff for positivity of 15 µg haemoglobin per g faeces was used. 6 months after the start of the programme, the cutoff was adjusted to 47 µg haemoglobin per g faeces, because the initial positivity rate was higher than expected and the positive predictive value was lower than expected. Decision analysis at that time showed that an increase to 47 µg haemoglobin per g faeces would result in the desired balance between true and false positive test results (11). Overall sensitivity of FIT for CRC was high (around 82%) and decreased slightly after the first invitation round (12–17). An overview of screening participation rates in the target population aged 55–75 years is shown in the appendix (Table 1). On average, the participation rate was around 72%. Participation rates were higher in women than in men (around 74% vs. 71%, respectively). Individuals with a positive FIT were invited to a precolonoscopy assessment and referred for colonoscopy if considered eligible. The overall participation rate for colonoscopy was around 85% and was similar for men and women (12–17). Relevant outcomes of screening within the Dutch CRC screening programme are advanced adenoma and CRC. Advanced adenoma is defined as any adenoma with histology of 25% or greater villous component, diameter of 10 mm or greater, or high-grade dysplasia. This study was approved by the privacy review board of the Netherlands Cancer Registry and did not require approval from an ethics committee in the Netherlands. Informed consent was not required due to the study design.

Procedures

We extracted data from three independent databases: the Netherlands Cancer Registry (NCR), Statistics Netherlands, and the Dutch nationwide registry of histopathology and cytopathology (PALGA). All newly diagnosed malignancies in the Netherlands are registered in the NCR. Data on CRC incidence were retrieved from the NCR and were available from Jan 1, 2010, to Dec 31, 2019. Detailed information on tumour localisation, stage distribution, and treatment was collected from the

patients' medical records by trained personnel and registered in the NCR. Tumour stage was coded using the TNM classifications of malignant tumours at that time and topography was classified according to the International Classification of Disease for Oncology (18–21). Data on stage distribution were only available for CRCs diagnosed from Jan 1, 2010, to Dec 31, 2018. To extract data on CRC-related mortality, we used cause of death information from Statistics Netherlands. Data on CRC-related mortality were available from Jan 1, 2010, to Dec 31, 2019. Within PALGA, it is recorded if the biopsy taken at colonoscopy was obtained after a positive FIT within the screening programme; we were therefore able to identify if a CRC was screening-detected or clinically detected.

Outcomes

The primary outcome was CRC incidence rates in people aged 55 years or older in 2010–19. This age range was chosen to estimate the effect of CRC screening in the long-term, because the effects of screening will continue after people reach the upper age limit of the screening programme. Additionally, we evaluated trends in early-stage and advanced-stage CRC incidence rates. To determine CRC incidence rates, we obtained information on all CRCs detected in 2010–19 through the NCR. Early-stage CRCs were defined as stage I and II cancers; advanced-stage CRCs were defined as stage III and IV cancers. Guidelines of the International Association of Cancer Registries on reporting incidence data were used to calculate age-standardised rates, using the European Standard Population (22). Hereafter, age-standardised CRC incidence rate will be referred to as CRC incidence. Next, we used data from Statistics Netherlands to calculate CRC-related mortality in 2010–19 in people aged 55 years or older. Hereafter, age-standardised CRC-related mortality will be referred to as CRC-related mortality. Lastly, we compared tumour localisation, stage distribution, and treatment of screening-detected CRCs with clinically detected CRCs diagnosed in 2014–18. For this analysis, we restricted cases to those diagnosed within the target population aged 55–75 years to avoid bias in the comparison because of age differences. We linked data from the NCR on CRCs diagnosed in 2014–18 to PALGA to identify mode of detection (i.e., screening-detected or clinically detected). Clinically detected CRCs included all CRCs not detected through FIT-based screening. Patients that did not meet the age criteria set for these analyses were excluded. Tumour localisation was categorised into right-sided colon (caecum to transverse colon, C18.0, C18.2–18.4), left-sided colon (splenic flexure to rectosigmoid, C18.5–18.7, C19), rectum (C20), and overlapping and unspecified (C18.8–18.9) (23). Appendiceal cancers (C18.1) were excluded from analyses. Treatment options included local excision (endoscopic resection, transanal endoscopic microsurgery, or

transanal minimally invasive surgery), oncological surgical resection, (chemo)radiotherapy, systemic therapy, a combination of the aforementioned treatments, other, or none. Treatment was analysed separately for colon and rectal cancers. Because local excision only is advised for stage I colon and rectal cancers (24), we also analysed treatments in these stage I cancers separately. When multiple synchronous primary CRCs were diagnosed, only the most advanced lesion was included in the analyses.

Statistical analysis

Joinpoint regression analyses were performed to detect changes in trends by calculating and comparing annual percentage change in overall, early-stage, and advanced-stage CRC incidence. The maximum number of join-points was limited to two with a minimal percentage point difference of 0.5. Data were summarised using standard descriptive statistics. To compare tumour characteristics and treatment of screening-detected CRCs with clinically detected CRCs, χ^2 testing was used. Calculated p values were two-sided and were considered significant if less than 0.05. Joinpoint regression analyses were performed using Joinpoint regression software (version 4.9.0.0) of the US National Cancer Institute. Further data management and analyses were performed using STATA (version 16.1).

Role of the funding source

There was no funding source for this study.

RESULTS

Between Jan 1, 2010, and Dec 31, 2019, 125,215 CRCs were diagnosed in individuals aged 55 years or older and were included in the analyses for CRC incidence (Figure 1).

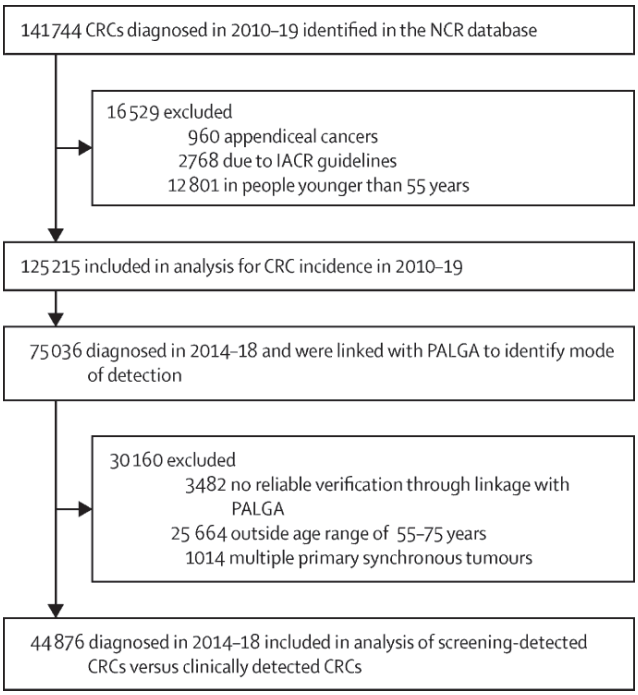

Figure 1 - Study profile

CRC=colorectal cancer. NCR=Netherlands Cancer Registry. IACR=International Association of Cancer Registries. PALGA=Dutch nationwide registry of histopathology and cytopathology.

CRC incidence in people aged 55 years or older decreased slightly in the period 2010–13 (annual percentage change –1.2% [95% CI –4.1 to 1.8]). Thereafter, CRC incidence temporarily increased from 214.3 per 100,000 population in 2013 to 259.2 per 100,000 population in 2015 after initiation of the screening programme (annual percentage change 10.1% for 2013–15; Figure 2). By 2019, CRC incidence had decreased to 181.5 per 100,000 population. The decrease in CRC incidence in the period 2015–19 (annual percentage change –8.7% [95% CI –10.4 to –7.0]) was significantly larger than the decrease in the period 2010–13.

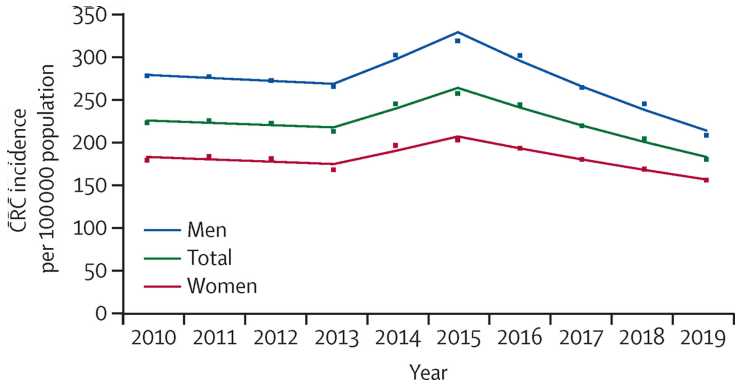

Figure 2 - Age-standardised CRC incidence rates in 2010–19 in people aged 55 years or older

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

Overall, CRC incidence was consistently higher in men than in women (Figure 2). In men, CRC incidence decreased in the period 2010–13 (annual percentage change –1.3% [95% CI –5.7 to 3.4]). CRC incidence in men then increased from 267.3 per 100,000 population in 2013 to 321.1 per 100,000 population in 2015 (annual percentage change 10.7% for 2013–15), and decreased to 209.8 per 100,000 population in 2019. The decrease in CRC incidence in men in the period 2015–19 (annual percentage change –10.2% [95% CI –12.8 to –7.5]) was significantly larger than the decrease in the period 2010–13. In women, CRC incidence also decreased in the period 2010–13 (annual percentage change –1.5% [95% CI –3.6 to 0.6]). CRC incidence in women increased from 169.3 per 100,000 population in 2013 to 204.4 per 100,000 population in 2015 (annual percentage change 8.9% for 2013–15), and decreased to 156.8 per 100,000 population in 2019. The decrease in CRC incidence in women in the period 2015–19 (annual percentage change –6.7% [95% CI –8.0 to –5.5]) was significantly larger than the decrease in the period 2010–13. The difference in decrease in annual percentage change between both periods was greater in men than in women.

Early-stage CRC incidence decreased slightly in the period 2010–13 before initiation of the screening programme, from 101.6 per 100,000 population to 92.2 per 100,000 population (annual percentage change –2.4% [95% CI –5.5 to 0.9]). There was a substantial increase in early-stage CRC incidence after introduction of the screening programme, with a maximum of 130.7 per 100,000 population in 2015 (annual percentage change 18.5% for 2013–15; Figure 3). After 2015, a decrease was observed until 2018, to 106.1 per 100,000 population (annual percentage change –7.7% [95% CI –10.6 to –4.6] for 2015–18). In advanced-stage CRC incidence, a different trend was observed to overall and early-stage CRC incidence. Advanced-

stage CRC incidence was 117.0 per 100,000 population in 2013; it increased only slightly until 2015, when it was 122.8 per 100,000 population (annual percentage change 0.9% [95% CI –0.7 to 2.5] for 2010–15). After 2015, a significant decrease was observed to an incidence of 94.7 per 100,000 population in 2018 (annual percentage change –8.3% [95% CI –11.5 to –4.9] for 2015–18; Figure 3).

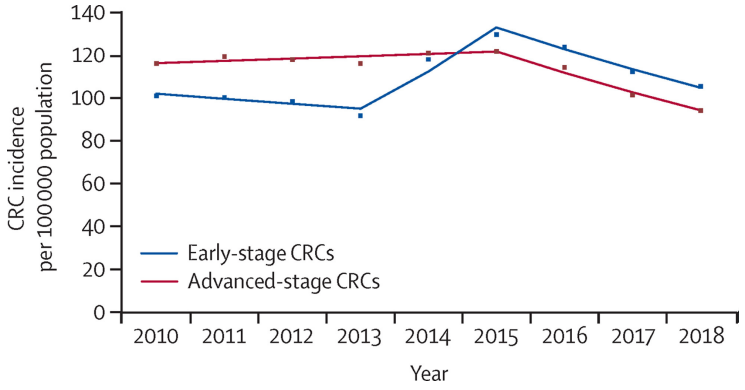

Figure 3 - Age-standardised incidence rates of early-stage CRCs and advanced-stage CRCs in 2010–18 in people aged 55 years or older

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

A total of 47,104 CRC-related deaths were registered between Jan 1, 2010, and Dec 31, 2019, which were used to determine CRC-related mortality. CRC-related mortality decreased from 87.5 deaths per 100,000 people in 2010 to 64.8 deaths per 100,000 population in 2019 (–3.0% [95% CI –3.8 to –2.3]; Figure 4). Men were more likely than women to die of CRC. CRC-related mortality in men decreased from 109.0 per 100,000 people in 2010 to 76.6 per 100,000 population in 2019 (annual percentage change –3.1% [95% CI –4.1 to –2.2]) and in women decreased from 71.2 per 100,000 population to 55.5 per 100,000 population, respectively (–3.1% [–3.9 to –2.3]). Trends in CRC-related mortality were similar over the whole study period and did not change after initiation of the screening programme (ie, no joinpoints were detected).

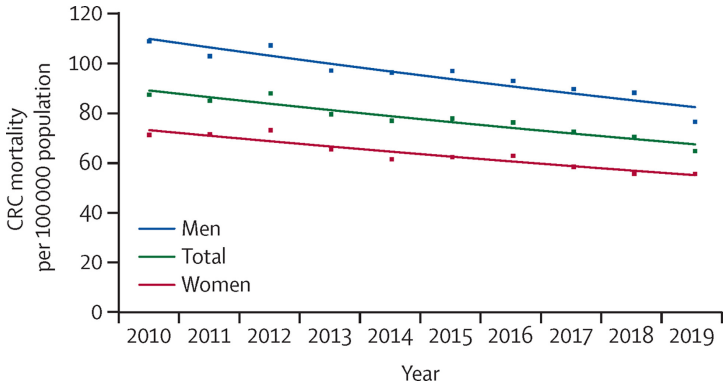

Figure 4 - Age-standardised CRC-related mortality rates in 2010–19 in people aged 55 years or older

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

Between Jan 1, 2014, and Dec 31, 2018, 75,036 CRCs were identified in the NCR. Of these CRCs, 71,554 (95.4%) could be reliably verified through linkage with PALGA and were included for further analyses (Figure 1). After excluding patients that did not meet the age criteria for this analysis or who had multiple primary synchronous tumours, we included 44,876 CRCs (screening-detected and clinically detected) observed in people aged 55–75 years. Of these, 13,565 (30.2%) CRCs were screening-detected and 31,311 (69.8%) were clinically detected (table). Median age was 67 years (IQR 63–72) in people with screening-detected CRCs and 67 years (62–72) in those with clinically detected CRCs (p<0.0001). Both screening-detected and clinically detected CRCs were more frequent in men than in women.

Table - Characteristics of the study population aged 55–75 years with screening-detected or clinically detected CRC diagnosed in 2014–18.

	Total (n = 44,876)	Screen-detected CRCs (n = 13,565)	Clinically detected CRCs (n = 31,311)	*p* value*
Age		67 (IQR 63-72)	67 (IQR 62-72)	<0.0001
Sex				
Men	26,646	8,276 (61.0)	18,370 (58.7)	
Women	18,230	5,289 (39.0)	12,941 (41.3)	<0.0001
Localisation				
Right-sided	13,452	3,300 (24.3)	10,152 (32.4)	
Left-sided	17,598	6,593 (48.6)	11,005 (35.2)	
Rectum	13,178	3,537 (26.1)	9,641 (30.8)	
Overlapping or NOS	648	135 (1.0)	513 (1.6)	<0.0001

Stage distribution				
Stage I	13,588	6,406 (47.2)	7,182 (22.9)	
Stage II	9,941	2,645 (19.5)	7,296 (23.3)	
Stage III	13,188	3,572 (26.3)	9,616 (30.7)	
Stage IV	7,586	719 (5.3)	6,867 (21.9)	
Unknown	573	223 (1.6)	350 (1.1)	<0.0001
Treatment colon cancers				
Number of cancers	31,698	10,028	21,670	
Local excision	2,814	1,749 (17.4)	1,065 (4.9)	
Surgical oncological resection	16,915	5,749 (57.3)	11,166 (51.5)	
Surgical oncological resection with (neo)adjuvant treatment	8,704	2,272 (22.7)	6,432 (29.7)	
Systemic treatment	2,052	173 (1.7)	1,879 (8.7)	
Other treatment	100	8 (0.1)	92 (0.4)	
None	1,113	77 (0.8)	1,036 (4.8)	<0.0001
Treatment rectal cancers				
Number of cancers	13,178	3,537	9,641	
Local excision	1,656	781 (22.1)	875 (9.1)	
Surgical oncological resection	3,356	1,212 (34.3)	2,144 (22.2)	
Surgical oncological resection with (neo)adjuvant treatment	5,666	1,148 (32.5)	4,518 (46.9)	
Systemic treatment	977	90 (2.5)	887 (9.2)	
Other treatment	1,137	287 (8.1)	850 (8.8)	<0.0001
None	386	19 (0.5)	367 (3.8)	
Treatment stage I colon cancers				
Number of cancers	9,760	4,825	4,935	
Local excision	2,647	1,661 (34.4)	986 (20.0)	
Surgical oncological resection	7,073	3,152 (65.3)	3,921 (79.5)	
None	40	12 (0.3)	28 (0.6)	<0.0001
Treatment stage I rectal cancers				
Number of cancers	3,828	1,581	2,247	
Local excision	1,626	760 (48.1)	866 (38.5)	
Surgical oncological resection	2,114	794 (50.2)	1,320 (58.7)	
None	88	27 (1.7)	61 (2.7)	<0.0001

Data are n, n (%), median (IQR), or p values. CRC=colorectal cancer. *p values for χ^2 testing comparing proportions of screening-detected CRCs versus clinically detected CRCs.

Tumour localisation differed significantly between screening-detected and clinically detected CRCs. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be left-sided (6,593 [48.6%] of 13,565 vs. 11,005 [35.2%] of 31,311; p<0.0001; table), and less likely to be right-sided (3,300 [24.3%] vs. 10,152 [32.4%]; p<0.0001). Left-sided CRCs were more frequently diagnosed in men than in women (Appendix Table 2). The proportion of left-sided cancers diagnosed in men was higher for cancers diagnosed through screening (4,251 [64.5%] of 6,593) than for cancers diagnosed through clinical detection (6,683 [60.7%] of 11,005, p<0.0001; Appendix Table 2).

Stage distribution differed significantly between screening-detected CRCs and clinically detected CRCs. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be stage I (6,406 [47.2%] of 13,565 vs. 7,182 [22.9%] of 31,311; p<0.0001), and less likely to be stage III or IV (4,291 [31.6%] vs. 16,483 [52.6%]; p<0.0001; table).

Screening-detected CRCs were more likely to be treated with local excision than were clinically detected CRCs, both in colon and in rectal cancers (p<0.0001 for both; table). 1,749 (17.4%) of 10,028 screening-detected colon cancers and 1,065 (4.9%) of 21,670 clinically detected colon cancers were treated with local excision only. For rectal cancers, 781 (22.1%) of 3,537 and 875 (9.1%) of 9,641, respectively, were treated with local excision only.

In the analyses of stage I colon and rectal cancers only, significant differences were observed in treatments between screening-detected and clinically detected cancers (p<0.0001 for both; table). 1,661 (34.4%) of 4,825 screening-detected stage I colon cancers were treated with local excision, compared with 986 (20.0%) of 4,935 clinically detected cancers. 760 (48.1%) of 1,581 screening-detected stage I rectal cancers were treated with local excision, compared with 866 (38.5%) of 2,247 clinically detected cancers.

DISCUSSION

This study evaluated CRC incidence, mortality, tumour characteristics, and treatment before and after the introduction of the Dutch national FIT-based CRC screening programme. We observed a decrease in overall CRC incidence, which was significantly larger than the small decrease in CRC incidence before the initiation of the programme. Advanced-stage CRC incidence also decreased significantly after the screening programme was initiated. CRC-related mortality decreased over time during the study period, but the trend did not change after introduction of the screening programme. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be diagnosed in men, to have a more favourable stage, and to be located in the left side of the colon. Screening-detected CRCs were more likely to be treated by local excision than were clinically detected CRCs, and this finding persisted when stage I CRCs were analysed separately.

Our results are similar to those showing overall CRC incidence reduction in several European countries that adopted organised FIT-based CRC screening programmes (25). In our study, after the start of the screening programme, an initial increase in CRC incidence was observed as expected, especially in early-stage CRC incidence, due to detection of prevalent (asymptomatic) CRCs (26). Similarly, in Slovenia and Denmark, where two FIT-based organised screening programmes have been implemented, a temporary increase and subsequent large decrease in overall CRC incidence were observed after initiation of the screening programmes. CRC incidence remained stable or decreased slowly in most countries that adopted opportunistic screening programmes or used screening modalities other than FIT (ie, colonoscopy or guaiac faecal occult blood testing [gFOBT]) (25). This difference in trends might be due to lower participation rates or lower sensitivity of these screening modalities compared with FIT.

An important addition of this study compared with previous work is that stage-specific CRC incidence was also assessed. Early-stage CRC incidence followed a similar, albeit more pronounced, pattern compared with overall CRC incidence. By contrast, advanced-stage CRC incidence followed a different pattern; from 2010 to 2015, advanced-stage CRC incidence increased slightly, followed by a decrease after 2015. Only one joinpoint was determined, in 2015, which suggests that the introduction of screening does not lead to an increase in diagnoses of advanced-stage CRC, as was observed for early-stage CRC. However, from 2015 onwards, a significant reduction in advanced-stage CRC incidence was observed compared with in 2010–15. The significant decrease in overall and advanced stage CRC incidence from 2015 onwards indicates that the Dutch CRC screening programme might have

contributed to early detection of CRCs and precancerous lesions. Therefore, we cautiously expect that CRC-related mortality might also decrease in the long-term due to the screening programme. It was not unexpected that we would not see a significant effect on CRC-related mortality yet. Given that screening brings diagnosis forward, and the average overall survival of patients with CRC exceeds 5 years, we did not expect to observe an effect of screening on CRC-related mortality for at least 7 years after the introduction of the programme (1,27,28).

Moreover, we compared screening-detected CRCs with clinically detected CRCs. Given the high participation in the Dutch screening programme and the high estimated sensitivity of FIT, the proportion of CRCs detected by screening (approximately one-third of all CRCs diagnosed in 2014–18 were screening-detected) might seem low. However, this is due to the gradual implementation of the programme, which was not completed until 2019. To illustrate, in 2014, only around 40% of the target population aged 55–75 years were invited for screening, which consisted mainly of individuals aged 65 years or older. This age distribution of people invited also explains the relatively high median age of individuals with screening-detected CRCs. Screening-detected CRCs were more frequently diagnosed at early stages than clinically detected CRCs, resulting in more favourable treatment strategies (i.e., local excision). Local excision was more likely to be performed in stage I screening-detected CRCs than in stage I clinically detected cancers. This difference in treatment might be due to a higher proportion of pT1 stage I CRCs and more rectal and left-sided cancers within screening-detected CRCs, as well as differences in high-risk features, such as differentiation grade and lymphovascular invasion. However, research on this is not yet available.

Minimal evidence is available on the effectiveness of FIT in lowering CRC incidence rates, mainly due to the observational nature of these studies (7). Furthermore, there is conflicting evidence on the effect of gFOBT screening on CRC incidence (29). However, sensitivity of FIT is much higher than gFOBT for detection of advanced adenoma, therefore a decrease in CRC incidence was anticipated, which is in line with our findings (6,30–33). Studies on screening with flexible sigmoidoscopy have previously shown a significant reduction of CRC incidence of approximately 20% after 11–12 years (34,35). Although we observed a smaller reduction in CRC incidence 5 years after the start of the programme compared with these studies, it remains to be seen how the programme affects CRC incidence in the long-term, given that FIT is repeated frequently in the population.

Our data are also relevant to other FIT-based screening programmes. We have shown that CRC incidence decreases in the long-term when using FIT every 2

years with a cutoff value for positivity of 47 µg haemoglobin per g faeces. Changes in CRC incidence might be affected by the screening invitation interval (e.g., annual or every 2 years testing), the age range invited, and lower or higher haemoglobin cutoffs for FIT positivity. A previous modelling study found that adopting lower positivity cutoffs, extending the age range, and offering more intensive screening (i.e., annual intervals) would lead to greater reductions in CRC incidence and mortality (36). Thus, for these more intensive programmes, our findings could be considered a conservative estimate of the potential effect.

We observed a greater difference in CRC incidence in men than in women after introduction of the programme; the difference in decrease in CRC incidence between 2010–13 and 2015–19 was greater in men than in women. Despite higher participation rates in women than in men (about 5% higher), CRC incidence reduction was lower in women than in men (12–17). The difference in CRC incidence reduction might be explained by a difference in FIT sensitivity, as higher detection rates for advanced neoplasia and higher sensitivity of FIT in men than in women have been previously reported (37,38). The lower sensitivity in women than in men could have two explanations: women have more proximal colon cancers than men, and a possible predominance of the serrated pathway (39). Together with the lower sensitivity of FIT for right-sided lesions, this might explain part of the observed differences in the effect of the screening programme between sexes. To account for these differences in sensitivity, especially in right-sided lesions, optimisation of faecal testing and different positivity cutoffs for men and women could be considered in the future. Further research on why the difference in participation rate does not outweigh the CRC detection rate, resulting in a difference in CRC incidence reduction, is needed.

A strength of this study is that it used data from three large national registries, combining essential information on all cancers detected. These unique registries each provide invaluable information for evaluation and thus quality assurance of the programme. The study includes data from before and after introduction of a national, organised, screening programme. The nature of the data enabled us to gather relevant information on all CRCs diagnosed during the study period and to evaluate long-term effects of screening for the first time after the start of the programme. The main limitation of this study is the ecological design, introducing confounders that might influence the observed associations between screening and CRC incidence and CRC-related mortality. We corrected for age by using age-standardised rates, but other confounders, such as diet, incidence of obesity, alcohol consumption, smoking, and physical activity levels could not be

accounted for (40). However, such changes are unlikely to be the main driver of the observed reduction in CRC incidence, because this study included data from a relatively short time period and major changes in lifestyle factors are not likely to have an effect in such a short term. Moreover, it is implausible that lifestyle would affect trends in advanced-stage CRC incidence differently than in early-stage CRC incidence. Therefore, despite the observational nature of our study, our findings suggest a positive effect of screening on CRC incidence in the long-term.

To further strengthen the evidence for the association between the implementation of the FIT-based screening programme and the decrease in (advanced-stage) CRC incidence, a case-control study could be conducted, for which a linkage through the NCR, the national information technology screening database, and Statistics Netherlands would be necessary. This would enable us to compare screening history of individuals with advanced-stage CRC (cases) with matched individuals without advanced-stage CRC (controls). However, such a study would require information on non-screened individuals, which for privacy law enforcement should be handled carefully, and is therefore beyond the scope of this research.

In conclusion, our data show that after introduction of the Dutch CRC screening programme, overall and advanced-stage CRC incidence decreased, which indicates that FIT-based CRC screening is effective. The decrease in advanced-stage CRC incidence coupled with the improved treatment options of screening-detected CRCs might decrease CRC-related mortality in the long-term.

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APPENDIX

Table 1: Screening process from 2014-2019

Year	Total target population aged 55-75	Number of individuals invited (%*)	Number of individuals participated (%**)
2014	1,925,110	741,914 (38.5)	529,056 (71.3)
2015	1,963,873	1,171,550 (59.7)	848,761 (72.4)
2016	2,000,291	1,457,976 (72.9)	1,063,651 (73.0)
2017	2,041,724	1,941,121 (95.1)	1,411,998 (72.7)
2018	2,081,355	2,186,186 (105.0)	1,589,322 (72.7)
2019	2,117,415	2,193,058 (103.6)	1,567,274 (71.5)

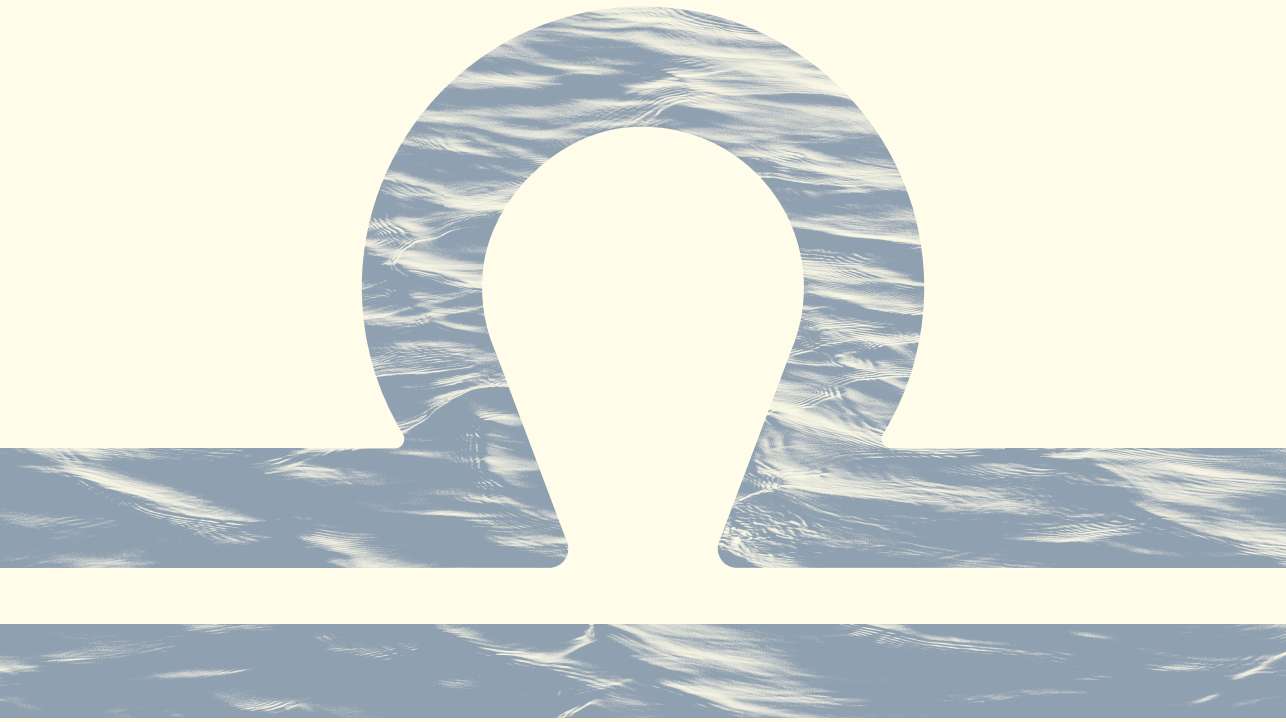
*of the total target population

**of the number of individuals invited

Table 2: Side distribution of localisation (2014-2018), screening-detected CRCs compared to clinically detected CRCs in individuals aged 55-75.

	Total (n = 44,876)	Screen-detected CRCs (n = 13,565)	Clinically detected CRCs (n = 31,311)	p value*
Localisation				
Right-sided				
Men	6,627	1,575 (47.7)	5,052 (49.8)	
Women	6,825	1,725 (52.3)	5,100 (50.2)	0.042
Left-sided				
Men	10,934	4,251 (64.5)	6,683 (60.7)	
Women	6,664	2,342 (35.5)	4,322 (39.3)	<0.0001
Rectum				
Men	8,728	2,375 (67.1)	6,353 (65.9)	
Women	4,450	1,162 (32.9)	3,288 (34.1)	0.18
Overlapping or NOS				
Men	357	75 (55.6)	282 (55.0)	
Women	291	60 (44.4)	231 (45.0)	0.90

Values are n (%). CRC, colorectal cancer; NOS, not otherwise specified. *: p values for chi-square testing comparing proportions of screening-detected versus clinically detected CRCs.



Chapter 3

Advanced-stage CRC incidence patterns following the phased implementation of the CRC screening programme in the Netherlands

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ABSTRACT

Background

From 2014, the Dutch colorectal cancer (CRC) faecal immunochemical testing-based screening programme was gradually rolled out by birth cohort. We evaluated changes in advanced-stage CRC incidence by timing of invitation to further strengthen the evidence for the effectiveness of CRC screening.

Methods

Data on advanced-stage CRC incidence in the period 2010–2019 by invitation cohort were collected through the Netherlands Cancer Registry. Crude rates of advanced-stage CRC incidence and cumulative advanced-stage CRC incidence were calculated. Observed advanced-stage CRC incidence and cumulative advanced-stage CRC incidence were compared with expected advanced-stage CRC incidence and cumulative advanced-stage CRC incidence by invitation cohort using trend lines extrapolating data prior to the introduction of screening.

Results

For the invitation cohort that was first invited for screening in 2014, advanced-stage CRC incidence increased before the introduction of screening from 94.1 to 124.7 per 100,000 individuals in the period 2010–2013. In 2014, the observed increase was higher than in preceding years, to 184.9 per 100,000 individuals. Hereafter, a decrease in incidence was observed to levels below expected incidence based on trends before the introduction of screening. A similar pattern was observed for invitation cohorts in subsequent years, coinciding with the first invitation to the screening programme. In 2019, the observed incidence for all invitation cohorts remained below expected incidence. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was significantly lower than the expected cumulative CRC incidence in the period 2010–2019.

Conclusions

In the period 2014–2019, an increase in advanced-stage CRC incidence was observed for all invitation cohorts first invited for screening, followed by a decrease below expected incidence, following the pattern of the phased implementation. The cumulative advanced-stage CRC incidence in invitation cohorts invited for screening multiple times was lower than expected based on trends from the pre-screening era.

These findings support a causal relationship between the introduction of the Dutch screening programme and a decrease in advanced-stage CRC incidence.

INTRODUCTION

The global burden of colorectal cancer (CRC) is high, with nearly two million new cases and one million deaths worldwide in 2020 (1). To reduce the burden of CRC, screening programmes have been implemented in many countries around the world. In the Netherlands, a faecal immunochemical testing (FIT)-based CRC screening programme has been gradually rolled out by birth cohort from 2014. Since 2019, all screening-eligible individuals are invited every two years to CRC screening.

The aim of CRC screening is to detect and treat CRC early to ultimately reduce CRC-related morbidity and mortality. To assure that CRC screening programmes achieve this aim, European guidelines for quality assurance in CRC screening and diagnosis prescribe regular monitoring of the early performance indicators for effectiveness (2). Previously, it has been described that CRC screening leads to a more beneficial stage distribution of screening-detected CRC than clinically detected CRC (3–7). However, overdiagnosis and lead-time bias could be introduced by screening and the, herewith, early detection of precursor lesions and CRC might not lead to a reduction in CRC-related mortality. Therefore, other surrogate indicators might be used, such as the incidence of advanced-stage CRC, which is associated with higher morbidity and mortality than early-stage CRC.

In previous publications, advanced-stage CRC incidence in the Netherlands as an early performance indicator was assessed and a significant decrease in advanced-stage CRC incidence after introduction of the screening programme was observed (6,7). However, when interpreting these results, understanding potential caveats of trend analyses in incidence rates is of great importance. Improved diagnostic methodology, changes in population size and age structure, differences in risk patterns over time and several other factors might introduce bias in the interpretation of trend changes in CRC incidence (8). Therefore, strengthening the causal relationship between the introduction of a screening programme and a decrease in the advanced-stage CRC incidence is deemed necessary. If the decrease in advanced-stage CRC incidence was indeed the result of the implementation of the screening programme, changes in the advanced-stage CRC incidence are to be expected at a later time point for birth cohorts that were invited at a later date. In this study, we assessed advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence by birth cohort to further strengthen the evidence for the association between the implementation of the screening programme and a decrease in advanced-stage CRC incidence.

METHODS

The Dutch CRC screening programme

In 2014, the Dutch national CRC screening programme was stepwise implemented by birth cohort (Table 1). In 2014, five birth cohorts (1938, 1939, 1947, 1949 and 1951) were first invited to participate in screening, while in 2015, six other birth cohorts (1940, 1946, 1948, 1950, 1952 and 1954) were first invited to participate, and so on. By 2019, all screening-eligible birth cohorts (aged 55–75) were at least invited once, and from 2019 onwards, all individuals were biennially invited to participate in FIT for haemoglobin (FOB-Gold; Sentinel Diagnostics®, Milan, Italy) at a cut-off for FIT-positivity of 47 µg Hb/g faeces. FIT participation rates within the screening programme were consistently high, at around 72% (9).

Table 1 - Overview of invitation cohorts 2014–2019.

	Birth cohorts first invited for screening					
Invitation cohort 2014[a]	1938	1939	1947	1949	1951	
Invitation cohort 2015[a]	1940	1946	1948	1950	1952	1954
Invitation cohort 2016[b]	1941	1945	1953	1955	1957	
Invitation cohort 2017[b]	1942	1944	1956	1958	1960	
Invitation cohort 2018[c]	1943	1959	1961	1963		
Invitation cohort 2019[c]	1962	1964				

a Three times invited for screening.

b Two times invited for screening.

c One time invited for screening.

Data

We retrieved CRC incidence data from the Netherlands Cancer Registry for individuals aged 45 and older in the period 2010–2019. Tumour stage was coded using the effective tumour, node, metastases classifications of malignancies (7th edition until to 2016, 8th edition from 2017 onwards (10,11)) and stored in the Netherlands Cancer Registry. Data from Statistics Netherlands were used to calculate population size by age cohort and calendar year. A total of 125,417 CRCs were identified in the period 2010–2019. Tumour stage was not reported in 3990 (3.2%) of cases. Only advanced-stage CRCs detected in individuals that were age 55 and older in the screening period were included.

Outcomes

In this retrospective observational study, we calculated crude rates of advanced-stage (stage III and IV) CRC incidence and the cumulative advanced-stage CRC incidence in the period 2010–2019 in individuals who were aged 55 and in the screening period. Incidence rates were grouped by invitation cohort. An invitation cohort consists of birth cohorts first invited for screening in the same calendar year. For example, invitation cohort 2014 consists of all birth cohorts first invited for screening in 2014. For some birth cohorts, the invitation extended beyond one calendar year; then, the calendar year in which most individuals were invited was used. Advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence was presented for both sexes combined and for men and women separately. We included cancers in the right-sided colon (cecum to transverse colon, C18.0, 18.2 – C18.4), left-sided colon (splenic flexure to rectosigmoid, C18.5-C18.7, C19), rectum (C20) and overlapping and unspecified (C18.8-C18.9). Appendiceal cancers (C18.1) were excluded for analyses.

Statistical analysis

Crude rates of advanced-stage CRC incidence were calculated by dividing the number of advanced-stage CRC per invitation cohort by the total population size of that cohort in each respective calendar year. Annual advanced-stage CRC incidence was displayed per 100,000 individuals. Next, we generated trend lines for each invitation cohort based on advanced-stage CRC incidence in the years before first invitation. Trend lines were generated by fitting a linear regression line using the natural logarithm of the incidence rates with the calendar year as regression variable. For invitation cohort 2014, trend lines were based on advanced-stage CRC incidence in the period 2010–2013; for invitation cohort 2015, trend lines were based on incidence in the period 2010–2014, and so on. Next, we calculated cumulative advanced-stage CRC incidence in the period 2010–2019 in all invitation cohorts by dividing the number of advanced-stage CRCs per invitation cohort by the number of individuals at risk per invitation cohort in 2010. We compared the cumulative advanced-stage CRC incidence to the expected cumulative advanced-stage CRC incidence in the period 2010–2019 for all invitation cohorts. The expected cumulative advanced-stage CRC incidence was calculated by dividing the number of expected advanced-stage CRCs per invitation cohort by the number of individuals at risk per invitation cohort in 2010. The number of expected CRCs was based on the trend lines

from the pre-screening era. Data were summarised using standard descriptive statistics. Calculated p values were two-sided and were considered statistically significant when <0.05.

Sensitivity analysis

We performed a sensitivity analysis to assess the robustness of results for the choice of trend line. For invitation cohort 2014 (birth cohort 1938; 76-year olds, 1939; 75-year olds, 1947; 67-year olds, 1949; 65-year olds), we constructed an alternative trend line using the observed advanced-stage CRC incidence for birth cohorts that had the same age in 2010 (1934, 1935, 1943, 1945) as the 2014 invitation cohort in 2014. We projected observed advanced-stage CRC incidence of these 2010 cohorts in the graph at time point 2014, to compare observed and expected advanced-stage CRC incidence at a particular age. Birth cohort 1951 (part of invitation cohort 2014) was not included in the sensitivity analysis since the respective comparison cohort in 2010 (1947) was invited in 2014.

RESULTS

A total of 45,990 advanced-stage CRCs were diagnosed in the period 2010–2019 in individuals who were 55 and older in the screening period. For invitation cohort 2014, advanced-stage CRC incidence increased prior to the introduction of screening, from 94.1 to 124.7 per 100,000 individuals in the period 2010–2013 (Figure 1). In 2014, the observed increase was larger than in preceding years, with an incidence of 184.9 per 100,000 individuals (+33.4% relative to trend). Hereafter, in 2015, a decrease in advanced-stage CRC incidence was observed (−21.9% relative to trend). When these birth cohorts were invited for the second time in 2016, no increase was observed, probably because a large part of the invitation cohort was not again invited to screening due to reaching the upper age limit. A slight increase was again observed in 2018 when this cohort was invited to screening for the third time, but this was lower than expected (−36.3% relative to trend). In 2019, at the end of our study period, the observed advanced-stage CRC incidence was lower than the expected incidence, with an observed incidence of 104.0 per 100,000 individuals versus an expected incidence of 192.2 per 100,000 individuals (−45.9% relative to trend).

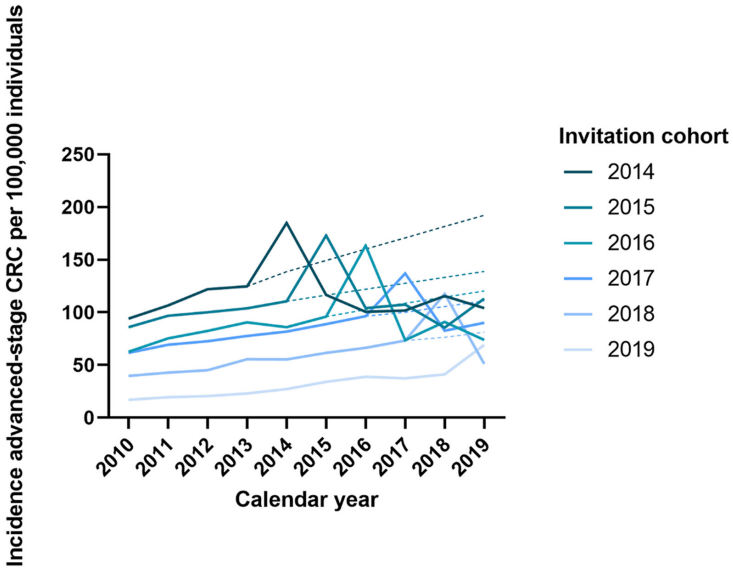

Figure 1 - Advanced-stage CRC incidence patterns in different invitation cohorts.

CRC: colorectal cancer.

A similar pattern was observed for invitation cohort 2015. In this cohort, advanced-stage CRC incidence increased from 85.9 to 110.6 per 100,000 individuals in the period 2010–2014. In 2015, advanced-stage CRC incidence substantially increased to

173.0 per 100,000 individuals (+48.7% relative to trend). This was followed by a decrease in 2016, after which an increase was observed when this invitation cohort was invited for screening for the second time (2017) and the third time (2019). However, observed advanced-stage CRC incidence in 2019 was lower than expected. Expected incidence was 138.8 per 100,000 individuals, whereas observed incidence was 113.0 per 100,000 individuals in 2019 (−18.6% relative to trend). For all other invitation cohorts (2016–2019), the same pattern was observed; advanced-stage CRC incidence increased in the year these birth cohorts were first invited to screening (between +36.7 and + 59.1% relative to trend), followed by a decrease, and an increase in the years, these birth cohorts were invited for the second time. In 2019, observed advanced-stage CRC incidence was far below the expected advanced-stage CRC incidence for all invitation cohorts. The cumulative advanced-stage CRC incidence in invitation cohort 2014 was 1.10% in the period 2010–2019 and was lower than the expected cumulative advanced-stage CRC incidence based on the trends from the pre-screening era (1.34%, $p < 0.0001$; Table 2). The cumulative advanced-stage CRC incidence in invitation cohorts 2015 and 2016 was also significantly lower than the expected cumulative advanced-stage CRC incidence. No significant differences were observed between the observed and expected cumulative advanced-stage CRC incidence in invitation cohorts 2017 and 2018. The cumulative advanced-stage CRC incidence in invitation cohort 2019 was slightly higher than the expected cumulative advanced-stage CRC incidence (0.32% versus 0.30%, $p = 0.034$; Table 2).

Table 2 - Cumulative observed and expected advanced-stage CRC incidence in the period 2010–2019.

Invitation cohort	No. individuals at risk (2010), n	Total advanced-stage CRCs from 2010-2019, n	Total expected advanced-stage CRCs from 2010-2019, n	Cumulative advanced-stage CRC incidence, %	Expected cumulative advanced-stage CRC incidence, %	*p* value
2014	919,000	10,108	12,294	1.10	1.34	<0.0001
2015	1,180,000	12,119	12,687	1.03	1.08	0.00029
2016	981,000	8,466	8,854	0.86	0.90	0.0031
2017	1,015,000	8,338	8,401	0.82	0.83	0.62
2018	896,000	5,294	5,196	0.59	0.58	0.34
2019	516,000	1,665	1,545	0.32	0.30	0.034

Similar patterns in advanced-stage CRC incidence were observed for men and women separately, although the incidence was higher in men than in women (Figure 2a–b). However, the increase in the first year was greater in men than in women. Differences between expected and observed advanced-stage CRC incidence in 2019 were slightly greater in men (between −19.6% and −49.6% relative to trend) than in women (between −16.2% and −40.9% relative to trend). The observed and expected cumulative advanced-stage CRC incidence were higher in men than in women, but patterns by sex were similar as for the population as a whole (Table 3). No significant differences were observed between the observed and expected cumulative advanced-stage CRC incidence in the male 2017–2019 invitation cohorts and the female 2016–2019 invitation cohorts.

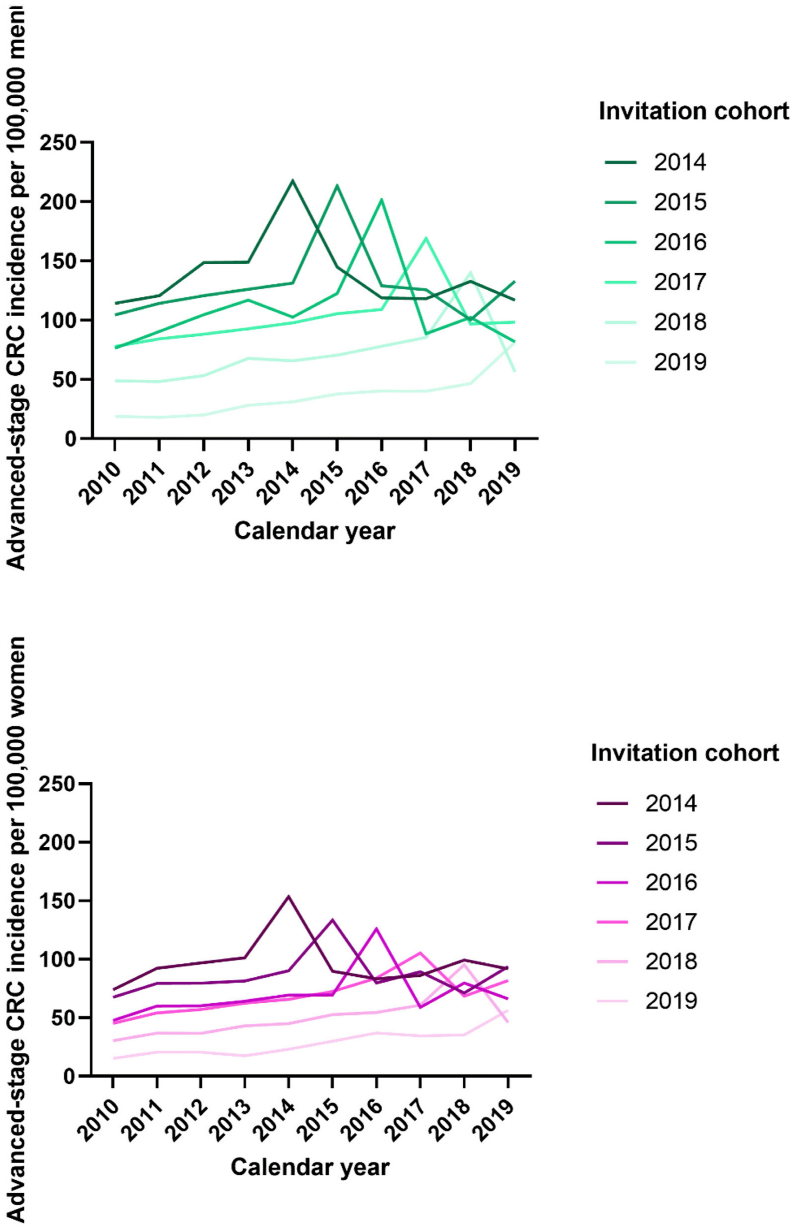

Figure 2(a), (b) - Advanced-stage CRC incidence patterns for men and women in different invitation cohorts.

Table 3 - Cumulative observed and expected advanced-stage CRC incidence in men and women in the period 2010–2019.

	No. individuals at risk (2010), n	Total advanced-stage CRCs from 2010-2019, n	Total expected advanced-stage CRCs from 2010-2019, n	Cumulative advanced-stage CRC incidence, %	Expected cumulative advanced-stage CRC incidence, %	*p* value
Men						
Invitation cohort 2014	456,000	5,830	7,186	1.28	1.58	<0.0001
Invitation cohort 2015	589,000	7,203	7,501	1.22	1.27	0.013
Invitation cohort 2016	495,000	5,107	5,521	1.03	1.12	<0.0001
Invitation cohort 2017	507,000	4,915	4,886	0.97	0.96	0.77
Invitation cohort 2018	450,000	3,101	3,045	0.69	0.68	0.47
Invitation cohort 2019	260,000	927	848	0.36	0.33	0.060
Women						
Invitation cohort 2014	464,000	4,278	5,123	0.92	1.10	<0.0001
Invitation cohort 2015	591,000	4,916	5,178	0.83	0.88	0.0068
Invitation cohort 2016	496,000	3,359	3,341	0.68	0.67	0.83
Invitation cohort 2017	508,000	3,423	3,515	0.67	0.69	0.27
Invitation cohort 2018	446,000	2,193	2,151	0.49	0.48	0.52
Invitation cohort 2019	256,000	738	697	0.29	0.27	0.28

The sensitivity analysis showed that the advanced-stage CRC incidence of birth cohorts invited to participate in screening in 2014 (1938, 1939, 1947, 1949) is different than that of birth cohorts of the same age 4 years earlier (1934, 1935, 1943, 1945; Figure 3a–d). Advanced-stage CRC incidence of 65-year olds in 2014 (birth cohort 1949) increased in 2014 and decreased in 2015, after which a slight increase was observed in 2016 (Figure 3a–d). A higher incidence was observed for birth cohort 1945 (65-year olds in 2010), implying that the difference between the observed and expected incidence based on the generated trend lines cannot only be attributed to by choice of trend lines. This was underlined by similar observed trends for other birth cohorts invited to screening in 2014 (1938, 1939 and 1947).

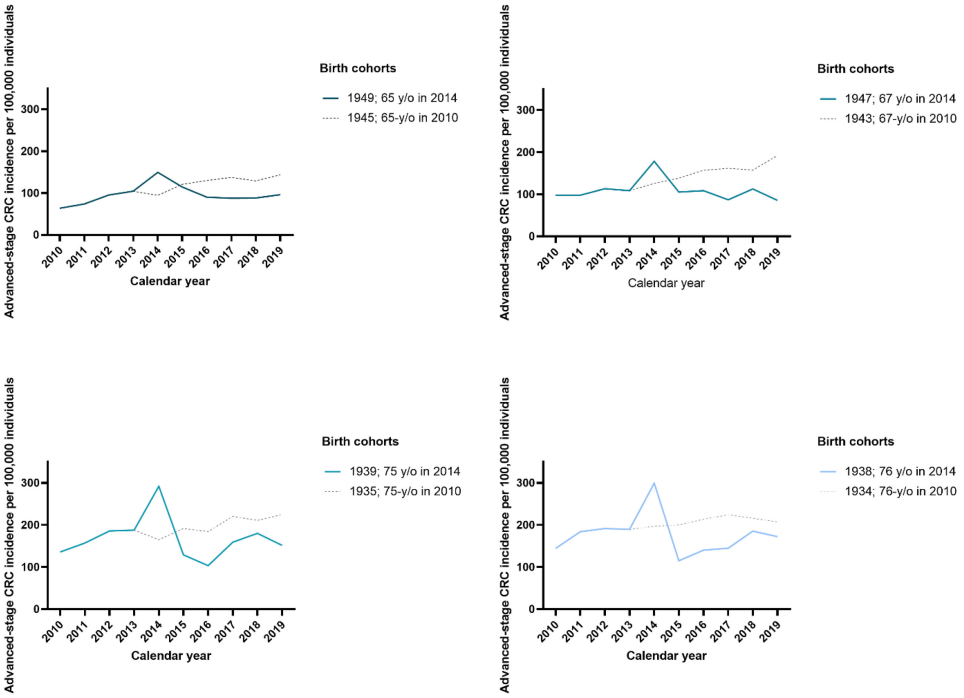

Figure 3(a), (b), (c), (d) - Sensitivity analysis: advanced-stage CRC incidence in birth cohorts from invitation cohort 2014 (1949, 1947, 1939, 1938) compared to cohort 2010 (1945, 1943, 1935, 1934).

DISCUSSION

This study evaluated patterns in advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence resulting from the phased rollout by birth cohort in the Dutch CRC screening programme, to estimate the effect of screening on CRC stage at diagnosis. We observed a temporary increase in advanced-stage CRC incidence in the first year individuals were invited. This increase was followed by a decrease below expected incidence levels. This pattern followed the phased implementation of the screening programme and was observed for all invitation cohorts. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was significantly lower than the expected cumulative advanced-stage CRC incidence in the period 2010–2019. Similar patterns in advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence were observed for men and women separately, although the incidence was higher in men than in women.

In previous publications, advanced-stage CRC incidence in the Netherlands was assessed as an early indicator for the effectiveness of the screening programme and a significant decrease in advanced-stage CRC incidence was observed after introduction of the programme (6,7). In this study, we further strengthened the causal relationship between the introduction of the programme and a decrease in advanced-stage CRC incidence. After introduction of the screening programme in 2014, an increase in advanced-stage CRC incidence was observed for all invitation cohorts in the years they were first invited to screening. This trend was mainly observed in the years these cohorts received their first screening invitation. At the end of the study period (2019), the observed advanced-stage CRC incidence was lower than the expected incidence based on trend lines in all invitation cohorts. This indicates the causal relationship between the introduction of the screening programme and a decrease in advanced-stage CRC incidence over time. To our knowledge, this is the first study assessing advanced-stage CRC incidence related to timing of invitation. Few previous studies reported on advanced-stage CRC incidence after introduction of FIT-screening. Levin et al. demonstrated a decreasing trend in advanced-stage CRC incidence after introduction of FIT besides primary colonoscopy screening in 2007 (12). At that time, sigmoidoscopy and guaiac faecal occult blood testing were discontinued. Chiu et al. demonstrated that advanced-stage CRC incidence and CRC-related mortality was lower for screened versus non-screened individuals (adjusted relative rate 0.66 and 0.60, respectively (13)). This indicated an association between the decrease in advanced-stage CRC incidence and CRC-related mortality in the long-term. However, in the study of Chiu, advanced-stage CRC was defined as ≥ stage II, and no data over time were shown. In an observational study

by Zorzi et al. on CRC-related mortality related to FIT-screening, an earlier decrease in age-standardised CRC-related mortality was observed for areas in Italy in which FIT-based screening was implemented early (2002–2004) compared to areas where screening was implemented at a later time point (2008–2009 (14)). The abovementioned results should be cautiously interpreted with regard to ours because multiple screening modalities were used side-by-side, different FIT cut-offs and screening intervals were applied, and CRC background risk differed. Still, when looking at trends in CRC screening performance indicators, similar patterns were observed in our study. Last, advanced-stage CRC incidence was higher in men than in women as was observed in multiple previous studies, but trends were similar (15). The larger differences between observed and expected advanced-stage CRC incidence in 2019 for men than women could be explained by the higher FIT-sensitivity in men than women (16,17).

We observed significant differences between cumulative advanced-stage CRC incidence and expected cumulative advanced-stage CRC incidence in the period 2010–2019 in the 2014–2016 invitation cohorts. This difference was not observed yet for the 2017 and 2018 invitation cohorts. In the 2019 invitation cohort, we actually observed a slightly higher cumulative advanced-stage CRC incidence than the expected cumulative advanced-stage CRC incidence. This pattern across all birth cohorts supports the hypothesis that screening is the main cause of changes in the cumulative advanced-stage CRC incidence. Indeed, first screening promotes the diagnosis of CRC, resulting in an initial peak in (advanced-stage) CRC incidence. This is exactly what we observe in the 2019 cohort, which was invited only once. After that first screening, time and repeated screening is needed to compensate for the peak in (advanced-stage) CRC incidence. Therefore, we do not see a statistically significant difference in the 2017 and 2018 invitation cohorts, but we do see a statistically significant difference in the earlier cohorts, which were invited for screening more often and longer ago. Interestingly, in men, the cumulative advanced-stage CRC incidence was significantly lower than the expected advanced-stage CRC incidence in the 2014–2016 invitation cohorts, whereas in women, only in the 2014 and 2015 invitation cohorts a significant difference was observed between the observed and expected cumulative advanced-stage CRC incidence. This could indicate that screening has a greater protective effect on the advanced-stage CRC incidence in men than in women. A major strength of this study is the availability of detailed data from a large national cancer registry, which allowed us to conduct analyses by birth cohort. Second, when assessing changes in trends of surrogate quality indicators, the fact that CRC survival has significantly improved in recent years due to advances in surgical oncological treatment, should also be taken into account. Modification of

(treatment) guidelines usually is quite time-consuming, hence using this surrogate quality indicator (i.e. advanced-stage CRC incidence patterns over time) is more reliable, as time effects are less influential. The main limitation of this study is the introduction of bias due to the ecological design. It is inevitable that randomised controlled trials (RCTs) are considered higher level evidence than (retrospective) cohort studies. Since RCTs on the efficacy of FIT-based screening are lacking and unlikely to be initiated in the future, we must rely on the results of previous guaiac faecal occult blood testing-based RCTs and FIT-based observational studies, such as our study. Despite the design of our study, we demonstrated a stronger association between the introduction of the screening programme and a decrease in advanced-stage CRC incidence than other cohort studies due to the analyses by birth cohort.

We used advanced-stage CRC reduction as outcome, rather than CRC mortality reduction, the ultimate outcome of screening. A reduction in CRC-related mortality is not to be expected until the mid-to-long-term after the introduction of a screening programme due to lead-time bias and the average survival of CRC. Therefore, adequate surrogate quality indicators for the eventual decrease in CRC-related mortality are important to identify. Cuzick et al. nicely discussed surrogate end-points for cancer screening trials and demonstrated these using data from the UK Flexible Sigmoidoscopy Screening Trial (18). Projected mortality based on stage-adjusted cancer incidence yielded most promising results and allowed the analysis of mortality to be advanced by more than three years. Though promising, a key requirement for this stage-based predicted mortality is the identification of cases and controls, which significantly complicates data retrieval. As demonstrated by Cuzick et al., the results presented in our study imply that we can conservatively assume that CRC-related mortality will also decrease in the mid-to-long-term. Our results are applicable to several other countries that introduced organised FIT-screening programmes, such as Slovenia and Denmark, but especially to countries that initiated FIT-screening at a later time point, such as Finland and England (15).

To conclude, we observed a short increase in advanced-stage CRC for all invitation cohorts first invited for screening in 2014–2019, followed by a decrease below expected incidence levels, coinciding with the pattern of the phased implementation. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was lower than the expected cumulative advanced-stage CRC incidence in the period 2010–2019. These findings support a causal relationship between the introduction of the Dutch CRC screening programme and a decrease in advanced-stage CRC incidence.

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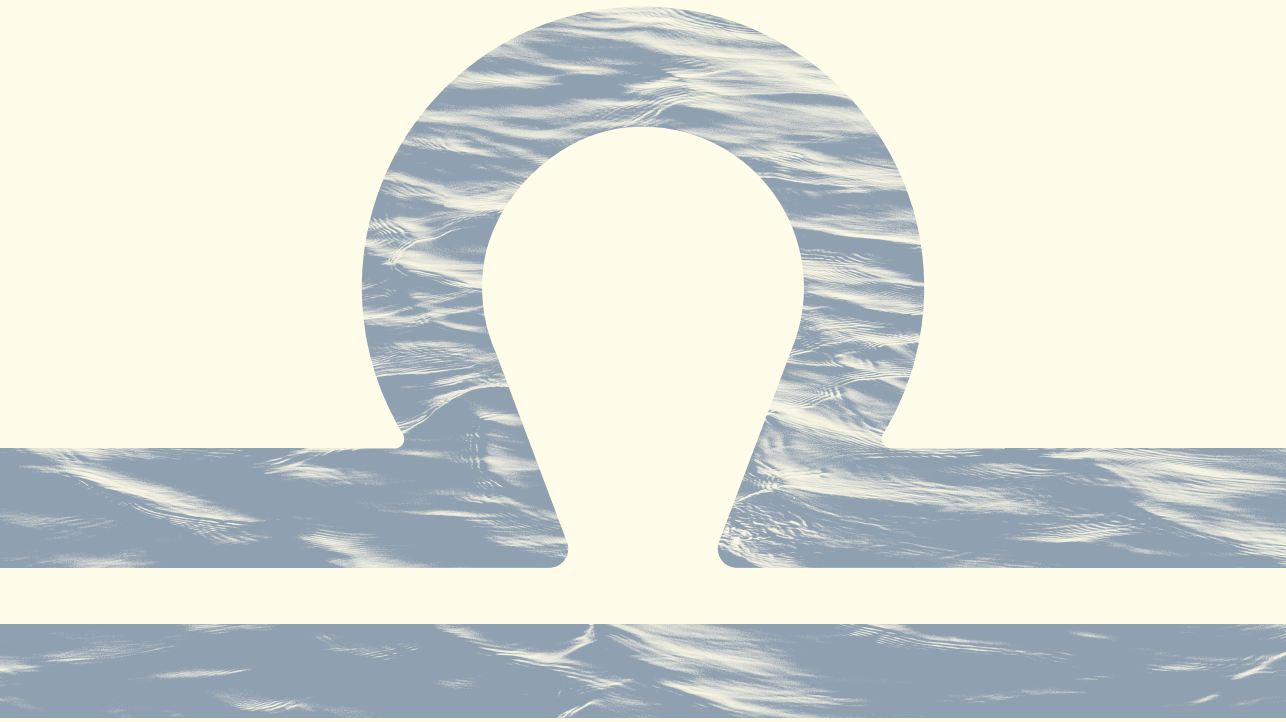

Chapter 4

Differences in treatment strategy of stage I CRCs: a population-based study of CRCs detected within and outside screening

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ABSTRACT

Background

Screen-detected colorectal cancers (CRCs) are often treated less invasively than stage-matched non-screen-detected CRCs, but the reasons for this are not fully understood. This study evaluated the treatment of stage I CRCs detected within and outside of the screening program in the Netherlands.

Methods

Data from the Netherlands Cancer Registry for all stage I CRCs diagnosed between January 1, 2008 and December 31, 2020 were analyzed, comparing patient, tumor, and treatment characteristics of screen-detected and non-screen-detected stage I CRCs. Multivariable logistic regression was used to assess the association between treatment (local excision only vs. surgical oncologic resection) and patient and tumor characteristics, stratified for T stage and tumor location.

Results

Screen-detected stage I CRCs were relatively more often T1 than T2 compared with non-screen-detected stage I CRCs (66.9% vs. 53.3%; P<0.001). When only T1 tumors were considered, both screen-detected colon and rectal cancers were more often treated with local excision only than non-screen-detected T1 cancers (odds ratio [OR] 2.19, 95%CI 1.93–2.49; and OR 1.29, 95%CI 1.05–1.59, respectively), adjusted for sex, tumor location, lymphovascular invasion (LVI) status, and tumor differentiation.

Conclusions

Less invasive treatment of screen-detected stage I CRC is partly explained by the higher rate of T1 cancers compared with non-screen-detected stage I CRCs. T1 stage I screen-detected CRCs were also more likely to undergo less invasive treatment than non-screen-detected CRCs, adjusted for risk factors such as LVI and tumor differentiation. Future research should investigate whether the choice of local excision was related to unidentified cancer-related factors or the expertise of the endoscopists.

INTRODUCTION

In the last decades, many countries have implemented colorectal cancer (CRC) screening programs to reduce the incidence and mortality of CRC (1,2). Reductions in CRC incidence and mortality can be achieved by the removal of precursor lesions and detection of CRC at an early stage. Early-stage CRCs have better survival rates and require less invasive treatment than advanced-stage CRCs. Therefore, a stage shift resulting from the implementation of CRC screening implies the need for less invasive treatment of CRC and a decrease in mortality may be expected (3–6).

In previous studies it has been shown that screen-detected CRCs are more likely to be treated less invasively (i.e. by local excision only) than those detected outside of a CRC screening program (non-screen-detected CRCs) (6,7). Remarkably, this phenomenon also occurred when treatment for only stage I CRCs was considered, with significantly more local excisions when these CRCs were detected through screening (6). The reasons why early-stage screen-detected CRCs are treated by less invasive methods compared with non-screen-detected CRCs, even if they are diagnosed at the same stage, are still not fully understood.

Several hypotheses could account for the observed difference in treatment within stage I CRCs. First, there may be an uneven T1/T2 distribution for stage I CRCs detected within and outside of the CRC screening program. If proportionately more T1 stage I CRCs are detected by screening, this may lead to a higher rate of local excision only for screen-detected rather than non-screen-detected stage I CRCs (8). Second, the location of screen-detected CRCs differs from non-screen-detected CRCs; screening detects relatively more left-sided colon cancers (6,9,10). As left-sided colon cancers are more easily removed than right-sided colon cancers, we hypothesize that the higher proportion of local excisions for screen-detected stage I CRCs is due to the unequal distribution of cancers in the colon and rectum (11). Third, the presence of prognostic factors (i. e. resection margin status, lymphovascular invasion (LVI), grade of differentiation, or tumor budding) may drive the decision to refer for (additional) surgical oncologic resection (12–15). If these prognostic factors differ between screen-detected and non-screen-detected stage I CRCs, this is likely to result in different rates of surgical oncologic resection. Finally, other (nontumor-related) factors may have determined the decision to refer for surgical oncologic resection.

The aim of this study was to describe the treatment of stage I CRCs detected within and outside of the CRC screening program in the Netherlands on a population level. Furthermore, we aimed to determine to what extent patient and tumor characteristics explain the difference in treatment of patients with stage I CRC.

METHODS

Dutch CRC screening program

Since 2014, the nationwide CRC screening program has been gradually implemented in the Netherlands (16). The target population of the program is men and women aged 55–75. The target population is invited to undergo screening biennially and receives an invitation letter including a fecal immunochemical test (FIT; FOB-Gold; Sentinel Diagnostics, Milan, Italy). Individuals with a positive FIT receive an invitation to undergo colonoscopy. Individuals with a negative FIT are invited for repeat FIT screening after 2 years.

Databases

All patients diagnosed with stage I CRCs between January 1, 2008 and December 31, 2020 were selected from the Netherlands Cancer Registry (NCR); the NCR registers all newly diagnosed malignancies in the Netherlands. Data from the NCR include: patient characteristics (sex and age) and tumor characteristics (incidence year; tumor, node, metastasis (TNM)-staging; location; histology; LVI; tumor differentiation; and treatment). Data are linked to the Dutch nationwide pathology databank (PALGA) to identify whether these CRCs were screen-detected or non-screen-detected tumors (99.2% of patients from the NCR could be reliably matched). When patients had multiple primary CRCs, the tumor with the first incidence date was included in the analyses. Patients with synchronous CRCs (i.e. more than one tumor with the same date of diagnosis) were excluded from the analyses, as their treatment differs from patients with one tumor.

Definitions

The prescreening era was defined as the incidence years 2008–2013. The screening era was defined as the incidence years 2014–2020. Only individuals aged ≥55 and <80 years were included to ensure a similar age distribution of individuals with screen-detected and non-screen-detected CRCs. The upper age limit of 80 years was chosen to allow for a delay in screening invitation, return of the FIT, and/or CRC diagnosis.

CRC stage was classified using the TNM staging system effective at the time of diagnosis (6th, 7th, or 8th editions (17–19)). Patients who received neoadjuvant treatment were excluded (1,956 [8.0%] stage I CRCs) as such treatment may interfere

with the accurate evaluation of the initial staging. Stage I CRCs were defined as T1Nx/N0 and T2Nx/N0 tumors. Hereafter, we will refer to T1Nx/N0 CRCs as T1 CRC and to T2Nx/N0 CRCs as T2 CRC. Location was defined as follows: right-sided colon (cecum to transverse colon, C18.0, C18.2– C18.4), left-sided colon (splenic flexure to rectosigmoid, C18.5–C18.7, C19), rectum (C20), and overlapping and unspecified (C18.8–C18.9). Appendiceal cancers (C18.1) were excluded from this study. LVI was defined as (suspicion of) invasion of the cancer cells into either the blood or lymphatic vessels. A three-tiered classification system was applied for grade: well (grade 1), moderately (grade 2), and poorly differentiated (grade 3).

Local excision included endoscopic resection, transanal endoscopic microsurgery (TEM), or transanal minimally invasive surgery (TAMIS). Surgical oncologic resection included all other forms of resection. When local excision was followed by surgical oncologic resection (secondary surgical oncologic resection), this was considered surgical oncologic resection.

Outcomes

Primary outcomes included the incidence and treatment of screen-detected versus non-screen-detected stage I CRCs, as a whole and separately for T1/T2 tumors. Secondary outcomes included tumor characteristics and factors associated with the treatment of screen-detected vs. non-screen-detected stage I CRCs.

Statistical analyses

Chi-squared testing was used to compare the characteristics of screen-detected and non-screen-detected stage I CRCs. The Wilcoxon–Mann–Whitney U test was used to compare the median ages of patients with screen-detected and non-screen-detected cancers. Two-sided P values <0.05 were considered statistically significant.

Join-point regression analyses were performed to evaluate changes in treatment by calculation and comparison of the annual percentage change (APC) in treatment of T1 CRC. Two join points were used as the maximum number of join points with a minimum difference of 0.5 percentage points. Multivariable logistic regression analyses were used to assess the association between treatment (local excision only versus surgical oncologic resection) and mode of detection (screen-detected vs. non-screen-detected), sex, age category, LVI status, tumor differentiation, and location of the tumor. The presence of multicollinearity was checked using the variance inflation factor (VIF). VIF values ≥ 5 were considered to

indicate collinearity and highly correlated variables were removed from the model. Separate models were constructed for T1 colon and T1 rectal cancers. As almost all T2 CRCs were treated by surgical oncologic resection, the number of patients with T2 CRCs treated by local excision only was insufficient to perform join-point and logistic regression analyses.

Join point regression analyses were performed using Join point regression software of the US National Cancer Institute. All other analyses were performed using R version 4.0.2.

Sensitivity analysis

A sensitivity analysis was performed to rule out selection bias in the referral of screen-detected versus non-screen-detected stage I (T1) CRCs. Selection bias may be present if a higher proportion of T1 cancers in one group is less often treated by surgical oncologic resection and is therefore not examined for lymph node metastases (LNM). We examined data from all T1 tumors diagnosed from 2014 to 2020 (stage I and IIIa/b) (Appendix Table 1). We compared the treatment of screen-detected T1 tumors with the treatment of non-screen-detected T1 tumors. Where there are similar treatments for screen-detected stage I T1 CRCs and non-screen-detected T1 CRCs, biases in the selection and conclusions with regard to the treatment of stage I T1 CRCs are less likely to arise.

RESULTS

In the period 2008–2020, 22,433 stage I CRCs were identified in patients aged 55–79 years. Of these cancers, 6,130 (27.3%) were detected in the period prior to the implementation of screening (2008–2013). In the screening period (2014–2020), 6,188 (27.6%) screen-detected and 10,115 (45.1%) non-screen-detected stage I CRCs were identified. A total of 277 (1.2%) CRCs with unknown T stage were excluded from the analyses.

Patient and tumor characteristics for stage I CRCs

In the prescreening era, stage I CRCs were comprised of 50.4% (n=3,052) T1 CRCs and 49.6% (n=3,008) T2 CRCs (Figure 1). In the screening era, screen-detected stage I CRCs comprised 68.5% (n=4,172) T1 CRCs and 31.5% (1,922) T2 CRCs. Non-screen-detected stage I CRCs consisted of 54.6% (n=5,464) T1 CRCs and 45.4% (4,538) T2 CRCs. The T1/T2 proportion differed significantly between screen-detected and non-screen-detected stage I CRCs (P<0.001). Patients with screen-detected CRCs were slightly younger than patients with non-screen-detected CRCs (P<0.001) (Table 1). For all stage I CRCs in the screening era, regardless of the mode of detection, the majority of patients were male, with the largest proportion of men in the T1 stage I CRC group (P<0.001) (Table 1).

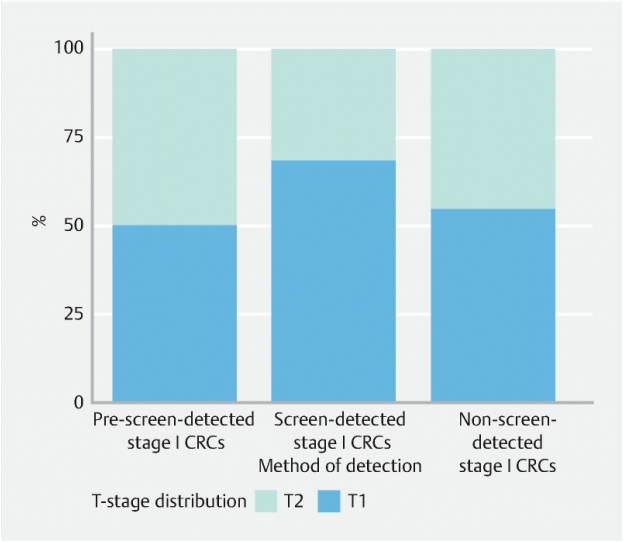

Figure 1 - T-stage distribution of stage I colorectal cancers (CRCs) by method of detection. Pre-screening CRCs were not taken into account in statistical analysis.

Table 1 - Characteristics of T1/T2 stage I colorectal cancers (CRCs) detected within and outside of the CRC screening program.

	Screen-detected T1 CRC	Non-screen-detected T1 CRC	*p* value	Screen-detected T2 CRC	Non-screen-detected T2 CRC	*p* value
n (total)	4,172	5,464		1,922	4,538	
Age (years, median, IQR)	67 (63-73)	69 (63-74)	***	67 (63-73)	70 (64-74)	***
Sex, n (%)			***			0.76
Men	2,643 (63.4)	3,230 (59.1)		1,108 (57.6)	2,596 (57.2)	
Women	1,529 (36.6)	2,234 (40.9)		814 (42.4)	1,942 (42.8)	
Location*			***			***
Left-sided	2,585 (62.9)	2,291 (42.7)		749 (39.3)	1,412 (31.5)	
Right-sided	528 (12.8)	1,428 (26.6)		695 (36.4)	1,921 (42.9)	
Rectum	999 (24.3)	1,643 (30.6)		463 (24.3)	1,149 (25.6)	
LVI*			0.33			0.75
No	2,824 (67.7)	3,511 (64.3)		1,409 (73.3)	2,969 (65.4)	
Yes	473 (11.3)	550 (10.1)		180 (9.4)	393 (8.7)	
Unknown	875 (21.0)	1,403 (25.7)		333 (17.3)	1,176 (25.9)	
Differen-tiation**			0.23			0.57
Grade 1	40 (1.0)	286 (5.2)		21 (1.1)	128 (2.8)	
Grade 2	3,749 (89.9)	4,528 (82.9)		1,739 (90.5)	3,999 (88.1)	
Grade 3	79 (1.9)	121 (2.2)		69 (3.6)	147 (3.2)	
Unknown/NA	304 (7.3)	529 (9.7)		93 (4.8)	264 (5.9)	

IQR, interquartile range; LVI, lymphovascular invasion; NA, not applicable.

*Category "unknown" was not taken into account for chi-squared testing.

**Chi-squared testing for grade 1 + grade 2 vs. grade 3 (category "unknown" was not taken into account).

***: <0.0001

In the prescreening era, a total of 33.6% (n=2,059) stage I cancers were right-sided, 47.1% (n=2,886) were left-sided, and 17.2% (n=1,051) were rectal cancers. In the screening era, location significantly differed between screen-detected and non-screen-detected stage I CRCs; screen-detected stage I cancers were more often located in the left side of the colon (54.7%, n=3,386) than non-screen-detected stage I cancers (37.0%, n=3,747; P<0.001).

No differences in LVI status were observed for screen-detected and non-screen-detected CRCs. For T1 CRCs, LVI was present in 67.7% (n=2,824) of screen-detected CRCs compared with 64.3% (n=3,511) of non-screen-detected CRCs (P=0.33) (Table 1). For T2 CRCs, LVI was present in 73.3% (n=1,409) of screen-detected CRCs vs. 65.4% (n=2,969) of non-screen-detected CRCs (P=0.75). The

majority of both screen-detected and non-screen-detected stage I CRCs showed moderate differentiation in both T1 (P=0.23) and T2 (P=0.57) CRCs (Table 1).

Treatment of stage I colon cancers

In the prescreening era, 33.1% (n=746) of T1 and 0.4% (n=11) of T2 colon cancers were treated by local excision only. In the screening era, local excision was performed on 56.4% (n=1,753) of screen-detected vs. 35.9% (n=1,332) of non-screen-detected T1 colon cancers (P<0.001) (Figure 2a). This difference was not observed in T2 colon cancers; the majority of patients were treated by surgical oncologic resection (99.6%) and no significant differences were observed in treatment between screen-detected and non-screen-detected T2 colon cancers (P=0.89) (Figure 2b). The proportion of T1 colon cancers treated by local excision slightly increased over time in screen-detected colon cancers (APC 1.5%, 95%CI 1.4% to 4.4%) (Figure 3a), as well as in non-screen-detected colon cancers (APC 3.2%, 95%CI 3.1% to 9.9%) (Figure 3b). However, no significant changes were observed in trends and no join points were identified.

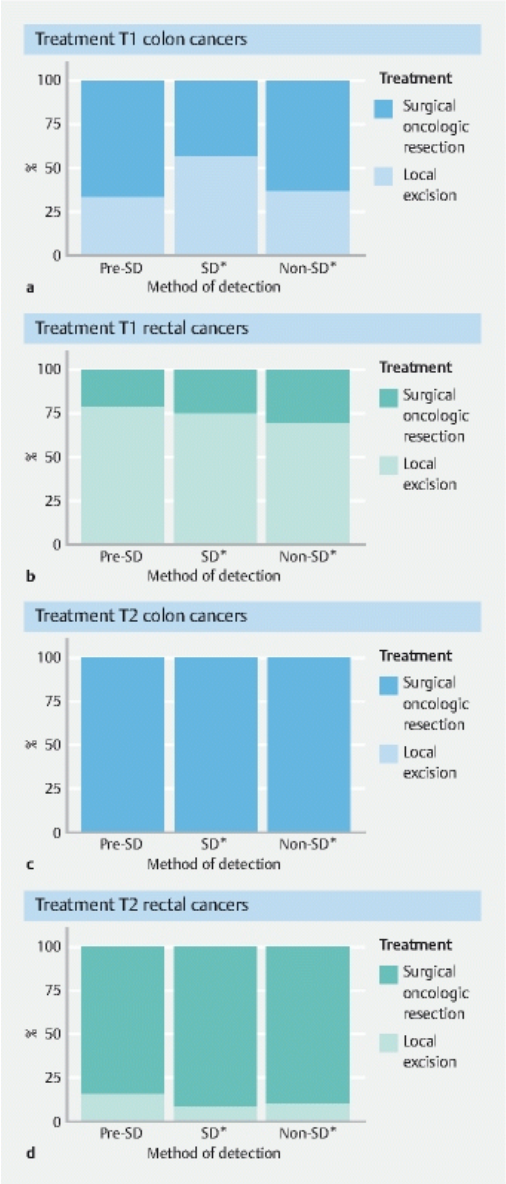

Fig. 2 Treatment of stage I colon and rectal cancers by T stage and method of detection.

SD: screen-detected. *: statistically significant difference.

Treatment of stage I rectal cancers

In the prescreening era, 79.1% (n=564) of T1 and 15.2% (n=47) of T2 rectal cancers were treated by local excision only. In the screening era, local excision was performed in 75.2% (n=751) of screen-detected vs. 69.2% (n=1,135) of non-screen-detected T1 rectal cancers (P<0.001) (Figure 2c). Again, treatment of T2 rectal cancers did not significantly differ: 91.8% (n=424) of screen-detected and 90.0% (n=1,033) of non-screen-detected T2 rectal cancers were treated by surgical oncologic resection (P=0.51) (Figure 2d). In the screening era, the proportion of T1 screen-detected rectal cancers treated by local excision decreased until 2016 and significantly increased after this: APC 2014–2016, −3.9% (95%CI −12.4% to 5.4%); APC 2016–2020, 3.2% (95%CI 0.7% to 5.8%) (Figure 3c). The proportion of T1 non-screen-detected rectal cancers treated by local excision increased from 2014 onwards; however, this trend was nonsignificant and no join points were identified (APC 2.7%, 95%CI −0.6% to 6.2%) (Figure 3d).

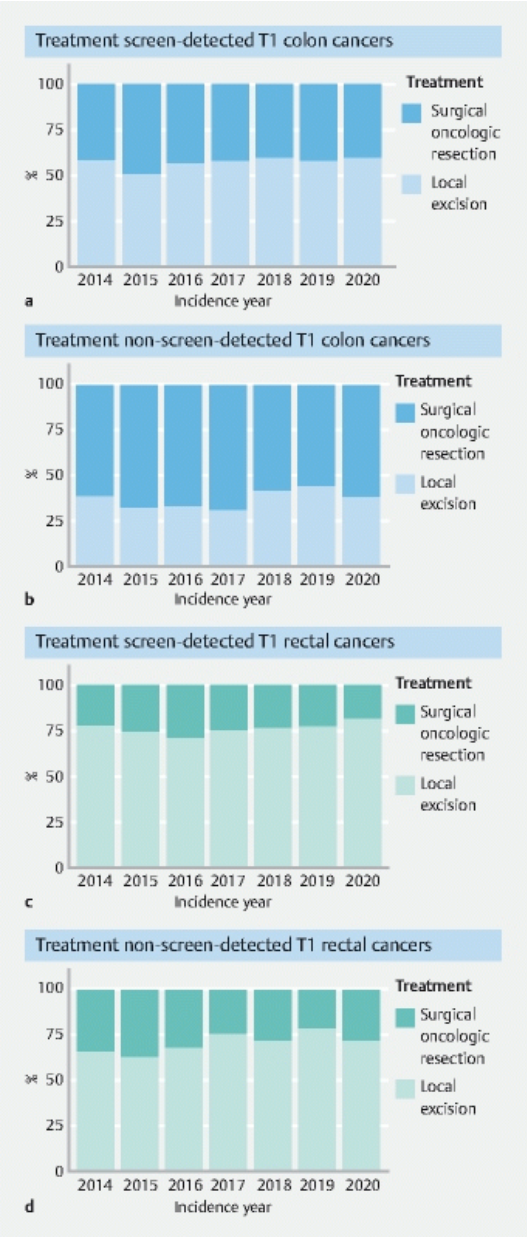

Figure 3 - Treatment of T1 colon and rectal cancers from 2014–2020 by method of detection.

Factors associated with the treatment of T1 tumors

In T1 rectal cancers, women had a higher likelihood of undergoing surgical oncologic resection than men (odds ratio [OR] 1.26, 95%CI 1.03 to 1.55) (Table 2). Patients with LVI were more likely to undergo surgical oncologic resection in both T1 colon (OR 3.15, 95%CI 2.61 to 3.81) and T1 rectal cancers (OR 1.55, 95%CI 1.17 to 2.03). Among patients diagnosed with T1 colon cancers, those with right-sided tumors were significantly more likely to undergo surgical oncologic resection than those with left-sided tumors (OR 4.20, 95%CI 3.61 to 4.90). Patients with poorly differentiated tumors were also more often treated by surgical oncologic resection compared with patients with well-differentiated tumors, in both T1 colon cancers (OR 6.96, 95%CI 3.63 to 12.85) and T1 rectal cancers (OR 3.19, 95%CI 1.26 to 8.43).

Table 2 - Multivariable logistic regression analyses for the association between treatment and patient and tumor characteristics for the separate T1 colon and T1 rectal cancer models.

	T1 colon cancers	**T1 rectal cancers**
	OR (95% CI)	*OR (95% CI)*
Sex		
Male	1	1
Female	1.03 (0.91-1.18)	1.26 (1.03-1.55)
Age category		
55-59 years	1	1
60-64 years	1.21 (0.98-1.51)	1.01 (0.72-1.43)
65-69 years	1.12 (0.91-1.37)	1.15 (0.83-1.59)
70-74 years	0.92 (0.74-1.13)	0.84 (0.60-1.17)
75-79 years	0.75 (0.60-0.94)	1.10 (0.76-1.59)
LVI		
No	1	1
Yes	3.15 (2.61-3.81)	1.55 (1.17-2.03)
Location		
Left	1	N/A
Right	4.20 (3.61-4.90)	N/A
Tumor differentiation		
Grade 1	1	1
Grade 2	1.58 (1.06-2.35)	1.32 (0.69-2.68)
Grade 3	6.96 (3.63-12.85)	3.19 (1.26-8.43)
Detection		
Screening	1	1
No screening	2.19 (1.93-2.49)	1.29 (1.05-1.59)

LVI: Lymphovascular invasion. OR: odds ratio. CI: confidence interval.

Upon adjusting for the previously mentioned risk factors, non-screen-detected T1 colon cancers had twice the likelihood of undergoing surgical oncologic resection in comparison with screen-detected T1 colon cancers (OR 2.19, 95%CI 1.93 to 2.49). A similar association was observed for T1 rectal cancers; however, the magnitude of the effect was smaller (OR 1.29, 95%CI 1.05 to 1.59).

Sensitivity analysis

When considering all T1 CRCs (stage I and stage III; n=10,245), 6.3% (n=278) of screen-detected T1 CRCs were stage III vs. 6.1% (n=355) of all non-screen-detected T1 CRCs (P=0.81) (Appendix Table 1). Local excision only was performed in 57.2% (n=2,543) of screen-detected T1 CRCs versus 43.6% (n=2,627) of non-screen-detected T1 CRCs (P<0.001).

DISCUSSION

The aim of this study was to describe the treatment of stage I CRCs detected within and outside of the CRC screening program in the Netherlands on a population level. Furthermore, we aimed to determine to what extent patient and tumor characteristics explain the difference in the treatment of patients with stage I CRC. We showed that two-thirds of all stage I CRCs detected through screening were T1 stage I CRCs. In contrast, only half of non-screen-detected stage I CRCs were T1 stage I. In addition, when only the T1 stage I colon and rectal cancers were considered, these were more likely to be treated with local excision when detected through screening.

We hypothesized that the less invasive treatment of screen-detected compared with non-screen-detected stage I CRCs could be explained by the unequal T1/T2 distribution within stage I CRCs. Screen-detected CRCs had a relatively higher proportion (13.6 percentage points) of T1 cancers compared with non-screen-detected CRCs. These findings suggest that the unequal T1/T2 distribution within stage I CRCs is an important explanation for the more frequent use of less invasive treatment for screen-detected stage I CRCs, as T1 tumors lacking high risk features for LNM can be safely treated by local excision. Fewer surgical oncologic resections may however have caused an underestimation of the T1 stage III CRCs owing to there being fewer lymph node dissections. However, as shown in the sensitivity analysis, the distribution between T1N0 and T1N+ for screen-detected and non-screen-detected CRCs was comparable, with only a 0.13 percentage point difference in T1N+ CRCs detected by screening. Therefore, the lower number of surgical oncologic resections among screen-detected T1 CRCs cannot be explained by the distribution of T1N0 and T1N+ tumors.

Several studies have compared rates of local excision and surgical oncologic resection of T1 CRCs. In the sensitivity analysis of all T1 CRCs in the current study, local excision rates were higher for screen-detected T1 CRCs (55.5%) than for non-screen-detected T1 CRCs (41.5%). These observed rates were higher than those found in four other studies from Italy (23.1%), the UK (31%), the USA (35.5%), and France (21.3%) (11,20–22). The reason for this is not fully understood, but it may be due to improvements in endoscopic techniques in recent years, making it easier to remove T1 CRCs through local excision only (23). Notably, some of the studies

mentioned were conducted many years ago, so may not reflect current trends in the management of T1 CRCs.

In addition to the explanation of less invasive treatment by the more favorable distribution of T1 and T2 stages for screen-detected stage I CRCs, we also observed differences in the treatment for screen-detected and non-screen-detected T1 stage I CRCs for both colon and rectal cancers. Non-screen-detected T1 colon cancers were twice as likely to be treated with surgical oncologic resection as were screen-detected T1 colon cancers, even after adjustment for well-known confounders (e. g. LVI and tumor differentiation). The same was true for rectal cancers, but to a lesser extent. Explanations for this phenomenon are unknown, but it may be related to the level of experience of endoscopists in assessing and/or removing malignant polyps in the right- and left-sided colon. Endoscopists first need to fulfill the eligibility quality criteria to be able to perform colonoscopies within the Dutch CRC screening program. Additionally, there are annual audits and colonoscopy results are benchmarked within the national screening program to ensure high quality endoscopies (i.e. adenoma detection rate of ≥ 40%, cecum intubation rate of ≥95%) (24). This may bias the screening program towards having more endoscopists who can assess polyps for local excision. Unfortunately, we were not able to distinguish whether endoscopies were performed by an expert endoscopist, or in an expert center or a general endoscopy center, which may also be related to the performance of the endoscopist, as well as data on resection margin or en bloc resection. In addition to endoscopist experience, observed treatment differences may ber elated to other tumor characteristics (i.e. morphology, residual tumor status, size of the tumor, and tumor budding) of CRCs that were not reported or other patient-related characteristics. For example, in our study we observed that men with rectal cancers were more often treated with local excision only compared with women.

Another explanation for more local excisions in the screen-detected stage I CRC group is tumor location. Among all T1 colon cancers, right-sided tumors were more often treated by surgical oncologic resection. Relatively more left-sided colon cancers are detected through FIT-based screening than outside of the screening program (6). This partly explains the larger proportion of local excisions only in patients with screen-detected T1 colon cancers, as left-sided and rectal tumors can more often be removed with noninvasive treatment methods. Other characteristics of the patient or tumor may have also driven the treatment decision. LVI status and

poor differentiation grade were associated with higher rates of surgical oncologic resection, which is in line with our expectations, the literature, and Dutch guidelines because of the risk of LNM (15,25,26). However, given the similar distribution of LVI and differentiation grade in both screen-detected and non-screen-detected T1 CRCs, this cannot explain the difference in treatment.

Despite the significant association between LVI and surgical oncologic resection, the proportion of tumors with LVI (i.e. 11% of T1 colon cancers) was much lower than the expected 18-30% found in the literature (27,28). An explanation for this could be the significant number of patients (approximately 25%) with unknown LVI status, which has also been observed in other population-based studies using national databases. We do not however anticipate a difference in the LVI status between the unknown cases in the screen-detected and non-screen-detected groups.

A major strength of this study is its large sample size, including all stage I CRCs diagnosed between 2008 and 2020, using nationwide population-based cancer registry data. The large sample size enabled us to carry out multiple subgroup analyses. By using a nationwide database, we could include all CRCs regardless of which hospital the diagnosis was made in (i.e. academic medical centers, teaching hospitals, or peripheral/general hospital).

The main limitation of this study is the absence of data on relevant risk factors (i.e. morphology, residual tumor status, and tumor budding) that could have driven the choice of treatment. This is due to the fact that some of these factors were only partly available in the NCR, while others were not registered until a later phase of the study. Moreover, complete information on co-morbidities or patient preferences is only accessible for a proportion of the patients included in the national database. Because these risk factors are not assessed and/or recorded in a standardized manner or available on a population level, we did not incorporate them in the statistical analyses. Standardized assessment and reporting of relevant risk factors is recommended.

Furthermore, we encountered the difficulty of distinguishing between secondary oncologic resections and direct referral for oncological resection, as the linkage between local excisions followed by surgical oncologic resection was not consistently reliable. Nonetheless, since 2019, this link has become more dependable, potentially enabling a subgroup analysis to be carried out in the future.

The difference in treatment between screen-detected and non-screen-detected stage I CRCs cannot be fully explained by the available risk factors in this study, suggesting that the mode of detection partially drives the more favorable treatment. The greater competence of endoscopists in identifying and assessing potentially malignant polyps to be eligible for local excision, along with the better health of the screened population may contribute to this difference. Many endoscopy centers performing local excisions within the screening program currently have an expert endoscopist who performs en bloc resections and/or surgeons who perform TEM or TAMIS, or appointments with referral centers.

Colonoscopies performed within the screening program are all performed by accredited endoscopists. However, no data were available on whether colonoscopies for local excision or colonoscopies outside of the screening program were performed by these accredited endoscopists or by general endoscopists. Furthermore no data were available on the type of center where local excisions were performed. This might introduce some bias in the results, as accredited screening endoscopists are also likely to perform colonoscopies outside of the screening setting, which implies equal expertise in the local treatment of screen-detected and non-screen-detected CRCs. Quality control measures set in the screening program might therefore also be imposed for endoscopies performed outside of a screening setting. Quality control measures should at least include whether an en bloc resection was performed and details about radicality (R0/R1 resection).

Long-term recurrence rates of locally excised T1Nx CRCs should confirm whether the decision for local excision only was justified, although a previous population-based study by Senore et al. suggested no difference in recurrence-free survival between local excision only vs. surgical oncologic resection for pT1 tumors with low risk features (11).

Another implication of the study is that the assessment of stage migration through population-based screening should not rely solely on TNM staging, as a large difference in treatment choice was observed between T1 and T2 stage CRCs. Subgrouping based on T and N classification may provide additional information that can facilitate in-depth evaluation of treatment patterns and outcomes in terms of CRC incidence and CRC-related mortality.

In conclusion, our findings support the idea that the higher level of less invasive treatment for screen-detected stage I CRCs can be attributed, at least in part, to the higher rate of T1 tumors in screen-detected stage I CRCs compared with non-screen-detected cases after adjusting for location, LVI presence, and tumor differentiation. Nevertheless, there are other factors that may account for the discrepancy in treatment between screen-detected and non-screen-detected cases that remain unclear. Future research should investigate if the choice of local excision was related to unidentified cancer-related factors or the expertise of the endoscopists. In the long-term, recurrence rate should confirm whether the choice of less invasive treatment was justified.

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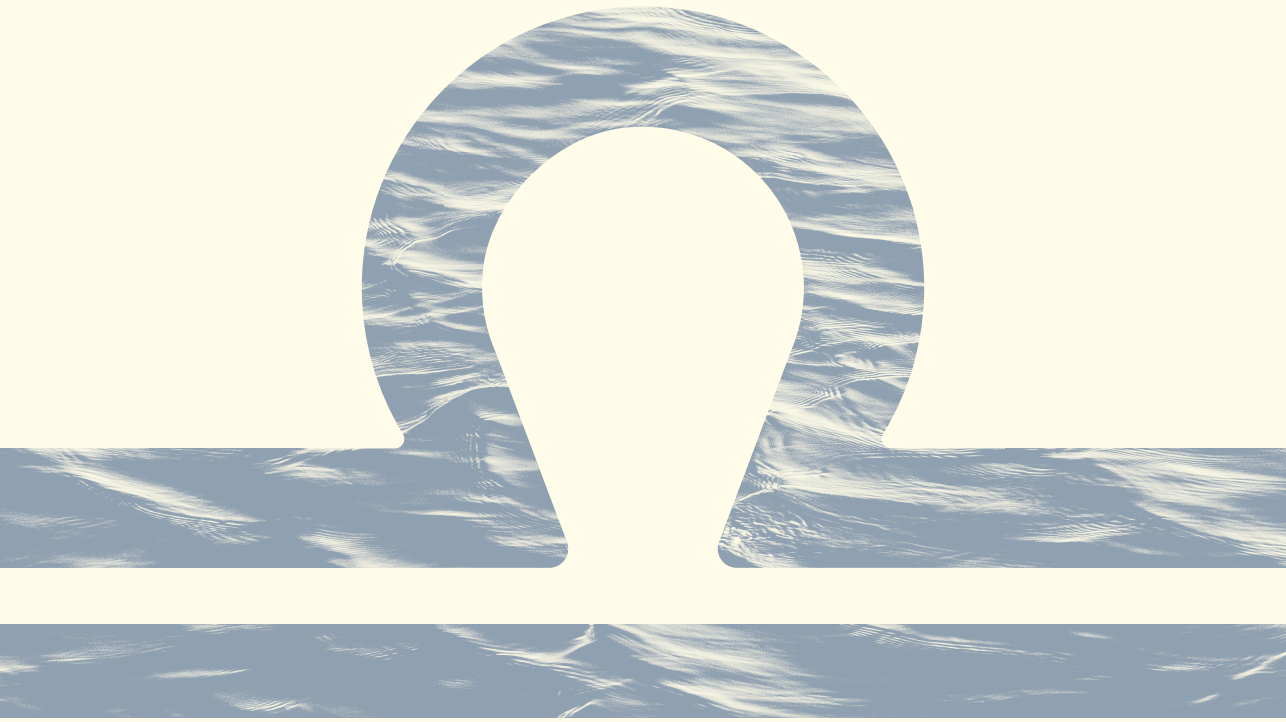
APPENDIX

Table 1 – T-stage distribution and treatment of all T1 CRCs diagnosed in the screening era

	Screen-detected T1 CRC	Non-screen-detected T1 CRC	*p* value
T-stage distribution			0.81
All T1 CRCs, n	4,445	5,800	
T1 stage I CRCs, n (%)	4,167 (93.7)	5,445 (93.9)	
T1 stage III CRCs, n (%)	278 (6.3)	355 (6.1)	
Treatment all T1 CRCs, n			<0.0001
Local excision, n (%)	2,543 (57.2)	2,527 (43.6)	
Surgical oncologic resection, n(%)	1,902 (42.8)	3,273 (56.4)	
Treatment T1 stage I CRCs			<0.0001
Local excision, n (%)	2,537 (60.9)	2,514 (46.2)	
Surgical oncologic resection, n(%)	1,630 (39.1)	2,931 (53.8)	
Treatment T1 stage III CRCs			0.39
Local excision, n (%)	6 (2.2)	13 (3.7)	
Surgical oncologic resection, n(%)	272 (97.8)	342 (96.3)	



Chapter 5

Advanced serrated polyps as a target of screening: detection rate and positive predictive value within a fecal immunochemical test-based colorectal cancer screening population

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ABSTRACT

Background

Advanced serrated polyps (ASPs) have a comparable risk to advanced adenomas for progression to colorectal cancer (CRC). The yield of most CRC screening programs, however, is based on advanced adenomas and CRC only. We assessed the ASP detection rate, and positive predictive value (PPV) including ASPs in a fecal immunochemical test (FIT)-based screening program.

Methods

We analyzed the findings of follow-up colonoscopies of FIT-positive screenees in the Dutch CRC screening program from 2014 until 2020. Data were retrieved from the national screening and pathology database. An ASP was defined as any serrated polyp of ≥ 10 mm, sessile serrated lesion with dysplasia, or traditional serrated adenoma. The ASP detection rate was defined as the proportion of colonoscopies with ≥ 1 ASP. PPV was originally defined as the proportion of individuals with a CRC or advanced adenoma. The updated PPV definition included CRCs, advanced adenomas, and/or ASPs.

Results

322,882 colonoscopies were included in the analyses. The overall detection rate of ASPs was 5.9%. ASPs were detected more often in women than men (6.3% vs. 5.6%; $P < 0.001$). ASP detection rates in individuals aged 55–59, 60–64, 65–69, and 70 + were 5.2%, 6.1%, 6.1%, and 5.9%, respectively ($P < 0.001$). The PPV for CRCs and advanced adenomas was 41.1% and increased to 43.8% when including ASPs. The PPV increase was larger in women than in men (3.2 vs. 2.4 percentage points).

Conclusions

5.9% of FIT-positive screenees had ASPs, but half of these were detected in combination with a CRC or advanced adenoma. Therefore, including ASPs results in a small increase in the yield of FIT-based screening.

INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide and causes substantial mortality and morbidity (1). CRC arises from polyps over the course of years. Until two decades ago, it was generally believed that adenomas were the sole precursors of CRC. In recent years, serrated polyps have also been identified as precursors and 15%–30% of all CRCs seem to arise from serrated polyps (2).

Advanced serrated polyps (ASPs) are serrated polyps that have a high risk of developing into CRC. Data on the prevalence of ASPs are sparse, partly owing to inconsistent terminology (3–5). In the most recent literature, ASPs are defined as either a serrated polyp ≥10mm in size, or one of the two serrated polyp subtypes, namely sessile serrated lesions (SSLs) with dysplasia, or traditional serrated adenomas (TSAs). This definition is based on large retrospective population studies that have reported an increased risk of metachronous CRC after the resection of these serrated polyp subtypes when compared with individuals without any significant lesions on baseline colonoscopy (6–8).

Despite the proven relevance of ASPs, they are usually not considered as a target lesion and are not accounted for in the yield of fecal immunochemical test (FIT) screening programs. Historically, the fact that serrated polyps were a relatively new concept, without a generally accepted and matured definition, has hampered their implementation into established performance indicators for screening.

Studies have shown the inferior diagnostic accuracy of FIT for the detection of large serrated polyps (≥10mm in size), with sensitivity varying between 5.1% and 18.4% (9–11). This may be explained by the low tendency of serrated polyps to bleed and the preferred proximal location of serrated polyps. Correct registration and classification of ASPs may help to set detection standards for future new screening tests. Timely detection of ASPs is especially relevant because these polyps follow a rapid transition to CRC once dysplasia develops.

The aim of this study was to determine the detection rate of ASPs in the Dutch FIT-based CRC screening program and to evaluate the additional yield of screening, taking into account ASPs, along with CRCs and advanced adenomas.

METHODS

Study design and population

We performed a cross-sectional analysis on colonoscopy and pathology data within the Dutch national CRC screening program (12). In this program, Dutch residents aged between 55 and 75 are biennially invited to perform a FIT. Screenees are referred for colonoscopy if they had a fecal hemoglobin (f-Hb) concentration above the set cutoff value for positivity. The FIT cutoff was 15 µg Hb/g feces at the introduction of the CRC screening program in 2014, and was increased to 47 µg Hb/g feces after 6 months (mid-2014).

All endoscopists performing screening colonoscopies within the national CRC screening program are required to perform high quality colonoscopies assessed by an upfront examination for accreditation, and regular monitoring and auditing (13). In short, all included endoscopists performed ≥200 colonoscopies per year, ≥50 polypectomies per year, achieved cecal intubation rates of ≥95%, adenoma detection rates of ≥30%, and removal rates of ≥90% of detected polyps. Reporting pathologists also require accreditation and regular monitoring, and were obligated to pass a validated e-learning on the histopathologic diagnosis of serrated polyps (14).

All colonoscopies that were performed in FIT-positive screenees between January 2014 and December 2020 were eligible for inclusion in our study. To ensure high quality data, colonoscopies were excluded from the analysis when the cecum was not reached and/or bowel preparation was insufficient (Boston Bowel Preparation Score <6) (15,16). Colonoscopies in which CRC was found were not excluded.

Data sources

Colonoscopy and pathology data were collected from the national screening information system (ScreenIT). As it was recognized that not all lesions were removed directly at the index colonoscopy, we considered all pathology findings until a period of 6 months after the index colonoscopy as screen-detected findings. Additional data on follow-up colonoscopies were retrieved from the Dutch nationwide pathology databank, PALGA (17).

Outcome definitions

Our main outcome parameter was the ASP detection rate, calculated as the proportion of colonoscopies in which at least one ASP was detected. The second

main outcome parameter was the incremental positive predictive value (PPV) when including ASPs as a relevant finding (i.e. advanced neoplasia). An updated definition of the PPV of FIT was calculated as the proportion of individuals diagnosed with advanced neoplasia (ASP, advanced adenoma, or CRC) within all screenees who underwent colonoscopy, and this was compared to the original definition of advanced neoplasia (advanced adenoma and CRC). CRCs were regarded as the most advanced lesions, followed by advanced adenomas, and then ASPs.

All CRCs were histologically confirmed as either adenocarcinoma, signet-cell carcinoma, or mucinous adenocarcinoma. Appendiceal cancers were excluded from analysis. Advanced adenoma was defined as any conventional adenoma of ≥10mm in diameter or adenoma with advanced histology (tubulovillous/ villous histological features or high grade dysplasia) (18). ASPs were defined as at least one serrated polyp of ≥10mm in diameter or an SSL with (low/high grade) dysplasia or a TSA (Figure 1) (19,20). Polyps with intramucosal carcinoma or carcinoma in situ were classified as high grade dysplasia in adenomas and as dysplasia in SSLs or TSAs. Non-relevant findings were categorized as "other findings," including nonadvanced serrated polyps and nonadvanced adenomas, and "no CRC and no polyp."

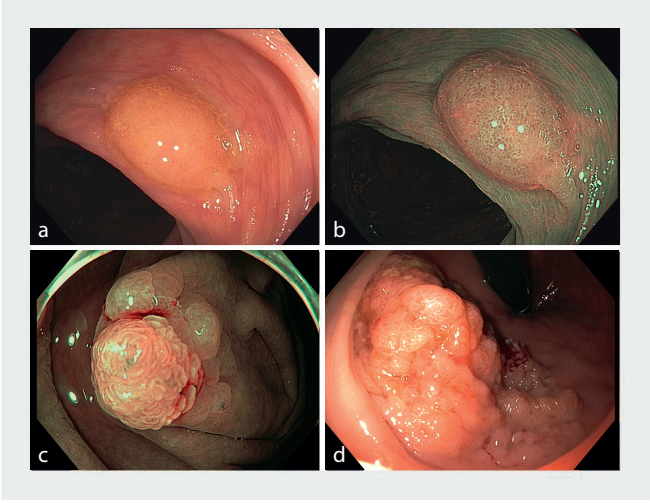

Figure 1 - Endoscopic images of three different types of advanced serrated polyps showing: a,b a sessile serrated lesion larger than 10mm in size on: a white-light endoscopy, with the typical mucus cap visible covering the polyp; **b** narrow-band imaging, with wide crypts recognizable as "black spots"; **c** a sessile serrated lesion with a focus of dysplasia seen as a villous pattern on top of the lesion; **d** a traditional serrated adenoma with typical polypoid and villous features.

Statistical analyses

Descriptive analyses for the ASP detection rate (and subgroups) are presented as counts and proportion of all colonoscopies, and median and interquartile range (IQR). Detection rates were stratified by sex, age (55–59, 60–64, 65–69, 70+ years), and invitation round (first/consecutive round). Differences between ASP subgroups were evaluated by using chi-squared testing for categorical variables and Mann-Whitney U testing for continuous variables.

The number needed to scope (NNS) for ASPs was defined as the total number of colonoscopies that would need to be performed in order to detect at least one ASP and was calculated by the inverse of the detection rate of ASPs. Furthermore, detection rates of each subgroup of ASP were evaluated, as well as the detection rate of ASPs stratified for polyp location and polyp size. The proximal colon was defined as being located proximal to the descending colon, including the splenic flexure. Analyses for polyp location and size were performed per polyp and therefore separately determined for index colonoscopies from the ScreenIT database and for colonoscopies within 6 months after the index colonoscopy from the PALGA database.

To identify risk predictors for the detection of ASPs, we performed univariate and multivariate logistic regression analysis including sex, age (55–59, 60–64, 65–69, 70+years) and invitation round (first/consecutive). Collinearity of the predictors were evaluated and considered absent with a tolerance level of >0.1. P values were two-sided and were considered statistically significant when <0.05. The PPV was stratified by sex and invitation round.

To evaluate whether the lower FIT cutoff influenced the PPV, we performed a sensitivity analysis calculating the PPV of individuals who were referred for colonoscopy using a FIT cutoff of 15 µg Hb/g feces. All analyses were performed in IBM SPSS Statistics 26.

Ethical approval

This study was conducted in accordance with the Dutch population screening act. Returning the FIT is considered as consent for the use of pseudonymized data of all screening colonoscopy and pathology reports, following the population screening act (WBO). All individuals had the right to object to the use of their data.

RESULTS

A total of 334,615 colonoscopies were performed during the study period, of which 11,733 (3.5%) were excluded, because of insufficient bowel preparation (2.8%; n=9,484) and/or no cecal intubation (2.0%; n=6,777). Of 322,882 included screenees who underwent a colonoscopy, the median (IQR) age was 66 (61–71) years and 133,552 (41.4%) were women (Table 1). In total 180,038 screenees (55.8%) were referred for colonoscopy after a positive FIT in the first invitation round, 142,844 (44.2%) were referred for colonoscopy after a positive FIT in consecutive rounds. In 310,387 cases (96.1%), screenees were tested with a FIT cutoff of 47 µg Hb/g feces and 11,896 screenees (3.7%) were tested with a FIT cutoff of 15 µg Hb/g feces.

Advanced neoplasia detection

The percentage of screenees with at least one CRC was 6.6% and this was 36.4% for advanced adenomas. In 19,014 screenees (5.9%), at least one ASP was detected (Table 1). ASPs were more often detected in women than in men (6.3% vs. 5.6%; P<0.001). The ASP detection rate differed by age, with lower detection rates for age group 55–59 years than the older age groups of 60–64, 65–69, and 70+ years (5.2% vs. 6.1% vs. 6.1% vs. 5.9 %; P<0.001). The proportion of screenees with at least one serrated polyp ≥10mm, SSL with dysplasia, or TSA were 4.1%, 1.3 %, and 0.9 %, respectively. Serrated polyps ≥10mm were more often diagnosed in women than in men (4.4% vs. 3.8%; P<0.001). The NNS to detect at least one ASP was lower for women than for men in age groups above 60 years (Figure 2). The opposite was true for advanced adenoma: the NNS to detect at least one advanced adenoma was lower for men than for women in these age groups. The NNS for CRC declined substantially with increases in the age groups for women and men.

Table 1 - Characteristics of the fecal immunochemical test (FIT)-positive screenees with advanced serrated polyps. Total FIT-positive colonoscopies

	Total FIT-positive colonoscopies	**≥1 ASP**	**p-value†**	**≥1 SP ≥10mm***	**p-value†**	**≥1 SSL with dysplasia***	**p-value†**	**≥1 TSA***	**p-value†**
	n= 322,882	n=19,014 (5.9%)		n=13,162 (4.1%)		n=4,214 (1.3%)		n=2,994 (0.9%)	
Sex, n (%)			p<0.001		p<0.001		p=0.20		p=0.02
Male	189,330 (59)	10,646 (5.6)		7,242 (3.8)		2,430 (1.3)		1,820 (1.0)	
Female	133,552 (41)	8,368 (6.3)		5,920 (4.4)		1,784 (1.3)		1,174 (0.9)	
Age, median (IQR)	66 (61-71)	66 (61-71)	-	65 (61-71)	-	67 (63-71)	-	67 (63-71)	-
Age groups, n (%)			p<0.001		p<0.001		p<0.001		p<0.001
55-59	59,891 (19)	3,128 (5.2)		2,262 (3.8)		559 (0.9)		406 (0.7)	
60-64	71,031 (22)	4,305 (6.1)		3,065 (4.3)		824 (1.2)		645 (0.9)	
65-69	102,607 (32)	6,279 (6.1)		4,314 (4.2)		1,458 (1.4)		944 (0.9)	
70+	89,353 (28)	5,302 (5.9)		3,521 (3.9)		1,373 (1.5)		999 (1.1)	
FIT-round, n (%)			p=0.79		p=0.94		p=0.06		p<0.001
first	180,038 (56)	10,620 (5.9)		7,335 (4.1)		2,289 (1.3)		1,773 (1.0)	
successive	142,844 (44)	8,394 (5.9)		5,827 (4.1)		1,925 (1.3)		1,221 (0.9)	
F-Hb (µg Hb/g feces), median (IQR)‡			-		-		-		-
15 µg/g	65 (28-171)	80 (31-186)		77 (30-185)		82 (32-186)		106 (31-193)	
47 µg/g	128 (72-208)	135 (75-213)		134 (74-213)		136 (75-212)		155 (80-221)	

ASP, advanced serrated polyp; SSL, sessile serrated lesion; TSA, traditional serrated adenoma; IQR, interquartile range; Hb, hemoglobin. F-Hb: fecal hemoglobin concentration.

* Screenees could be included in more than one column if they had more than one different subtype of ASP.

† Chi-squared test for categorical variables.

‡ Missing data for 599 screenees.

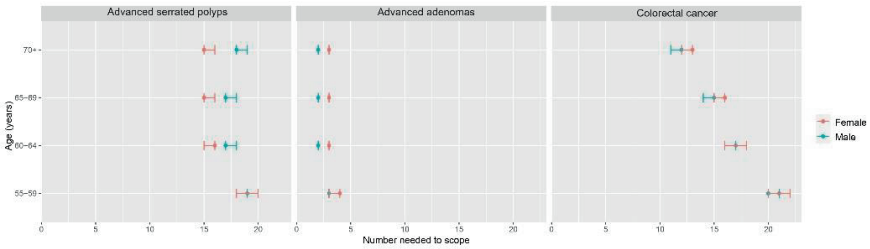

Figure 2 - Number needed to scope in order to detect at least one advanced serrated polyp, advanced adenoma, and colorectal cancer, according to age group and sex.

Predictors for advanced serrated polyp detection

Multivariate logistic regression analysis showed that individuals in older age groups were more likely to have an ASP diagnosis than individuals of 55–59 years (60–64 years, odds ratio [OR] 1.17, 95%CI 1.12–1.23; 65–69 years, OR 1.19, 95%CI 1.14– 1.24; and 70+years, OR 1.15, 95%CI 0.09–1.20). Men were less likely to have an ASP diagnosis than women (OR 0.89, 95% CI 0.87–0.92) (Table 2). Invitation round was not significantly associated with the detection of an ASP (OR 1.00, 95%CI 0.98– 1.03).

Table 2 - Association between the presence of an advanced serrated polyp and patient characteristics.

	Univariate OR (95%CI)	Multivariate OR (95%CI)
Sex, male	0.89 (0.87–0.92)	0.89 (0.87–0.92)
Age groups, years		
55-59	reference	reference
60-64	1.17 (1.12–1.23)	1.17 (1.12–1.23)
65-69	1.19 (1.13–1.24)	1.19 (1.14–1.24)
70+	1.15 (1.09–1.20)	1.15 (0.09–1.20)
FIT round, first	1.00 (0.97–1.03)	*NA*

OR: odds ratio; FIT, fecal immunochemical test; NA, not applicable.

Location and size of advanced serrated polyps

ASPs were more often detected in the proximal colon than in the distal colon, both at the index colonoscopy (63.4% vs. 36.6%) and in colonoscopies in the following 6 months (57.8% vs. 42.2%) (Table 3). Serrated polyps ≥10mm were more often located in the proximal colon (65.3% at the index colonoscopy;

56.0% in the following 6 months), which was also true for SSLs with dysplasia (69.9% and 75.2%, respectively). TSAs however were more common in the distal colon (73.8% and 67.1%, respectively), as were advanced adenomas (69.5% and 55.0%). At the index colonoscopy, the median size of serrated polyps ≥10mm was 12 mm, the median size of SSLs with dysplasia was 7 mm, and that of TSAs was 10 mm. The median size of advanced adenomas was in line with the size of ASPs at 11 mm.

Table 3 - Location and size of the serrated polyps identified by subtype.

	Advanced Serrated Polyps	**SP ≥10mm**	**SSL with dysplasia**	**TSA**
No. polyps, n (%)*				
Index colonoscopy (n=695,571)	23,905 (3.4)	19,353 (2.8)	4,772 (0.7)	3,089 (0.4)
6 months (n=45,803)	2,198 (4.8)	1,393 (3.0)	614 (1.3)	394 (0.1)
Index colonoscopy†, n(%)				
Proximal	13,866 (63.4)	11,641 (65.3)	3,058 (69.9)	671 (26.2)
Distal	7,990 (36.6)	6,187 (34.7)	1,319 (30.1)	1,893 (73.8)
6 months†				
Proximal	1,088 (57.8)	654 (56.0)	407 (75.2)	108 (32.9)
Distal	795 (42.2)	513 (44.0)	134 (24.8)	220 (67.1)
Size in mm, median (IQR) ‡				
Index colonoscopy	10 (10-15)	12 (10-15)	7 (4-10)	10 (5-15)
6 months	12 (10-15)	12 (10-15)	10 (6-14)	13 (7.5-22)

SSL, sessile serrated lesion; TSA, traditional serrated adenoma; IQR, interquartile range.

* Polyps could be included in more than one column if a serrated polyp ≥10mm also had dysplasia.
† For index colonoscopies, the location was missing for advanced serrated polyps, serrated polyps ≥10mm, SSLs with dysplasia, and TSAs in 2049, 1525, 395, and 525 cases, respectively, and for procedures within 6 months after the index colonoscopy in 315, 226, 73, and 66 cases, respectively.

‡ Polyp size for the index colonoscopy was based on the colonoscopy report, whereas for colonoscopies within 6 months, it was based on the pathology report.

Positive predictive value including advanced serrated polyps

Based on the most advanced lesion, the PPVs for CRC, advanced adenoma, and ASP were 6.6%, 34.5%, and 2.7%, respectively (Figure 3), meaning, in 2.7% of all FIT-positive screenees, at least one ASP was present in the absence of a CRC or advanced adenoma. As such, the PPV for relevant findings was 41.1% using the current definition of the national CRC screening program, which increased to 43.8% using our suggested updated definition including ASP. This PPV did not significantly change after exclusion of those colonoscopies performed in screenees using the lower FIT cutoff of 15 µg Hb/g feces. For the remaining 11,896 colonoscopies the PPV for CRC was 5.9%, for advanced adenoma 37.5%, and for ASP 2.2%. The PPV using the current definition was 36.3% for women and 44.5% for men and increased to 39.5% and 46.9%, respectively, when including ASPs. This increase of 3.2 percentage points for women and 2.4 percentage points for men was significantly different ($P<0.001$). The increase in PPV owing to the inclusion of ASPs was lower in the first invitation round (from 47.5% to 49.9%) than in consecutive rounds (from 32.9% to 36.0%; $P<0.001$).

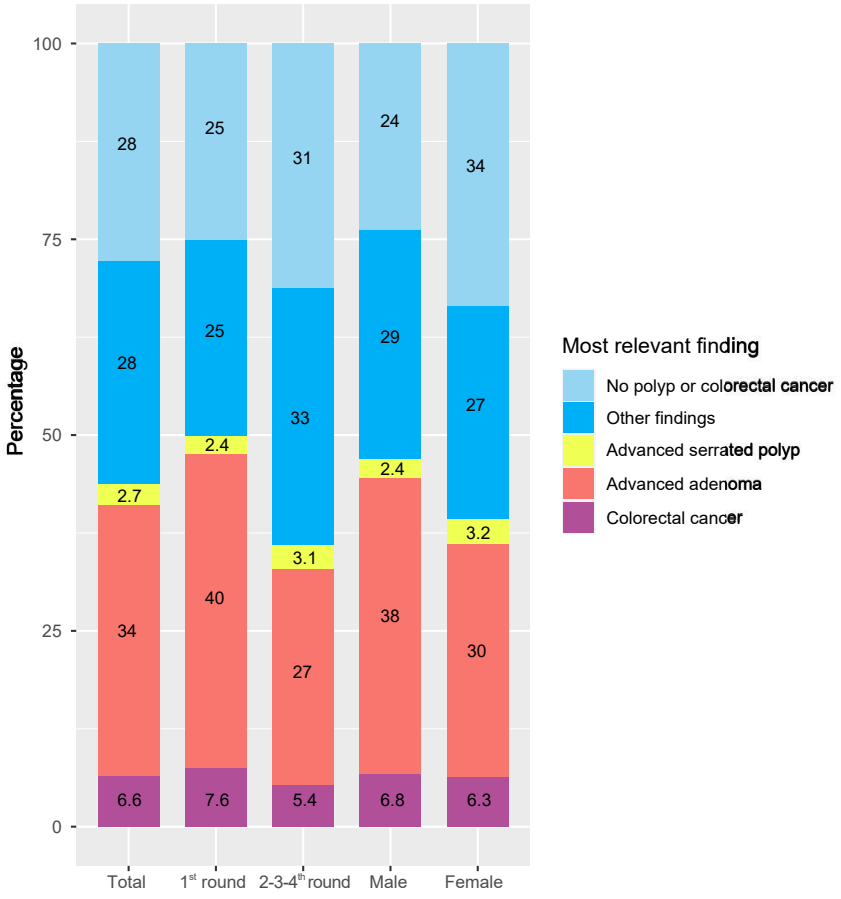

Figure 3 - Positive predictive value of the screening program based on the updated definition for advanced neoplasia including advanced serrated polyps.

Note: proportions have been rounded so they do not completely align with the numbers in the text.

DISCUSSION

In this study within the Dutch FIT-based CRC screening program, a considerable proportion of FIT-positive screenees who underwent follow-up colonoscopy had at least one ASP (5.9%). These lesions were more frequently detected in women and individuals in the older age groups (>60 years). Including ASPs in the yield of FIT-screening increased the PPV for advanced neoplasia from 41.1% to 43.8%.

Results from this study demonstrate that in a FIT-based CRC screening program, the additional yield of ASPs is modest at best. Definitions for yield and detection rates should be distinguished here because half of the screenees who had an ASP had a concurrent CRC or advanced adenoma so, following the original definition, were already considered as having a relevant finding (a positive finding when evaluating yield).

No previous studies have reported the additional yield of screening when including ASPs in terms of the PPV for advanced neoplasia, nor have they reported on the PPV for ASPs using our definition (i.e. any serrated polyp ≥10mm, SSL with dysplasia, or TSA). One study reported on the PPV for advanced neoplasia including CRC, advanced adenomas, and SSLs ≥10mm in a colonoscopy cohort, showing a PPV of 41%, which was comparable with our result (43.8%) (11). The estimated individual PPVs were 9% for CRC, 27% for advanced adenoma, and 3% for ASP, which are also consistent with our findings (6.6%, 34.5%, and 5.9%, respectively). However, this study by Redwood et al. was based on only 661 screenees who were scheduled for an average-risk screening or surveillance colonoscopy, making comparison with our setting of organized FIT-based screening difficult.

Our observation that FIT has a higher PPV for ASP in consecutive rounds, while detection rates were comparable, might be a result of the poor sensitivity of FIT for ASPs. In contrast, a higher bleeding risk associated with CRCs and advanced adenomas most likely explains these lesions being detected more often in the first screening round. This hypothesis is also supported by the fact that the PPV was not significantly higher when individuals who received a colonoscopy after testing positive at a lower FIT cutoff of 15 µg Hb/g feces were evaluated separately. Of note, when evaluating the current literature regarding the yield of CRC population

screening, one should take into consideration that a small proportion of serrated polyps might have been classified among advanced neoplasia owing to the limited reproducibility of the optical and pathological diagnosis of serrated polyps.

Some studies have reported detection rates of the different categories of ASPs in FIT-based or primary colonoscopy screening; however, none of these studies have used our definition of ASP and assessed it within an organized FIT-based CRC screening program. A study comparing three FIT-based national CRC screening programs showed comparable detection rates with our study, with detection rates for serrated polyps ≥10mm of 1.2%–2.5%, for SSLs with dysplasia of 0.2%–0.6%, and for TSAs of 0.1% (21). Studies reporting on primary colonoscopy screening demonstrated detection rates for serrated polyps ≥10mm of 1.1%–2.6%, for SSLs with dysplasia of 0.2%–1.5%, and for TSAs of 0.1%–0.8% (21–23).

Interestingly, when we compare these different screening settings, the ASP detection rates seem highly similar and in line with our results. Possibly this is also a result of the low sensitivity of FIT for ASPs, meaning that the detection of ASPs is a coincidental finding, rather than their being detected by FIT.

Therefore, the detection rate of ASPs likely corresponds to the ASP prevalence in the general population, instead of a preselected high risk population. Hence, here lies a great potential for a screening test that also targets screenees with ASPs. The ColoGuard (Exact Sciences; Madison, Wisconsin, USA) for instance, a multitarget stool DNA test including methylation markers, seems to have a promising higher sensitivity for ASPs, because SSLs with dysplasia are characterized by high DNA methylation levels (9,11). Screening with such tests could result in higher overall detection rates of ASPs, and therefore timely detection and resection of ASPs. The main restriction for the worldwide implementation of the ColoGuard are its complex logistics owing to the required large stool samples, lower specificity, and higher costs compared with FIT (24,25).

In this FIT-screening setting, ASPs were more often detected in women and older screenees. This finding is in line with previous studies, in which female sex has already been described as a risk factor for SSLs with

dysplasia and serrated polyp-derived CRCs (26–29). The differences between women and men were small however and were considered clinically less relevant. Nevertheless, it is important to note that this higher detection of ASPs in women is contrary to the known higher performance of FIT in men to detect advanced adenoma and CRC that our results have confirmed (30–32). These major sex differences in the performance of FIT testing might be relevant in the near future when a more personalized strategy based on risk factors, such as previous hemoglobin concentration, age, and sex could be used. If ASPs are not taken into consideration, women might be invited for CRC screening at an older age than men. As a consequence, relatively large numbers of ASPs would be missed and could develop into CRC.

Despite the modest increase in PPV when including ASPs as target lesions, this study substantially contributes to our under- standing of ASPs for the following reasons. First, the extensive organization of FIT-based screening programs depends completely on the cutoff value for positivity, and is led by multiple factors, including: colonoscopy capacity, the proportion of false positives and false negatives that is deemed acceptable, cost-effectiveness, and public health policies. Decision-making regarding false positives and false negatives should be based on the yield and expected CRC-related mortality reduction of a program, thereby taking into account all relevant lesions. Although modest, the increase in PPV by 2.7 percentage points is of importance, and reflects screenees who are currently incorrectly classified as false positives. Second, estimation of the detection rates of ASPs within a FIT-based screening program are necessary to enable any comparison with other screening tests, for example the multitarget stool tests. Third, accurate registration of (advanced) serrated polyps is essential to monitor and optimize the quality of (proximal) serrated polyp detection among endoscopists, which is highly relevant in clinical practice because higher serrated polyp detection rates are associated with a lower risk of interval postcolonoscopy CRC (33).

For the interpretation of our results, some limitations must be taken in consideration. First, colonoscopy reports were not linked automatically per polyp to pathology reports in the standardized database, impeding proper evaluation of polyp size, as this requires pathological polyp diagnosis and estimated polyp size by the endoscopist. We estimated an incorrect linkage of polyp type and polyp size in about 2% of all polyps. This included half of the

group of polyps within a FIT-positive screenees that had the same pathological diagnosis (serrated polyp or adenoma) and also shared the same location. This proportion, however, was too low to have influenced our outcomes significantly. Second, relevant findings like CRC and advanced adenoma were more often detected at the start of the screening program, owing to the fact that relatively older individuals were invited in the first years. The results we are currently presenting might therefore evolve over time. Third, the relative high cutoff value in our screening program might have influenced our outcomes; however, given the low sensitivity of FIT for ASPs, this might not have significantly affected the detection rates or PPVs for ASPs (34).

A strength of this study derives from the nationwide, prospective, and comprehensive data collection within our CRC screening program, which allowed for the analysis of a large sample of FIT-positive screenees referred for colonoscopy. Colonoscopies were performed across the Netherlands and the data is of high quality because of the thorough training and quality monitoring of endoscopists and pathologists in the screening program. Essential for this study was the quality of histopathological diagnosis, especially the subclassification of serrated polyps, which was assured by an obligatory e-learning module for all participating pathologists. This e-learning was shown to be effective (14).

In conclusion, we demonstrated a considerable detection rate of ASPs within colonoscopies performed after a positive FIT, while the additional yield of screening was 2.7 percentage points. We believe that, although this is a rather modest increase in the yield of screening, it nevertheless has some important clinical implications. As ASPs are high risk premalignant lesions, and reference standards for FIT and other new screening tests are needed, our results support taking these lesions into account when determining the yield of screening in a FIT-based population. Routinely monitoring the detection rate and PPV of relevant colorectal lesions including ASPs should be standard practice in organized CRC screening programs.

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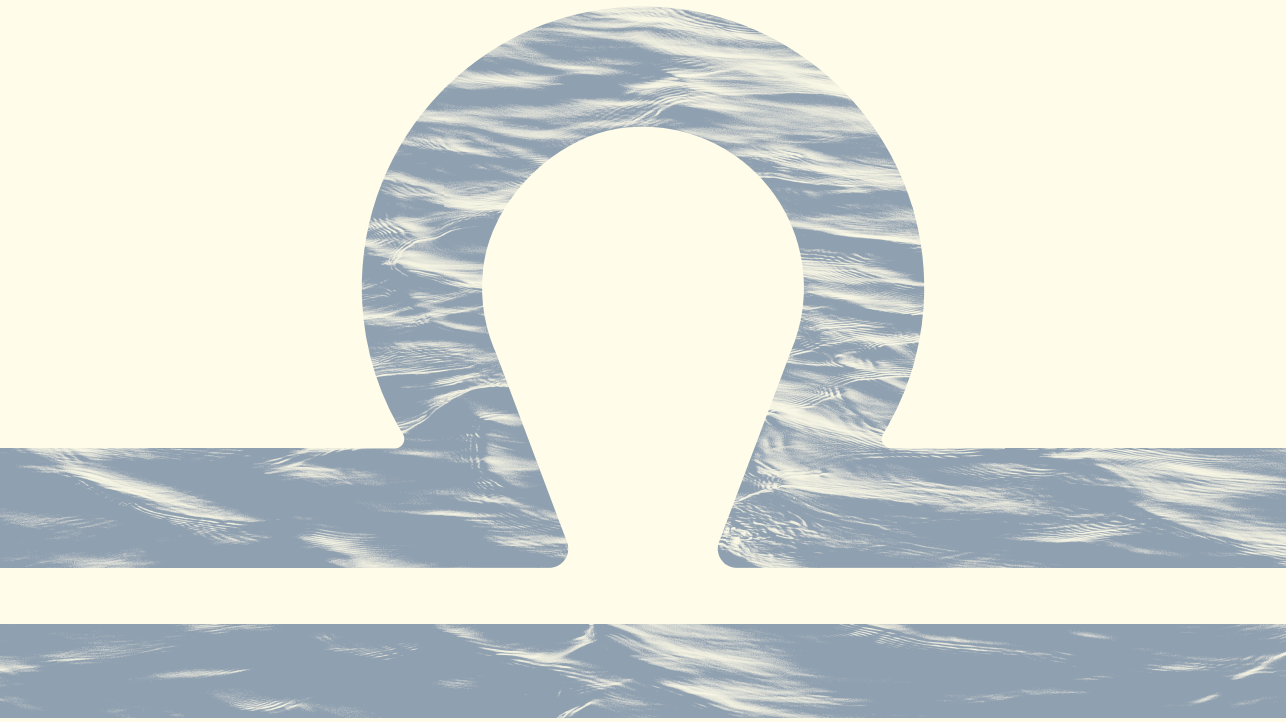
Part II

Towards personalized colorectal cancer screening for average-risk individuals in the Netherlands



Chapter 6

Factors associated with interval colorectal cancer after negative FIT: results of two screening rounds in the Dutch FIT-based CRC screening program

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ABSTRACT

The interval colorectal cancer (CRC) rate after negative fecal immunochemical testing (FIT) is an important quality indicator of CRC screening programs.

We analyzed the outcomes of two rounds of the FIT-based CRC screening program in the Netherlands, using data from individuals who participated in FIT-screening from 2014 to 2017. Data of individuals with one prior negative FIT (first round) or two prior negative FITs (first and second round) were included. Outcomes included the incidence of interval CRC in FIT-negative participants (<47 µg Hb/g feces [µg/g]), FIT-sensitivity, and the probability of detecting an interval CRC by fecal hemoglobin concentration (f-Hb). FIT-sensitivity was estimated using the detection method and the proportional incidence method (based on expected CRC incidence). Logistic regression analysis was performed to estimate whether f-Hb affects probability of detecting interval CRC, adjusted for sex- and age-differences.

Incidence of interval CRC was 10.4 per 10 000 participants after the first and 9.6 after the second screening round. FIT-sensitivity based on the detection method was 84.4% (95%CI 83.8-85.0) in the first and 73.5% (95% CI 71.8-75.2) in the second screening round. The proportional incidence method resulted in a FIT-sensitivity of 76.4% (95%CI 73.3-79.6) in the first and 79.1% (95%CI 73.7-85.3) in the second screening round. After one negative FIT, participants with f-Hb just below the cut-off (>40-46.9 µg/g) had a higher probability of detecting an interval CRC (OR 16.9; 95%CI: 14.0-20.4) than had participants with unmeasurable f-Hb (0-2.6 µg/g). After two screening rounds, the odds ratio for interval CRC was 12.0 (95%CI: 7.8-17.6) for participants with f-Hb just below the cut-off compared with participants with unmeasurable f-Hb.

After both screening rounds, the Dutch CRC screening program had a low incidence of interval CRC and an associated high FIT-sensitivity. Our findings suggest there is a potential for further optimizing CRC screening programs with the use of risk-stratified CRC screening based on prior f-Hb.

INTRODUCTION

Organized colorectal cancer (CRC) screening programs have been adopted widely with the aim to reduce CRC-related mortality. These programs are mostly based on fecal immunochemical testing for occult human hemoglobin (FIT). The quantitative nature of FIT (µg Hb/g feces) allows for adjusting the cut-off for a positive test result. Several factors can be considered to determine the optimal cut-off; that is, positivity rate, colonoscopy capacity and sensitivity of FIT for CRC.

The incidence of interval CRCs after a negative FIT may serve to indicate the sensitivity of FIT, based on the occurrence of false-negative FITs. Evaluation of the sensitivity of FIT and the incidence of interval CRC is necessary to assess the quality of the program (1). Besides, it can reveal information on characteristics of interval CRCs that might provide insight on the number of cancers missed in FIT-based screening. Previous research showed that higher fecal Hb (f-Hb) concentrations in prior screening rounds were associated with higher detection of CRC or advanced neoplasia (AN) in subsequent screening rounds, as well as a higher probability of detecting interval CRC after negative FIT (2–8). Still, the small sample sizes in those studies call for validation of this risk factor in larger populations.

In the Netherlands, an organized FIT-based screening program went ahead in 2014, inviting all individuals eligible for screening every two years. The complete target population has been invited from 2019 onwards and participation rates are consistently high (around 72%). A previous study from our group found that the Dutch CRC screening program revealed a low incidence of interval CRC and an associated high sensitivity of FIT after one screening round (5). Only few studies are available on the incidence of interval CRC and sensitivity after multiple screening rounds, especially detailed data on specific screening rounds are scarce (9).

In this study, we evaluated the incidence of interval CRC and sensitivity of FIT within the framework of the FIT-based CRC screening program in the Netherlands, both after one screening round (one prior negative FIT) and after two screening rounds (two prior negative FITs). In addition, we assessed characteristics (i.e., localization and stage distribution) of these interval CRCs, as well as the probability of detecting interval CRC based on f-Hb concentrations at prior screening.

METHODS

Dutch national screening program

In 2014, the Dutch national CRC screening program was introduced, for which all individuals aged 55 to 75 were invited biennially for FIT-based screening (FOB-Gold, Sentinel Diagnostics, Milan, Italy). The program was gradually rolled out by birth cohort. Since 2019, all individuals in the target population (around 4.4 million) have been invited at least once. Those with a positive FIT were referred for colonoscopy; in case of a negative FIT, participants were invited for a second test 24 months later. Initially, a FIT positivity cut-off of 15 µg Hb/g feces was used; this was adjusted to 47 µg Hb/g feces in June 2014. The rationale for this choice has been described previously (10).

Data collection

Real-time data from the Dutch CRC program stored in the national screening information system (ScreenIT) were linked with data from the Netherlands Cancer Registry (NCR). This would enable identifying CRCs diagnosed after a positive and after a negative FIT. Data from the NCR, including complete data on incidence and stage distribution, covered the period from January 1, 2014 to November 1, 2019. To ensure complete follow-up for analyses on interval CRC (24 months), only participants tested between January 1, 2014 and November 1, 2017 were included in the analyses. To maintain homogeneity within groups, only participants tested at the positivity cut-off of 47 µg Hb/g feces that was initiated in June 2014 were included. First screening round participants were defined as participants with one prior negative or positive FIT at the first invitation round. Second screening round participants were defined as participants with one prior negative FIT at the first invitation round and subsequent negative or positive FIT at the second invitation round.

Definitions

A negative FIT was defined as a FIT with f-Hb concentration <47 µg Hb/g feces. A positive FIT was defined as a FIT with f-Hb concentration ≥47 µg Hb/g feces. Interval CRC was defined as CRC diagnosed after a negative FIT and before invitation to the next screening round, according to the proposed nomenclature by the World Endoscopy Organization (11). For participants who were not eligible for the subsequent screening round because they had reached the upper age limit, interval

CRC was defined as CRC diagnosed within 24 months after a negative FIT. Screening-detected CRC was defined as CRC diagnosed within 180 days after a colonoscopy following a positive FIT. The episode sensitivity of FIT was defined as the percentage of individuals in the screened population who were identified by the FIT and confirmed as truly positive (i.e., having CRC) at colonoscopy. Episode sensitivity reflects the full diagnostic process of CRC screening per screening round (12).

Interval CRC was categorized as right-sided (caecum to transverse colon, C18.0, C18.2-C18.4), left-sided (splenic flexure to rectosigmoid, C18.5-C18.7, C19), rectum (C20), or overlapping and not otherwise specified (NOS; C18.8-C18.9) (13). Appendiceal cancers (C18.1) were excluded from analyses. In case of synchronous CRCs, the CRC with the most advanced stage was included in the analyses. Stage distribution was determined using the effective Tumor, Node, Metastases (TNM)-classification at year of diagnosis (seventh edition in 2014-2016, eighth edition from 2017).

Outcomes

Primary outcomes were the incidence of interval CRC, the episode sensitivity and the probability of detecting interval CRC by f-Hb concentration after the first and second round, respectively. The incidence of interval CRC was calculated by dividing the number of interval CRCs by the total number of participants with a negative FIT in the same screening round, and is presented per 10 000 participants with a negative FIT. Furthermore, we determined the probability of detecting interval CRC by f-Hb concentration, corrected for sex- and age-differences. Secondary outcomes were localization and stage distribution of interval CRCs and screening-detected CRCs diagnosed after the first and second round.

Statistical analysis

We estimated the incidence of interval CRC and episode sensitivity of FIT for CRC after the first and second screening round of the Dutch national CRC screening program. Episode sensitivity was estimated in two ways: through the detection method and the proportional incidence (PI) method. Episode sensitivity according to the detection method was calculated from the number of screening-detected CRCs (SD-CRC) per round divided by the sum of interval CRCs and screening-detected CRCs for that specific round, using the formula: Sensitivity(detection method) = $\frac{\text{SD-CRC}}{\text{IC+SD-CRC}}$.

Episode sensitivity according to the PI method was calculated from the expected CRC incidence extrapolating data from the pre-screening era. A log-linear Poisson model served to estimate the expected CRC incidence from age-specific CRC incidence trends in the Netherlands in the pre-screening era (2009-2013). Based on this estimate, the expected sex- and age-specific CRC incidences for the first (2014-2017) and second (2016-2017) round were calculated. Trends were standardized by sex- and age distributions of the study population. Next, the proportional incidence or rate ratio (RR) of interval CRC (IC) was estimated as the number of interval CRCs divided by the length of the interval multiplied by the expected annual CRC incidence (E) for that specific sex- or age group, using the formula: $RR = \frac{IC}{\text{Interval length(years)} \times E}$ The mean interval length was 1.97 years (23.7 months) in the first round and 1.96 years (23.5 months) in the second round. The episode sensitivity was calculated using the formula: Sensitivity (PI method) $= 1 - RR$.

The incidence of interval CRC and the sensitivity of FIT are summarized using standard descriptive statistics, displaying the 95% confidence interval (CI). Chi-square testing was performed to compare localization and stage distribution of interval CRCs with screening-detected CRCs after the first and second round, respectively. Calculated p values are two-sided and are considered statistically significant when <.05.

Logistic regression analysis was performed to determine the odds ratio (OR) of interval CRC after the first and after the second round, based on f-Hb concentration, adjusted for sex- and age-differences. Only data of individuals who participated in both rounds were used to determine the number of interval CRCs after the second round. F-Hb concentrations were categorized as: unmeasurable (0-2.6 µg Hb/g feces; below limit of detection), >2.6 to 10 µg Hb/g feces, >10 to 20 µg Hb/g feces, >20 to 30 µg Hb/g feces, >30 to 40 µg Hb/g feces and >40 to 46.9 µg Hb/g feces. Five age categories were defined with respect to interval CRCs after the first round: 55-59, 60-64, 65-69, 70-74 and ≥ 75 years. Complete data on interval CRCs after the second round were available for only three age categories: namely 60-64, 65-69 and ≥70 years.

We evaluated the probability of detecting an interval CRC using multiple models. Model 1 concerned the OR of detecting interval CRC based on f-Hb concentration of participants with a negative FIT at the first round. Model 2 concerned the OR of detecting interval CRC based on the last measured f-Hb concentration of participants with a negative FIT at the second round. Lastly, f-Hb concentrations at both the first and second round of participants with a negative FIT

in both rounds were incorporated (Models 3a-c). These models were variations of model 2. Model 3a included dichotomous (0-2.6 vs. >2.6-46.9 µg Hb/g feces) f-Hb concentrations of the first round as well as categorical f-Hb concentrations of the second round. Model 3b included summed f-Hb concentrations of both rounds, dividing this added value into quantiles. Model 3c included categorical f-Hb concentrations of both rounds, as opposed to only the last f-Hb concentration measured in the second round (Model 2). Goodness-of-fit of the models was determined by comparing Akaike Information Criterion (AIC) scores of the different models.

Data management and analysis were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The first round included 2,302,711 individuals of whom 2,153,582 (93.5%) had a negative FIT, and 2,256 of the latter had been diagnosed with an interval CRC (Figure 1 and Table 1). Median age of the FIT-negative participants was 67 years (interquartile range [IQR]: 63-73). At the first round, 149,129 (6.5%) participants had a positive FIT, of whom 12,183 had been diagnosed with a screening-detected CRC (Figure 1).

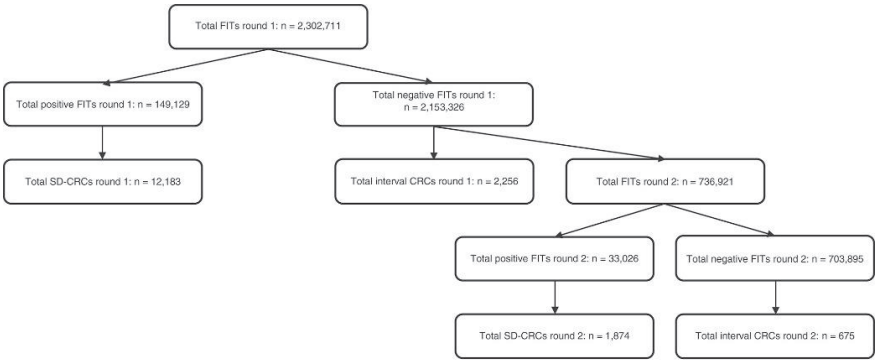

Figure 1 - Flowchart displaying numbers for first and second round. CRC, colorectal cancer; FIT, fecal immunochemical test; SD-CRC, screening-detected colorectal cancer

Table 1 - Characteristics study population

	First screening round		**Second screening round**	
	Negative FIT, n (%)	*Interval CRC,* n (%)	*Negative FIT,* n (%)	*Interval CRC,* n (%)
Total	2,153,582	2,256	703,895	675
Men	1,024,314 (47.6)	1,178 (52.2)	334,559 (47.5)	366 (54.2)
Women	1,129,268 (52.4)	1,078 (47.8)	369,336 (52.5)	309 (45.8)
Age distribution				
56-59	336,917 (15.6)	122 (5.4)	-	-
60-64	767,684 (35.6)	594 (26.3)	76,543 (10.9)	46 (6.8)
65-69	626,627 (29.1)	729 (32.3)	532,388 (75.6)	519 (76.9)
70-74	171,944 (8.0)	279 (12.4)	94,964 (13.5)	110 (16.3)
≥75	250,410 (11.6)	532 (23.6)	-	-
Prior f-Hb concentration (µg Hb/g feces)				
Unmeasurable (0-2.6)	1,907,528 (88.7)	1,143 (50.7)	654,010 (92.9)	441 (65.3)
>2.6-10	127,256 (5.9)	324 (14.3)	21,513 (3.1)	69 (10.2)
>10-20	62,479 (2.9)	292 (12.9)	13,305 (1.9)	66 (9.8)
>20-30	26,723 (1.2)	195 (8.6)	6,895 (1.0)	39 (5.8)
>30-40	18,603 (0.9)	181 (8.0)	5,149 (0.7)	35 (5.2)
>40-46.9	10,993 (0.5)	121 (5.4)	3,023 (0.4)	25 (3.7)

Median age in FIT-positive participants was 65 years (IQR: 61-71). The incidence of interval CRCs in participants with a negative FIT was 10.4 per 10,000 (Table 2). The episode sensitivity of FIT was 84.4% (95%CI 83.8-85.0) as determined with the detection method, and 76.4% (95%CI 73.3-79.6) as determined with the PI method (Table 2 and Appendix Table 1).

Table 2 - Incidence of interval CRC after negative FIT and sensitivity of FIT

		Number			Incidence rate/10,000			RR	SENSITIVITY (DETECTION METHOD) (%, 95%CI)	SENSITIVITY (PI METHOD) (%, 95%CI)
		Population screened	IC	SDC	IC	SDC	CRC predicted*	IC	SDC/SDC + IC	1-RR
ROUND 1	**Sex**									
	Male	1,113,736	1,178	7,584	10.6	68.1	50.6	0.21	86.6 (85.8-87.3)	79.0 (74.7-83.7)
	Female	1,188,975	1,078	4,599	9.1	38.7	33,1	0.28	81.0 (80.0-82.0)	72.5 (68.3-77.0)
	Age (yrs)									
	55-59	353,178	122	899	3.5	25.5	17.4	0.20	88.1 (86.1-90.0)	79.9 (66.9-95.4)
	60-64	813,106	594	3,248	7.3	40.0	29.5	0.25	84.5 (83.4-85.7)	75.3 (69.4-81.6)
	65-69	673,110	729	3,985	10.8	59.2	46.1	0.23	84.5 (83.5-85.6)	76.6 (71.2-82.3)
	70-74	187,583	279	1,511	14.9	80.6	62.9	0.24	84.4 (82.7-86.1)	76.3 (67.9-85.8)
	≥75	275,734	532	2,540	19.3	92.1	83.5	0.23	82.7 (81.3-84.0)	76.9 (70.6-83.7)
	Total	**2,302,711**	**2,256**	**12,183**	**9.8**	**52.9**	**41.6**	**0.24**	**84.4 (83.8-85.0)**	**76.4 (73.3-79.6)**
ROUND 2	**Sex**									
	Male	334,559	366	1,066	10.9	31.9	56.6	0.19	74.4 (72.2-76.7)	80.7 (72.9-89.4)
	Female	369,336	299	808	8.1	21.9	36.1	0.22	73.0 (70.4-75.6)	77.5 (69.2-86.8)
	Age (yrs)									
	60-64	76,542	46	143	6.0	18.7	29.1	0.21	75.7 (69.5-81.8)	79.4 (59.4-106.0)
	65-69	532,388	519	1,416	9.7	26.6	45.5	0.21	73.2 (71.2-75.2)	78.7 (72.2-85.7)
	≥70	94,964	110	315	11.6	33.2	62.3	0.19	74.1 (70.0-78.3)	81.4 (67.5-98.1)
	Total	**703,895**	**675**	**1,874**	**9.6**	**26.6**	**45.9**	**0.21**	**73.5 (71.8-75.2)**	**79.1 (73.3-85.3)**

Abbreviations: CI, confidence interval; CRC, colorectal cancer; IC, interval colorectal cancer; PI, proportional incidence; RR, rate ratio; SDC, screening-detected colorectal cancer; Yrs, years.

* Based on expected CRC incidence using Poisson log linear regression to extrapolate CRC incidence data from the pre-screening era. Displayed for the screening interval of 1.97 years in the first round and 1.96 years in the second round.

The second round included 736,921 individuals, of whom 703,895 (95.5%) had a negative FIT, and 675 of the latter had been diagnosed with an interval CRC (Figure 1 and Table 1). Median age of the FIT-negative participants was 67 years (IQR: 66-69). At the second round, 33,026 (4.5%) participants had a positive FIT, of whom 1,874 had been diagnosed with a screening-detected CRC (Figure 1). The median age of the FIT-positive participants was 67 years (IQR: 65-69). The incidence of interval CRC in participants with a negative FIT was 9.6 per 10,000 (Table 2).

After the second round, the episode sensitivity of FIT was 73.5% (95%CI 71.8-75.2) as determined with the detection method and 79.1% (73.3-85.3) as determined with the PI method (Table 2 and Appendix Table 2). The incidence of interval CRC after the first round was significantly higher than after the second round (P=0.04). Furthermore, the incidence of interval CRC was significantly higher in men than in women in both the first (P=0.003) and second (P=0.002) round (Table 1).

Stage distribution and localization

After both the first and second round, the stage distribution of interval colon cancers was less favorable than that of the screening-detected colon cancers (P<0.0001, Figure 2A). After the first round, 17.9% of interval colon cancers were assigned stage I, compared with 46.3% of screening-detected colon cancers. By contrast, 28.1% of interval colon cancers were assigned stage IV, compared with 7.2% of screening-detected colon cancers. The same pattern was observed after the second round (Figure 2B). In both rounds, interval colon cancers were more often located right-sided than were the screening-detected colon cancers (50.8% vs. 27.3% in the first round and 54.1% vs. 36.2% in the second round; P<0.0001, Figure 3A, B).

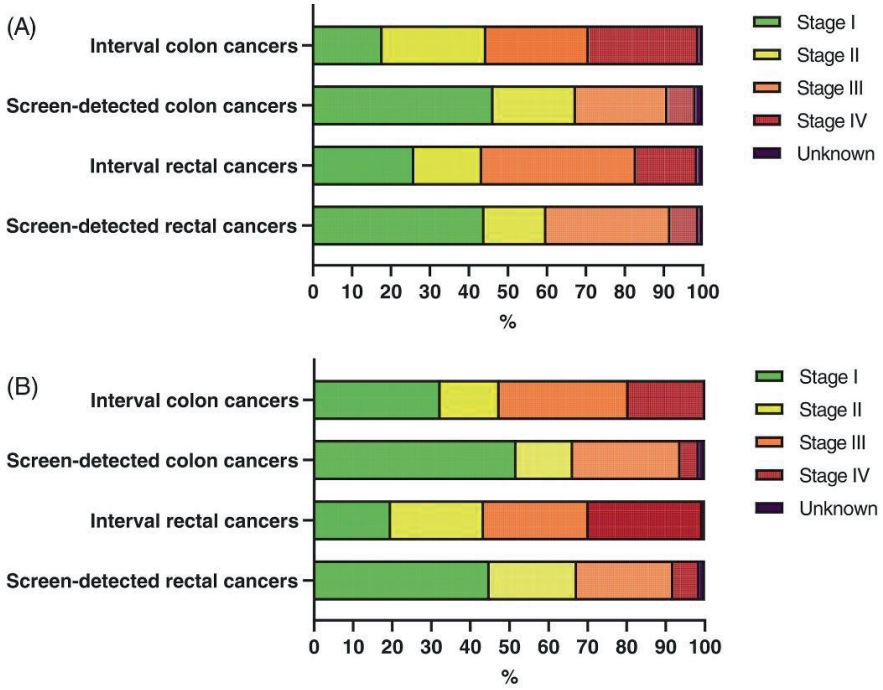

Figure 2 - (A) Stage distribution interval and screening-detected cancers after the first round. (B) Stage distribution interval and screening-detected cancers after the second round.

After both the first and second round, the stage distribution of interval rectal cancers differed from that of screening-detected rectal cancers ($P<0.0001$, Figure 2A, B). After the second round, 26.0% of interval rectal cancers were assigned stage I, vs. 44.0% of screening-detected rectal cancers. By contrast, 15.7% of interval rectal cancers were assigned stage IV, vs. 7.2% of screening-detected rectal cancers. The proportions of cancers diagnosed in the rectum were quite comparable between interval and screening-detected cancers, both in the first round (25.9% vs. 26.1%, respectively) and in the second round (26.5% vs. 28.3%, respectively; Figure 3A, B).

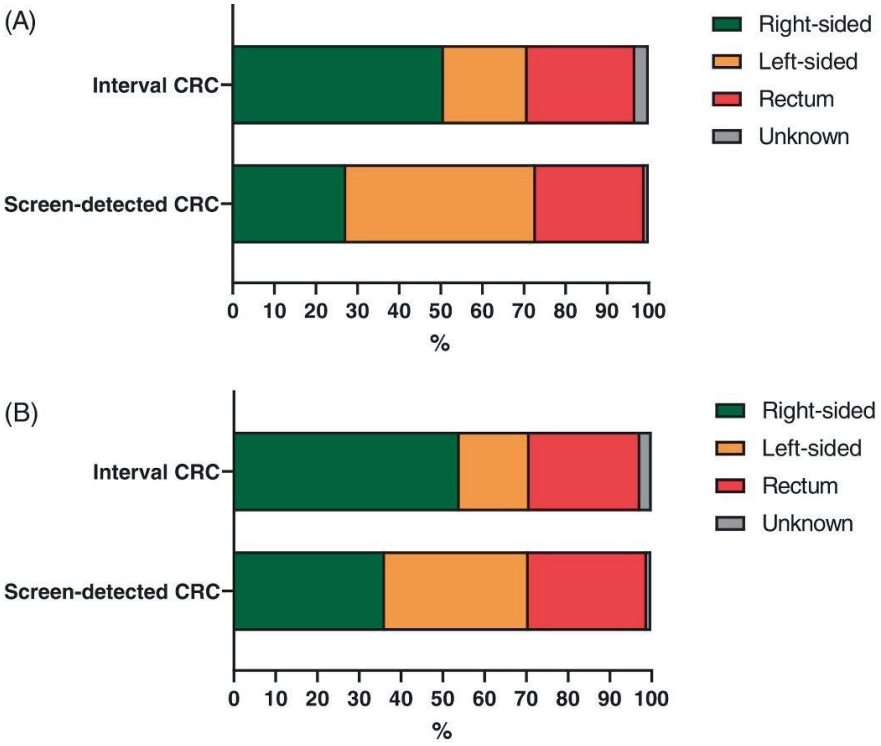

Figure 3 - (A) Localization interval and screening-detected cancers after the first round. (B) Localization interval and screening-detected cancers after the second round.

Association between f-Hb concentration and interval CRC after the first round

The vast majority (88.7%) of participants with a negative FIT had an unmeasurable f-Hb concentration after the first round (Table 1). With increasing f-Hb concentrations, the corresponding percentage of participants decreased. The probability of detecting an interval CRC increased with increasing f-Hb concentrations and during the period until the next invitation after 24 months (Figure 4A). In participants with the highest f-Hb concentration just below cut-off (>40-46.9 µg Hb/g feces), 1.08% had an interval CRC detected at 24 months, as opposed to 0.06% in those with an unmeasurable f-Hb concentration (Figure 4A). After the first round, participants in the category with the highest f-Hb concentrations (>40-46.9 µg Hb/g feces) had an OR of 16.9 (95% CI 13.9-20.3) for detection of interval CRC

compared with participants with unmeasurable f-Hb concentration, when adjusted for sex- and age-differences (Model 1; Table 3).

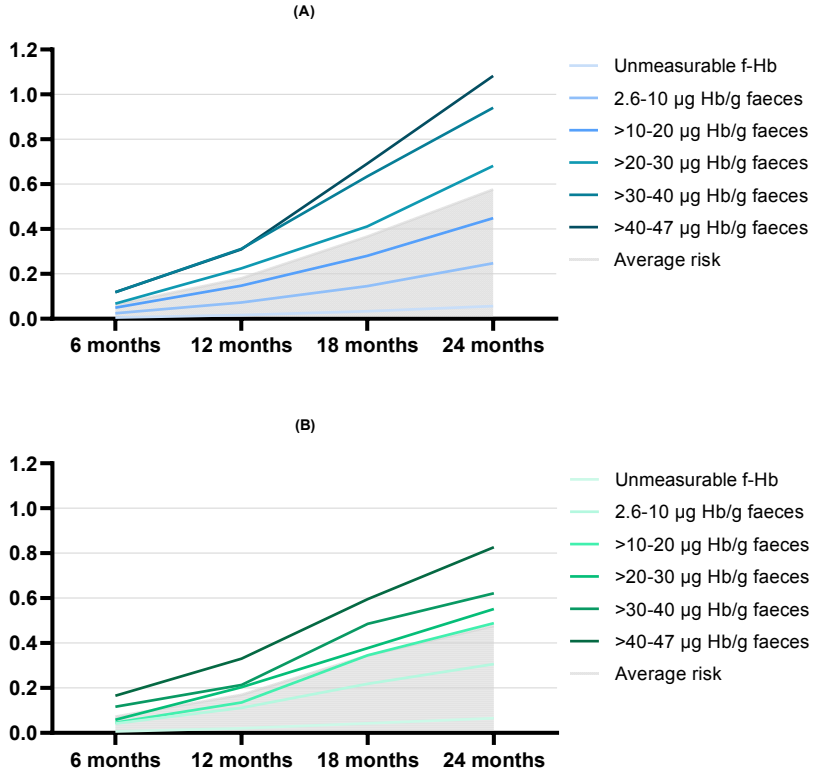

Figure 4 - (A) Probability of detecting interval CRCs after the first round by subgroups of f-Hb concentrations. (B) Probability of detecting interval CRCs after the second round by subgroups of f-Hb concentrations.

Table 3 – Multivariable logistic regression analysis: association between f-Hb concentration and interval CRC in the first and second round, adjusted for sex- and age-differences

	First screening round (Model 1) Odds ratio, 95%CI	Second screening round (Model 2) Odds ratio, 95%CI
Sex		
Men	REF	REF
Women	0.9 (0.9-1.0)	0.8 (0.7-1.0)
Age category*		
56-60	REF	-
60-64	1.8(1.5-2.2)	REF
65-69	2.4(2.0-2.9)	1.6(1.2-2.1)
70-74	3.8(3.0-4.7)	1.8(1.3-2.6)
≥75	4.3(4.6-5.3)	-
Prior f-Hb concentration (µg Hb/g feces)*		
Unmeasurable (0-2.6)	REF	REF
>2.6-10	4.0 (3.5-4.5)	4.7 (3.6-6.0)
>10-20	7.2(6.3-8.1)	7.2 (5.5-9.3)
>20-30	11.1(9.5-12.9)	8.2 (5.8-11.2)
>30-40	14.9 (12.7-17.4)	9.9 (6.9-13.7)
>40-46.9	16.9(13.9-20.3)	12.0 (7.8-17.6)

Abbreviations: 95% CI, 95% confidence interval; CRC, colorectal cancer; f-Hb, fecal hemoglobin.
* P <0.05.

Association between f-Hb concentration and interval CRC after the second round

After the second round, again, most participants with a negative FIT had an unmeasurable f-Hb concentration (92.9%, Table 1). The probability of detecting an interval CRC increased with higher f-Hb concentrations and during the period until the next invitation (Figure 4B). In participants with the highest f-Hb concentration just below cut-off (>40-46.9 µg Hb/g feces), 0.83% had an interval CRC detected at 24 months, as opposed to 0.07% in participants with unmeasurable f-Hb concentrations (Figure 4B).

Similar to the first round, multivariable analysis showed a strong correlation between f-Hb concentration and detection of interval CRC after the second round, when adjusted for sex- and age-differences. Participants with the highest f-Hb concentrations (>40-46.9 µg Hb/g feces) had an OR of

12.0 (95% CI 7.8-17.6) for detection of interval CRC compared with participants with unmeasurable f-Hb concentrations (Model 2; Table 3).

Lastly, we compared different models for estimating the probability of detecting an interval CRC after the second round. These models were a variation of model 2 and took into account f-Hb concentrations of the first round as well. Model 3a included dichotomous f-Hb concentrations of the first round and categorical f-Hb concentrations of the second round (AIC: 10,236.53, Appendix Table 3). Model 3b included summed f-Hb concentrations of both rounds, dividing this added value into quantiles (AIC: 10,268.59, Appendix Table 4). The model that discriminated best was the one that included categorical f-Hb concentrations of the first and second round separately (Model 3c, AIC: 10,232.83, Table 4).

This model performed better than the model taking into account only the f-Hb concentration measured in the second round (AIC: 10,275.10). Thus, the goodness-of-fit of the model incorporating f-Hb concentrations of two consecutive rounds (model 3c) was superior to the goodness-of-fit of the model only incorporating the last measured f-Hb concentration (model 2).

DISCUSSION

This study evaluated the incidence of interval CRC and sensitivity of FIT after the first and the second screening round of the Dutch national FIT-based CRC screening program. In both rounds, the incidence of interval CRC was low, whereas the sensitivity of FIT was high. Compared with screening-detected CRC, interval CRC was more often diagnosed in men, more often at an advanced stage, and was more often located at the right side of the colon. Importantly, the higher the f-Hb concentration, the higher the odds of detection of interval CRC, both after the first and the second round. The goodness-of-fit of the used model increased when f-Hb concentrations of both rounds (as opposed to only the last measured f-Hb concentration) were included to estimate the OR of interval CRC after the second round. This would suggest that not only the last measured f-Hb concentration but also the prior screening history might be predictive for the detection of interval CRC.

Our results showed a high sensitivity of FIT in the Dutch CRC screening program. A systematic review on FIT-sensitivity found a pooled sensitivity of FIT for CRC of 0.71 (95%CI 0.56-0.83) in 12 studies that used a positivity cut-off for FIT of >20 µg Hb/g feces (14). The measured FIT-sensitivity in our study was slightly higher, but from that review it was not clear which round was assessed in the various studies. Furthermore, the sensitivity of FIT was calculated with a screening colonoscopy as the gold standard (i.e., reference), whereas we have approximated the sensitivity from the interval CRC rate. The latter approach could result, however, in an over- or underestimation of the actual FIT-sensitivity. Overestimation might occur when prevalent early-stage CRCs went unrecognized as interval CRCs during the relevant time period. Underestimation might occur when interval CRCs actually were advanced adenomas at the time of prior FIT, which also impacts sensitivity estimates.

We approximated the FIT-sensitivity in two ways: with the detection method and the proportional incidence method. The decrease in sensitivity over two rounds found with the detection method can be explained by the first round being a prevalence round, and subsequent rounds are incidence rounds. The sensitivity was estimated by dividing the number of screening-detected CRCs by the sum of interval CRCs and screening-detected CRCs. In

the first round, prevalent cancers will most likely be detected through screening. Because most of the prevalent cancers will be diagnosed after the first round and the number of interval cancers detected will remain stable, we might expect a plateau phase in sensitivity of FIT after multiple screening rounds. This phenomenon has been described in several previous studies (9,15,16).

The proportional incidence method allows for comparisons between programs, as it makes use of data on the (expected) background incidence of CRC in the target population. Moreover, the resulting estimate is unaffected by the effect of overdiagnosis. A very important caveat when calculating expected trends based on the CRC incidence in the pre-screening era is that time trends cannot be taken into account. This phenomenon may lead to overestimation of the protective effect of the FIT. Still, our results testify to the satisfactory performance of the FIT in the Dutch CRC screening program. When calculating the sensitivity of FIT in a CRC screening program, there are a few caveats worth mentioning. From a screening program perspective, estimating sensitivity per screening round ensures that we can obtain the relevant measure of FIT sensitivity: CRC detection before clinical manifestation. Nevertheless, from a screening participant's point of view, one could argue that individuals with a screen-detected CRC at the second screening round and a negative FIT at the first screening round are false negative test results and that this should be taken into account when estimating the sensitivity of the FIT in the first screening round. However, it is unknown what percentage of these screen-detected CRCs were actually missed cancers in earlier screening, since colonoscopy is not performed in FIT-negative individuals. Furthermore, it is unclear what percentage of screen-detected CRCs should be included in this calculation, as it is unlikely that early-stage screen-detected CRCs were missed CRCs in the previous screening round. When advanced-stage screen-detected CRCs in the subsequent round are included in the calculation, this would (somewhat) reduce the FIT sensitivity. The evaluation of FIT-based screening programs does not yet take this phenomenon into account when estimating the sensitivity of FIT (15,17–21). Cancer screening researchers should discuss and reach consensus on the calculation of FIT

sensitivity, similar to the consensus statement on post-colonoscopy cancers (22).

The finding that interval CRCs were more often diagnosed at the right side of the colon seems to underline the hypothesis that the FIT-sensitivity is higher for left-sided cancers and that right-sided lesions are more frequently missed by FIT. A reason for this could be that approximately 75% of advanced serrated lesions are right-sided, and tend to bleed less than do (advanced) adenomas. Furthermore, they are hypothesized to progress much faster into carcinoma than do adenomas once dysplasia has established (23,24). A second hypothesis could be the degradation of hemoglobin, which may occur at a greater extent in right-sided lesions, leading to lower concentrations of fecal hemoglobin. Unexpectedly, in the present study the proportion of rectal cancers diagnosed was similar for interval and screening-detected cancers. Further research is necessary to find the reason for these missed rectal cancers.

Previous f-Hb concentrations appear to have a greater predictive value for developing AN in future rounds than, for example, age, lifestyle or family history (4,25–27). In this study, we used different models to estimate the probability of detecting an interval CRC after both rounds. We found that the model that incorporated f-Hb concentrations of both the first and second round performed better to estimate probability of detecting an interval CRC after the second round than did the model that included only the last measured f-Hb concentration after the second round. This indeed goes to show that prior screening history could be predictive for detection of interval CRC. When we assessed the predictive value of the variation in both f-Hb concentrations (i.e., the delta) on the probability of detecting interval CRCs, this model was not significant. We expected a higher association between this delta and detection of interval CRC after the second round. However, when information on CRCs of multiple screening rounds becomes available, the prior screening history—that is, the variation in f-Hb concentrations—could allow identifying individuals at highest probability of detecting an interval CRC with the use of more advanced statistics such as a (linear) mixed model.

Although the incidence of interval CRC was low after both rounds, the largest proportion of interval CRCs was diagnosed at an advanced stage. As

these are associated with higher morbidity and mortality, the importance of preventing these interval CRCs is self-evident. Of note, we found substantial differences in the probability of detecting an interval CRC by f-Hb concentration, like in recent studies from Spain and Italy (8,28). There are several options to address participants at highest probability of developing an interval CRC, hereby increasing benefits of the screening program. In case of a history of multiple previous f-Hb concentrations just below the cut-off, they can be offered colonoscopy. Alternatively, the screening interval can be shortened, thereby intensifying FIT-based screening. Clearly, the first option would require additional colonoscopy capacity. In our study, this would require approximately 10% additional colonoscopy capacity per screening round. Both options warrant close consultation with public health officials, while considering that information on multiple screening rounds should be available to make well-balanced decisions on these strategies, especially with intensifying FIT-screening. In the Netherlands, every year approximately two million individuals were invited to participate in the screening program, of whom about 72% participated (29). Around 95% of them had a negative FIT. In this study, we found that only 10% of all participants with a negative FIT had detectable f-Hb concentrations below the cut-off (>2.6-47 μg Hb/g feces). Importantly, around 50% of all interval CRCs had been diagnosed in this small population. The associated higher probability of detecting an interval CRC in this small population, coupled with the large proportion of participants with a negative FIT and an unmeasurable f-Hb concentration, indicates possibilities for risk-stratified CRC screening. Such a program could improve the harm-benefit balance, increase the yield of AN (in terms of detection rate and positive predictive value) and imply a lower burden of screening for participants at low risk. Still, factors such as acceptability, participation and use of resources need to be considered as well (30).

We reported on probability of detecting interval CRCs for different categories of f-Hb concentration, thus making these data generalizable to programs using other cut-offs. Obviously, the generalizability is highly dependent on the set-up of the program (i.e., population-based vs. opportunistic screening). Another important strength of this study is the large sample size, enabling us to combine essential information on interval CRC in

a national, organized screening program. The main limitation of this study is that we could incorporate only data from two rounds. This is due to a data acquisition delay of information on CRC, such as the stage distribution. We hope that after having analyzed information from multiple rounds of FIT screening we will be able to identify which and how patterns of f-Hb concentrations influence the probability of detecting interval CRCs.

To conclude, we found that the CRC screening program in the Netherlands has a low incidence of interval CRC and an associated high FIT-sensitivity, after one and two consecutive screening rounds. The probability of detecting interval CRCs increased with increasing fecal hemoglobin concentrations. Our findings suggest there is a potential for further optimizing CRC screening programs with the use of risk-stratified CRC screening based on prior fecal hemoglobin concentrations.

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APPENDIX

Table 1 - Incidence of interval CRC after negative FIT and sensitivity of FIT after the first screening round

		NUMBER			INCIDENCE RATE/10,000			RR	SENSITIVITY (DETECTION METHOD) (%, 95%CI)	SENSITIVITY (PI METHOD) (%, 95%CI)
		POPULATION SCREENED	IC	SDC	IC	SDC	CRC PREDICTED*	IC	SDC/SDC + IC	1-RR
YEAR	**SEX**									
	Male	**1,113,736**	**1,178**	**7,584**	**10.6**	**68.1**	**50.6**	**0.21**	**86.6 (85.8-87.3)**	**79.0 (74.7-83.7)**
2014		149,000	173	1,184	11.6	79.5	61.4	0.19	87.3 (85.5-89.0)	81.1 (69.9-94.1)
2015		392,748	442	2,813	11.3	71.6	51.8	0.22	86.4 (85.2-87.6)	78.2 (71.2-85.8)
2016		335,548	340	2,268	10.1	67.6	49.2	0.21	87.0 (85.7-88.3)	79.5 (71.5-88.4)
2017		236,440	223	1,319	9.4	55.8	43.7	0.22	85.5 (83.8-87.3)	78.5 (68.8-89.5)
	Female	**1,188,975**	**1,078**	**4,599**	**9.1**	**38.7**	**33.1**	**0.28**	**81.0 (80.0-82.0)**	**72.5 (68.3-77.0)**
2014		155,816	192	705	12.3	45.2	40.1	0.31	78.6 (75.9-81.3)	69.4 (60.2-79.9)
2015		415,218	400	1,704	9.6	41.0	33.9	0.28	81.0 (79.3-82.7)	71.7 (65.0-79.1)
2016		359,594	333	1,357	9.3	37.7	32.4	0.29	80.3 (78.4-82.2)	71.3 (64.0-79.4)
2017		258,347	163	833	6.3	32.2	28.5	0.22	83.6 (81.3-85.9)	77.9 (66.8-90.8)
	AGE YRS)									
	55-59	**353,178**	**122**	**899**	**3.5**	**25.5**	**17.4**	**0.20**	**88.1 (86.1-90.0)**	**79.9 (66.9-95.4)**
2014**										
2015**										
2016		131,000	54	351	4.1	26.8	17.5	0.23	86.7 (83.4-90.0)	76.6 (58.6-100.0)
2017		222,177	68	548	3.1	24.7	17.3	0.18	89.0 (86.5-91.4)	82.1 (64.7-104.1)
	60-64	**813,106**	**594**	**3,248**	**7.3**	**40.0**	**29.5**	**0.25**	**84.5 (83.4-85.7)**	**75.3 (69.4-81.6)**
2014		65,329	54	289	8.3	44.2	29.8	0.28	84.3 (80.4-88.1)	72.1 (55.2-94.2)
2015		307,754	219	1,298	7.1	42.2	29.6	0.24	85.6 (83.8-87.3)	76.0 (66.5-86.7)
2016		306,822	242	1,224	7.9	39.9	29.4	0.27	83.5 (81.6-85.4)	73.2 (64.5-83.0)
2017		133,201	79	437	5.9	32.8	29.3	0.20	84.7 (81.6-87.8)	79.9 (64.1-99.6)
	65-69	**673,110**	**729**	**3,985**	**10.8**	**59.2**	**46.1**	**0.23**	**84.5 (83.5-85.6)**	**76.6 (71.2-82.3)**
2014		174,659	177	989	10.1	56.6	46.2	0.22	84.8 (82.8-86.9)	78.2 (67.4-90.6)
2015		434,841	488	2,580	11.2	59.3	46.1	0.24	84.1 (82.8-85.4)	75.7 (69.3-82.7)

2016		60,976	63	404	10.3	66.3	45.9	0.22	86.5 (83.4-89.6)	77.6 (60.6-99.3)
2017**										
	70-74	**187,583**	**279**	**1,511**	**14.9**	**80.6**	**62.9**	**0.24**	**84.4 (82.7-86.1)**	**76.3 (67.9-85.8)**
2014**										
2015**										
2016		110,092	159	886	14.4	80.5	63.0	0.23	84.8 (82.6-87.0)	77.1 (66.0-90.1)
2017		77,490	120	625	15.5	80.7	62.9	0.25	83.9 (81.3-86.5)	75.4 (63.0-90.1)
	≥75	**275,734**	**532**	**2,540**	**19.3**	**92.1**	**83.5**	**0.23**	**82.7 (81.3-84.0)**	**76.9 (70.6-83.7)**
2014		64,828	124	611	18.1	94.2	82.7	0.22	83.1 (80.4-85.8)	78.1 (65.5-93.2)
2015		65,369	135	639	20.7	97.8	83.3	0.25	82.6 (79.9-85.2)	75.2 (63.5-89.0)
2016		86,252	155	760	18.0	88.1	83.9	0.21	83.1 (80.6-85.5)	78.5 (67.1-92.0)
2017		59,285	118	530	19.9	89.4	84.0	0.24	81.8 (78.8-84.8)	76.3 (63.7-91.4)
	TOTAL	**2,302,711**	**2,256**	**12,183**	**9.8**	**52.9**	**41.6**	**0.24**	**84.4 (83.8-85.0)**	**76.4 (73.3-79.6)**

Abbreviations: IC: interval colorectal cancer. SDC: screening-detected colorectal cancer. CRC: colorectal cancer. RR: rate ratio. CI: confidence interval. PI: proportional incidence. Yrs: years.

* based on expected CRC incidence using Poisson log linear regression to extrapolate CRC incidence data from the pre-screening era. Displayed for the screening interval of 1.97 years in the first round and 1.96 years in the second round.

**too few people screened/too few cancers for displaying/significance.

Table 2 - Incidence of interval CRC after negative FIT and sensitivity of FIT after the second screening round

		NUMBER			INCIDENCE RATE/10,000			RR	SENSITIVITY (DETECTION METHOD) (%, 95%CI)	SENSITIVITY (PI METHOD) (%, 95%CI)
		POPULATION SCREENED	IC	SDC	IC	SDC	CRC PREDICTED*	IC	SDC/SDC + IC	1-RR
YEAR	**SEX**									
	Male	**334,559**	**366**	**1,066**	**10.9**	**31.9**	**56.6**	**0.19**	**74.4 (72.2-76.7)**	**80.7 (72.9-89.4)**
2016		98,273	125	332	12.7	33.8	55.5	0.23	72.6 (68.6-76.7)	77.1 (64.7-91.9)
2017		236,286	241	734	10.2	31.1	57.0	0.18	75.3 (72.6-78.0)	82.1 (72.4-93.2)
	Female	**369,336**	**299**	**808**	**8.1**	**21.9**	**36.1**	**0.22**	**73.0 (70.4-75.6)**	**77.5 (69.2-86.8)**
2016		105,951	93	220	8.8	20.8	36.0	0.24	70.3 (65.2-75.4)	75.5 (61.6-92.6)
2017		263,385	216	588	8.2	22.3	36.1	0.23	73.1 (70.1-76.2)	77.3 (67.6-88.3)
	AGE YRS)									
	60-64	**76,542**	**46**	**143**	**6.0**	**18.7**	**29.1**	**0.21**	**75.7 (69.5-81.8)**	**79.4 (59.4-106.0)**
2016**										
2017		74,517	44	142	5.9	19.1	29.1	0.20	76.3 (70.2-82.5)	79.7 (59.3-107.1)
	65-69	**532,388**	**519**	**1,416**	**9.7**	**26.6**	**45.5**	**0.21**	**73.2 (71.2-75.2)**	**78.7 (72.2-85.7)**
2016		202,190	216	551	10.7	27.3	45.7	0.23	71.8 (68.7-75.0)	76.6 (67.0-87.5)
2017		330,198	303	865	9.2	26.2	45.4	0.20	74.1 (71.5-76.6)	79.7 (71.2-89.2)
	≥70	**94,964**	**110**	**315**	**11.6**	**33.2**	**62.3**	**0.19**	**74.1 (70.0-78.3)**	**81.4 (67.5-98.1)**
2016**										
2017		94,955	110	315	11.6	33.2	62.3	0.19	74.1 (70.0-78.3)	81.4 (67.5-98.1)
	TOTAL	**703,895**	**675**	**1,874**	**9.6**	**26.6**	**45.9**	**0.21**	**73.5 (71.8-75.2)**	**79.1 (73.3-85.3)**

Abbreviations: IC: interval colorectal cancer. SDC: screen-detected colorectal cancer. CRC: colorectal cancer. RR: rate ratio. CI: confidence interval. PI: proportional incidence. Yrs: years.

* based on expected CRC incidence using Poisson log linear regression to extrapolate CRC incidence data from the pre-screening era. Displayed for the screening interval of 1.97 years in the first round and 1.96 years in the second round.

**too few people screened/too few cancers for displaying/significance.

Table 3 - Multivariable logistic regression analysis: association between dichotomous f-Hb concentrations in the first screening round, f-Hb concentration in the second round, and interval CRC in the 2nd screening round, adjusted for sex- and age-differences (Model 3a)

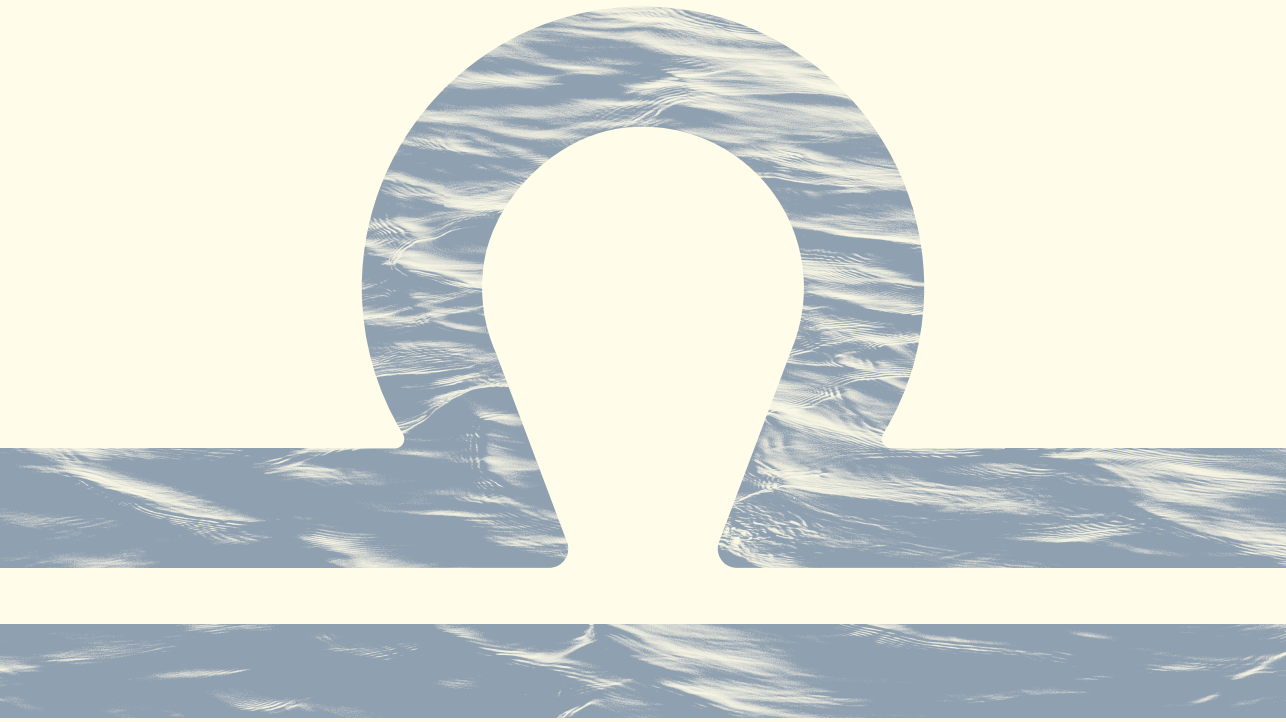
	Odds Ratio, 95% CI
Sex	
Men	REF
Women	0.9(0.7-1.0)
Age category	
60-64	REF
65-69	1.5(1.2-2.1)
≥70	1.8(1.3-2.5)
F-Hb concentration round 1 (µg Hb/g feces)	
Unmeasurable (0-2.6)	REF
>2.6-46.9	1.8 (1.5-2.1)
F-Hb concentration round 2 (µg Hb/g feces)	
Unmeasurable (0-2.6)	REF
>2.6-10	3.9(3.0-5.1)
>10-20	6.0(4.5-7.7)
>20-30	6.7(4.7-9.3)
>30-40	8.1 (5.6-11.3)
>40-46.9	9.7(6.3-14.4)

Abbreviations: 95% CI = 95% Confidence interval. f-Hb = fecal hemoglobin.

Table 4 - Multivariable logistic regression analysis: association between summed f-Hb concentrations from the first and second round (quantiles), and interval CRC in the 2nd screening round, adjusted for sex- and age-differences (Model 3b)

	Odds Ratio, 95% CI
Sex	
Men	REF
Women	0.9 (0.8-1.0)
Age category	
60-64	REF
65-69	1.4 (1.2-1.7)
≥70	1.5 (1.1-1.9)
Summed f-Hb concentration round 1 + round 2, quantiles (µg Hb/g feces)	
Unmeasurable (0-2.6)	REF
1st quantile	1.9 (1.4-2.7)
2nd quantile	2.7 (2.0-3.6)
3rd quantile	5.2 (4.2-6.5)
4rd quantile	8.3 (6.9-10.0)

Abbreviations: 95% CI = 95% Confidence interval. f-Hb = fecal hemoglobin.



Chapter 7

Personalized colorectal cancer screening: study protocol of a mixed-methods study on the effectiveness of tailored intervals based on prior f-Hb concentration in a FIT-based colorectal cancer screening program

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ABSTRACT

Background

In 2014, the national population-based colorectal cancer (CRC) screening program was implemented in the Netherlands. Biennial fecal immunochemical testing (FIT) for hemoglobin (Hb) is used at a cut-off of 47 µg Hb per gram feces. The CRC screening program successfully started, with high participation rates and yield of screening. Now that the program has reached a steady state, there is potential to further optimize the program. Previous studies showed that prior fecal Hb (f-Hb) concentrations just below the FIT cut-off are associated with a higher risk for detection of advanced neoplasia (AN) at subsequent screening rounds. We aim to achieve a better balance between the harms and benefits of CRC screening by offering participants tailored invitation intervals based on prior f-Hb concentrations after negative FIT.

Methods

This mixed-methods study will be performed within the Dutch national CRC screening program and will consist of: (1) a randomized controlled trial (RCT), (2) focus group studies, and (3) decision modelling. The primary outcome is the yield of AN per screened individual in personalized screening vs. uniform screening. Secondary outcomes are perspectives on, acceptability of and adherence to personalized screening, as well as long-term outcomes of personalized vs. uniform screening. The RCT will include 20,000 participants of the Dutch CRC screening program; 10,000 in the intervention and 10,000 in the control arm. The intervention arm will receive a personalized screening interval based on the prior f-Hb concentration (1, 2 or 3 years). The control arm will receive a screening interval according to current practice (2 years). The focus group studies are designed to understand individuals' perspectives on and acceptability of personalized CRC screening. Results of the RCT will be incorporated into the MISCAN-Colon model to determine long-term benefits, harms, and costs of personalized vs. uniform CRC screening.

Discussion

The aim of this study is to evaluate the yield, feasibility, acceptability and (cost-) effectiveness of personalized CRC screening through tailored invitation intervals based on prior f-Hb concentrations. This knowledge may be of guidance for health policy makers and may provide evidence for implementing personalized CRC screening in The Netherlands and/or other countries using FIT as screening modality.

Trial registration:

ClinicalTrials.gov, NCT05423886, June 21, 2022,
https://clinicaltrials.gov/ct2/show/NCT05423886

INTRODUCTION

In 2014, a national population-based colorectal cancer (CRC) screening program was implemented in the Netherlands. Biennial fecal immunochemical testing (FIT) for hemoglobin is used at a cut-off of 47 µg (µg) hemoglobin (Hb)/g (gram) feces. The CRC screening program successfully started, with high participation rates and yield of screening resulting in a decrease in overall and advanced-stage CRC incidence (1–3). Now that the program has reached a steady state, there is potential to further optimize the program.

Every year, about 2.2 million people are invited to participate in the Dutch CRC screening program. The participation rate is about 72% (4). About 4.5% of participants has a positive FIT, meaning they have a fecal hemoglobin (f-Hb) concentration above the pre-set FIT cut-off [4]. Of these participants, about 85% undergo a colonoscopy, with around 40% of these people having a relevant finding (6% CRC and 36% advanced adenoma (AA)) (4). This implies that about 98% of participants in CRC screening do not experience any benefit from screening; 95.5% of participants because they have a negative FIT and 2.7% because they have a positive FIT without relevant findings at colonoscopy.

Ideally, screening should be offered primarily to those who would benefit most, that is, those who are at high risk of the disease. Personalized screening has been discussed for a long time (about 25 years) (5). To date, however, such an approach has not taken off, due to the limited predictive power of a number of known risk factors (6). A risk model that combined genetic information with lifestyle factors, family history and sex had a discriminatory power of 63% for predicting CRC risk (7).

There is increasing evidence that f-Hb concentration is a good predictor of future diagnosis of advanced neoplasia (AN) (Table (Table1). Models incorporating f-Hb concentrations could reach a discriminatory power of about 80% (6–10). The major advantage of this predictive factor is that the f-Hb concentration is automatically obtained within FIT-based CRC screening programs and thus is readily available information. The likelihood that the integration of tailored invitation intervals based on prior f-Hb concentration after negative FIT lowers the participation rate is therefore smaller than if another (not automatically obtained) risk factor would be used to personalize CRC screening. Sex and age are also automatically registered, but their predictive value is much lower than the f-Hb concentration (odds ratios for

AN: 1.6 (male sex) and 0.9–1.1 (increasing age) vs. 2.5–21.8 (increasing f-Hb concentrations), respectively (8). In addition, a strong association was observed between the measured f-Hb concentration in participants with a negative FIT and the risk of developing interval CRC in the Dutch CRC screening program (11). Interval CRC is defined as CRC diagnosed after a negative FIT and before invitation to the next screening round (12). Participants in the category with an f-Hb concentration just below the FIT cut-off (15–46.9 µg Hb/g feces) are 13 times more likely to develop an interval CRC compared to participants with an unmeasurable f-Hb concentration (0 µg Hb/g feces) [*personal communication*].

Table 1 - Risk of AN and/or CRC in subsequent screening rounds in high-risk individuals compared to low-risk individuals

Program	FIT cut-off	Comparison high- vs. low-risk individuals	Main outcome	Risk of AN and/or CRC in subsequent round
Dutch pilot studies (13)	10 µg Hb/g feces	8–10 µg Hb/g feces vs. 0 µg Hb/g feces	AN	HR: 8
Flemish CRC screening program (14)	15 µg Hb/g feces	Males aged 74 and 200 µg Hb/g feces vs. females aged 56 and 15 µg Hb/g feces	CRC	OR: 15
Dutch CRC screening program (15)	47 µg Hb/g feces	15–46.9 µg Hb/g feces vs. 0 µg Hb/g feces	AN	OR: 23
Scottish CRC screening program (16)	80 µg Hb/g feces	60.0–79.9 µg Hb/g feces vs. 0.0–19.9 µg Hb/g feces	AN	OR: 38

Abbreviations: CRC: colorectal cancer, FIT: fecal immunochemical testing, µg Hb/g: microgram hemoglobin per gram, AN: advanced neoplasia, HR: hazard ratio, OR: odds ratio

Almost half of all interval CRCs occur in a small group of participants (3.5%) with an f-Hb concentration between 15 and 46.9 µg Hb/g feces (17). Two-thirds of these cancers occur in the second year after screening (17). This means that one-third of interval CRCs could potentially have been prevented by inviting only 3.5% of participants to screening one year earlier. Based on more recent data, we expect around 85% of participants to have an f-Hb concentration of 0 µg Hb/g feces and thus to be at lowest risk of developing an interval CRC. If the interval between invitations for this group would be extended by one year, this would represent a 40% reduction in the screening burden for the population as a whole.

Now that the FIT-based CRC screening program has been fully rolled out in the Netherlands, has high participation rates and shows favorable results, there is potential for further optimization of the CRC screening program. We designed a mixed-methods study consisting of: (1) a parallel group, two-arm, superiority randomized controlled trial (RCT), (2) focus group studies, and (3) decision modelling. The aim of this mixed-methods study is to identify the yield and (cost-) effectiveness of personalized CRC screening, whether it could be feasible within population-based CRC screening programs, and whether the population is able to understand and accept it.

METHODS

Objectives

The aim of this study is to evaluate the yield, feasibility, acceptability and (cost-) effectiveness of personalized CRC screening through tailored invitation intervals based on prior f-Hb concentrations. Table 2 describes the aims, outcomes, and designated components of the study.

Table 2 - Aims, outcomes and designated components of the PERFECT-FIT study

Aim	*Outcome*	*Component of the mixed-methods study*
Yield	Detection rate	RCT
Effectiveness	Detection of AN Cost-effectiveness Long-term outcomes (incidence & mortality)	RCT Decision modeling Decision modeling
Feasibility	Participation rate Information needs in personalized screening	RCT Focus group I
Acceptability	Information needs in personalized screening Perspectives on personalized screening	Focus group I Focus groups II and III

Abbreviations**:** RCT: randomized controlled trial, AN: advanced neoplasia, PERFECT-FIT: personalized colorectal cancer screening: effectiveness of tailored intervals based on prior f-Hb concentration in a FIT-based colorectal cancer screening program

The primary objective of this study is to compare the yield (detection rate; DR) of AN per participant of personalized CRC screening (intervention arm) to uniform biennial CRC screening (control arm). AN is defined as AA or CRC. AA is defined as an adenoma with high grade dysplasia, and/or > 25% villous component, and/or ≥ 10 mm diameter. The DR is defined as the number of individuals with AN per 1000 screened individuals. Currently, advanced serrated polyps (ASPs) are not yet considered as relevant findings of the Dutch FIT-based screening program. However, this could change in the near future, due to new insights into the relevance of the serrated pathway in carcinogenesis. If ASPs are added to the relevant findings of the national CRC screening program, we will also evaluate the yield of the RCT with an updated definition of AN (AA + ASP + CRC).

The secondary objectives are to determine perspectives on, acceptability of and adherence to personalized CRC screening. Furthermore, we aim to evaluate the (cost-) effectiveness of personalized CRC screening compared to the current screening strategy.

This study was approved by the Health Council and fell under the Population Research Act. It was registered at Clinical Trials (NCT05423886) and started on October 14th, 2022.

Study design

This study is a mixed-methods study consisting of three parts: (1) a parallel group, two-arm, superiority randomized controlled trial (RCT), (2) focus group studies, and (3) decision modelling. This study will be performed over a time period of three years (Figure 1). A concise time schedule can be found in the Appendix.

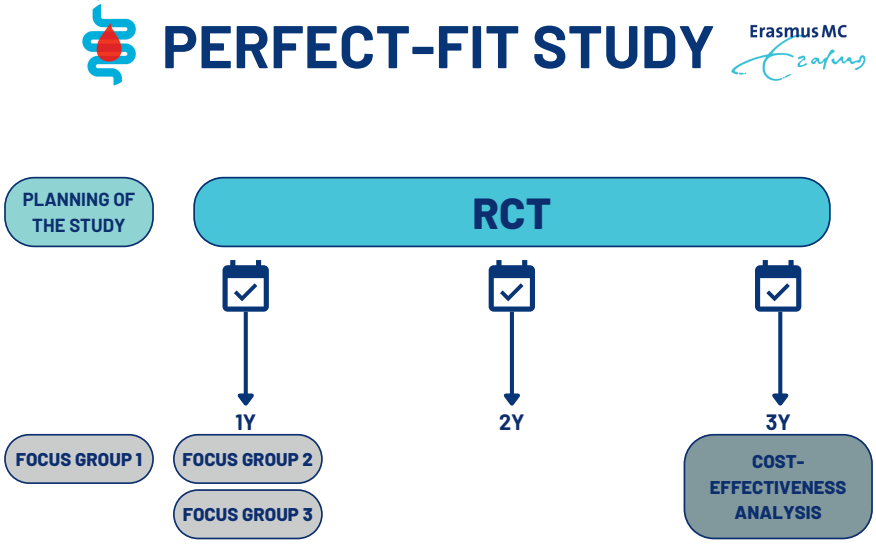

Figure 1 - Time schedule of the PERFECT-FIT study.

Abbreviations: FIT: fecal immunochemical testing, RCT: randomized controlled trial, PERFECT-FIT: personalized colorectal cancer screening: effectiveness of tailored intervals based on prior f-Hb concentration in a FIT-based colorectal cancer screening program.

RCT

Outcomes

We will conduct a prospective, parallel group, two-arm, superiority RCT within the Dutch national, population-based CRC screening program to evaluate the yield of personalized CRC screening by determining the DR of AN (and potentially the updated definition of AN including ASPs) in the intervention and control arm. Furthermore, feasibility will be determined by comparing participation rates between the intervention and control arm.

Study procedures

The design and logistics of this proposed study will be embedded in the nationwide FIT-based CRC screening program. Screening-eligible individuals with a prior negative FIT (irrespective of screening round) within the Dutch CRC screening program will be included. These individuals will have had a negative FIT ≤ 8 months before inclusion and will have a maximum age of 72, in order for them to undergo at least one more round of screening after participating in the RCT. Individuals will be randomly selected by the CRC screening authority (Bevolkingsonderzoek-Nederland; BVO-NL) from the Mid-West area in the Netherlands.

Individuals who meet the inclusion criteria will be approached by the screening organization (BVO-NL) to participate in the study. Information about the trial will be provided to participants through an information leaflet. Participants will receive the information leaflet by mail, including an informed consent form and a return envelope. General practitioners in the relevant region will receive additional information about the RCT. All individuals will be asked to give informed consent and participate in scientific research, both in the intervention and control group. If individuals choose not to participate, no reminder will be sent and they will receive a standard invitation for screening conform current practice.

After providing informed consent, participants will be randomized 1:1 to the control or intervention arm by block randomization according to a computer-generated randomization schedule using permuted blocks. Block sizes will not be disclosed for privacy purposes. Participants will be randomized using R version 4.0.2. Concealment of allocation will be ensured by data transmission through a digital research environment. All participants will be informed whether they have been randomized to the control or intervention arm and will receive a notification letter regarding their invitation interval. Participants in the control arm will receive an invitation to perform FIT at the regular invitation interval, after two years of their prior negative FIT. Individuals in the intervention arm receive information on their prior f-Hb concentration and their corresponding invitation intervals (Figure 2). They are notified on whether they had little (> 15–46.9 µg Hb/g feces), very little (> 0–15 µg Hb/g feces), or no blood in their stool (0 µg Hb/g feces). They will receive an invitation to perform FIT at the designated invitation interval corresponding with their f-Hb concentration (little blood: 1 year; very little blood: 2 years; no blood: 3 years, Figure 2).

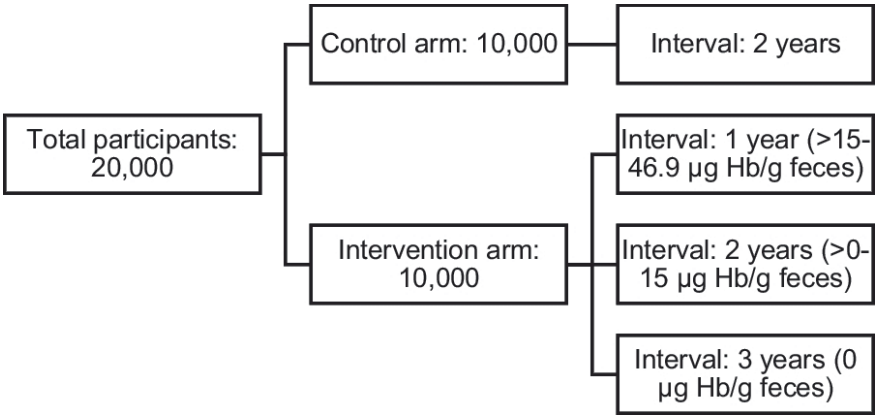

Figure 2 - Randomization of participants in the RCT.

Abbreviations: µg Hb/g: microgram hemoglobin per gram, RCT: randomized controlled trial.

If an individual does not respond to the invitation, a reminder will be sent after six weeks, conform current practice. Study participants will receive the result of the FIT (negative or positive) according to current practice and in case of a positive FIT also an invitation for an intake appointment for a colonoscopy. The existing IT infrastructure of the CRC screening program, ScreenIT, will be used and adjusted to facilitate allocating personalized invitation intervals within the screening process. After all participants have performed their FIT within the study, they return to the regular CRC screening program and will again be invited after two years to perform FIT if appropriate.

Sample size calculation

The power calculation is based on the main endpoint of this study: the yield (DR) of AN (CRC + AA) in the control arm versus the intervention arm. To detect a difference in DR of 0.5% between the intervention and control arm, 20,000 FIT participants are needed. With 20,000 inclusions, we have sufficient power to demonstrate a difference in detection rate of 2.2% in the intervention arm vs. 1.7% in the control arm. Given the high adherence rates of previous participants to subsequent screenings (93%), we conservatively assume that 40% of the invited population is willing to participate in this trial. This means that 50,000 individuals need to be invited to this RCT to demonstrate superiority in yield of risk-based screening. However, if participation rates are lower than expected, more invitations will be sent out until we have reached the total of 20,000 inclusions.

Data management

All data will be entered electronically by scanning a barcode. The original informed consent forms will be entered into the system and kept on file at the study site. Files are stored in numerical order in a safe, accessible location. Participant records will be retained for at least 15 years after study completion. All reports, data collection, trial and administrative forms will be identified only by an encoded ID number to ensure participant confidentiality. All records with names or other personal identifying information, such as a locator form or informed consent form, are stored separately from study records with ID numbers. All local databases will be protected with password-protected access systems. Forms, spreadsheets, logbooks, and other lists that link participant IDs to other identifying information are stored in a separate locked file in a restricted area. The datasets generated and/or analyzed in this study are not publicly available, but are available on request from BVO-NL. A data transfer agreement will be drawn up in the event of data sharing between BVO-NL and the PERFECT-FIT study team. Data Integrity is enforced through a Data Management Plan; data is owned by BVO-NL and is protected according to the General Data Protection Regulation and other applicable guidelines.

Study procedures: logistics

1. A study invitation letter will be sent to a selection of screen-eligible individuals who had a negative FIT ≤ 8 months earlier and are still eligible for a subsequent screening round. Invitation letters are sent out in batches of 10,000 invitations. The study invitation will include an information letter and an informed consent form (for the RCT as well as focus groups). Invitees who wish to participate in the study send the informed consent form to the investigators.

2. Informed consent will be returned in a prepaid, pre-addressed return envelope that is sent to the researchers. The barcode on the informed consent will be scanned by one researcher and will be checked by a second researcher.

3. All patients who consent for participation and meet the inclusion criteria will be randomized into either the control or intervention arm by using 1:1 block randomization. No blinding will be performed, as both the investigators and the participants will be informed of the assigned invitation interval. Information on informed consent and randomization of study participants is stored in the eCRF CASTOR.

4. BVO-NL supplies information on f-Hb concentrations of participants that gave consent to participate in the RCT. The researchers assign a screening interval to the participant based on their assigned group and, if applicable, prior f-Hb concentration.

5. Study participants will receive a confirmation letter, stating when the client will be invited again according to the study design (intervention arm: 1, 2 or 3 years and control arm: 2 years).

6. Study participants will receive their FIT within the RCT and will perform the FIT conform the regular screening process.

7. During the study, only the invitation interval of study participants in the intervention arm (1 and 3 years) will be changed. Study participants will receive the regular CRC screening program outcome letter (negative FIT at a cut-off of 47 µg Hb/g feces or positive FIT with an invitation for a follow-up colonoscopy). After participating in the study, all study participants will return to the regular screening program and will be invited to participate in CRC screening two years after the previous invitation date, unless the participant had a positive FIT and was referred for colonoscopy.

8. Individuals returning their consent forms too late (> 3 weeks after receiving their information leaflet and informed consent form) will be excluded from the study and thus follow the regular screening process.

9. A monitoring report provided by BVO-NL will be used to track the progress of the study (including invitations sent and participation rate). If needed, the number of invitations sent will be expanded to reach 20,000 inclusions.

10. At three time points during the study (i.e. 1, 2 and 3 years after inclusion), researchers will receive a report of results from participants who have given informed consent for the study. From study invitees who did not participate in the study (no informed consent), the researchers will receive a report with aggregated/anonymous data (i.e., information on age, sex and f-Hb concentration) to be able to assess generalizability of the results to the entire population.

11. Upon completion of the study, BVO-NL will verify that the study invitees will receive another invitation to the CRC screening program, two years after performing their FIT within the study, according to current practice (unless the participant had a positive FIT).

12. In case participants have logistical questions about the study or the regular CRC screening program, they can visit the study website or ask them by e-mail. There will also be a telephone line available for questions, which will be answered by the researchers of the Erasmus MC.

Focus group studies

At three time points during the study, a focus group study will be conducted.

Focus group I

The first focus group study aims to gain insight in information needs among individuals eligible for CRC screening (i.e., acceptability and feasibility of personalized CRC screening). Individuals' perspectives on personalized CRC screening and information needed to make a well-informed choice whether to participate or not are unknown. The study population consists of individuals that are eligible for CRC screening (i.e. men and women aged 55 to 75 years). This focus group will be conducted online. As this is a qualitative focus group, no formal sample size calculation is required. We aim at including a minimal number of 4 individuals and a maximum of 8 individuals per focus group. Inclusions are continued until thematic

saturation is reached; we expect to reach saturation after 3 focus groups (i.e., a minimum number of 12 participants, a maximum number of 24 individuals).

Focus group II and III

Focus group studies two and three are conducted during the RCT (Figure 1). In these focus group studies, we would like to determine the acceptability of personalized CRC screening. We deliberately chose not to add an additional questionnaire to assess individuals' view on personalized screening, as this may jeopardize participation. It is important to obtain additional information on individuals' motivations for participating in personalized CRC screening, as well as their perspectives on tailored screening intervals. Focus groups will be conducted in two groups:

- among participants in the intervention arm with a 1-year screening interval;
- among participants in the intervention arm with a 3-year screening interval.

An informed consent form for the focus groups is added to the information leaflet and informed consent form for the RCT. Those individuals that give their consent will be invited for the focus groups when randomized in the intervention arm and having received an invitation interval of 1 or 3 years. Moderators will consist of one of the study coordinators and an independent moderator.

All focus groups will be audio recorded (starting after introduction and verbal consent for recording). The recordings will be transcribed with all identifiers removed. Recordings will be transcribed by an experienced typist as soon as possible after the focus groups. Subsequently, the data will be coded manually and managed using NVivo software. Coding will be translated to English. Analysis will be performed using a framework analysis, a qualitative analytic technique (18).

Decision modelling

We will use the well-established MIcrosimulation SCreening ANalysis for CRC (MISCAN-Colon) model (19,20) to estimate harms, benefits, resources and costs of uniform screening with a biennial interval and compare that with those of personalized screening intervals of 1, 2 or 3 years based on prior f-Hb concentrations.

Outcome of the modelling study is the long-term (cost-) effectiveness of personalized screening by using prior f-Hb concentrations. Long-term outcomes include CRC incidence, CRC-related mortality, (quality-adjusted [QA]) life-years [LYs]

gained, false-positive tests, colonoscopy complications, and costs, which will be compared for personalized screening versus uniform screening in the Dutch population.

MISCAN-colon was developed by the Department of Public Health of Erasmus MC to evaluate the cost-effectiveness of different CRC screening policies, and it has been used to inform CRC screening policy in the Netherlands, the United States, Canada, and Australia (20–23). In brief, the MISCAN-Colon model simulates the life histories of a large population of individuals from birth to death and has a natural history component that tracks the progression of underlying colorectal disease in the absence of screening. As each simulated individual ages, there is a chance that one or more adenomas may develop depending on age, sex, race and individual risk. Adenomas can progress from small (1–5 mm) to medium (6–9 mm) to large (≥ 10 mm) size, and some may eventually become malignant. A preclinical cancer (i.e., not detected) has a chance of progressing through different stages and may be detected by symptoms at any stage. With screening, adenomas and preclinical cancers may be detected depending on the sensitivity of the screening test for that lesion and, for endoscopic tests, whether the lesion is within reach of the endoscope.

Cost-effectiveness analysis

First, we will adjust the MISCAN-Colon model to include f-Hb concentration as a predictive factor for CRC. Next, we will validate model-predicted yield of CRC and AA at different screening intervals to those observed in the results of the RCT. If necessary, the model will be adjusted to improve its predictions. Finally, we will use the model to simulate the 2024 Dutch population and follow this population for a lifetime under two screening strategies: one in which the population is screened every 2 years from age 55 to age 75, and one in which the population is screened in the same age range, but with screening intervals varying between 1 and 3 years based on the f-Hb concentration measured at the prior screening round. Benefits, harms and costs will be compared in a formal incremental cost-effectiveness analysis to determine which of the two strategies is optimal from a cost-effectiveness and health care perspective.

DISCUSSION

The aim of this study is to evaluate the yield, feasibility, acceptability and (cost-) effectiveness of personalized CRC screening through tailored invitation intervals based on prior f-Hb concentrations. This personalized approach could contribute to a better balance between the harms and benefits of CRC screening on both an individual and population level.

Introducing tailored invitation intervals results in both direct and indirect consequences of personalized CRC screening. Direct consequences are the detection of precancerous lesions or CRC at an earlier stage, as well as reduction of the number of interval CRCs in individuals at higher risk for CRC, by offering specific individuals a shorter invitation interval. In the long-term, this could contribute to a lower burden of CRC-related morbidity and mortality. By inviting participants with an f-Hb concentration just below the cut-off (> 15–46.9 µg Hb/g feces) at a shorter interval, it is expected that, compared to uniform CRC screening, slightly more people will test false positive compared to true positives. Still, the balance of benefits and harms in the high-risk group is expected to be at least as favorable as that of individuals in the low-risk groups. In these low-risk groups, less intensive screening intervals ensures lower burden of screening. There will potentially be an increase in the incidence of interval CRCs in this group because participants will be invited to CRC screening one year later. However, our hypothesis is that the reduction in screening burden clearly outweighs the potential small increase in incidence of interval CRCs. Altogether, it is expected that the balance between harms and benefits of personalized CRC screening will be more favorable compared to uniform CRC screening.

Indirect consequences of implementing personalized CRC screening include ethical and communication challenges (24). When introducing personalized CRC screening to individuals, there could be confusion between screened individuals living in the same household if they are invited after different time intervals. Another disadvantage could be that those individuals who receive a longer invitation interval will experience stress from the longer waiting time, because of the increased risk of interval CRC. Therefore, providing clear and explicit information on the different invitation intervals based on an individual's risk is of great importance. The focus group studies will provide invaluable information on perspectives on and acceptability of personalized CRC screening that can be used when personalized CRC screening is potentially introduced at a population level.

It is inevitable that the direct and indirect consequences of personalized CRC screening versus uniform CRC screening will need to be assessed, should personalized screening eventually be implemented at the population level. Possible benefits of a personalized screening approach (i.e., increase in detection of AN, decrease in false-positives, overtreatment, etc.) should be monitored closely, as well as predicted long-term outcomes (i.e., CRC incidence, CRC-related mortality, QALY's gained, cost-effectiveness). If successful, this study will not only provide evidence for personalized CRC screening, but will also be an important benchmark for quality assurance in future implementation of personalized CRC screening, similar as previous pilot studies preceding the implementation of the Dutch CRC screening program have been for the current uniform program (13,25–29).

Some limitations or our study should be mentioned. The design of our study is fixed and based on the current test (FIT; FOB-Gold; Sentinel Diagnostics, Milan, Italy), cut-off (47 µg Hb/g feces) and age range (individuals aged 55–75) used in the Dutch CRC screening program. Nevertheless, even if the CRC screening program would be modified in terms of test, cut-off or age range, we expect that the results of our study are still relevant: the effect of the risk factor f-Hb holds for all ages, and the literature shows that it also holds for other cut-offs and FIT brands (8,11,13–17,30–32). Furthermore, even if the decision should be made to use another test instead of FIT, the study is still informative on the acceptability of risk-based screening in general. Obviously, there will always be organizational and political aspects that need to be considered when planning the real-time implementation of personalized CRC screening (24). Nevertheless, by embedding this study in the current and ongoing CRC screening program in the Netherlands, it is hoped and expected that (most of) these challenges can be overcome.

We expect there are many future directions in personalized CRC screening; more information will become available on outcomes of multiple screening rounds and on well-known risk factors such as age and sex. Furthermore, in the future other risk factors might also be collected by default within the IT infrastructure, such as lifestyle and genetic (i.e., single nucleotide polymorphisms) factors (24). If we can implement these risk factors in (advanced) prediction models, the risk prediction for personalized CRC screening can be even further improved, for example through better identification and categorization of the risk groups. If this study demonstrates that personalized CRC screening is successful, such a development would only make risk-based screening more favorable than uniform screening.

In conclusion, the aim of this study is to identify the yield and (cost-) effectiveness of personalized CRC screening, whether it could be feasible within population-based programs, and whether the population is able to understand and accept it. This knowledge may be of guidance for health policy makers and may provide evidence for implementing personalized CRC screening in the Netherlands and/or other countries.

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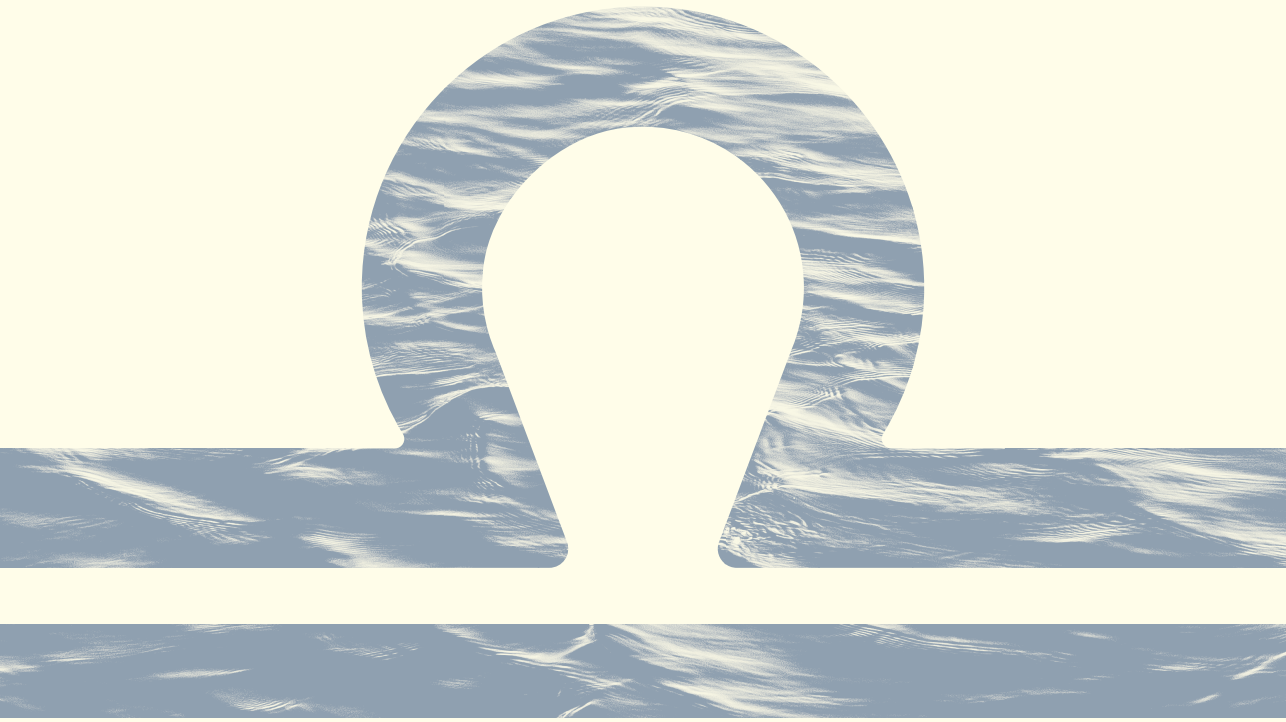
APPENDIX

Time schedule of the PERFECT-FIT study.

Tasks		Year 1		Year 2		Year 3		Year 4	
	2021-2	2022-1	2022-2	2023-1	2023-2	2024-1	2024-2	2025-1	2025-2
Permission Population Research Act									
Focus group									
Adjustment IT infrastructure									
Invitation to RCT									
Invitation to FIT,1 year									
Invitation to FIT, 2 year									
Invitation to FIT, 3 year									
Analysis outcomes									



Chapter 8

Personalized colorectal cancer screening strategies: information needs of the target population

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ABSTRACT

Prior faecal Hemoglobin (f-Hb) concentrations of a negative fecal immunochemical test (FIT) can be used for risk stratification in colorectal cancer (CRC) screening. Individuals with higher f-Hb concentrations may benefit from a shorter screening interval (1 year), whereas individuals with undetectable f-Hb concentrations could benefit from a longer screening interval (3 year). Individuals' views on personalised CRC screening and information needed to make a well-informed decision is unknown. We conducted three semi-structured focus groups among individuals eligible for CRC screening (i.e. men and women aged 55 to 75) in the Netherlands. Thematic analysis was used to analyse participants' information need on personalised CRC screening strategies. Fourteen individuals took part. The majority were positive about CRC screening and indicated that they would participate in personalised CRC screening. The rationale for a longer interval among those at lowest risk was, however, unclear for many. The preferred information on individual risk was variable: ranging from full information to only information on the personalised strategy without mentioning the risk. It was not possible to address everyone's need with a single approach. Additional communications, e.g. public media campaigns, billboards, videos on social media, were also suggested as necessary. This study showed that preferences on receiving information on individual CRC risk varied substantially and no consensus was reached. Introducing a personalised screening programme will require careful communication, particularly around the rationale for the strategy, and a layered approach to deliver information.

INTRODUCTION

In 2014, a nationwide faecal immunochemical test (FIT)-based colorectal cancer (CRC) screening programme was initiated in the Netherlands (1). A cut-off of 47 µg Hemoglobin per gram (Hb/g) faeces is considered as positive. Positives are referred for follow-up colonoscopy and negatives are invited for repeat testing in two years. Having a faecal Hb (f-Hb) concentration just below the cut-off is associated with a higher risk for the detection of CRC and/or advanced adenomas (AA) at consecutive screening and having an interval CRC(2,3). Individuals with f-Hb concentrations close to 47 µg Hb/g faeces may therefore benefit from a shorter screening interval (i.e. increase the benefit), whereas individuals with undetectable f-Hb concentrations could benefit from a longer screening interval (i.e. decrease the harms) (4). A nationwide randomised controlled trial (RCT) is currently being carried out within the Dutch CRC screening programme to assess feasibility, acceptability and (cost-) effectiveness of such personalised screening intervals based on f-Hb concentration in those with a prior negative FIT (4).

Public preferences for cancer risk communication and acceptability of risk-stratified screening have been studied previously, mainly in the context of breast cancer screening (5–8). The acceptability of risk-based screening varies. It may be acceptable by the public when the rationale behind the strategies is explained and the public can see that the strategies result in greater benefit to the population as a whole (9). In contrast, receiving more- or less-intensive screening based on individual risk causes anxiety (10). Explaining the benefit of risk-stratified screening in an understandable manner, especially for those receiving less-intensive screening, appears to be crucial (11). Thus, transparency and public education is required for personalised screening strategies to be acceptable to the public. Evidence on individuals' information needs regarding risk stratification based on personal CRC risk is scarce. In this study, we aimed to gain insight into information needs to make a well-informed decision to participate in personalised CRC screening.

METHODS

PERFECT-FIT study

The focus group was conducted as part of a nationwide mixed-method study: "Personalised CRC screening: effectiveness of tailored intervals based on prior f-Hb concentration in a FIT-based programme (PERFECT-FIT)". The study is described in detail in the study protocol (4). In short, the aim of the PERFECT-FIT study is to evaluate the effectiveness, feasibility and acceptance of personalised CRC screening through tailored invitation intervals based on prior f-Hb concentrations; one year with f-Hb concentrations of >15–46.9 µg Hb/g faeces, two year with f-Hb concentrations of >0–15 µg Hb/g faeces and three years with f-Hb concentration of 0 µg Hb/g faeces. In the current uniform CRC screening programme in the Netherlands, the cut-off for a positive FIT is set at ≥ 47 µg Hb/g faeces and all individuals that tested negative are re-invited after two years, irrespective of their f-Hb concentration. At present, the target population is not informed of the quantitative amount of f-Hb concentration but only whether a follow-up colonoscopy is recommended. Anyone can request their f-Hb concentration at any time, provided they are aware of it.

The focus group in this paper, which consisted of three sessions, was conducted before the start of the national RCT. The online sessions took place between February and May 2022. The online platform Microsoft TEAMS was used. The first session was led by an experienced moderator (IK), with one expert on CRC screening (ETZ). The second and third sessions were led by ETZ, with an additional expert on CRC screening (EB). A topic guide was developed; the English translation can be found in the Appendix.

Study population focus group

Qualitative research methods allow for the in-depth exploration of the individual experiences and perspectives. Participants can build on the responses of each other, allowing for exploration and contradiction of individual's perspectives. We aimed for between four to five individuals per focus group session (12,13).

Participants were recruited through GENERO, a networking organisation for elderly people in the Southwest region in the Netherlands. Due to an insufficient number of individuals identified through GENERO for session 3, individuals were also

recruited through a nationwide network for immigrants (NOOM) living in the Netherlands.

To be eligible to participate in this study, a participant had to meet all of the following inclusion criteria: eligible for CRC screening, i.e. aged 55 to 75; having provided informed consent; having access to a laptop, computer, or iPad/Tablet with camera and microphone; and Dutch language proficiency. Subjects who did not meet all the inclusion criteria were excluded from participation in this study. All participants received financial compensation for participating in the focus groups (25 euros per person).

Qualitative data and thematic analysis

All focus group sessions were audio recorded. The recordings were transcribed with all personal identifiers removed. The full transcripts were read by two researchers (ETZ and LdJ) to familiarise themselves with the data. Subsequently, they coded the data and generated the main themes. Only the main themes and quotations were translated from Dutch into English. Codings were discussed among the researchers and the final themes and subthemes. Coding and analyses were performed using thematic analysis approach (14). Data was coded and managed using NVivo software (QSR International).

Ethical considerations

Study participants were recruited by our contacts at GENERO and NOOM, by sending an information letter. Individuals who indicated to our contacts to be interested were contacted by one of the investigators by phone, received information about the focus groups and all of them gave their verbal consent. The study was conducted according to the principles of the Declaration of Helsinki. Ethical approval was received from the medical ethical committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands (MEC-2021-0663).

RESULTS

A total of 14 individuals participated in the three focus groups; four to five per session. Men (50%) and women (50%) were equally represented. The median age was 69 (interquartile range 66–73 years; Table 1). Five (36%) individuals had a migrant background. Eleven participants had previously participated in the national CRC screening programme (79%). Two (14%) individuals had been diagnosed with CRC or AA through the screening programme.

Table 1 – Demographics of study participants of the focus groups.

Gender, n (%)	
Men	7 (50)
Women	7 (50)
Age	
Median (min-max)	69 (66-73)
Migrant background, n (%)	
Yes	5 (36)
No	9 (69)
Participation in national CRC screening programme, n (%)	
Yes	11 (79)
No	3 (21)
CRC or AA detected through screening, n (%)	
Yes	2 (14)
No	12 (86)

Abbreviations: CRC: colorectal cancer. AA: advanced adenomas.

Three overarching themes were identified (Figure 1):

1) views on CRC screening in general;
2) engagement of the target population;
3) information need about personalised CRC risk and screening.
4)

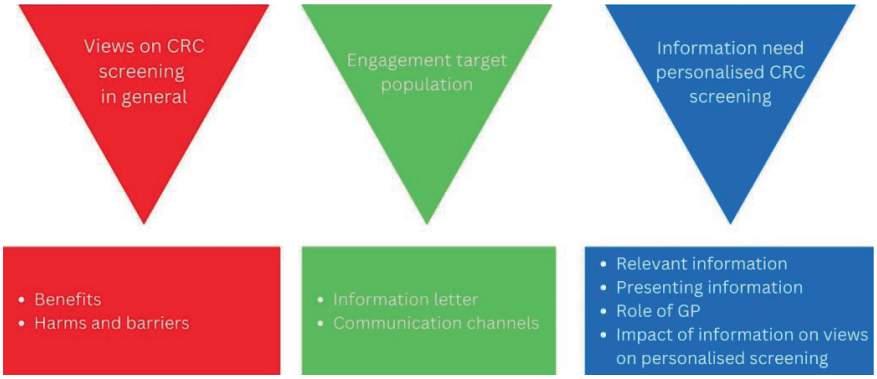

Figure 1 - Summary of main themes and sub-themes of the focus groups on information needs on personalised risk in CRC screening.

Abbreviations: CRC, colorectal cancer; GP, general practitioner.

Views on CRC screening

Benefits of CRC screening in general

The majority of participants understood that CRC screening leads to early detection of CRC or can even prevent CRC. A small number of participants had had a positive FIT and undergone a follow-up colonoscopy in the past. In two participants a relevant finding (CRC or AA) was detected at colonoscopy. Their experience, including the perceived benefits of CRC screening, was shared with the other participants and well-received (Table 2a).

Table 2a - Focus group quotations 'Benefits of CRC screening in general'.

"It is, of course a form of cancer that has no symptoms. So by the time you have symptoms, you are already at a fairly advanced stage. And if you can prevent that in this way [screening], yeah, it's just a win–win" (Focus group 1).

Harms and barriers of CRC screening in general

Similar disadvantages of CRC screening or the organisation of the screening programme were addressed across all three focus groups (Table 2b). Stool collection was considered an unpleasant and complex task, although it was debated that it most likely only has a negative impact on individuals in doubt to participate. The deductible excess is an obligatory amount that first needs to be paid out of pocket

before the health insurance reimburses healthcare costs. It was discussed that this might be a barrier for individuals to participate in screening, although it was felt again likely to have negative effects only on individuals in doubt to participate. Stopping screening at the age of 75 years was extensively debated; there was misunderstanding about the fact why 75-years-old individuals were no longer entitled to participate. Besides the barriers to participate in FIT-based CRC screening, harms of CRC screening were not explicitly mentioned during the focus group.

Table 2b - Focus group quotations 'Harms and barriers of CRC screening in general'.

"The collection is a hassle and I have the impression that when people are already in doubt, the whole hassle [of collecting stool], is a deciding factor not to participate" (Focus group 1).
"What I hear from people is that they are 76 years old and they can no longer participate. That can be explained, but it goes through people's minds" (Focus group 1).
"It stops at 75, doesn't it? The fact that you never receive an invitation again, is that because of medical reasons or is it financial?" (Focus group 2).

Engagement of the target population

Information letter

The information letter format and content were important considerations for participants; one individual had even kept his first information letter (since October 2015) (Table 2c). An important topic was language. Although the information letter refers to the website for information in different languages, the letter must first be opened and read in Dutch to find this reference to the website. It was suggested to add a small leaflet with information in several languages to make it more identifiable for migrant populations, especially because first-generation immigrants at an older age have more difficulty using the internet. Using pictures or infographics were considered helpful in understanding the information. The majority of participants that had participated in CRC screening said that they had already made the decision to participate before receiving the invitation.

Table 2c - Focus group quotations 'Information letter'.

"Yes, it is a good idea of use pictures, just like Ikea" (Focus group 2).
"There is some information about how to do it, but I think indeed for people, especially for our migrants who are not sufficiently proficient in the Dutch language. If you explain it with pictures, well, that will also make it clearer" (Focus group 2).
"I think that a purple envelope [colour of the Dutch invitation envelope] is not enough. There should be something else to make it more recognisable. Maybe more in the life-world of people, so to speak and maybe this is even more difficult for men" (Focus group 3). *"This is of course also an old-fashioned way of passing on this [information on CRC screening and invitation] by letter…. Maybe there are other ways as well" (Focus group 3).*

Communication channels

A hardcopy information letter alone was considered insufficient to inform all individuals within the target population (Table 2d). They all preferred various communication channels to be informed about CRC screening. Several suggestions were made to inform and better engage the target population in CRC screening; public media campaigns, billboards, videos on social media, posters in the waiting room of the general practitioner (GP), interviews in magazines and encouragement through key figures in communities. Social media, for example Facebook, was suggested as a platform to share information through a video. This video should be available in different languages to also address the language barrier. It was pointed out that there was a public media coverage at the launch of the national CRC screening programme. This publicity was considered informative and when individuals were eventually invited, the letter came as no surprise.

Table 2d - Focus group quotations 'Communications channels'.

"Before the population screening started, there was a lot of publicity in the press. So when the invitation letter came in it complemented the whole thing. It didn't influence my decision whether to participate or not" (Focus group 1).

"I have the impression that people do not read letters. The more information they [invitation letter] contain, the less people read them. So it is important that the information is also presented through advertisements or on regional or national television. The information about CRC screening is already in people's mind and the details just need to be given in the information letter" (Focus group 3).

"You really need to find someone who can give you more information, so to speak. People who know how the organisation works and who know the culture and the differences……. When you reach them, you don't have to reach out to everyone. People who really have a public function. We have to look for them" (Focus group 2).

"You could also use the billboards we have in the city. We have so many billboards where you can also present the information" (Focus group 2).

Another topic that was addressed regarding communication is the use of key figures in communities to involve individuals from different cultures who may not be reached with the traditional information leaflet.

Information need personalised CRC screening

Relevant information - risk communication

The PERFECT-FIT RCT on tailored invitation intervals (1, 2 or 3 years) using prior f-Hb concentration was used as an example when discussing cancer risk communication. During the sessions, it became clear that what was considered as relevant information varied substantially among focus group participants. Some participants preferred to receive detailed information on their f-Hb concentration and whether they were at higher or lower risk of developing CRC (Table 2e). Other participants clearly indicated that they preferred not to receive detailed information, but only which risk group they fall into and that they will be re-invited after a certain time interval. In all three sessions they came to the conclusion that it is probably impossible to address everyone's needs.

Table 2e - Focus group quotations 'Risk communication'.

"I have the feeling that no matter what you write down, you will never please everyone. One person will think they are getting too much information, the other person will think they are getting too little information. One person wants the test earlier, another wants it later. We are, of course, a country of experts" (Focus group 1).
"I wonder if you have to give such an explanation. What I would suggest is that if you test negative two or three times, you say that the interval will be extended. That you can determine that based on your personal data. But I won't start saying you have a little bit of blood" (Focus group 1)
"I actually think that if there is blood found in the stool during the population screening, but not to such an extent that it is alarming, I am shocked not to report it, I think that is actually a bit misleading. You could say in the result letter that there is indeed blood in the stool. It is not yet necessary to have a colonoscopy or something like that, but it should be monitored for this or that reasons" (Focus group 3).

The meaning of a negative FIT was new to the participants; no communication is provided to the public on the predefined cut-off for a negative FIT. All focus group participants were unaware that having a negative FIT does not mean that there was no blood in their stool sample. Hearing that their stool may have contained blood came as a surprise to many of the study participants; one person felt misled. The response to the information that a previous negative FIT indicates that their stool may have contained blood ranged from acceptant to surprise or alarmed.

Relevant information – costs

During the discussion on the rationale behind shortening and lengthening the screening interval, some participants were under the impression that the decision to introduce personalised CRC was cost-driven (Table 2f). They had not appreciated that the aim of the current RCT is to improve the balance of the benefits and harms of CRC screening by intensifying screening in those at highest risk (i.e. shortening the screening interval) and lessening screening in those at lowest risk (i.e. extending the screening interval).

Table 2f - Focus group quotations 'Costs'.

"I think it's very important, if you start with it, to do it very carefully, for example in a public campaign or I don't know what to call it. But just to clarify that [that people think it might be cost-driven] a lot" – "Yes, because it will be understood as retrenchment" (Focus group 1). *"What is the idea behind extending up to three years? Is it just costs, or are there other reasons?" (Focus group 3).*

Presenting information

Similar to the discussions around the information provision on the current Dutch uniform CRC screening programme, suggestions were made to use figures or infographics to communicate different risk profiles (Table 2g). The participants also favoured layered information, with some information provided in the results letter and additional information available elsewhere for those wanting more details. This was particularly important when providing information about the amount of blood in their stool as it was felt that detailed information on this might frighten individuals. Another recommendation that recurred in all sessions was that it would be beneficial to raise public awareness before personalised screening is implemented nationally, as discussed in the Methods section.

Table 2g - Focus group quotations 'Presenting information'.

"The best thing would be if it will be presented in different ways, so that you get repetition. Because of course people take in information in different ways" (Focus group 3).

Role of the general practitioner

Instead of sending information by letter, another option discussed was to refer individuals to their general practitioner (GP) (Table 2h). The GPs are aware of patients' medical records and can communicate information that is relevant to them based on their medical condition and communicate this in a way that is most likely to be understandable to individuals. Some participants said that they would contact their GP directly if they were given a 1-year interval, as they would be concerned if it indicated that they were at higher risk for CRC. Others realised that the GP could be the right person, but that GPs would have restricted time for this additional task.

Table 2h - Focus group quotations 'Role of the general practitioner'.

"Yes, but they [Population Screening Information Line] cannot, in my opinion, respond to your personal situation. The person who can do that is the doctor. So if your doctor knows the background information, he/she can give an explanation" (Focus group 1).

Impact of information on views on personalised screening

Shortening the invitation interval when at high risk was well-accepted and understood by the participants (Table 2i). Views on extending the invitation interval for those at lower risk for CRC were diverse. From the study participants' perception, performing the stool test is not a harm (burden). They felt that individuals who have already decided to participate accept harms involved in screening and to them there is no benefit in extending the interval to three years. To them, it is better to choose the safer option than the riskier one. However, not all participants were negative about extending the interval, as some believed they were in good health and did not need more intensive screening.

Table 2i - Focus group quotations 'Impact of information on views on personalised screening'.

"But I think it is better to have one too many than one too few" (Focus group 3).
"Yes, I agree, because I think that you should stick to the two years…….. If you have to wait three years for the next screen, people think it will be much too late. I don't know how aggressive this cancer is, I have no idea" (Focus group 3).
"No, I would not mind [3-year interval]. If I am so healthy that they do not want to see me three years I will explain that as something positive" (Focus group 2).
"I think that at some point people will be willing to participate in screening, that they will take the risk of that tension. And then it makes absolutely no difference whether it is every three years or every two years" (Focus group 3).

Focus group participants clearly stated that they would participate in personalised screening, regardless of whether the information presented met their needs. This was due to their positive view on CRC screening in general and belief that CRC screening will lead to benefits. The participants that had not participated in CRC screening before, said they would reconsider their choice to not participate, as a result of the discussion during the focus group.

DISCUSSION

In this study we gained insights into information needs regarding risk communication in personalised CRC screening. No consensus was reached during the focus group on the preferred method for communicating individuals' CRC risk. Several suggestions were made, which ranged from "I want to know everything" to "I only want to know which risk group I am in".

The variation is in line with findings of other studies which have shown that the presentation of risk in a single format is not optimal (15,16). In a study on optimal communication about breast cancer risk, women's preferences varied from preferring not to be given detailed information to the more detailed information on individual breast cancer risk (15). In another study on risk communication of cardiovascular disease, it was also concluded that a combination of different formats of risk communication is preferred (16). Our findings reaffirm that it will be challenging to address everyone's needs and a layered approach to deliver information on individual's CRC risk is required. Different formats need to be designed and evaluated in larger cohorts.

The findings of this qualitative study emphasise that the public particularly need understandable information on the balance between the harms and benefits of CRC screening, given that personalised screening aims to improve this balance. Increasing the benefits by intensifying screening was well-accepted among our participants, but lessening screening to reduce the harms of screening was received differently. This is consistent with the findings of previous research, in which it has been shown that lessening screening was not accepted by the public and highlights further the importance of clearly communicating the rationale and evidence behind the personalised approach (7,11,17–19). Explaining these benefits is also essential to avoid that the general perception will be that optimising CRC screening is only cost-driven. The discussion on stopping age of screening was beyond our research scope, but gave insight in the issue of informing the population about the optimal balance between harms and benefits of screening. The stopping age was chosen based on the harm/benefit ratio of CRC screening per age (20). This optimal harm/benefit ratio may however be perceived differently by the target population, having another view on the benefit and especially the harms of screening at an older age (11,21). The public seems not well informed and may disagree with the rationale for stopping CRC screening at the age of 75, similar to the disagreement with the rationale for lengthening the screening interval to reduce potential harms of screening.

Individuals that previously participated in CRC screening indicated that they had already made the decision to participate before receiving their invitation letter. Moreover, the indicated that they would participate in personalised CRC screening, regardless of whether CRC risk communication met their preference. This is in line with previous research, in which participants reported that receiving a low risk estimate would have no impact on whether they chose to participate, while receiving a high risk might have a positive impact (22). Literature consistently showed that the concept of personalised screening seems to have no negative impact on individuals' view on cancer screening (22–24). We can carefully conclude that individuals also seem to accept new screening strategies if they are positive towards uniform CRC screening. Further research is needed to examine whether engaging individuals in CRC screening in general might actually be more important than addressing everyone's need in communication of personal' CRC risk.

Focus group participants shared their views on the minimum requirements for informing and engaging the target population in a personalised CRC screening programme. The organisational structure may already be optimal: sending a pre-invitation letter, then mailing an invitation including a test kit and a reminder letter if necessary (25,26). Despite the success of the media campaign when CRC screening started in 2014, focus group participants indicated that there is no general awareness of the CRC screening programme at present and a hardcopy letter is insufficient. Especially relevant, as it is known that non-participants read no information (24,27). A media campaign accompanying the introduction of a personalised screening programme could therefore potentially raise the public awareness of the personalised approach before participation (28). Other suggestions to raise awareness were information leaflets in different languages, infographics, social media, national campaigns, billboards, interviews in magazines, and key figures in the community.

The main strength of our study was using focus groups rather than interviews which gave the benefit of providing a way for participants to build on each other's responses and consider aspects that they might not have considered themselves. This was particularly important around the variation in preferences for information, only by the group discussion we became aware that there is not one preferred format. Another strength was the inclusion of individuals who had previously chosen not to take part in screening and thereby we were able to capture the views of a hard-to-reach group. In line with this, the participants were diverse in

terms of gender and migrant background, the result of recruiting the participants through the elderly network within a large multicultural city. Lastly, the personalised CRC screenings strategy discussed in the focus group was not a hypothetical scenario, but based on real scenario of a nationwide RCT (4). Our method of recruitment - through an elderly network – is also a limitation and may have introduced some selection bias; participants were relatively old (69 years) and did not cover the full age range (55–75) of the screening programme. The lack of younger individuals in this study sample may have influenced the results of the study. Younger people may have had different information preferences, using different types of social media or communicating their individual CRC risk. However, this is in line with our conclusion; that communication should happen using a layered approach and through multiple channels. Also few individuals had been diagnosed with CRC or a precancerous stage, and these patients may have a more positive view towards CRC screening in general. Another limitation was that not all participants were ready for the discussion on personalised screening because they had outstanding questions on the CRC screening programme in general. Positively, this enabled us to obtain relevant insights that can be useful for communication methods within the current uniform CRC screening programme.

In conclusion, this study showed that preferences for receiving information about individual CRC risk varied widely and no consensus was reached. A layered approach to deliver information is required. Nevertheless, the provision of information may have minimal impact on the decision to participate in personalised CRC screening.

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APPENDIX

Questionnaire for the semi-structured focus group (translation of original Dutch questionnaire)

Theme I: Bowel cancer population screening

1. What do you already know about the Dutch uniform colorectal cancer (CRC) screening programme?
    a. Have you participated in CRC screening before?
    b. What are reasons to participate in CRC screening?
2. Can you take me along in your choice process to participate in CRC screening?
    a. Did you discuss your choice to participate with anyone else?
    b. Did you inform or visit your GP?
    c. Did you read the invitation letter?
    If yes:
    What did you find difficult when reading the information about the CRC screening programme?
    What did you find helpful when reading the information about the CRC screening programme?
    If not, why not?

In the current CRC screening programme you will receive a stool test at home every two years. You can perform this at home and send it back by post. The laboratory then checks whether there was blood in your stool, which is often invisible. With the stool test you can have a favourable or unfavourable result. If the result is unfavourable, the lab (laboratory) found blood in your stool. Further research is then required. With a favourable result, the laboratory found little or no blood in your stool. This means that no further investigation is required. Until now, all people with a favourable result were invited again every two years. However, the risk of CRC differs in people who previously had a favourable result. People without blood in the stool have a lower risk of CRC than people with very little or little blood, even though this risk is still very low. In CRC screening based on individual risk, people with little blood are invited earlier than people without blood. This means that not everyone is invited every two years with a favourable result, but the screening interval is based on personal risk.

3. Do you think that information about the results and personal risk can influence people's opinions about the CRC screening programme, and if so, how?
    a. Now you have the knowledge about the cut-off value and a favourable result, do you prefer to know that a favourable result does not always mean that no blood was found in the stool?
    b. What is your response or feeling that, despite a favourable result, there may have been a little blood in your stool?
    c. Would you have needed more information about a favourable result?
    d. If so, what would you like to have known before participating?

Theme II: Personalized colorectal cancer screening

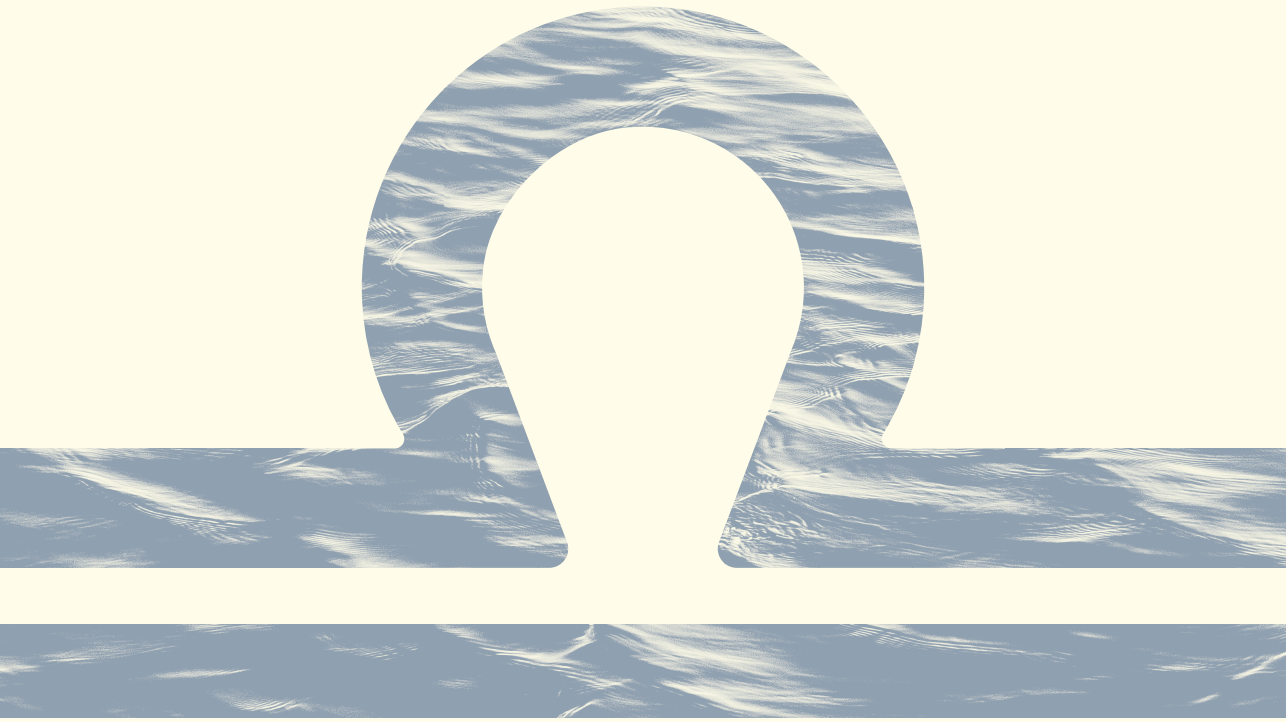
We are conducting a scientific study with people who had a favourable result in the previous screening round. However, there is a difference in CRC risk among individuals with a prior favourable result. In the study, we do not invite all individuals after 2 years as standard, but after one, two or three years. Depending on whether people had no blood (3 years), very little blood (2 years) or little blood (1 year) in the stool. The majority of people have no blood in their stool (85%). In the context of this study, we would like to find out what information people consider desirable in order to make a well-informed choice about participation in a population CRC screening based on personal risk.

4. The above information is new to you, as it was previously communicated that there was no blood in your stool. Do you have questions about this?
5. Would you participate in CRC screening on personal risk?
    a. What are reasons for not participating?
    b. What is a reason to participate?
6. What information do you think is necessary to make a good choice about participation in a CRC screening based on personal risk?
    a. How would you best understand information from, for example, the invitation folder regarding a higher or lower risk of colorectal cancer?
    b. What information is helpful in making a good choice regarding participation in CRC screening using personal risk?

   c. How would you like to get this information presented? (Short folder, letter, website, film)?
7. How do you feel about some people being invited after 1 year, and the majority of people after 3 years?
8. Does anyone have anything to add that hasn't been discussed?

Part III

Colorectal cancer in testicular cancer survivors treated with platinum-based chemotherapy



Chapter 9

Somatic hits in mismatch repair genes in colorectal cancer among non-seminoma testicular cancer survivors

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ABSTRACT

Background

Non-seminoma testicular cancer survivors (TCS) have an increased risk of developing colorectal cancer (CRC) when they have been treated with platinum-based chemotherapy. Previously we demonstrated that among Hodgkin lymphoma survivors (HLS) there is enrichment of rare mismatch repair (MMR) deficient (MMRd) CRCs with somatic hits in MMR genes. We speculate that this phenomenon could also occur among other cancer survivors. We therefore aim to determine the MMR status and its underlying mechanism in CRC among TCS (TCS-CRC).

Methods

Thirty TCS-CRC, identified through the Dutch pathology registry, were analysed for MMR proteins by immunohistochemistry. Next-generation sequencing was performed in MMRd CRCs without MLH1 promoter hypermethylation (n=4). Data were compared with a male cohort with primary CRC (P-CRC, n=629).

Results

MMRd was found in 17% of TCS-CRCs vs.. 9% in P-CRC (p=0.13). MMRd was more often caused by somatic double or single hit in MMR genes by mutation or loss of heterozygosity in TCS-CRCs (3/30 (10%) vs.. 11/629 (2%) in P-CRCs (p<0.01)).

Conclusions

MMRd CRCs with somatic double or single hit are more frequent in this small cohort of TCS compared with P-CRC. Exposure to anticancer treatments appears to be associated with the development of these rare MMRd CRC among cancer survivors.

BACKGROUND

Testicular cancer (TC) survivors have an increased risk of developing colorectal cancer (CRC) (1–7). This increased risk appears to be associated with platinum-based chemotherapy, which was associated with a hazard ratio (HR) for CRC of 3.9 (95% confidence interval (CI) 1.7–8.9) (8,9). Such an association between platinum-based treatment and risk of second primary gastrointestinal (GI) malignancies has also been described in childhood cancer survivors (10).

The increased risk of second primary CRC in TC survivors (TCS-CRC) may be due to mutagenic and genome destabilising effects of cancer treatment on normal colonic mucosa (11). These changes can result in premature ageing of the colonic mucosa and/or cancer development at an earlier age among cancer survivors (12,13). These treatment-induced changes may also activate pathogenetic processes that result in molecular profiles that are different from those of primary CRC. Previously, we have shown that Hodgkin lymphoma (HL) survivors treated with abdominal radiotherapy and/or procarbazine-containing chemotherapy have a higher frequency of mismatch repair (MMR) deficient (MMRd) CRC compared with CRC patients in the general population (14). This higher frequency was due to the enrichment of somatic double hit in MMR genes by either mutations or loss of heterozygosity (LOH). Also, MMRd cases with somatic single hit occurred in this group. These findings suggested a novel association of prior anticancer therapy with somatic MMR gene mutations or LOH. We hypothesise that this association may not be specific to the context of HL. Instead, we contemplate that this phenomenon could also occur in other cancer survivors that received other types of anticancer treatments. To examine this hypothesis, we evaluated whether MMR status and the underlying mechanism of MMRd in TCS-CRC differs from CRC occurring in the general population (primary CRC, P-CRC).

METHODS

Patients and tissue samples

The population-based Netherlands Cancer Registry (NCR) was used to identify CRC after non-seminoma TC, diagnosed before the age of 50 years, irrespective of non-seminoma treatment. Patients were diagnosed with non-seminoma TC between 1989 and 2011. This range is caused by the fact that CRC develops predominately 10 years after treatment for TC, and therefore CRC was still diagnosed in 2019. A total of 36 CRC were identified at least one year after the diagnosis of non-seminoma TC. These cases were subsequently linked to the PALGA (the nationwide network and registry of histopathology and cytopathology) registry to obtain pathology reports and formalin-fixed paraffin-embedded (FFPE) material (15). Tissue from 30 TCS-CRCs was available for analyses. Non-seminoma TC treatment data were retrieved through the NCR. All data collection and analyses were pseudonymised.

Histopathology

Histopathology of 30 of 36 (83%) retrieved samples was reassessed on haematoxylin & eosin (H&E)-stained slides according to standard protocol by an experienced gastrointestinal pathologist (PS). One patient had a metachronous CRC, of which both CRCs were completely evaluated, leading to 30 CRCs in 29 TC patients.

Immunohistochemistry

Immunohistochemistry (IHC) was performed for MMR proteins according to standard protocols for Ventana immunostainer (MLH1 (Agilent/DAKO, Cat. # M3640), MSH2 (Roche/Ventana, Cat. # 8033684001), MSH6 (Epitomics, cat. # AC-0047EU), PMS2 (Roche/Ventana, Cat. # 8033692001). IHC was performed on tissue microassay when available. In case of biopsy material, whole sections were cut for IHC.

Molecular analyses

The AllPrep DNA/RNA FFPE extraction kit (QIAGEN, Germany) was used to isolate DNA of FFPE material of CRC in TC survivors following the manufacturer's instructions. The concentrations were measured using the Qubit 2.0 Fluorometer with the Qubit dsDNA Assay Kit (Provenience).

Additionally, we evaluated the mutational status in common CRC-related genes, i.e. KRAS, NRAS, BRAF and PIK3CA, using a gene panel (Sequenom Massarray, Agena Bioscience, San Diego, California, USA) that also included AKT1, DDR2, EGFR and MEK1.

Due to very high concordance of MMR IHC and MSI PCR between between MMR status and microsatellite status in colorectal cancer (16–19), we did not perform MSI PCR.

Assessment of mechanism behind MMR deficiency

Promoter methylation of MMR genes was evaluated in MMRd tumours by a multiplex ligation-dependent probe amplification (MLPA) kit (ME011-B2 kit; MRC Holland, Amsterdam, the Netherlands). This probemix included a total of 25 probes for the promoter region of six different MMR genes (MLH1, MSH2, MSH6, PMS2, MSH3, MLH3). Gene positivity was defined as 33% of probes per gene with a cut-off for positivity of 0.2 at probe level.

In case of MMRd without MLH1 promoter methylation, further analysis was performed on both tumour tissue and normal tissue to screen MMR genes for mutations and LOH via Next Generation Sequencing (NGS) using the msCRCv2 panel with supplier's materials and protocols (Life Technologies, Carlsbad, CA, USA) as described previously (20). Details of the panel can be found at https://www.palga.nl/datasheet/LUMC/MMR_Panel_MSCRCv2_LUMC.pdf.

The mechanism underlying MMRd was classified as follows: (1) MLH1 promoter methylation, (2) Lynch syndrome, (3) somatic double hit by mutations or LOH and (4) somatic single hit by mutation or LOH. For statistical analysis, cases with somatic double or single hit were grouped together. We included all cases of MMRd in our analysis, including MMRd explained by Lynch syndrome to provide an overview on all MMRd subgroups.

Control group of CRC <70 years in the general population

The frequencies of MMRd and its mechanism of inactivation were compared to data of sporadic CRC in a general population cohort, referred to as primary CRC (P-CRC) (21,22). This included 1,117 patients prospectively collected between 2007 and 2009 at ages ≤70. For this study, we selected male patients (n=629) only to ensure comparability with our cohort. This control group was selected because it was a

relatively young cohort within the general population and because of the availability of the required data (MSI status, MMR status, MLH1 promoter methylation, etc).

Statistical analyses

Data was analysed using IBM SPSS V.22.0 database software. Data were compared between groups using $\chi 2$ tests or Fisher's exact tests for categorical data and Mann–Whitney U-test for continuous data that were not normally distributed. The significance level was defined as two-sided $p \leq 0.05$.

RESULTS

Patient characteristics

FFPE material of 30 out of 36 TCS-CRCs (83%) was available for analyses (Figure 1). One TC survivor had developed a second CRC after 1 year. The non-seminoma TC were diagnosed at a median age of 39 years (IQR 22–45 years) in the 29 patients (Table 1). In most cases, data on TC therapy could not be retrieved. Of patients for whom data could be retrieved (n = 9), all had received platinum-based chemotherapy (8/9 cisplatin and 1/9 carboplatin). Patient characteristics of the non-seminoma TC are described in Table 1.

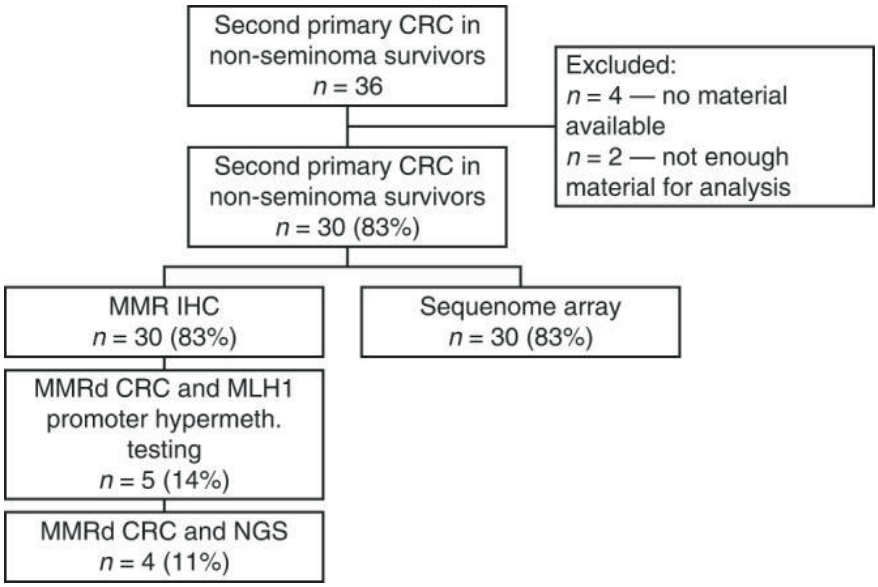

Figure 1 – Study flowchart. The flowchart of colorectal cancer (CRC) diagnosed in non-seminoma testicular cancer survivors treated with platinum-based chemotherapy.

Table 1 - Baseline characteristics of non-seminoma testicular cancer (TC) survivors with second primary colorectal cancer (CRC).

	N (%) (N = 29)*
Age of non-seminoma TC diagnoses	
Median (range)	39 (22–45)
Treatment period	
1989–1999	22 (76%)
2000–2011	7 (24%)
Stage non-seminoma	
I	9 (40%)
II	3 (15%)
III	4 (20%)
IV	4 (20%)
Unknown	9
Treatment non-seminoma	
Chemotherapy only	8 (89%)
Radiotherapy + chemotherapy	1 (11%)
Unknown	20

*Only characteristics of those patients from whom samples were retrieved are presented in the table of which one patient developed two CRCs.

The median interval between non-seminoma TC diagnosis and CRC was 19 years (IQR 2–29 years). Median age at diagnosis of TCS-CRC was 55 years (range 35–68), which was significantly younger than the median age at diagnosis of the P-CRC (diagnosed ≤70 years) (61 years, IQR 27–71 years, $p<0.01$). The tumour location did not significantly differ between TCS-CRC and P-CRC. All TCS-CRC (n = 30) were conventional adenocarcinomas. KRAS, NRAS and BRAF mutation occurred in 35, 7 and 3% of TCS-CRCs, respectively. Patient and CRC characteristics are described in Table 2.

Table 2 - Characteristics of second primary colorectal cancer (CRC) in non-seminoma survivors and primary CRC.

	Second primary CRC in non-seminoma survivors (n=29)	*Primary CRC <70 years (n=629)*	*P value*
Interval between TC diagnosis and CRC (median, range, years)	19 (2–29)	N/A	–
Age at diagnosis of CRC (median, range, years)	55 (35–68)	61 (27–71)	<0.01
Year of CRC diagnosis (range)	1994–2019	2007–2009	N/A
	Total CRC n = 30 (n, (%))	*Total CRC n = 629 (n, (%))*	
Location			0.59
Proximal*	8 (29%)	153 (25%)	
Distal	12 (43%)	218 (36%)	
Rectum	8 (28%)	228 (38%)	
Unknown	1	30	
Stage			0.18
I	10 (50%)	123 (28%)	
II	3 (15%)	123 (28%)	
III	6 (30%)	173 (39%)	
IV	1 (5%)	25 (6%)	
Unknown	9	184	
MMR status			0.13
Proficient	25 (83%)	575 (91%)	
Deficient	5 (17%)	54 (9%)	
MMR staining			0.20
Staining present	25 (83%)	576 (92%)**	
MLH1 and PMS2 deficiency	3 (10%)*	38 (6%)	0.38
MSH2 and/or MSH6 deficiency	2 (7%)	14 (2%)	0.12
Mechanism of MMR deficiency			0.02
Somatic *MLH1* hypermethylation	1 (3%)	30 (5%)	0.18
Lynch syndrome	1 (3%)	13 (2%)	0.64
Somatic double or single hit in MMR genes	3 (10%)	11 (2%)	<0.01

*In one there was loss of MLH1 and PSM2 staining, which also included secondary loss of MSH6 staining.
**One case with MMR proficient IHC result while MSI PCR showed MSI.

MMR status of second primary colorectal cancer in non-seminoma survivors

MMRd occurred in 17% (5/30) of TCS-CRC compared with 9% (54/629) in P-CRC (p=0.13). Three of five MMRd cases (60%) demonstrated combined absence of MLH1 and PMS2 staining. One of these cases also showed absence of MSH6 staining, which is recognised as secondary inactivation resulting in loss of MSH6 on IHC (23). The remaining two cases demonstrated either isolated absence of MSH6 staining or combined absence of MSH2 and MSH6 staining. Of all five MMRd cases, treatment given for non-seminoma TC was unknown.

Underlying mechanism of MMR deficiency in colorectal cancer in non-seminoma survivors

Of the three cases with MLH1/PMS2 deficiency, the first one had somatic hypermethylation of the MLH1 promoter. The second was explained by Lynch syndrome (germline MLH1 mutation accompanied by second somatic hit) and the third case by somatic double hit in the MLH1 gene by mutation and LOH (Table 3). In the fourth case, which demonstrated MSH2/MSH6 deficiency on IHC, there was somatic single hit in the MSH2 gene by LOH. In this case, we also detected LOH of MSH6, but these genes are in close proximity of each other on chromosome 2. It was therefore classified as a somatic single hit. Finally, for the case with isolated MSH6 deficiency, we found three mutations in the MSH6 gene (Table 3). These three mutations included one frameshift mutation with known pathogenicity and two missense mutations of unknown pathogenicity. Therefore, we classified this case as having somatic single hit.

Table 3 - Outcome of next-generation sequencing (NGS) of the four mismatch repair deficient (MMRd) colorectal cancer (CRC) in non-seminoma testicular cancer (TC) survivors (exclusion of the MMRd CRC explained by MLH1 hypermethylation).

No.	Age at TC	Age at CRC	IHC loss	Material	Chr:ChrPos	Gene	HGVS. Coding	Class**	Type	LOH	Conclusion of MMR	Mechanism of MMR deficiency
1*	37	40	MLH1 PMS2	Tumour Normal	3:37053310 3:37038205 3:37053310	MLH1 MLH1 MLH1	NM_000249.3:c.546-1G>A NM_000249.3:c.207+5G>A NM_000249.3:c.546-1G>A	4 4 4	Splice-site Splice-effect Splice-site	No LOH No LOH	2 mutations 1 mutation	Lynch syndrome
2	31	57	MLH1 PMS2	Tumour Normal	3:37053595	MLH1 No pathogenic mutation	NM_000249.3:c.677+5G>T	4	Splice-site	LOH of *MLH1*	1 mutation + LOH	Somatic double hit
3	22	50	MSH2 MSH6	Tumour Normal		No pathogenic mutation No pathogenic mutation				LOH of *MSH2* and *MSH6*	LOH	Somatic single hit
4	26	35	MSH6	Tumour Normal	2:48026606	MSH6 No pathogenic mutation	NM_000179.2:c.1484delG NM_000179.2:c.890C>A NM_000179.2:c.728G>A	4 3 3	Frameshift Missense Missense	No LOH	1 mutation	Somatic single hit

Abbreviations: TC: testicular cancer, CRC: colorectal cancer, IHC: immunohistochemistry of mismatch repair (MMR) genes, Chr:ChrPos chromosome and chromosome position, HGVS.: a series of variance on one chromosome, LOH: loss of heterozygosity.

* Of one CRC, two samples of FFPE material were available.

** Class: prediction of pathogenicity of gene variant (benign (1), likely benign (2), uncertain (3), likely pathogenic (4) or definitely pathogenic (5)).

The distribution of molecular mechanisms underlying the MMRd was different between TCS-CRC and P-CRC (p=0.02; Table 2). This difference was primarily due to enrichment of MMRd cases showing somatic double or single hit in MMR genes by mutation/LOH (10 vs.. 2%, p<0.01). The frequency of MLH1 promoter hypermethylation was similar to the P-CRC cohort (resp. 3 vs.. 5%, p=0.18). Also, the frequency of Lynch syndrome was similar in TCS-CRC compared with P-CRC (resp. 3 vs.. 2%, p=0.48).

DISCUSSION

In this study, we aimed to determine whether TCS-CRC have different pathogenesis compared to P-CRC for which we evaluated the MMR status and its underlying mechanism. We have found that 17% of TCS-CRC are MMRd. MMRd status is significantly more often caused by double or single somatic hit compared to P-CRC (10 vs. 2%, $p<0.01$). In other words, we have shown that a rare subgroup of CRC with MMR deficiency, i.e. CRC with somatic double or single hit in MMR genes by mutation or LOH, is more common in TCS-CRC. Cases explained by MLH1 promoter hypermethylation or Lynch syndrome are equally frequent in both cohorts.

In a previous study on HL survivors, we demonstrated a significant enrichment of somatic double hit as cause of MMRd (7/54, 13%) compared to the general population (8/1,111, 0.7%) (14). In that study, we primarily focussed on cases demonstrating somatic double hit, but we also found significantly more cases with somatic single hit (3/54, 6%) compared to CRC in the general population (3/1,111, 0.3%, $p<0.01$). The combined frequency of these two rare MMRd subgroups was 19% (10/54), which is much higher than in the general population reference cohort for that study (11/1,111, 1%, $p<0.01$).

The present data show an enrichment of a rare subgroup of MMRd cases, i.e. with somatic double or single hit in MMR genes, as previously observed in the study on HL survivors (14). This enrichment becomes more apparent when comparing these frequencies to data from a recent meta-analysis taking all age-groups into account which showed that somatic double and single hit in MMR genes only occurs in 1.8% and 0.7% of all CRCs, respectively (24). This underscores the rarity of this MMR subgroup in CRC in the general population and contrasts the frequency among second primary CRC. These data are of great importance, because the repeated link between anticancer treatment and the occurrence of these rare MMRd CRC among cancer survivors raises the question whether various anticancer treatments may cause the development of this MMRd subgroup among cancer survivors. The patient cohort with HL survivors was predominately treated with alkylating agents such as procarbazine and/or radiotherapy, while the large majority of

patients with non-seminoma TC are treated with platinum-based chemotherapy (25). In the current study, we unfortunately did not have information on treatment of patients with MMRd CRC. Also, experimental data explaining the mechanisms underlying these associations is lacking. Still, there is a link between the MMR system and cisplatin exposure, as it was shown that the MMR mechanism is important in repairing DNA damage caused by cisplatin (26–30). Furthermore, a link between the MMR system, radiotherapy and alkylating agents has been described (14). We previously hypothesised that pre-existing epithelial intestinal cells with some level of MMR dysfunction are targeted by anticancer treatments, which could then lead to the development of MMRd CRC.

Previously, patients with MMRd CRC have been referred to as having Lynch-like syndrome (LLS) when neither MLH1 promoter hypermethylation nor germline mutations in MMR genes were detected. Since then, it has become clear that in a significant part of these cases, acquired somatic double or single hit in MMR genes can be found (31). Cases with double hit in MMR genes can be regarded as fully clarified. However, MMR deficient cases with only a single detectable hit in an MMR gene are not fully clarified. Since inactivation of both alleles is necessary to result in complete loss of expression of MMR genes it can be deduced that a second hit is present although it was not identified. The lack of second hit is most likely explained by genetic alterations that are not detected by the methods used, such as certain types of LOH, epigenetic alterations or complex genomic alterations resulting in silencing of the other MMR gene. In studies examining patients with LLS, there also remains a subgroup where no somatic changes can be detected (31).

In our analysis, we found one TC survivor with corresponding MMR gene mutation both in CRC tumour tissue as well as in normal colonic tissue. Therefore, this single patient was regarded to have Lynch syndrome. The remaining patients did not carry MMR mutations in normal colonic tissue. For these patients it could therefore be concluded that the MMR gene hits were unique to the CRC and not involved in the carcinogenesis of the prior testicular cancer. An increased risk of testicular cancer among Lynch syndrome patients has never been reported (32) and 97% of germ cell tumours from various

locations among Lynch syndrome patients are microsatellite stable (33). Also, the rate of MMRd in testicular cancers has been reported to be very low, i.e. much less than 1% (34,35). These observations contrast the relatively high percentage of MMRd in second primary CRC among TC survivors and agree with our finding that second primary MMRd CRC of TC survivors are largely unrelated to Lynch syndrome. This is also analogous to our previous findings on second primary MMRd CRC among Hodgkin lymphoma survivors (14).

Limitations of this study are the small sample size and the incomplete information on prior treatment for non-seminoma TC. Studies on MMRd CRC with somatic double or single hit usually lack information on whether these patients received previous anticancer therapy (31,36–38). However, when combining results from three recent studies with a total of 30 patients with MMRd due to somatic double hit, one of these patients had a previous history of HL and another of leukaemia (39–41). None of these studies reported other prior cancer types or anticancer therapies. Even though treatment for TC was unknown in most cases in the present study, a large majority of non-seminoma TC patients do receive treatment with platinum-based chemotherapy, as the relapse risk varies between 15 and 50% depending on the presence of lymph-vascular invasion (25). Clinical experience shows that a majority of the patients treated for TC will have received chemotherapy and, to a lesser extent, radiotherapy. The increased risk for developing CRC appears to be associated with the dosage of platinum-based chemotherapy in TC survivors (1–10,42). An elevated risk of developing CRC was even present 35 years after treatment (4,5,42). We suggest that platinum-containing chemotherapy is associated with this increased risk, especially since platinum levels in serum remain elevated for a long period after treatment and is still detectable in tissues of various organs (43–47). However, whether long-term retention in colorectal tissue, a fast-turnover tissue, is possible, remains unknown.

To conclude, somatic double or single hit in MMR genes is significantly more frequent in secondary CRCs that develop in non-seminoma TC survivors compared to primary CRC in the general population. Since similar results were shown in HL survivors, this may suggest an association between prior anticancer treatment and MMRd with double or single hit in MMR genes.

Furthermore, our results could imply that this phenomenon is neither specific to a certain primary cancer nor a single type of prior anticancer treatment. These findings need confirmation in larger cancer survivor cohorts.

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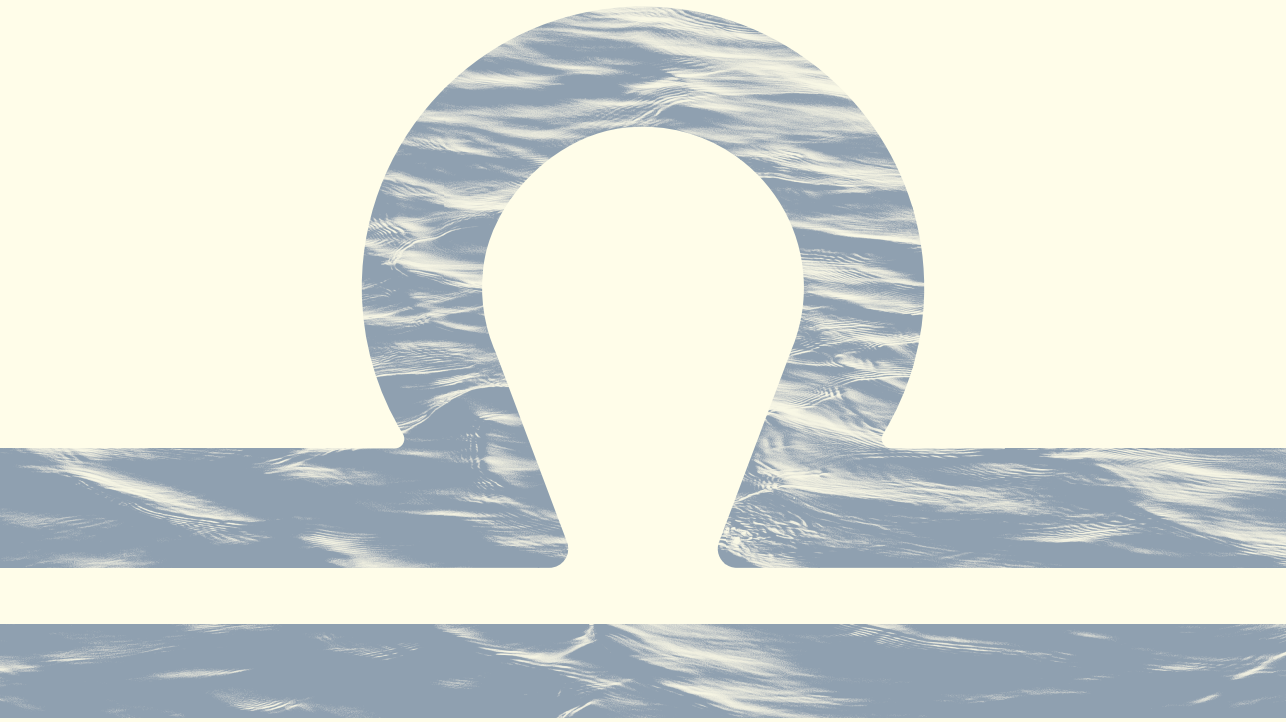

Chapter 10

Prevalence of neoplasia at colonoscopy among testicular cancer survivors treated with platinum-based chemotherapy

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ABSTRACT

Testicular cancer survivors (TCS) treated with platinum-based chemotherapy have an increased risk of colorectal cancer (CRC). We determined the yield of colonoscopy in TCS to assess its potential in reducing CRC incidence and mortality. We conducted a colonoscopy screening study among TCS in four Dutch hospitals to assess the yield of colorectal neoplasia. Neoplasia was defined as adenomas, serrated polyps (SPs), advanced adenomas (AAs: ≥10mm diameter, high-grade dysplasia or ≥25% villous component), advanced serrated polyps (ASPs: ≥10mm diameter or dysplasia), or CRC. Advanced neoplasia (AN) was defined as AA, ASP, or CRC. Colonoscopy yield was compared to average-risk American males who underwent screening colonoscopy (n=24,193) using a propensity score matched analysis, adjusted for age, smoking status, alcohol consumption and body mass index. A total of 137 TCS underwent colonoscopy. Median age was 50 years among TCS (IQR 43-57) vs. 55 years (IQR 51-62) among American controls. A total of 126 TCS were matched to 602 controls. The prevalence of AN was higher in TCS than in controls (8.7% vs. 1.7%; p=0.0002). Non-advanced adenomas and SPs were detected in 45.2% of TCS vs. 5.5% of controls (p<0.0001). No lesions were detected in 46.0% of TCS vs. 92.9% of controls (p<0.0001). TCS treated with platinum-based chemotherapy have a higher prevalence of neoplasia and AN than matched controls. These results support our hypothesis that platinum-based chemotherapy increases the risk of colorectal neoplasia in TCS. Cost-effectiveness studies are warranted to ascertain the threshold of AN prevalence that justifies the recommendation of colonoscopy for TCS.

INTRODUCTION

Over the past few decades, the proportion of second malignant neoplasms (SMNs) among all cancer diagnoses has increased substantially (1). There are several known risk factors for SMNs, including environmental and lifestyle factors and aging, but also late side effects of prior cancer treatment. Due to the improved prognosis of cancer patients resulting in longer survival, the likelihood of developing an SMN increases. Especially among patients who received intensive (multimodality) treatment, the late side effects of the initial cancer treatment contribute to the development of these SMNs (2). Population-based CRC screening programs have been widely implemented for average-risk individuals, with the aim of reducing CRC incidence and mortality by removing precursor lesions and early detection (3). A variety of screening modalities are used, including fecal immunochemical testing (FIT), multi-target stool DNA tests, sigmoidoscopy, and colonoscopy (3). For high-risk individuals, who may have at least two times the risk of developing CRC in their lifetime compared to those at average risk, surveillance programs are offered. Testicular cancer survivors (TCS) treated with platinum-based chemotherapy can be considered a high-risk group, as one study reported an almost 4-times higher CRC risk among platinum-treated TCS compared to TCS not treated with platinum-based chemotherapy (4) and several other studies also reported higher risk of gastrointestinal malignancies (5,6). Treatment options for TC patients have improved over the past decades, resulting in very high 5-year overall survival rates of 73-99%, depending on the presence and localization of metastases (7). TC patients treated with chemotherapy usually receive bleomycin or ifosfamide, etoposide and cisplatin (7). Cisplatin has been associated with numerous late side effects, including endothelial dysfunction, atherosclerosis, but also increased CRC risk (8,9). This risk increased as higher platinum doses were administered (4). The effectiveness of colonoscopy screening for TCS treated with (cis-)platinum-based chemotherapy has not yet been established. In this study, we evaluated the yield of colonoscopy in TCS treated with platinum-based chemotherapy.

METHODS

Study design

The design of the CATCHER (Diagnostic Yield of Colonoscopy Surveillance in Testicular Cancer Survivors Treated With Platinum-based Chemotherapy) study was described in detail previously (10). In short, this prospective, cross-sectional study aimed to evaluate the yield of colonoscopy in detecting colorectal neoplasia, including advanced neoplasia (AN), in TCS treated with platinum-based chemotherapy.

Population

The CATCHER study is nested in a well-defined Dutch multicenter cohort of 5,848 1-year TCS treated from 1976-2007 in 13 hospitals in the Netherlands (4). TCS were eligible for inclusion in the CATCHER study if they met the following criteria: 1) First TC diagnosis <50 years of age, 2) TC treatment consisted of ≥3 cycles of platinum-based chemotherapy, 3) TC treatment was administered at least 8 years ago, 4) current survivors' age should be ≥35 and ≤75 years, and 5) detection and treatment of colorectal neoplasia is considered beneficial when weighed against comorbidities. Individuals were excluded if undergoing surveillance colonoscopy for other indications (including hereditary CRC, familial CRC, inflammatory bowel disease, and history of adenomas or CRC) or if they underwent colonoscopy in the past 3 years [10]. In total, 1,801 individuals treated in one of the four participating centers in the CATCHER study (Netherlands Cancer Institute, Radboud University Medical Center, University Medical Center Utrecht, and Erasmus University Medical Center) met these eligibility criteria (4).

Control population

An effort was made to find an optimal cohort as a control population that included average-risk men who were offered a first colonoscopy screening with an age range overlapping with the CATCHER cohort. The only available Dutch colonoscopy screening cohort study included men aged 50-75. Due to the substantially older median age (61 years, $p<0.0001$; data not shown), this Dutch cohort did not meet our comparison criteria (10,11). Additionally, colonoscopies in this study were performed in 2009-2010 (11). Therefore, we searched for an international comparison cohort of men who were offered a first colonoscopy at young(er) ages. The New Hampshire Colonoscopy Registry (NHCR) cohort fulfilled all criteria for a

valid comparison to our CATCHER cohort. This population-based, statewide registry collects colonoscopy data throughout the state of New Hampshire in the United States (US) of America (12). NHCR data selected included first screening colonoscopies in average-risk individuals from the recommended CRC screening age (50 years and older before 2021, now 45 years and older (13), as well as colonoscopy data from young(er) individuals, who are defined as 'average-risk screening equivalent' if they have a low risk of AN (i.e., symptoms such as constipation or abdominal pain), and no family history of CRC in a first degree relative (12). Data on colonoscopies were collected from October 2004 to November 2021. We excluded data from the NHCR on colonoscopies performed in men of non-white race, as the CATCHER population consisted solely of males of white race. Individuals with a prior colonoscopy or indication for surveillance were also excluded.

Outcomes

The primary outcome was the yield of colorectal neoplasia by colonoscopy, defined as the most advanced lesion at colonoscopy and the number of neoplasia detected.

Definitions

Colorectal neoplasia was defined as either an adenoma, a serrated polyp (SPs), advanced adenoma (AA), advanced serrated polyp (ASPs), or CRC. AA was defined as any adenoma with a size ≥10 millimeters and/or high-grade dysplasia and/or histologically confirmed villous component ≥25%. ASP was defined as at least one SP ≥10 millimeters, a sessile serrated lesion with dysplasia, or a traditional serrated adenoma (14). AN was defined as either AA, ASP, or CRC. Each individual was categorized based on the most advanced lesion: 1) AN, 2) non-advanced adenomas or non-advanced SPs, and 3) no relevant findings. Any neoplasia was defined as either non-advanced adenomas, non-advanced SPs, or AN. Only complete colonoscopies (cecal intubation) with adequate bowel preparation (CATCHER cohort: Boston Bowel Preparation Scale ≥6, NHCR cohort: adequate (excellent, good, or fair) bowel preparation (15) were included.

Methods - Study procedures

A total of 537 randomly selected individuals from the eligible CATCHER cohort were sent an invitation letter by mail (Figure 1). The invitation letter contained brief information about the risk of CRC and study procedures. If no response was received, two reminder letters were sent. Individuals could respond by mail or telephone and

were contacted by the study coordinator or physician at one of the four participating centers for instructions on further study procedures. The usual colonoscopy procedures were followed in the event of relevant colonoscopy findings. Experienced gastrointestinal pathologists performed routine histologic evaluation of all resected lesions. Follow-up after colonoscopy was performed according to standard clinical care.

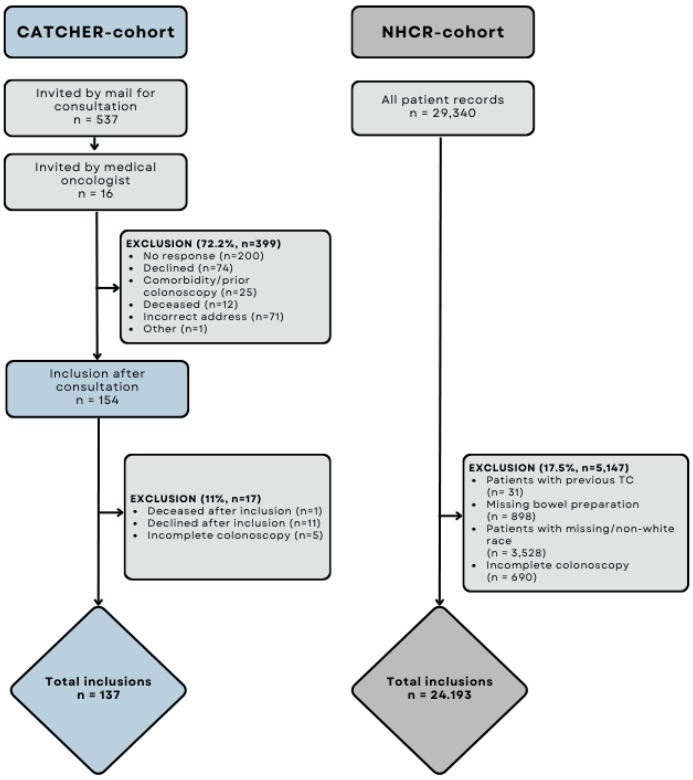

Figure 1 - Flow diagram of study inclusions.

Abbreviations: NHCR: New Hampshire Colonoscopy Registry. TC: testicular cancer.

Statistical analysis

Categorical data were compared using a chi-square or Fisher's exact test; continuous data were compared using Mann-Whitney-U tests. Two-sided p-values <0.05 were considered statistically significant. We performed a propensity score matching analysis to balance the baseline characteristics of the CATCHER and NHCR cohort to

reduce potential confounders using a logistic regression model, adjusting for age, smoking status, alcohol consumption, and body mass index (BMI) (16). Each propensity score matching was performed using a 1:5 ratio and a 'nearest-neighbor' algorithm. Covariate data (BMI, alcohol consumption, or smoking status) were unavailable for 11 participants in the CATCHER cohort, who were therefore excluded in the propensity score analysis. Baseline covariates and distributions of standardized mean differences before and after matching are displayed in Appendix Figure 1 and Tables 1-3. We compared colonoscopy outcomes between the CATCHER and the NHCR cohort. Data management and analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Funding

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RESULTS

Out of the 537 TCS who were invited to participate, 154 (28.7%) responded and were subsequently scheduled for a colonoscopy intake (Figure 1). We excluded 11 TCS, who declined participation after inclusion, one patient who died of COVID before colonoscopy and five participants due to incomplete colonoscopy, leaving 137 (89%) individuals, who underwent colonoscopy between February 20, 2020, and November 25, 2022, for analysis.

Baseline characteristics

The median age of participants at TC diagnosis was 27.5 years (interquartile range [IQR]: 23-34; Table 1). TC histology was predominantly non-seminoma (n=108, 78.8%), followed by 15.7% seminoma (n=21). Forty-three (31.4%) participants received 3 cycles of platinum-based chemotherapy and 91 (66.4%) received ≥4 cycles. Seven participants (5.1%) received both radiotherapy and platinum-based chemotherapy.

Table 1 - Characteristics of the CATCHER study population.

Characteristic	
Age at TC treatment, median (IQR), y	27.5 (23-34)
Time since TC treatment, median (IQR), y	20.0 (16-26)
Histology of TC, n (%)	
Seminoma	21 (15.3)
Non-seminoma	108 (78.8)
Unknown	8 (5.8)
Stage of TC at initial diagnosis, n (%)	
I	28 (20.4)
II	37 (27.0)
III	10 (7.3)
IV	5 (3.6)
Unknown	57 (41.6)
Number of cycles of (cis)platin, n (%)	
3	43 (31.4)
4	76 (55.5)
≥5	15 (10.9)
Unknown	3 (2.2)
RT treatment for TC, n (%)	7 (5.1)
Age at colonoscopy, median (IQR), y	50 (43-58)
ASA-score at colonoscopy	
1	68 (49.6)
2	64 (46.7)
3+	4 (2.9)
Unknown	1 (0.7)

BMI, median (IQR), kg/m2	26.0 (23.5-28.6)
Smoking status	
Current smoker	14 (10.2)
Former smoker	41 (29.9)
Never smoked	76 (55.5)
Unknown	6 (4.4)
Alcohol consumption	
≥15 units/week	9 (6.6)
<15 units/week	99 (72.3)
No alcohol	21 (15.3)
Unknown	8 (5.8)

Abbreviations: TC: testicular cancer; IQR: interquartile range; RT: radiotherapy; BMI: body mass index.

Findings CATCHER cohort

The median time between TC treatment (last cycle of platinum-based treatment) and colonoscopy was 20 years (IQR: 16-26). Median age at colonoscopy was 50 years (IQR 43-57 years). The ASA score at time of colonoscopy was 1 in 49.6% of individuals, 2 in 46.7% of individuals, and 3 in 2.9% of individuals (Table 1). In total, 181 colorectal neoplasia were detected among 74 (54.0%) of 137 participants. The median number of neoplasia detected was 1 (IQR 0-2). The most advanced lesion was AN in 8.8% of participants, non-advanced adenomas/SPs in 45.3%, while no lesions were found in 46.0% (Table 2). No CRCs were detected in the CATCHER cohort. One participant was hospitalized for one day of observation for rectal bleeding after polypectomy; no other adverse events occurred.

Table 2 - Most advanced lesions in the CATCHER vs. the NHCR cohort, stratified per age category.

Most advanced lesion, n (%)	*CATCHER*	*NHCR*	*p value*
Total	137	24,193	<0.0001
No lesions	63 (46.0)	15,615 (64.5)	
Non-advanced adenomas and/or non-advanced SPs	62 (45.3)	7,249 (30.0)	
Advanced neoplasia	12 (8.8)	1,329 (5.5)*	
30-39 year olds			0.36
No lesions	12 (70.6)	197 (81.1)	
Non-advanced adenomas and/or non-advanced SPs	4 (23.5)	39 (16.0)	
Advanced neoplasia	1 (5.9)	7 (2.9)	
40-49 year olds			0.00091
No lesions	27 (51.9)	873 (74.7)	
Non-advanced adenomas and/or non-advanced SPs	22 (42.3)	238 (20.4)	
Advanced neoplasia	3 (5.8)	58 (5.0)	
50-59 year olds			0.00098
No lesions	16 (37.2)	8,713 (64.4)	
Non-advanced adenomas and/or non-advanced SPs	23 (53.5)	4,101 (30.3)	
Advanced neoplasia	4 (9.3)	721 (5.3)	
60-69 year olds			0.013
No lesions	8 (34.8)	4,870 (63.4)	
Non-advanced adenomas and/or non-advanced SPs	13 (56.5)	2,383 (31.0)	
Advanced neoplasia	2 (8.7)	434 (5.6)	
70-80 year olds			-
No lesions	0	962 (61.7)	
Non-advanced adenomas and/or non-advanced SPs	0	488 (31.3)	
Advanced neoplasia	2	109 (7.0)	

*= AN included 37 (0.2%) CRCs in the NHCR cohort. Abbreviations: SP: serrated polyp. CRC: colorectal cancer.

Findings NHCR cohort

Median age at colonoscopy in the NHCR cohort was 55 years (IQR 51-62 years). In total, 22,819 colorectal neoplasia were detected among 8,578 (35.5%) of 24,193 men. The median number of neoplasia was 0 (IQR 0-1) in the NHCR cohort. The most advanced lesion was AN in 5.5% of participants, non-advanced adenomas/SPs in 30.0%, while no lesions were found in 64.5% (Table 2). A total of 37 (0.2%) CRCs were detected in the NHCR cohort.

Comparison of colonoscopy findings in the CATCHER and NHCR cohorts

We compared the distribution of the most advanced lesions by age category, as the cohorts differed in age (Table 2, Figure 2). The prevalence of any neoplasia was significantly higher in the CATCHER cohort than in the NHCR cohort when combining all age groups (54.0% vs. 35.5%, p<0.0001); significant differences between the CATCHER cohort and the NHCR cohort were also observed in age categories 40-49,

50-59, and 60-69 years. The largest difference was observed in the 50-59 age category, where any neoplasia was found in 62.8% (n=27) in the CATCHER cohort compared to 35.6% (n=4,822) in the NHCR cohort (p=0.0002).

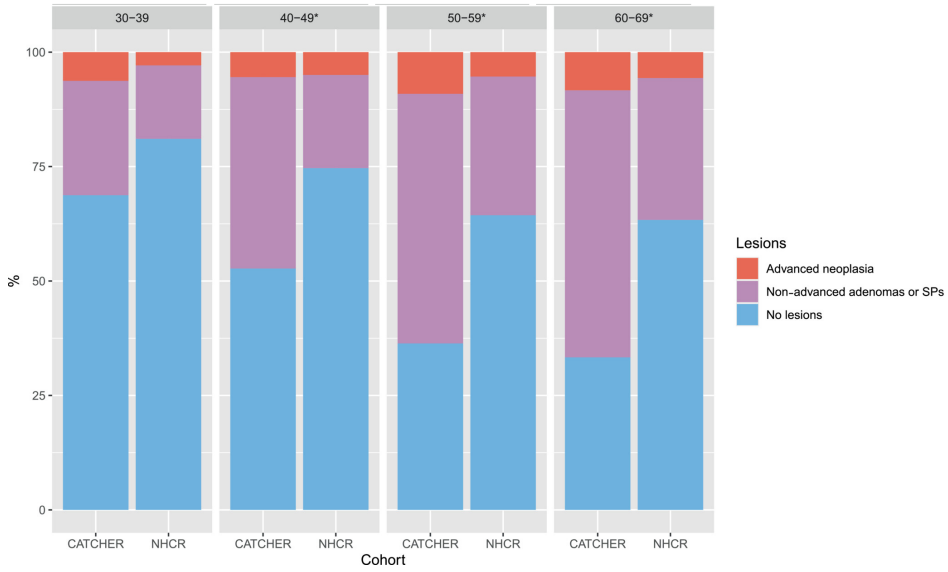

Figure 2 - Distribution of most advanced lesions in the CATCHER and the NHCR cohort. Abbreviations: SPs: serrated polyps. *: statistically significant difference.

Based on propensity score matched analysis, 126 individuals (92%) from the CATCHER cohort were matched to 602 individuals from the NHCR cohort (Appendix Figure 1; Tables 1-3). The propensity score matched analysis revealed an even more striking difference in the distribution of most advanced lesions than the overall group analyses (Figure 3). In 45.2% (n=57) of the CATCHER cohort, the most advanced lesion was a non-advanced adenoma/SP, compared to 5.5% (n=33) of the NHCR cohort (p<0.0001). AN was the most advanced lesion in 8.7% (n=11) of the CATCHER cohort compared to 1.7% (n=10) of the NHCR cohort (p=0.0002). In the CATCHER cohort, 46.0% (n=58) had no lesions compared to 92.9% (n=559) in the NHCR cohort (p<0.0001). The median number of any neoplasia was 1 (IQR 0-2) in the CATCHER cohort vs. 0 (IQR 0-0) in the NHCR cohort (p<0.0001).

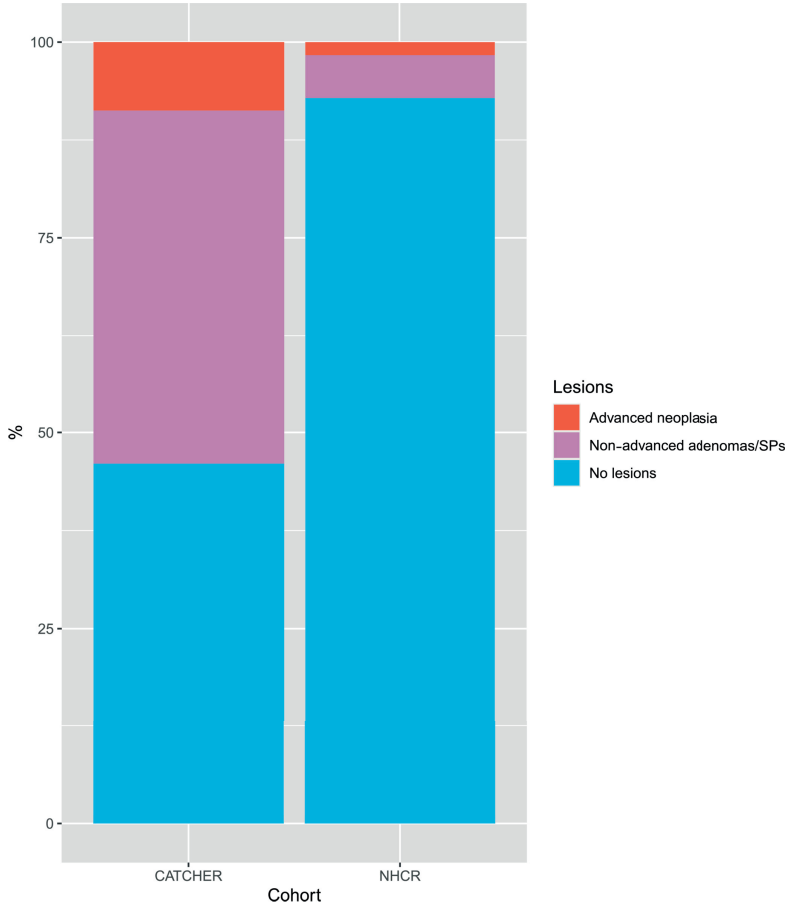

Figure 3 - Most advanced lesions in the CATCHER vs. the NHCR cohort after propensity score matched analysis.
Abbreviations: SPs: serrated polyps.

DISCUSSION

This study demonstrates a higher prevalence of AN and any neoplasia (non-advanced adenomas/SPs and AN) in TCS treated with platinum-based chemotherapy compared to age-matched controls at average risk of CRC. These findings were supported by the propensity score matched analysis. No CRCs were detected in TCS treated with platinum-based chemotherapy.

The propensity score matched analysis shows that the prevalence of AN in TCS is much higher than in the NHCR cohort (8.7% vs. 1.7%, p=0.0002) after correction for baseline covariates associated with higher risk of neoplastic lesions. These findings are in line with the previously observed high risk of CRC (4). As expected, the prevalence of any neoplasia and AN increases with age in both TCS and the comparison cohort. Although our study was initially powered on the yield of AN (10), there is evidence that removal of non-high-risk polyps may also contribute to a reduction in CRC-related mortality (17). Furthermore, the presence of non-advanced adenomas is associated with development of AN overtime (18) and with recurrence of (advanced) adenomas at follow-up colonoscopy (19).

While the increased risk of AN is clear, additional evidence is needed to establish recommendations for CRC screening in TCS. Cost-effectiveness studies are warranted to determine whether or not the increase in prevalence of AN is high enough to merit a colonoscopy recommendation for TCS treated with platinum-based chemotherapy, and how this recommendation may vary based on the patients' age and the number of years since treatment. FIT-screening may be a non-invasive alternative for colonoscopy, and CRC screening recommendations for childhood cancer survivors (CCS), who are also at higher risk of developing (gastrointestinal) SMNs, may help guide CRC screening recommendations for TCS. However, the added value of alternative screening modalities has not been extensively investigated in CCS (20), and currently, colonoscopy screening repeated every five years, or multitarget stool DNA tests repeated every three years is only advised in the US for CCS treated with radiotherapy, starting at age 30 or five years after radiation (whichever occurs last) (21). European guidelines on screening for gastrointestinal SMNs in CCS are more heterogeneous and do not provide clear recommendations on CRC screening (21,22), and furthermore, it should be noted that background risk of gastrointestinal SMNs differs for different primary cancers, as well as the availability of healthcare resources in many countries. Notwithstanding, efforts are

being made to harmonize recommendations to provide CCS and their healthcare providers with clear guidelines (22–24). Defining the optimal strategy for each country will be aided by cost-effectiveness studies.

We hypothesize that the development of CRC in TCS may differ from that observed in the general population due to (epi)genetic changes caused by specific anti-cancer treatments [8]. Increasing evidence suggests that sporadic CRCs result from the stepwise accumulation of multiple somatic mutations, which is also observed in CRCs in TCS (25). Kuijk et al. showed that both capecitabine-oxaliplatin chemotherapy and radiotherapy are mutagenic in colorectal stem cells and that the mutational burden was significantly increased in normal non-cancerous cells, in addition to the typical accumulation of mutations associated with aging, applying whole genome sequencing (26). They found the pattern of single base substitutions (SBS) to be consistent with an SBS mutational signature from the Catalogue of Somatic Mutations in Cancer that has been ascribed to prior platinum-based treatment. However, this study was performed shortly after oxaliplatin treatment (several months), and the pharmacokinetics of oxaliplatin are different from those of cisplatin (27). Further research on cisplatin accumulation in tissues of TCS, its relationship to colorectal neoplasia development and mutations in colonic mucosa is important to understand carcinogenesis and thus how best to prevent CRC in CCS.

A major strength of this study was the availability of detailed data on this well-defined cohort of TCS treated with platinum-based chemotherapy. Our results are applicable to a large population of TCS throughout the world, as TC patients are currently still treated with chemotherapy regimens similar to those in our cohort. Furthermore, our results may also be applicable to other cancer survivors treated with cisplatin for bladder, head and neck, lung, and ovarian cancer. Lastly, the availability of detailed data on the large NHCR comparison cohort allowed us to compare our results directly with those of average-risk individuals with similar patient characteristics. This showed that colonoscopy did indeed result in a higher yield of AN and any colorectal neoplasia in TCS treated with platinum-based chemotherapy.

This study has some limitations; first, when weighing the screening colonoscopy detection rate of colorectal neoplasia and AN in a high-risk population, the choice of the comparison cohort will strongly impact conclusions drawn and clinical implications of the results. Despite the fact that the overall CRC incidence is

higher in the Netherlands than in the US, the CRC incidence in men aged 45-59 is slightly lower in the Netherlands than in the US, which means that our results can be considered a conservative estimate (28,29). In addition, the NHCR is one of the few registries to include data on average-risk screening equivalents who are younger than the starting age of screening. Second, the colonoscopy participation rate of TC survivors was relatively low (28.7%). However, a lower participation rate of 22% was reported in a Dutch primary colonoscopy screening trial in the general population (30). In a similar colonoscopy screening study in Hodgkin lymphoma (HL) survivors, the participation rate was somewhat higher (41%), which we hypothesize to be due to the fact that many HL survivors still received (follow-up) care when invited by their radiotherapist or medical oncologist to participate in colonoscopy (31). Individuals in the CATCHER cohort were almost all invited by mail, and we observed a higher participation rate in one of the participating centers where individuals were invited by their medical oncologist. This underscores the importance of clear risk communication at all levels of care, and ideally, TC survivors should be made aware of the increased risk of CRC, lifestyle recommendations and alarm symptoms, while still under the care of their medical oncologist, similar to how cardiovascular risks associated with cisplatin are communicated. TC survivors with bowel symptoms that may indicate CRC, or with additional CRC risk factors, should be referred for colonoscopy at a very low threshold. Last, individuals in the CATCHER cohort who had already developed CRC (at an early age) were excluded from the pool of eligible individuals. Unfortunately, data on CRC in these TCS were not available due to the enforcement of privacy laws in the Netherlands (no informed consent for retrieval of their data was given). However, based on this, the results of our study could only be an underestimate of the true risk of AN in TCS.

In conclusion, TCS treated with platinum-based chemotherapy have a higher prevalence of any colorectal neoplasia and AN compared with matched average-risk individuals. This increased risk already emerges at ages when population-based screening is not yet offered. These results support epidemiological observations showing that platinum-based chemotherapy increases the risk of colorectal neoplasia in TCS. Cost-effectiveness studies are warranted to determine the threshold of AN prevalence increase that would justify recommending colonoscopy for TCS as the test of choice for CRC screening and for TCS who are younger than the recommended age to begin CRC screening. Our results emphasize the importance of clear risk communication to TCS and their treating physicians. Insight

into how platinum-based chemotherapy contributes to CRC carcinogenesis in TCS is of great importance and may also have implications for other cancer survivors treated with similar treatment regimens.

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APPENDIX

Table 1 - Characteristics of the NHCR study population.

Characteristic NHCR	
Age at colonoscopy, median (IQR), y	55 (51-62)
BMI, median (IQR), kg/m2	28 (25-31)
Smoking status	
Current smoker	2.118 (8.8)
Former smoker	8.440 (34.9)
Never smoked	13.362 (55.2)
Unknown	273 (1.1)
Alcohol consumption	
≥20 units/week	508 (2.1)
<20 units/week	16.343 (67.6)
No alcohol	7.035 (29.1)
Unknown	307 (1.3)

Abbreviations: IQR: interquartile range; y: years; BMI: body mass index.

Table 2 - Characteristics of the CATCHER and NHCR cohorts after propensity score matching.

	CATCHER	*NHCR*
n	126	602
Age, median (IQR), y	49.5 (42.3-57.0)	50 (43.0-58.0)
Smoking status, n (%)		
Never smoked	74 (58.7)	335 (55.6)
Former/current smoker	52 (41.3)	267 (44.4)
Alcohol consumption, n (%)		
No	21 (16.7)	105 (17.4)
<15-20 units/week	97 (77.0)	457 (75.9)
≥15-20 units/week	8 (6.3)	40 (6.6)
BMI, n (%)		
<25 kg/m^2	47 (37.3)	203 (33.7)
25 - <30 kg/m2	62 (49.2)	314 (52.2)
≥30 kg/m^2	17 (13.5)	85 (14.1)

Abbreviations: IQR: interquartile range; y: years; BMI: body mass index.

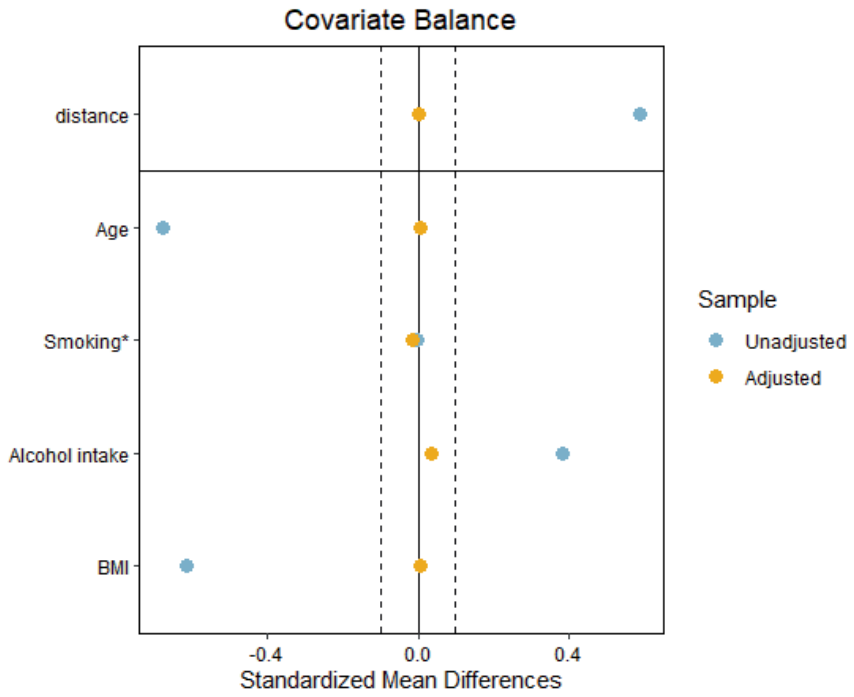


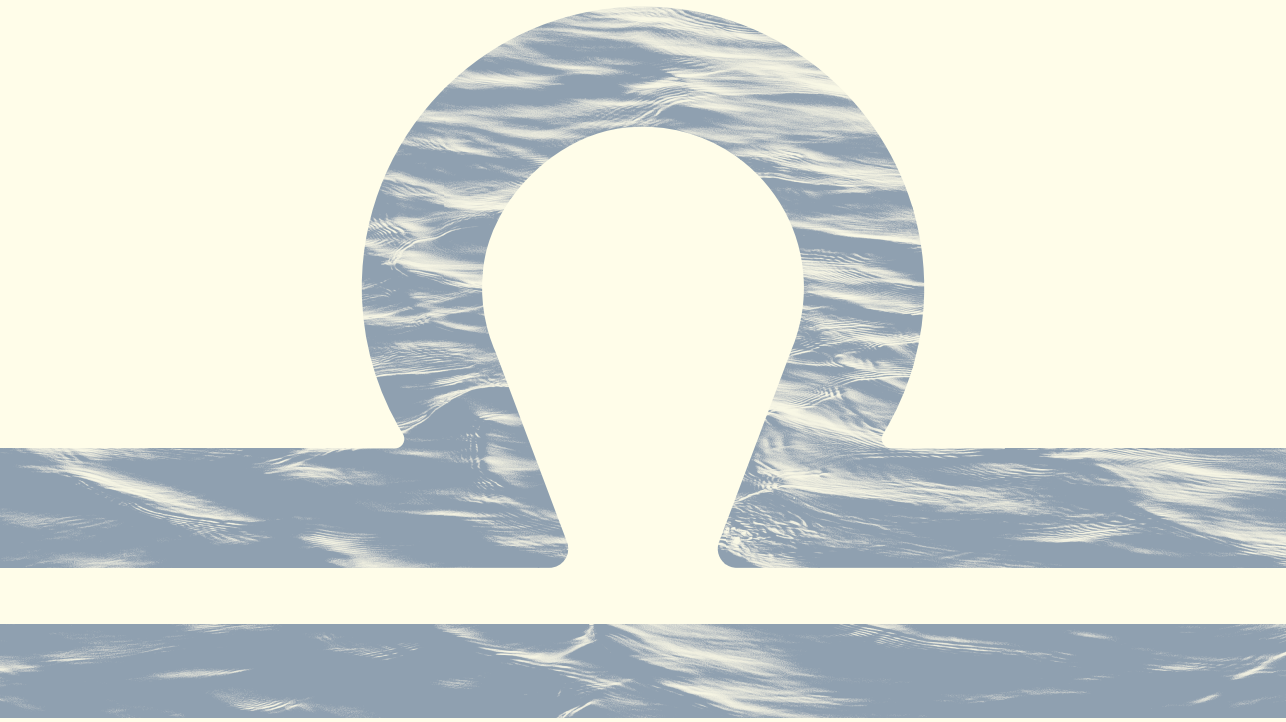
Figure 1 - Standardized mean differences distributions of baseline covariates before and after propensity score matching of the CATCHER and NHCR cohort.

Abbreviations: BMI: body mass index.

Table 3 - Standardized mean differences distributions and variance ratio of baseline covariates before and after propensity score matching of the CATCHER and NHCR cohort.

	SMD before matching	*Var. Ratio before matching*	*SMD after matching*	*Var. Ratio after matching*
Distance	0.5859	10.1327	0.0005	1.0087
Age	-0.6745	1.5277	0.0056	1.0930
Smoking status	-0.0025	.	-0.0289	.
Alcohol consumption	0.3826	0.9360	0.0351	0.9977
BMI	-0.6128	0.8420	0.0059	0.9291

Abbreviations: SMD: standardized mean difference; BMI: body mass index.



Chapter 11

Platinum retention in plasma, urine and normal colonic mucosa in cisplatin-treated testicular cancer survivors

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SUBMITTED

ABSTRACT

Background

Testicular cancer survivors (TCS) treated with platinum-based chemotherapy have increased cancer risk. Platinum retention in healthy tissue may contribute to carcinogenesis. We assessed total platinum concentrations in plasma, urine, and normal colonic mucosa samples in TCS treated with cisplatin.

Methods

Plasma (n=131) and urine (n=115) samples were collected from TCS treated with ≥3 cycles cisplatin who participated in a colonoscopy-screening study in four Dutch hospitals. During colonoscopy, 60 biopsies of normal colonic mucosa (n=2 per patient) were obtained. Samples were analyzed for total platinum concentrations using inductively coupled plasma mass spectrometry and compared with controls (plasma: 10, urine: 3, normal colonic mucosa: 9).

Results

The median age at colonoscopy was 50 years (interquartile range (IQR): 43-57) and the median time since treatment was 20 years (IQR:16-26). Median platinum concentrations in plasma (38 pg/mL; IQR: 24-61 pg/mL) and urine (376 pg/mL; IQR: 208-698 pg/mL) remained elevated in TCS up to 40 years post-treatment and were higher than in controls (all controls were below limits of detection [plasma: 25 pg/mL, urine: 6 pg/mL]). The median platinum concentration in normal colonic mucosa was 0.58 pg/mg (IQR: 0.33-1.59 pg/mg) in the transverse and 0.51 pg/mg (IQR:0.26-1.25 pg/mg) in the descending colon.

Conclusions

Cisplatin treatment is associated with long-term retention of platinum in various patient sample types. This might increase cancer risk by causing somatic mutations, potentially explaining the elevated risk of second malignant neoplasms in TCS. The long-term effects of platinum retention should be monitored to understand carcinogenesis and to provide guidelines for early second cancer detection.

INTRODUCTION

Cisplatin is widely used in treatment of various malignancies, such as ovarian, bladder, head-and-neck, esophageal, breast, brain and lung cancer. Cisplatin is also essential in the systemic treatment of testicular cancer (TC), typically consisting of bleomycin, etoposide/ifosfamide, and cisplatin (1). The use of cisplatin has resulted in remarkably high 5-year overall survival rates around 90%, depending on the stage at diagnosis (1,2). Despite its efficacy, cisplatin is associated with several adverse effects, including nephrotoxicity, ototoxicity, cardiotoxicity and neurotoxicity. There is accumulating evidence that in some cases, prior anti-cancer treatment is associated with the development of second malignant neoplasms (SMNs) (3). Treatment with cisplatin-based chemotherapy has been associated with increased risk of developing gastrointestinal (GI) and other SMNs in TCS (4). Uptake of cisplatin into cells occurs both through passive diffusion as well as various modes of transport. Within the cell, cisplatin subsequently induces DNA damage by multiple mechanisms of action, both directly by forming DNA cross-links and indirectly through multifaceted cellular damage. Depending on the response, the cell may survive or undergo apoptosis (5). While most cisplatin will covalently bind to proteins and is cleared by the kidneys, a small amount accumulates in rapidly growing tissues, both tumor tissue as well as proliferating healthy tissue (5). The retention and accumulation of cisplatin in healthy tissues may exert long-term carcinogenic effects and may ultimately lead to the formation of SMNs.

Platinum has previously been demonstrated in plasma and urine of TCS treated with (cis)platinum-based chemotherapy even more than a decade after treatment (6,7). Other platinum-based agents, such as oxaliplatin, have also been measured in human tissues, albeit for shorter periods after treatment and at lower concentrations (8). The causation of late side-effects by platinum-based chemotherapy is complex, and understanding the contribution of long-term retention of cisplatin to carcinogenesis of SMNs might be crucial for effective prevention or early detection of SMNs in TCS. This study aims to investigate whether platinum is still detectable in plasma, urine, and normal colonic mucosa of TCS up to 40 years after cisplatin-based chemotherapy. In addition, we assessed the correlation between platinum concentrations in urine and plasma and platinum concentrations in normal colonic mucosa.

METHODS

Participants, collected samples and samples analyzed

All samples were retrieved from participants in the CATCHER study, a colonoscopy screening study in four hospitals in the Netherlands, which aimed to evaluate the diagnostic yield of colonoscopy in TCS treated with platinum-based chemotherapy. The CATCHER study design has been described previously (9). All participants met the following criteria: 1) TC diagnosis before age 50, 2) TC treatment consisted of at least 3 cycles of cisplatin-containing chemotherapy, 3) TC treatment was at least 8 years ago, 4) age at enrollment ≥35 and ≤75 years, 5) detection of colorectal neoplasia was considered beneficial taking into account co-morbidities. This study was approved by the Medical Ethical Committee (study number M19CTR, clinical trial number: NCT04180033) and the institutional review board (study numbers IRB22-083 and IRB22-222) of the Netherlands Cancer Institute. Data and materials were anonymously processed. Patient-derived tissue and data were collected, stored, and used in accordance with the Code of Conduct for the Proper Secondary Use of Human Tissue in the Netherlands, Dutch Federation of Biomedical Scientific Societies, The Netherlands.

A total of 154 individuals provided informed consent to participate in the CATCHER study. Colonoscopy was performed in 137 individuals. Plasma and urine samples were collected at the enrollment visit or prior to colonoscopy. A total of 131 plasma and 115 urine samples were collected and for 106 individuals, both plasma and urine samples were available. Nine individuals provided a urine sample only and 25 individuals provided a plasma sample only. A random selection of 30 individuals was made from the study participants who underwent colonoscopy. For each patient, one transverse colon biopsy and one descending colon biopsy were used for analyses, for a total of 60 normal colon tissue samples. Biopsies from normal colonic mucosa of the transverse and descending colon were obtained during colonoscopy and neoplasia was removed according to standard protocol. For 29 participants, samples from plasma, urine and normal colonic mucosa were available.

The Institutional Review Board approved the search for (biobanked) control samples consisting of patients treated at the Netherlands Cancer Institute who had never received platinum-based chemotherapy and who were matched for male sex and age to the CATCHER study participants. We obtained 10 plasma, three urine, and nine normal colonic mucosa samples as control samples.

Outcomes

Primary outcomes were total platinum concentrations in plasma, urine, and normal colonic mucosa samples of the transverse and descending colon. Secondary outcomes were platinum half-lives in plasma and urine, and median platinum concentrations by most advanced lesion at colonoscopy. The most advanced lesion at colonoscopy was categorized into i) no lesions, ii) non-advanced adenomas or non-advanced serrated polyps (SPs), and iii) advanced neoplasia (AN). Advanced neoplasia was defined as either advanced adenomas (AAs), advanced serrated polyps (ASPs), or CRC. AA was defined as any adenoma measuring ≥10 mm and/or having high-grade dysplasia and/or histologically confirmed villous component ≥25%. ASP was defined as at least one SP ≥10 mm, sessile serrated lesion with dysplasia, or traditional serrated adenoma.

Clinical parameters

Information regarding cumulative cisplatin dose and follow-up time were collected from patient files for all TCS included in the colonoscopy screening study. TCS received either 3, 4, or >4 cycles of cisplatin during treatment; 3 cycles of cisplatin are defined as <350 mg/m2, 4 cycles as 350-450 mg/m2, and >4 cycles as >450 mg/m2.

Sample retrieval and measurement of platinum

Inductively coupled plasma mass spectrometer (ICP-MS) was used to quantify the total platinum concentration in plasma, urine and normal colonic mucosa samples. The total platinum concentration refers to all platinum-containing species within the sample, including the intact cisplatin molecule as well as any platinum metabolites or forms bound to proteins or biomolecules. Sample preparation is described in detail in the Appendix. Pretreated, diluted samples were introduced into the ICP-MS (ICP-MS 7800, Agilent Technologies, Santa Clara, CA, USA) for quantification of total platinum concentrations. Calibration standards and quality control samples were prepared from carboplatin in human plasma (10). The concentration range of the calibration standards were 50-5000 pg/mL. For the quantification of total platinum concentrations in normal colonic mucosa samples, the concentration range of the calibration standards was 10-1000 pg/mL. To fit the calibration data (response ratio Pt 194/Ir 191 vs. the concentration), linear regression was applied with a weighting factor of $1/x^2$, where x is the total platinum concentration. Quality control (QC)

samples were included in each analytical run (at least 6 samples containing platinum at low, medium and high concentration over the calibration range). For every analytical run, the measured platinum concentrations of at least 2/3rd of the QC samples should be within the ±15% deviation from the nominal concentration and at least 50% at each level should meet this criterion. For all executed analytical runs, the acceptance criteria were met.

The platinum concentration in the study samples was quantified if the concentration was measured within the concentration range of the calibration standards. In plasma and normal colonic mucosa samples, however, total platinum concentrations were frequently below the lower limit of quantitation (LLOQ). Therefore, the limit of detection (LOD) was defined as a signal to noise ratio of at least 3 and the concentration of samples between the LLOQ en LOD were semi-quantitatively reported. The lower limit of quantitation (LLOQ) for plasma was set to 50 pg/mL (lowest calibrations standard concentration) and the LOD at 25 pg/mL. For normal colonic mucosa samples, the LLOQ and LOD were 10 pg/mL and 2 pg/mL, respectively.

Statistical analyses

Descriptive statistics were used to summarize the data, including median and interquartile range (IQR). Differences in platinum concentrations between groups were analyzed using the Mann-Whitney-U or Kruskal-Wallis test. Associations between platinum concentrations and time since last cisplatin cycle were assessed using scatter plots. Correlations between plasma and urine concentrations of platinum were evaluated by the Pearson correlation coefficient. Plasma and urine platinum half-lives were estimated from single measurements at various time points since treatment of participants in the CATCHER cohort. Linear regression analysis of ln-transformed plasma or urine platinum concentrations (dependent variable) and time since TC treatment (independent variable) was used to approximate platinum half-lives [Model 1]. Observations were excluded when platinum concentrations were below the LOD. Outliers were identified by computing z-scores for each data point. Data points with a z-score exceeding the threshold of 3 were considered outliers and were also excluded. Platinum half-lives were estimated using the following formula: $\frac{-\ln(2)}{coeff\ (model\ 1)}$. Data were analyzed using R version 4.0.2.

RESULTS

The median age of TCS at colonoscopy was 50 years (IQR: 43-57) and the median time since treatment was 20 years (IQR: 16-26; Table 1). Median age at TC diagnosis was 27.5 (IQR 23-34). Most TCS received three or four cycles of cisplatin. No CRCs were detected during colonoscopy.

Table 1 – Characteristics of the study population.

	Age at enrollment (median (y), IQR)	Time since TC treatment (median (y), IQR)	Age at TC diagnosis (median (y), IQR)	Cycles of cisplatin (n, %)
Study participants (n=154)	50 (43-58)	20 (16-27)	28 (23.3-34)	3: 50 (32.5) 4: 85 (55.2) ≥5: 16 (10.4) Unknown: 3 (1.9)
Participants who underwent colonoscopy (n=137)	50 (43-57)	20 (16-26)	27.5 (23-34)	3: 43 (31.4) 4: 76 (55.5) ≥5: 15 (10.9) Unknown: 3 (2.2)
Plasma samples (n=131)	50 (43-58)	20 (16-27)	28 (23.5-34)	3: 41 (31.3) 4: 72 (55.0) ≥5: 15 (11.5) Unknown: 3 (2.2)
Urine samples (n=115)	50 (32-59)	21 (17-27.8)	28 (23-33.5)	3: 36 (31.3) 4: 65 (56.5) ≥5: 12 (10.4) Unknown: 2 (1.7)
Normal colonic mucosa samples (n=30)	49 (40-55)	17 (15-21)	29 (24-34)	3: 11 (36.6) 4: 15 (50) ≥5: 4 (13.3) Unknown: 0
Plasma + urine samples (n=106)	50.5 (43-59)	20 (16-28)	28 (24-34)	3: 32 (30.2) 4: 60 (56.6) ≥5: 12 (11.3) Unknown: 2 (1.9)
Plasma + urine + normal colonic mucosa samples (n=29)	49 (40-55)	17 (15-21)	29 (24-34)	3: 11 (37.9) 4: 15 (51.7) ≥5: 3 (10.3) Unknown: 0

Abbreviations: TC: testicular cancer. IQR: interquartile range. Y: years.

Platinum in plasma

The median platinum concentration in plasma (n=131) was 38 pg/mL (IQR: 24-61 pg/mL). A total of 34.4% of platinum plasma concentrations in TCS was equal to or above the LLOQ (50 pg/mL), 41.2% was between the LLOQ and the LOD (25 pg/mL); and 24.4% was below the LOD and not used for the calculations (Figure 1A). All platinum concentrations in control samples (n=10) were below the LOD. The estimated platinum half-life in plasma was 13.3 years (Figure 1B).

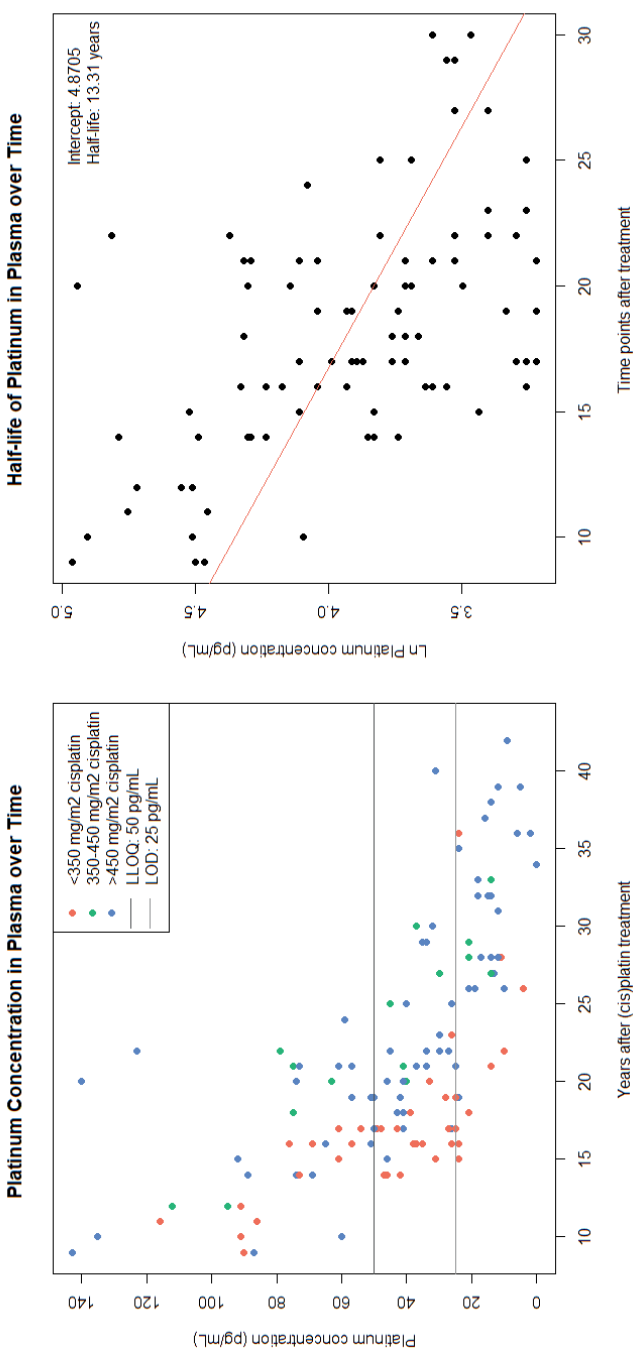

Figure 1A&B - Correlation between platinum concentration in plasma and years after cisplatin treatment and half-life of platinum in plasma.

Platinum in urine

The median platinum concentration in urine (n=115) was 376 pg/mL (IQR: 208-698 pg/mL). Almost all (94.8%) platinum urine concentrations in TCS were above the LLOQ (50 pg/mL), 4.6% was between the LLOQ and the LOD (6 pg/mL), and only one sample was below the LOD and excluded from the dataset (Figure 2A). All platinum concentrations in control samples (n=3) were below the LOD. The estimated platinum half-life in urine was 9.8 years (Figure 2B).

Platinum in normal colonic mucosa

The median platinum concentrations were similar in the transverse colon (n=30, 0.58 pg/mg [IQR: 0.33-1.59]; Figure 3A) and in the descending colon (n=30, 0.51 pg/mL [IQR 0.26-1.25]; p=0.62; Figure 3B). A total of 55% of platinum concentrations in normal colonic mucosa of TCS was above the LLOQ (10 pg/mL), 40% was between the LLOQ and the LOD (2 pg/mL); and 5% was below the LOD and not used for the calculations. The LLOQ concentrations are dependent on the weight of the biopsies. Based on a mean biopsy weight of 3.5 mg of study participants, the LLOQ and LOD were 0.5 pg/mg and 0.1 pg/mg, respectively. All platinum concentrations in control samples (n=9) were below the LOD.

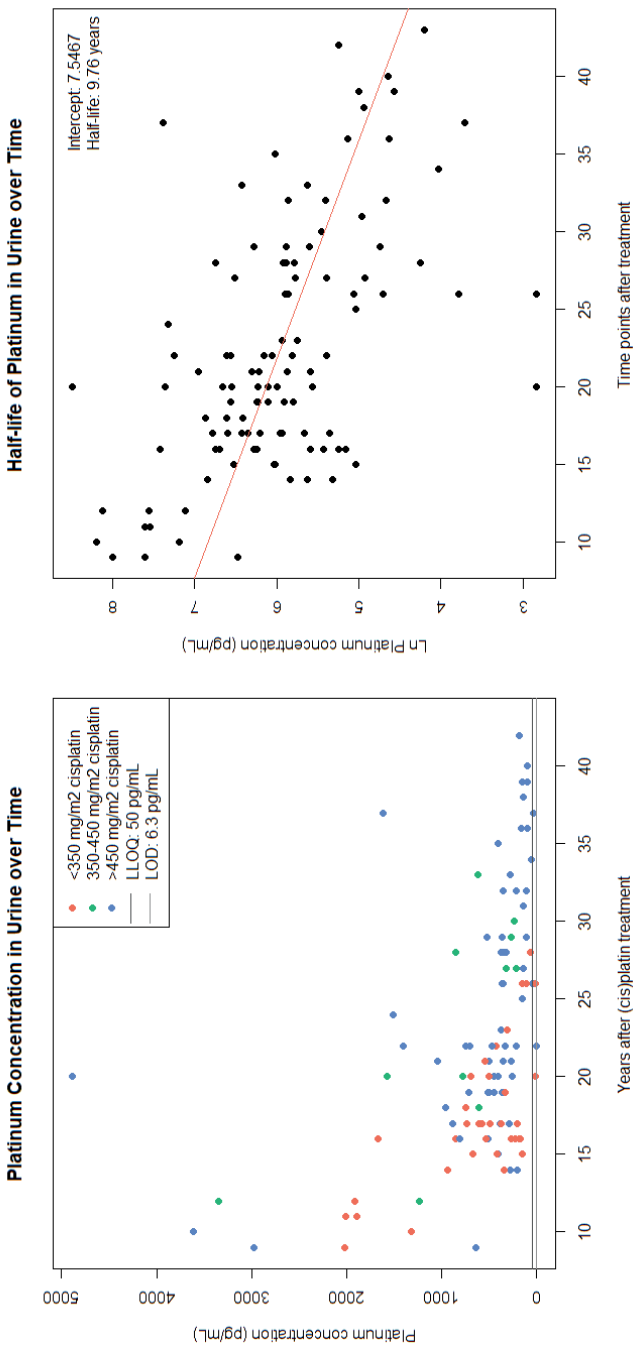

Figure 2A&B - Correlation between platinum concentration in urine and years after cisplatin treatment and half-life of platinum in urine.

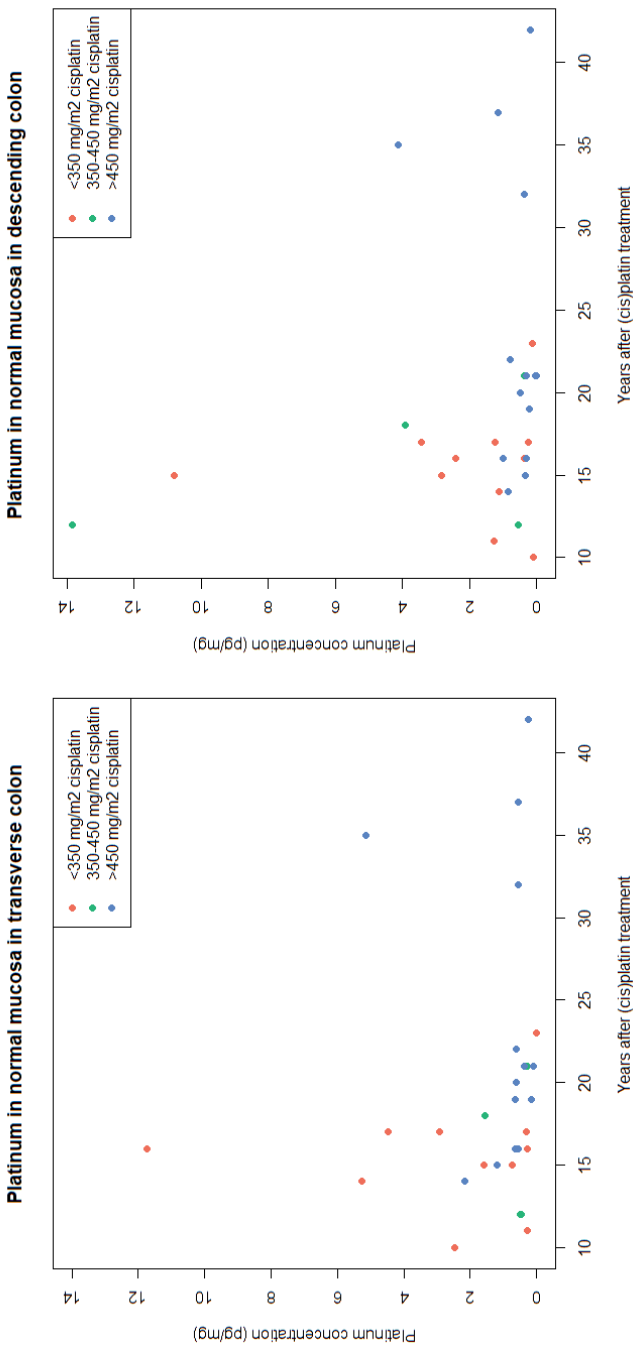

Figure 3A&B - Correlation between platinum concentration in the mucosa of the transverse and descending colon and years after cisplatin treatment.

Correlation platinum concentrations in different samples and clinical findings

Platinum concentrations tended to be higher in individuals with a shorter interval between cisplatin treatment and study enrollment (Figures 1A, 2A, 3A&B). There was a statistically significant correlation between plasma and urine platinum concentrations (Pearson correlation coefficient r = 0.78 (95%CI 0.69-0.85, p<0.001; Figure 4). In 29 samples in which platinum concentrations could be determined for both plasma, urine and normal colonic mucosa, the correlation between platinum concentrations in plasma and urine was less clear (r=0.69) and not statistically significant (p=0.43; Appendix Figure 1). There was relatively poor correlation between platinum concentrations in plasma or urine and the platinum concentration in the normal colonic mucosa samples (plasma-colon: r=0.13 (p=0.28), urine-colon: r=0.04 (p=0.15); Appendix Figure 1). The median platinum concentration did not increase in any of the samples when no adenomas, non-advanced adenomas/SPs, or advanced neoplasia were detected during colonoscopy. Median platinum concentrations in plasma (p=0.7), transverse colon (p=0.06), and descending colon (p=0.53) did not differ between individuals with no lesions, non-advanced adenomas/SPs or AN as their most advanced lesion detected at colonoscopy (Appendix Figure 2).

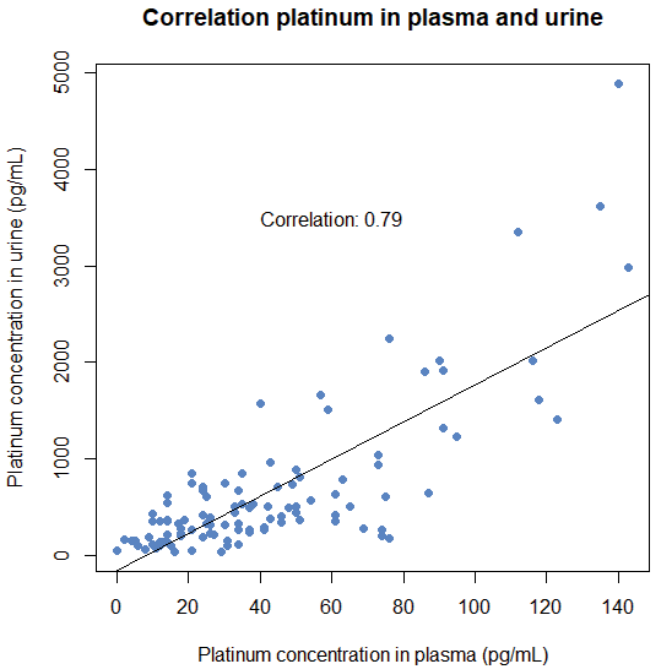

Figure 4 - Correlation between measured platinum in plasma and urine of TC-survivors treated with platinum-based chemotherapy.

DISCUSSION

In this study we found measurable platinum concentrations up to 40 years after treatment, in plasma, urine, and normal colonic mucosa samples from TCS treated with cisplatin. Platinum concentrations were higher in all three different types of patient samples compared to control samples.

The measured platinum concentrations decreased with time since cisplatin treatment. Several other studies have shown long-term retention of platinum in plasma and urine (6–8,11,12). However, no study has shown that platinum persists in these tissues beyond 20 years after treatment and has evaluated correlations between platinum concentrations in plasma, urine and normal colonic mucosa. To our knowledge, this is the first study which quantified platinum concentrations in normal colonic mucosa of patients exposed to cisplatin during cancer treatment. Almost all normal colonic mucosa of cisplatin-treated TCS contained higher platinum concentrations than controls (i.e., measurable platinum above the LOD), suggesting that platinum may not only be measurable for a very long time in plasma and urine, but might also be retained in various tissues of the human body.

A recent epidemiologic cohort study showed a higher risk of developing CRC in TCS treated with platinum-based chemotherapy compared to TCS not treated with platinum-based chemotherapy (HR: 3.9) (4). Based on these findings, we evaluated platinum concentrations in normal colonic mucosa in TCS and correlated them with the most advanced lesion detected by colonoscopy. Although we did not find a correlation between platinum concentrations in colonic mucosa and clinical outcomes (i.e., AN or CRC development), it has been hypothesized that long-term accumulation of platinum in (healthy) tissues may be associated with early ageing through cellular senescence (13). However, cisplatin leads to DNA damage, which could also occur in healthy tissue at the time of cisplatin treatment, therefore increasing the risk of developing cancer in TCS and shifting the cancer risk to a younger age. This is supported by a recent study showing that oxaliplatin treatment leads to increased mutational load in stem cells of normal colonic mucosa (14). The long-term retention of platinum in plasma is likely due to the slow release of platinum from regenerating tissues throughout the human

body. Brouwers et al. found that long after treatment, platinum in plasma still had remaining protein binding capacity, implicating that even years after treatment, around 10% of circulating platinum may still be reactive in patients. Furthermore, given the extensive binding of cisplatin to proteins, it is to be expected that platinum is gradually released into the bloodstream when tissues regenerate, after which renal excretion is initiated (7,8).

In a study conducted by Hjelle et al., it was demonstrated that out of 76 TCS, of whom 12 developed an SMN, a lower risk of SMNs was associated with more rapid decreases in plasma platinum levels (15). Taken together, we hypothesize that the long-term presence/retention of active platinum among TCS treated years before with cisplatin may contribute to the accumulation of somatic mutations in normal tissues, which might enhance the mutations that developed during the cisplatin treatment. This treatment-related accumulation of DNA mutations then adds to age-related accumulation of somatic mutations caused by endogenous mutagenic processes, thus leading to higher risk of developing SMNs. The emergence of other fourth-generation platinum agents, which appear to show a similar mechanism of action but a reduced carcinogenic effect on non-malignant cells in vitro and in vivo, promises lower rates of late side effects in the future (16).

The major strength of our study was our ability to assess platinum concentrations in different types of patient samples from TCS in a well-defined cohort up to 40 years after initial treatment using ICP-MS, a highly sensitive technique for quantification in different samples. In addition, we were able to assess correlations between measurements in the different samples and colonoscopy outcomes in relation to platinum measurements in plasma, urine, and normal colonic mucosa. Further research is needed to determine the relationship between platinum exposure and the subsequent development of CRC in normal colonic mucosa.

Almost all urine samples had platinum concentrations above the LLOQ, whereas this has not occured for plasma samples, although most platinum concentrations in plasma were well above the LOD and higher than those in unexposed controls. The inability to distinguish between unchanged cisplatin and its metabolites or adducts limits the use of ICP-MS to measure

platinum in biological samples. As a result, information on the composition of platinum components was not obtained. The renal function at time of treatment could also have influenced long-term platinum concentrations in biological samples. Unfortunately, no data were available on the glomerular filtration rate at time of cisplatin treatment, although none of the study participants suffered from renal insufficiency at the time of sample acquisition. A previous study also showed that plasma and urinary platinum concentrations were strongly correlated years after cisplatin treatment, which was confirmed by the high correlation between platinum in plasma and urine in our study (7). These observations suggest that the effect of renal excretion on plasma platinum concentrations at follow-up is minimal, which was underlined by the fact that the platinum half-life in plasma was comparable to that in urine.

In conclusion, the use of cisplatin can result in long-term exposure to low doses of circulating platinum and platinum accumulation/retention in various types of patient samples, and may be associated with an increased risk of cancer through induction of somatic mutations and thereby partly explain the increased SMN risk in TCS. Individuals exposed to cisplatin should be carefully monitored because of the potential long-term effects of platinum accumulation, and fourth-generation platinum agents may offer future solutions to alleviate risk of these late effects.

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APPENDIX

Sample collection and pre-treatment

Plasma was collected from whole blood samples in 6 or 10 mL K_2EDTA-containing tubes. The tubes were centrifuged at 1500g for 10 minutes at room temperature. After centrifugation, the plasma was pipetted into 1 or 2 mL labeled cryovials and stored at -20°C. Urine was collected in urine containers and pipetted into 1 or 2 mL labeled cryovials and stored at -20°C. Colon biopsies were obtained from normal looking colorectal tissue during colonoscopy, after which fresh frozen material was stored at -20°C or -80°C. Each colon tissue sample was weighed before storage.

Plasma and urine (calibration standard, quality control sample or study sample) were thawed at room temperature and 150 µL of each sample was transferred to 10 mL PP tubes. Subsequently 2850 µL of 0.01% EDTA-triton solution (Sigma Aldrich chemistry ©) and 30 µL of Internal Standard Working Solution (10,000 pg/mL Iridium in 0.01% EDTA-triton solution, Merck, Darmstadt, Germany) were added. The diluted samples were mixed for 5 seconds before analysis.

Normal colonic mucosa samples were weighed and digested with 160 µL digestion solvent (10 mM $CaCl_2$ 50 mM TRIS-buffer (pH 7.5). After incubation (for at least 16 h at 37 °C and 1,000 rpm), the digested samples (150 µL) were then diluted to a final volume of 850 µL with 0.01% EDTA-triton solution. A volume of 10 µL of Internal Standard Working Solution (10,000 pg/mL Iridium in 0.01% EDTA-triton solution) was added and the diluted samples were mixed for 5 seconds before analysis.

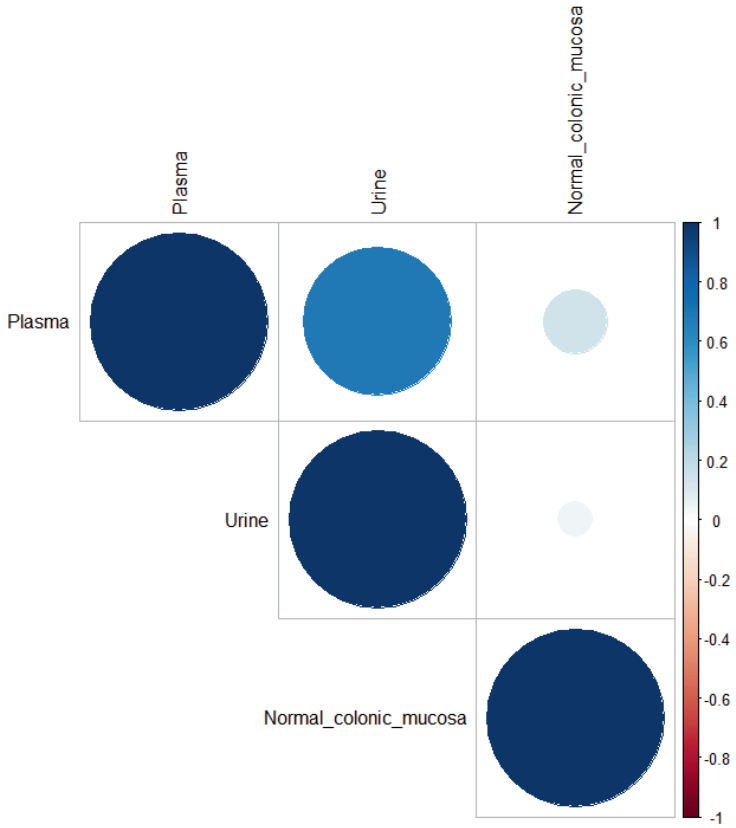


Figure 1 - Correlation between platinum concentrations in plasma, urine, and normal colonic mucosa of 29 participants in the CATCHER study.

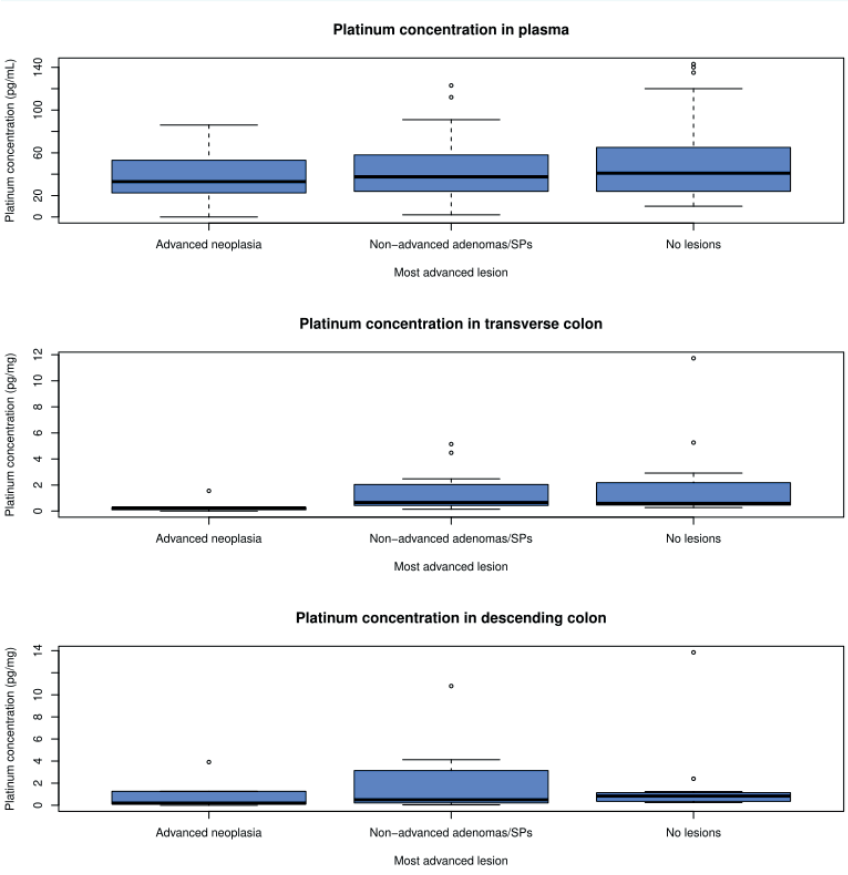
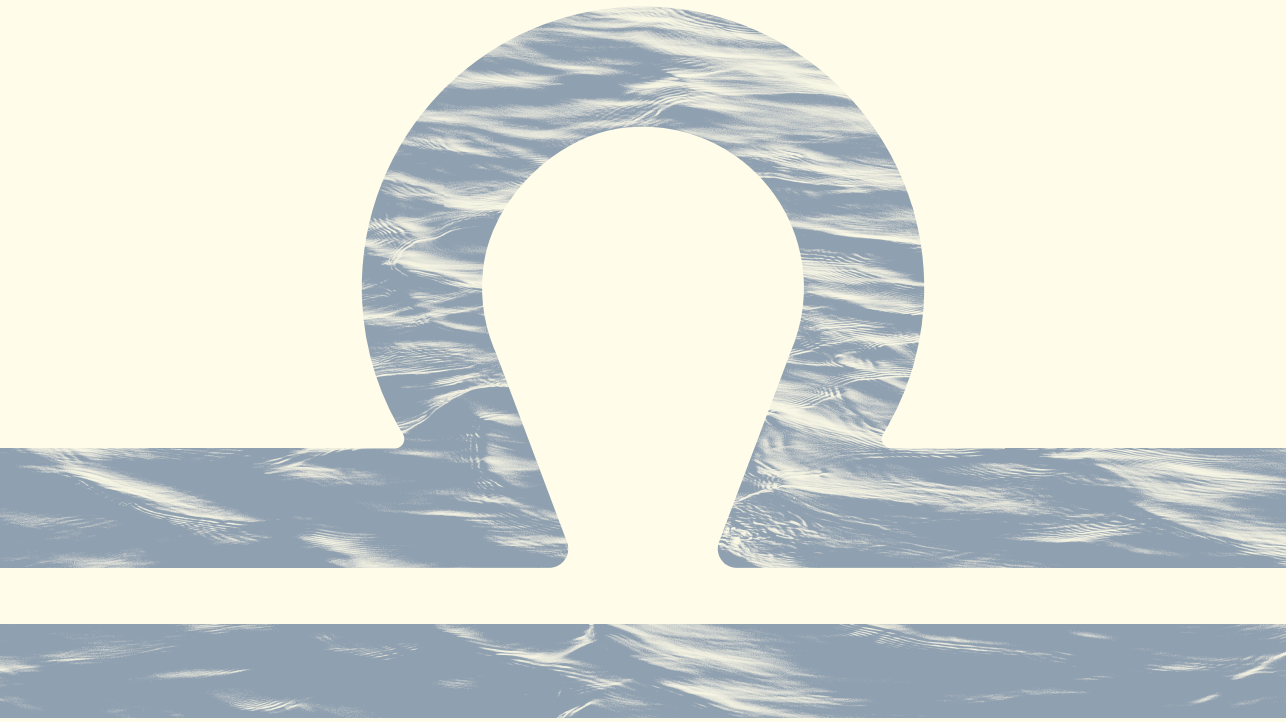


Figure 2 - Median platinum concentrations in plasma, transverse and descending colon according to findings at colonoscopy.



Chapter 12

Discussion

''Do we wish to turn the world's healthy citizens into fearful patients-to-be who, in the not too distant future, might be asked to deliver, for example, annual samples of feces, urine, sputum, vaginal smear, and blood, and undergo X-ray and ultrasound examination with all it entails in terms of psychological morbidity and the potential for harm because of further testing and interventions due to false positive findings?''

This rhetorical question was posed by Professor Peter C. Gøtzsche in the Lancet in 1997, after expressing reservations about the results of two trials on the effectiveness of guaiac fecal occult blood testing (gFOBT) screening in reducing colorectal cancer (CRC) mortality. Before I reflect on this question in this final chapter, I will first elaborate on short- middle- and long-term outcomes of CRC screening for average- and high-risk populations. Second, this final chapter will explore pathways to optimize (personalized) screening for these populations. This final chapter consists of three parts; part I focuses on the evaluation of CRC screening for average-risk individuals, part II on personalized CRC screening for average-risk individuals, and part III on CRC screening for and aspects of CRC in high-risk individuals.

12.1 PART I: EVALUATION OF COLORECTAL CANCER SCREENING FOR AVERAGE-RISK INDIVIDUALS

The goal of CRC screening is to reduce the (late-stage) CRC incidence and the CRC-related mortality. This can be achieved through removal of precursor lesions, as well as detection of CRC at an earlier stage. To ensure that these goals are achieved, short-, middle- and long-term outcomes should be monitored. The following paragraphs concern these outcomes after the introduction of the CRC screening program in the Netherlands in 2014, which are described in Chapters 2-5 of this thesis.

Evaluation of middle- and long-term outcomes of CRC screening

Shift of the CRC stage distribution

Chapter 2 concluded that the Dutch fecal immunochemical testing (FIT)-based screening program results in a more favorable stage distribution (stage I and II) of screen-detected CRCs compared to clinically detected CRCs (66.7% vs. 46.2%), which is also observed in several other European countries (1). Similar percentages

were reported in Flanders, Slovenia, Denmark and Germany. FIT-based screening is also applied Flanders, Slovenia, and Denmark, and screen-detected CRCs were detected at an early stage in 64.2-69.1% of cases, whereas non-screen-detected CRCs were detected at an early stage in 40.4-45.6% of cases (1,2). In Germany, colonoscopy is used in addition to FOBT, and screen-detected CRC by FOBT was early-stage in 68% vs. 50% of symptom-detected CRC (3). Overall, these results are promising and may indicate a reduction in CRC-related morbidity and, in the long-term, CRC-related mortality.

Overall, early-stage and late-stage CRC incidence

By 2019, the short-term outcomes indicated that the introduction of the CRC screening program in the Netherlands contributed to the reduction of the burden of the disease. In **Chapter 2**, I described that the CRC incidence increased in 2013-2015 when the CRC screening program was first introduced, but thereafter I observed a significant decrease until 2019, dropping to below the level before the introduction of screening. Similarly, after 2014, compared with the pre-screening period (2010-2014), an increase in early-stage CRC incidence was observed in 2013-2015, and again a significant decrease was observed until 2019. These results are not surprising, given that screening is aimed at detecting CRC at an early stage. Furthermore, the increase in CRC incidence in the first years after the introduction of the screening program can be explained by the fact that prevalent, asymptomatic CRCs in the target population are detected in the first screening round. This was also observed in several other European countries, such as Slovenia and Denmark (4). In Italy, where FIT-based screening was implemented early (2002-2004), the same phenomenon was also described (5–7). Retrospective cohort studies on the effectiveness of biennial FIT-screening have shown that CRC incidence in screened vs. non-screened individuals was reduced by 10%-22% (incidence rate ratio (IRR): 0.90; hazard ratio (HR): 0.78) (7,8). In a meta-analysis, it was even described that FIT-based screening could lead to a 59% relative incidence reduction (relative risk (RR) 0.41) (9).

The ecological design of these studies can introduce challenges and limitations in the interpretation of the effectiveness of CRC screening on long-term outcomes, because of possible confounders and the lack of ascertainment whether changes in incidence are directly attributable to the screening program. Therefore, strengthening the evidence for the relation between the introduction of CRC screening and the decrease in (late-stage) CRC incidence and, ultimately, CRC

mortality, is important. Surrogate performance indicators can be used to overcome the limitations as mentioned above. It was described by Cuzick et al. that a surrogate performance indicator (the late-stage CRC incidence) could advance expectations in mortality trend changes by more than three years (10). If the late-stage CRC incidence decreases after initiation of a screening program, this will probably result in a decrease in CRC-related mortality in the long-term. This was underlined by a study conducted in Taiwan, which showed significant reductions in individuals exposed to screening vs. non-exposed individuals in late-stage CRC incidence and CRC mortality (adjusted RR 0.66 and adjusted RR 0.60, respectively) (11).

I observed a slight increase in the incidence of late-stage CRC incidence between 2010 and 2015 in **Chapter 2**. This was followed by a significant decrease until 2019, when the late-stage CRC incidence decreased to rates below observed in the pre-screening era. In a similar join point regression analysis performed in Flanders, the same patterns in late-stage CRC incidence were observed after introduction of the program (2). A decreasing trend in the late-stage CRC incidence was also seen after introduction of FIT-based screening besides colonoscopy in the Kaiser Permanente Northern California cohort (12). At that time, in 2007, sigmoidoscopy and gFOBT as screening modalities were discontinued.

In **Chapter 3**, late-stage CRC incidence patterns following the phased implementation by birth cohorts of the CRC screening program were assessed. In the years these birth cohorts were first invited to screening, a peak in late-stage CRC incidence was observed. This was followed by a decrease below levels before the introduction of screening. This so-called 'wave' pattern builds up the evidence for the causal relation between the introduction of screening and a reduction in late-stage CRC incidence. A study from the Basque country evaluated these patterns in a joinpoint regression analysis on overall CRC incidence. In this study, age cohorts not invited to screening indeed showed different, non-significant trends compared to age cohorts invited to screening, which showed a significant decrease in CRC incidence (13), implying that our findings could indeed indicate the beneficial effect of screening on the late-stage CRC incidence.

Shift to less invasive treatment

In **Chapter 2**, treatment of screen-detected CRC was less invasive than that of clinically detected CRC, with local excision performed in 17.4% of screen-detected colon cancers compared with 4.9% of clinically detected colon cancers.

This pattern was also observed for rectal cancer, namely 22.1% vs. 9.1%. A more favorable stage distribution and more local treatment of screen-detected CRC lead to lower morbidity and, in the long-term, might lead to decreased CRC mortality. In Chapter 2, a less invasive treatment (i.e., more local excisions) was also observed when only considering stage I CRCs.

Therefore, in **Chapter 4**, the reasons for the less invasive treatment of screen-detected stage I CRCs were examined. Of all stage I CRCs detected by screening, 68.5% were T1N0/Nx, compared with 54.6% of all non-screen-detected stage I CRCs. When only T1 stage I colon and rectal cancers were considered, these were more likely to be treated by surgical oncologic resection when detected outside the screening program compared to screen-detected T1 cancers (colon: odds ratio (OR) 2.2, and rectum: OR 1.3, respectively). This observation holds true even after adjusting for factors such as tumor location, presence of lymphovascular invasion, and tumor differentiation.

Although explanations for the higher proportion of local excisions for screen-detected stage I CRCs are unknown, these findings may be related to unknown cancer-related factors or the competence of the endoscopists identifying these early cancers suitable for local excision within the CRC screening program. The expertise of endoscopists who perform screening colonoscopies might be superior to that of endoscopists who do not perform screening colonoscopies. To perform endoscopies within the Dutch CRC screening program, endoscopists are subject to quality accreditation criteria. These quality criteria include dedicated e-learnings, exam endoscopies, and annual visitations to evaluate colonoscopy quality indicators including a minimum adenoma detection rate (ADR) and cecal intubation rate (14). In addition to these criteria, a new e-learning has just been developed for the endoscopic evaluation of advanced lesions for piecemeal endoscopic mucosal resection or for en bloc local excision. Training for all endoscopists to better recognize early invasive lesions and optimization of subsequent management should be strived for. Further centralization or accreditation criteria for resection of T1 cancers might lead to more R0 resections of early invasive tumors.

Of course, long-term recurrence rates of locally excised T1 cancers should be determined to confirm whether the choice for local excision was justified. However, in a population-based study by Senore et al. no differences between recurrence-free survival of pT1 tumors with low-risk features were found when comparing local excisions and surgical oncologic resections (15). Finally, the results

presented suggest that the assessment of a shift in stage distribution as a result of the screening program should not be based on TNM staging alone. Treatment of T1 and T2 differed widely, and further evaluation of outcomes (i.e., CRC incidence and CRC mortality) based on T and N subgroups is recommended.

CRC-related mortality

The previously mentioned decrease in (late-stage) CRC incidence and shift in stage distribution is promising and would, in theory, lead to decreased CRC-related mortality as a result of the introduction of screening. In **Chapter 2**, a decrease in CRC-related mortality was observed from 2010-2019, however no changes in trends were observed after the introduction of the CRC screening program in the Netherlands. One would not expect this decrease in trend until at least 7 years after introduction of CRC screening, given the lead time bringing diagnosis forward with an estimated 2 years, and the average overall survival of patients with CRC exceeding 5 years. In Italy, FIT-based screening was gradually introduced in several areas. In areas where screening was introduced early (2002-2004), mortality rates in 2006-2011 were 22% lower than in areas where screening was introduced late (2008-2009) (5). In observational studies with similar changes in CRC incidence but earlier introduction of CRC screening than in the Netherlands, decreases in mortality trends were indeed observed in time periods between 6-15 years after the introduction of FIT-based screening programs (16,17). These results are of importance, since no randomized controlled trials (RCTs) have been initiated on the effectiveness of FIT and will likely not be initiated in the future.

Several RCTs of individuals who were screened through gFOBT have shown a significant reduction in CRC-related mortality (18–23) with an RR reduction of around 18% (RR 0.82, 95%CI 0.73-0.92) (24,25). FIT has demonstrated to yield higher participation rates than gFOBT and higher sensitivity for CRC and advanced adenomas (AA) (although depending on the cut-off level), suggesting that the effectiveness of FIT in lowering CRC mortality might be greater than gFOBT. Reductions from 10%-72% in CRC-related mortality attributable to FIT were demonstrated, which is most probably related to the FIT cutoff applied and participation rates, but is also highly correlated to the study design (7,8,26,27).

Ideally, to further strengthen this evidence, one would perform a case-control study, which would enable to compare the screening history of cases (CRC-related death) to matched controls (no CRC-related death). Another possibility would be target trial emulation, through which the causal effect of CRC screening

on long-term outcomes is estimated (28,29). In target trial emulation, a hypothetical RCT can be conducted. One would define in- and exclusion criteria to select individuals from an observational cohort to match the target trial population. Hereafter, an intervention (in this case, CRC screening) is emulated and events are censored based on the target trial design. This method allows for addressing biases and confounding. One important condition is the availability of high-quality detailed observational data and an important challenge here is that all of these analyses would require demographic data of non-participants, which is currently hampered by the General Data Protection Regulation.

I believe we can safely say that the Dutch CRC screening program yields promising results in terms of short-term performance indicators, stage distribution, and (late-stage) CRC incidence, and I do expect that we will soon observe a reduction in CRC-related mortality as well. The prospect of approaching the evaluation of the ultimate outcome of screening, i.e. the CRC-related mortality, is a welcome development. However, it is still important to continue to assess short-term indicators for quality assurance of the program. This allows for early identification of problems or possible changes in the program, as the impact on long-term outcomes may only appear after a much longer period of time. In the following section, I will focus on some of these short-term indicators.

Evaluation of short-term performance indicators of CRC screening

Several performance indicators can be measured to ensure quality assurance of CRC screening programs. These indicators are defined in European guidelines and include, but are not restricted to, participation rates (in FIT and in colonoscopy), the detection rate (DR), the positive predictive value (PPV), the test sensitivity and specificity of the FIT, and interval cancer rates.

In **Chapter 5**, the DR and PPV were evaluated with the addition of advanced serrated polyps (ASPs) to the definition of relevant findings, as these have been shown to account for a considerable proportion (~10%-30%) of precursor lesions of CRC. The DR of ASPs from 2014-2020 was 5.9%. In 2.7% of all FIT-positive individuals, at least one ASP was present in the absence of AA or CRC, resulting in a PPV of 43.8% when including ASPs (compared to 41.1% without ASPs). Although these numbers do not indicate that the yield of the screening program with the current definition is greatly underestimated, it might indicate that the sensitivity of FIT for ASPs is low. This was indeed observed previously (30),

where sensitivity for ASPs was at least 10% lower than for AAs at different cutoffs for FIT positivity. Nonetheless, it is also possible that the prevalence of ASPs is very low or that the detection of ASPs is often associated with the detection of AAs. If new stool tests are introduced that are more sensitive for these lesions, it is worthwhile to include these lesions in the current definition of relevant lesions in the future. This could be, for example, the multitarget stool DNA (mt-sDNA) test, which yielded higher DR for ASPs than FIT, also when corrected for having metachronous AA or CRC (31).

I also assessed the FIT sensitivity for CRC in the screening program, which is interconnected with the interval cancer rate. In **Chapter 6**, the sensitivity of the FIT for CRC was assessed after two rounds of the Dutch CRC screening program. In screening, there are three ways to determine sensitivity: program sensitivity, episode sensitivity, and test sensitivity. In FIT-based screening, episode sensitivity is preferred because it best reflects the sensitivity of the entire diagnostic process (FIT + colonoscopy). However, as we do not perform colonoscopies in FIT-negative individuals, we assessed the FIT sensitivity to estimate the performance of the test. Two ways were used to calculate the FIT sensitivity; i) the detection method, which is based on the number of screen-detected CRCs and interval CRCs, ii) the proportional incidence method, which is based on the number of interval CRCs and the expected background incidence in the Dutch population (32).

The detection method resulted in a FIT sensitivity for CRC of 84.4% in the first and 73.5% in the second round, whereas the proportional incidence method yielded a sensitivity of 76.4% in the first and 79.1% in the second round. Several other studies found similar sensitivities of FIT, ranging from 74-84%, using the detection method (33–35). In a meta-analysis, with a FIT cut-off of ≥20 µg Hb/g feces, the pooled FIT sensitivity was 71%, which is very similar to the sensitivity found in our study (36). Another study from Italy that used the proportional incidence method found sensitivities ranging from 71.5%-86.9% (6). Both methods come with some limitations. The detection method is an approximation, as some missed CRCs have not appeared as an interval CRC but are detected at the next screening round and are therefore not included in the calculation. This method can lead to both overestimation (not all missed CRCs express as interval CRC before the next screening round) and underestimation (interval CRCs that were actually AA at the previous FIT) of the FIT sensitivity. The second method, the proportional incidence method, is suggested in the European guidelines and is based on the expected background incidence in the population (32). This method allows for

comparisons with other programs; however, it should be noted that the background incidence is based on extrapolated CRC incidence from the pre-screening era. Therefore, it cannot account for changes in CRC incidence trends as a result of the CRC screening program (i.e., lower incidence because of detection and removal of precancerous lesions), possibly resulting in an overestimation of the FIT sensitivity. Nevertheless, it can be concluded that the FIT sensitivity for CRC in the Dutch screening program is satisfactory and comparable to other programs considering results from either of both methods.

Future perspectives

Now that the CRC screening program in the Netherlands is fully rolled-out, all eligible individuals are invited to participate every two years from the age of 55, and the program yields promising results, the effectiveness of the program might be improved by several other interventions, which I will elaborate on in the next sections.

Promotion of health behavior

'If we compare with the considerable risks the citizens expose themselves to because of smoking and other unhealthy lifestyles, I believe that the answer should be no [To screening, red.]' Following the rhetorical question posed by Gøtzsche in 1997, screening would inevitably not be beneficial if individuals continue putting themselves at risk for disease by continuing unhealthy behavior. I do believe that combining primary and secondary prevention, using screening as a teachable moment, should be one of our priorities. We should empower the target population to make healthier lifestyle choices, including improved nutrition, promotion of physical activity, and smoking cessation. An example of combining these strategies can be found in the integrated healthcare agreement, where several targets have been posed for 2030. This includes indicated prevention (people with an increased risk of disease), care-related prevention (patients), the strengthening of health skills and self-care, lifestyle as (part of) treatment and the connection with the municipal domains through a (regional) prevention infrastructure. Continuous effort should be put in making the target population more aware of the risks associated with certain lifestyle habits.

Participation in screening

The participation rate has a great impact on the yield of AAs and CRCs in population-based CRC screening programs. The participation rate in the Netherlands has always been one of the highest in the world. However, there has recently been a downward trend in the participation rate, especially among younger individuals, first-time participants and men (37–39). This is a worrying development and needs attention. Nevertheless, I believe increasing participation rates should never be a goal in itself. Individuals should always be able to make autonomous choices, but it might be that a (large) proportion of non-responders does not make informed choices when they do not participate (40).

Previous studies have shown that involving the general practitioner in this choice process can help to increase participation rates, as can the introduction of national campaigns that reach people in a variety of ways (i.e., through television, radio, social media, and educational programs). Furthermore, lower socio-economic status (SES) is known to be associated with lower participation rates (41) and targeted interventions to increase awareness through community-based initiatives could be a solution to inform these individuals with lower SES. A recent study from the Netherlands found that several factors are independently negatively associated with participation in the CRC screening program, i.e., being single/living with other residents, having a migrant background, a lower income, and male sex (42).

We can distinguish between nonmodifiable (e.g., gender, ethnicity, education level, income, demographics) and modifiable factors (e.g., knowledge of CRC and screening and structural barriers) (43). These modifiable factors are of particular interest when trying to enhance participation rates, and might be related to the nonmodifiable factors (i.e., different individuals have different information needs and prefer different information channels). Using a systematic approach that includes public campaigns and community outreach initiatives to engage the target population to make an informed choice on whether or not to participate, as well as investigating reasons for not participating in non-responders, can help overcome barriers to participation.

Digitalization of care

In Denmark, a decision aid was tested in an RCT, and it was shown that the participation rate increased by 8% by using a web-based decision aid sent electronically with the second reminder to participate in screening compared to no

intervention. Nonetheless, this decision aid had no effect on knowledge or attitude towards screening (44).

Incorporating various digitalization technologies into the current infrastructure of the screening program could simplify many processes for healthcare professionals, policy makers, and certainly participants. A study is currently conducted to use a digital intake tool for colonoscopy, which would eliminate the need for FIT-positive individuals to travel to a hospital for a colonoscopy intake appointment. This could improve the accessibility of the program and remove barriers to participation. This tool can also be used to identify eligibility of individuals for colonoscopy and in the process, can avoid unnecessary health care costs. The effectiveness of this intervention is, however, largely based on the accurate identification of patients with comorbidities, and whether the target population understands it.

Altering the age to start or stop screening

Recently, the American Cancer Society recommended that CRC screening should start at age 45 in the United States (US), based on the increasing incidence of CRC in younger individuals and the fact that this screening strategy was shown to be cost-effective in modeling studies (45,46). An increase in CRC incidence has also been observed in Europe (47), albeit smaller than in the US, and as the European guidelines on CRC screening recommend starting screening at age 50, this may be considered in the Netherlands in the future. However, the Health Council recommended in December 2022 to conduct a study on a one-time FIT for individuals aged 50 years, which was not adopted by the Ministry of Health because this was already evaluated in the extensive piloting phase of the screening program. A cost-effectiveness study has evaluated whether lowering the starting age or even extending the stopping age of screening should be considered to expand the CRC screening program in the Netherlands (48). It was shown that, from a cost-effectiveness perspective, extending the age range beyond 75 years would be more effective than screening individuals below 55 years. However, the cost-effectiveness of an intervention is not the only factor at play, and colonoscopy capacity is one of those factors that is very important to consider. This study also showed that if colonoscopy capacity is limited, it would be more cost-effective to screen people below the age of 55 (48).

Alternative screening modalities

Alternative screening modalities could be used in order to increase the yield of CRC and AAs/ASPs, either by increasing the sensitivity and specificity of the test for these lesions, or by increasing the participation rate. A critical issue here is the cost of the test (and thus cost-effectiveness) and facilitating the up-scaling of tests with potential higher sensitivity and specificity.

The mt-sDNA test which uses an algorithm testing for 7 DNA markers for CRC in addition to FIT seemed promising. This test yielded a sensitivity for CRC of 93%, and the sensitivity for ASPs is superior to FIT only, as described earlier (33,49). However, the mt-sDNA test is more expensive than FIT and a large amount of stool needs to be collected for analysis. Therefore, the mt-sDNA test is not as cost-effective as FIT in a population-based screening program, and not feasible (50).

Another test being assessed to improve the (cost-)effectiveness of CRC screening is the multitarget FIT (mt-FIT), which is currently studied in a large trial within the Dutch CRC screening program. The mt-FIT measures calprotectin and serpin F2 in addition to f-Hb and was shown to increase detection of AAs, improving the diagnostic accuracy of the detection of AN (51). Besides, several other tests were developed to measure proteins or DNA in stool, blood, or exhaled air. These tests have not yielded promising results yet (52–57).

Another, ground-shifting, development is the use of multicancer early detection (MCED) tests. MCED uses new technologies in one test assay, enabling testing at once for multiple cancers. However, these tests are not yet cleared for use in large populations, and the MCED consortium is working hard to initiate trials to test the feasibility and (cost-)effectiveness of these tests. At the moment, in the United Kingdom, the NHS Galleri trial is being executed, in which individuals aged 55-77 are invited to provide blood samples, in which an MCED test is performed (58). Although these MCED tests might sound promising, some important limitations and challenges should be mentioned. First, it should be noted that not all cancers have established benefits from early detection and treatment. Also, it is unclear what protocols of diagnostic work up should be offered to individuals who test positive, as it would not be feasible to offer a PET-CT to all individuals with a positive test. Next, it is unclear what the assessment interval should be after a positive MCED but no subsequent detection of cancer. Last, the potential for overdiagnosis, false positives and unnecessary and expensive invasive follow-up procedures can have significant negative consequences for a population. Returning

to Professor Gøtzsche's rhetorical question, offering MCED tests to a large population raises complex ethical challenges, and the potential future of these tests remains to be determined. Emphasizing the principles of minimizing harm and respecting individual rights and autonomy becomes crucial.

In the context of FIT-based CRC screening, I do believe that at the population level, the benefits of CRC screening outweigh the potential harms. According to recent monitoring reports of the CRC screening program in the Netherlands, nearly 14 million invitations to participate in the screening program have been sent to the target population since 2014. Approximately 10 million people participated in the screening program, resulting in an average participation rate of approximately 72%. The CRC screening program yielded 23,801 CRCs and 132,778 AAs between 2014 and 2021 (37,38). Although these results are satisfactory, there is always room for improvement. This was too envisioned, by professor David Lieberman in 1996:

''The time has come to encourage colon screening, despite its limitations, while continuing to research ways to improve identification of high-risk subgroups, increase compliance, reduce costs, and develop better screening methods.''

In Part II, I will further lay out some of the aspects mentioned by Prof. Lieberman.

12.2 PART II: PERSONALIZED COLORECTAL CANCER SCREENING FOR AVERAGE-RISK INDIVIDUALS

Currently, in countries where screening is offered to average-risk individuals, with a few exceptions, a one-size-fits-all approach is applied, with a preset age range, screening interval, and screening modality. However, even for average-risk individuals, risk factors can be identified that could stratify these populations into higher or lower risk for CRC. This risk-stratification could be based on several individual-level factors, including sex, age, familial history, lifestyle and/or genetic variations (including single nucleotide polymorphisms) (59,60), and screening history (i.e., fecal hemoglobin [f-Hb] concentration). All of these factors could add up to a risk calculation for individuals, that can be used to assign them a personalized approach in terms of age to initiate and stop screening, screening modality, and screening interval. The ultimate goal of this personalized approach, compared to uniform screening, is to further improve the balance of the benefits and harms of screening, by increasing benefits in those at highest risk and reducing harms in those at lowest risk.

Fecal hemoglobin concentration in personalized CRC screening

While the aforementioned risk factors have been studied using multiple risk prediction models, the diagnostic accuracy was modestly satisfactory, and incorporation of the previous f-Hb concentration seemed to best improve the accuracy of the models to the point that it might actually be beneficial to use them for risk stratification at this point in time (61–63). This is underlined by the results presented in **Chapter 6** of this thesis, where it was observed that the risk of interval CRC after negative FIT increased with increasing f-Hb concentrations. Individuals with f-Hb concentrations just below the cut-off were 17 times more likely to develop interval CRC than individuals with unmeasurable f-Hb concentrations in the first screening round, and 12 times more likely in the second screening round. While several models were used to assess the interval CRC risk at the second screening round using both the first and second screening round f-Hb concentrations, this model did not perform better than the model using only the most recently measured f-Hb concentration. However, a previous study showed that two consecutive f-Hb concentrations were independent predictors of incident advanced neoplasia (AN) at subsequent screening (64). Information on multiple f-Hb concentrations from consecutive rounds of screening should confirm whether

this holds true in the future, as these findings could be different for detecting (interval) CRC in a subsequent screening round.

Given the promising performance of prior f-Hb concentrations as a risk predictor for CRC, a mixed-methods study was initiated to study the yield, feasibility, acceptability, and (cost-)effectiveness of personalized CRC screening using tailored invitation intervals based on prior f-Hb concentrations. **Chapter 7** describes the study protocol of this study, called PERFECT-FIT. The PERFECT-FIT study consists of an RCT, focus group studies, and a cost-effectiveness analysis. The RCT concerns the enrollment of 20,000 individuals; 10,000 in the intervention and control arm, respectively. Individuals in the intervention arm are offered tailored intervals based on their prior f-Hb concentration (1 year for individuals with f-Hb concentrations >15-46.9 µg Hemoglobin (Hb)/gram (g) feces, 2 years for individuals with f-Hb concentrations >0-15 µg Hb/g feces, and 3 years for individuals with f-Hb concentrations of 0 µg Hb/g feces. The inclusion started in October 2022, and by August 2023, all 20,000 individuals were enrolled in the study. If personalized screening is shown to be effective, its acceptance by the target population is an incredibly important component of its eventual implementation. A number of factors are at play here, including the participation rate in the RCT, individuals' experiences with a changed invitation interval, the reasons why people do not want to participate in the RCT (which might introduce selection bias), as well as the information needs of the target population.

Information need of the target population in personalized screening

Chapter 8 presents the results of a focus group study conducted before the enrollment period of the RCT, exploring the information needs of individuals eligible to participate in personalized CRC screening. Here, it became clear that the information needs of the target population vary widely and that it is a challenge to use a single approach to risk communication and information provision for individuals. This was also observed in a study on optimal communication on the risk of breast cancer, in which some women expressed preferring no detailed information, while others preferred more detailed information (65). One solution may be to use a multifaceted information approach. The need for good communication, particularly regarding the rationale for the possible new screening policy, was highlighted as an important issue. Other studies indeed found that non-participants often did not read the information letters, and media campaigns might potentially be (cost-) effective interventions for increasing participation rates (66).

Fortunately, this study found that learning about personal risk did not appear to be a factor for people when deciding whether or not to participate in personalized CRC screening, which was underlined by previous research that demonstrated that communicating risk had no impact on participation of low-risk individuals, and even positive impact on participation of high-risk individuals (67).

The focus groups that will be conducted within the RCT among individuals in the 1- or 3-year interval should show whether this does indeed turn out to be the case. Here, we will evaluate the perspectives of individuals being assigned a different screening interval, as well as their motivations for participating in the RCT.

Future perspectives

The PERFECT-FIT study uses three different screening invitation intervals for individuals with a negative FIT, while in the long-term, it may be possible to apply risk stratification in prediction models using an algorithm for each separate individual. Incorporating various risk factors such as sex, age, familial history, lifestyle and/or genetic variations (including single nucleotide polymorphisms) might even further improve the ability of an algorithm to predict the risk of CRC (68). Although these algorithms could serve as a "perfect" solution for CRC risk prediction, they present difficulties in incorporation for integration into the current screening setup. Other changes in program design may be a first step toward personalized CRC screening.

Different screening strategies for men and women

Different screening strategies could be offered to men and women. Lifetime risk for CRC in men is somewhat higher than in women, namely 4.4% and 4.1%, respectively. However, increases in age-specific CRC incidence and mortality occur later in women than in men (69). Lower DRs for CRC and higher incidence of interval CRC were reported in women than in men, possibly due to the lower positivity rate in women compared to men (70,71). Furthermore, sensitivity of the FIT seems lower in women, as well as the PPV (72–74).

In Finland and the Stockholm-Gotland area in Sweden, different cutoffs for men and women have been evaluated to overcome these issues. In Finland, they found similar positivity rates in women and men when using different cutoffs for FIT positivity (at 40 µg Hb/g feces for women and at 80 µg Hb/g feces for men) (75). The Finnish CRC program also performed a pilot study, using cutoffs of 25 µg Hb/g feces for women and 70 µg Hb/g feces for men (76). The authors found a positivity

rate of 2.8% in men and 2.4% in women, which was lower than expected, especially in women. Also, the DRs of CRC and AA only moderately improved. Hereafter, a modelling study was initiated to evaluate the most beneficial FIT cut-offs, screening interval and age range of the target population for the national screening program in Finland (76).

As the risk of CRC differs for men and women in specific age groups (i.e., 50-59 and 60-69), different starting ages of screening can be considered (69). Whether these strategies are cost-effective remains to be seen, and it was shown that these strategies could mainly be beneficial for countries where screening is offered at ages above 50 years (69). Another adjustment could be different cutoffs for FIT positivity in men and women. However, to date, cost-effectiveness analyses have shown that implementing different cutoffs by sex would not yield satisfactory results, and that sex stratification was not more cost-effective than uniform screening (77–79).

Implementation and challenges of personalized CRC screening

The abovementioned alterations to the current screening strategy could improve the program in terms of yield, but are challenging in terms of implementation. In determining the optimal screening strategy, public health officials and screening organizations should decide whether the goal of altering the screening strategy is to achieve equal CRC detection rates in different groups of the target population, the highest sensitivity, or CRC incidence and mortality reductions. There are several challenges that remain for personalized CRC screening programs.

Linkage between screening IT systems and cancer registries is crucial for obtaining accurate data to evaluate the optimal (personalized) screening strategy, often lacking globally (15). While the Netherlands has a very accurate data linkage system, there is still room for improvement, as seen in the NORDICC trial, where Dutch follow-up data was initially unavailable due to data protection laws. In this RCT, screening-naïve individuals were invited to a single screening colonoscopy (80). However, fortunately, the Ministry of Health has shown willingness to facilitate the use of secondary data for healthcare improvement., and also provide data on the NORDICC trial. Also, global consortia play a critical role in advancing CRC screening by enabling data pooling, standardization, sharing of best practices, and informing policy makers.

Population-level implementation is challenging in terms of ethics, organization, execution, and acceptance of the target population (68). In theory, personalized screening could lead to more efficient and equitable use of services. However, the implementation of personalized screening would require a change in the organizational framework for CRC screening and a different use of resources.

Furthermore, translating risk scores into an individualized screening strategy will be demanding at the individual and population levels. At the individual level, communicating an individual's risk for CRC may cause confusion, and studies are needed on how and when to communicate this risk. At the population level, incorporating an algorithm offering clinically actionable recommendations into the current screening framework would also be challenging (68). Last, it is very important to keep evaluating personalized screening strategies in terms of feasibility, (cost-)effectiveness, and acceptability of the target population. In Figure 1, some of the most important challenges are summarized.

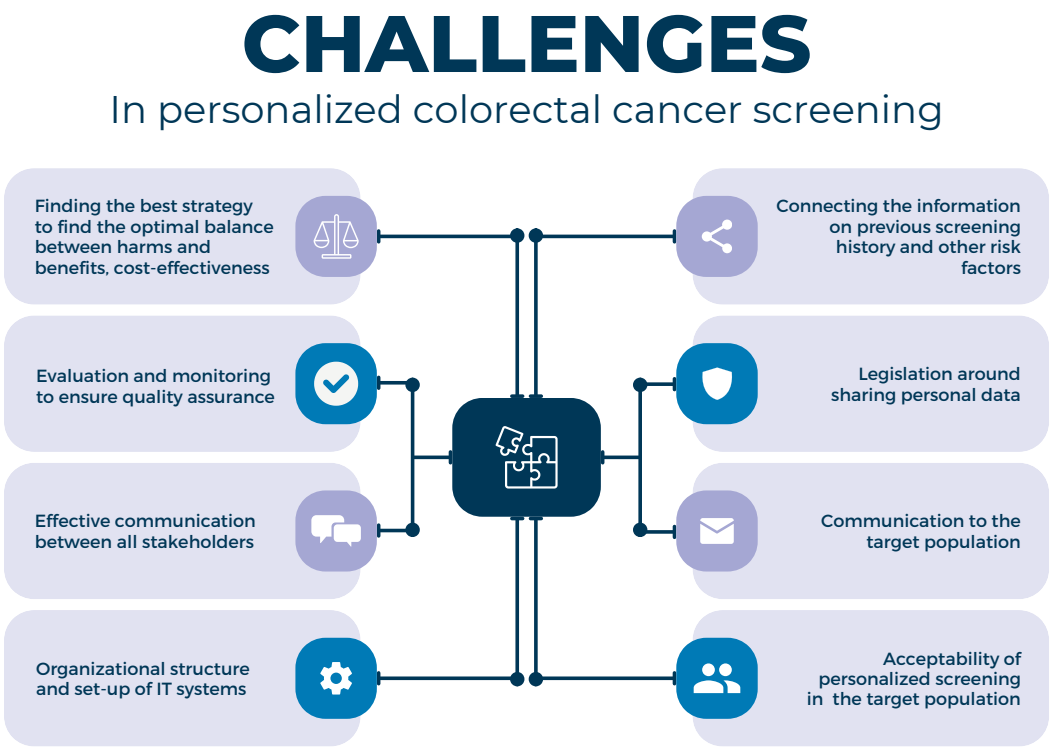


Figure 1 - Challenges in the implementation of personalized colorectal cancer screening

12.3 PART III: COLORECTAL CANCER SCREENING AND ASPECTS OF COLORECTAL CANCER IN HIGH-RISK INDIVIDUALS

As with personalized CRC screening for average-risk individuals, a personalized approach can also be used for high-risk individuals. These high-risk individuals have at least twice the lifetime risk of developing CRC as average-risk individuals. This personalized approach may include risk stratification for individuals based on family history and lifestyle factors, but also applies to childhood cancer survivors (CCS) based on their prior treatment regimens. One of these high-risk groups includes testicular cancer survivors (TCS).

Treatment regimens for TCS usually consist of bleomycin, etoposide/ifosfamide, and cisplatin/carboplatin (81). In addition to the known long-term effects of treatment for testicular cancer, such as ototoxicity, neurotoxicity, cardiovascular toxicity, pulmonary toxicity, infertility and metabolic syndrome, there is increased risk of second malignant neoplasms (SMNs) in TCS (82). A higher incidence of SMNs and mortality has been reported in TCS, with a standardized incidence rate (SIR) of 1.65 (95%CI: 1.57-1.73) and a standardized mortality rate (SMR) of 2.0 (95%CI: 1.7-2.4) (83,84).

The SIR for TCS treated with chemotherapy versus surgery alone is 1.43 (95%CI: 1.18-1.73) (85). A large epidemiologic study found that the HR of colorectal SMNs is 3.9 (95%CI 1.7-8.9) in TCS treated with platinum-based chemotherapy compared to TCS not treated with platinum-based chemotherapy (86). Also, this risk increased with increasing doses of platinum-based chemotherapy (86).

In the Netherlands, no CRC screening guidelines for any CCS are in place yet. In the United States (US), CCS treated with abdominal radiotherapy had a higher polyp prevalence and risk of CRC compared with average-risk individuals (87,88). These findings led to the introduction of CRC surveillance from the age of 35 or beginning at 10 years after radiation, repeated every five years (colonoscopy) or every three years (mt-sDNA tests) in the US (89). Based on these findings, it could be argued that TCS should be offered CRC screening at an earlier age, rather than waiting to be invited to the population-based CRC screening program at age 55, similar to other high-risk groups.

Colorectal cancer screening in testicular cancer survivors

In **Chapter 10**, I evaluated the yield of colonoscopy in TCS treated with platinum-based chemotherapy. I found that the prevalence of AN and any

neoplasia (including non-advanced adenomas/serrated polyps (SPs)) was significantly higher compared with a control cohort of age-matched average-risk American males. The propensity score matched analysis (adjusted for age, smoking status, alcohol consumption and body mass index) revealed a prevalence of AN of 8.7% in TCS vs. 1.7% in the control cohort (p=0.0002). Furthermore, the prevalence of non-advanced adenomas/SPs was 45.2% in TCS vs. 5.5% in the control cohort (p<0.0001) after propensity score matching.

There is conflicting evidence as to whether non-advanced adenomas/SPs are associated with an increased risk of CRC. However, it was described that having tubulovillous or villous adenomas does carry higher CRC risk than having no polyps (90). Also, it was described that the risk for metachronous AN was higher for individuals with non-advanced lesions than for individuals with no lesions (RR: 1.8; 95%CI 1.3-2.6) (91). Regarding the ultimate goal of CRC screening and surveillance, one study found that removing non-advanced lesions may contribute to reduced CRC-related mortality (92). Another, more recently published, systematic review did not find statistical differences in standardized mortality rates of low-risk polyp groups compared with the general population (93).

While the prevalence of AN was significantly higher in TCS than in the average-risk cohort, no CRCs were detected in the TCS cohort, and additional cost-effectiveness studies are needed to determine whether the increase in AN prevalence justifies offering colonoscopy screening to TCS, and at what age. It was found that the prevalence of AN in older cohorts (e.g., age categories 50-59 and 60-69), was higher than in younger cohorts and that the difference in AN prevalence with the control cohort was more pronounced. This was also observed for non-advanced adenomas and SPs. In **Chapter 9,** it was found that the median age at diagnosis of second primary CRC in TCS was 55 years (range 35-68), which was lower than the median age of individuals with CRC in a general population cohort with primary colonoscopy screening offered below the age of 70 (61 years, range 27-71; p<0.01). Furthermore, another study on subsequent primary gastrointestinal (GI) cancers in CCS found that most GI cancers developed 26-30 years after the first primary cancer (94). This could indicate that although the risk of CRC in TCS is higher from a young(er) age, the right age to begin screening by colonoscopy may be later than the age of 45.

Last, TCS should be made aware of the increased risk of CRC, lifestyle recommendations, and alarm symptoms while still under the care of their medical oncologist, similar to the manner in which cardiovascular risks associated with

cisplatin are communicated. The overall benefit of colonoscopy in TCS should be considered together with the increased risk of other SMNs, as well as cardiovascular toxicity after following chemotherapy regimens in TCS. Last, TCS with bowel symptoms that may indicate CRC, or with additional CRC risk factors, should be referred for colonoscopy at a low threshold.

Mutational signature of colorectal cancer among testicular cancer survivors treated with cisplatin

There are several pathways that might lead to CRC in TCS. It has been hypothesized that cellular senescence leading to chronic inflammation results in premature aging in TCS, which may contribute to carcinogenesis (95). Also, it may be that anti-cancer therapies (e.g., cisplatin) lead to somatic mutations, which in turn lead to the formation of second primary CRC in TCS.

Cellular senescence initially supports cells to respond to stressors (such as DNA damage, telomere shortening, or oncogenic signals) to prevent cells from becoming cancerous. However, senescent cells can persist in tissues and disrupt homeostasis and promote chronic inflammation (96). This well-known process initiated by telomere shortening can cause senescent cells to interfere with surrounding tissues, leading to the development of aging and age-related diseases (97,98). Age-related diseases include cardiovascular disease, neurodegenerative and metabolic disorders, and cancer. The aforementioned phenomenon can also be caused by many types of anti-cancer therapies, referred to as therapy-induced senescence (TIS) (99). TIS can lead to the elimination of cancer cells, but it can also lead to chronic inflammation and senescence, which in turn can result in carcinogenesis (100). This can be both intrinsic (i.e., generation of reactive oxygen species and chronic inflammatory response) and extrinsic (i.e., radiation therapy and macromolecular damage) (101). This senescent state caused by therapy has been described in several CCS cohorts (102,103).

Since the mid-1980, we recognize cisplatin as being mutagenic; it was described that in E.Coli, >90% of mutations caused by cisplatin are single base substitutions (104). The working mechanism of cisplatin is based on DNA damage by inhibition of RNA transcription, which leads to oxidative stress and the formation of reactive oxygen species. This could lead to somatic mutations that target specific genes or regions of the genome, affecting normal (stem) cells and leading to uncontrolled growth and division of cells, resulting in formation of sporadic CRCs. In sporadic CRCs, we identify two groups of gene alterations: i) the

hypermutated group (16% of all sporadic CRCs): DNA mismatch repair deficiency (MMRd) and/or polymerase ε (POLE) mutations, ii) the non-hypermutated group (84% of all sporadic CRCs): chromosomal instability, oncogenic activation of KRAS/PIK3CA and mutation and loss of heterozygosity (LOH) of APC and TP53. However, there are several overlapping (somatic) mutations found in both groups, and about 140 genes (tumor suppressor genes as well as oncogenes) among the 20,000 identified genes in the human genome can be distinguished as drivers of sporadic CRCs. Nevertheless, the genomic signature of sporadic CRC is thought to be unique with 2-8 driver gene alterations that are highly heterogeneous within patients (105).

Taken together, it may be that multiple pathways lead to (CRC) carcinogenesis in TCS, taking into account MMRd, but also for example APC mutations. It could be that treatment in TCS, as well as in other CCS, leads to a cascade of somatic mutations and loss of heterozygosity (LOH) in both or other genes, leading to carcinogenesis in these cancer survivors.

In **Chapter 10**, it was observed that the frequency of MMRd of CRC in TCS was higher than that of CRC in a general population cohort, however no significant difference was found (17% vs. 9%, p=0.13). MMRd was more often explained by somatic double or single hits in MMR genes (10% vs. 2%, p<0.01), while the prevalence of MLH1 promoter hypermethylation or Lynch syndrome was similar in TCS and CRC diagnosed within the general population cohort. Nonetheless, most CRCs with MMRd in TCS were somatic events and not related to Lynch syndrome. Furthermore, common mutations were found in CRCs in TCS, namely KRAS (in 35% of cases) NRAS (in 7% of cases), and BRAF (in 3% of cases).

It is not inconceivable that the higher prevalence of somatic MMRd in combination with the aforementioned aging process that begins earlier in life than in average-risk individuals leads to the formation of CRC in TCS treated with platinum-based chemotherapy. Cisplatin treatment may immediately cause genetic damage after administration that leads to aging and, together with somatic mutations over a lifetime, leads to formation of CRC. Another possibility is that the platinum, about 10% of which we know retains in several human tissues after treatment, is slowly released and gradually causes an accumulation of mutations that eventually reaches a threshold that leads to carcinogenesis.

Platinum retention in testicular cancer survivors treated with cisplatin

As described earlier, treatment with cisplatin is associated with multiple adverse effects. It is known to cause nuclear DNA damage through passive diffusion into the cell, after which RNA transcription is inhibited leading to oxidative stress (106). As cisplatin enters the body, around 90% is protein-bound and quickly cleared by the kidneys. Only a small proportion resides in targeted tissues, as well as in healthy tissue. Several studies have shown that platinum can retain in plasma and urine of TCS treated with cisplatin for up to 20 years (107–109). It was also described that serum platinum concentration quartiles are associated with adverse effects, such as tinnitus, higher luteinizing hormone levels, and hearing impairment (110). Furthermore, higher dosages of cisplatin at time of treatment for TCS were correlated with higher risk of CRC in the retrospective cohort study by Groot et al. (86), which might have implications for the follow-up on SMNs in these individuals.

In **Chapter 11**, platinum concentrations in plasma, urine, and normal colonic mucosa for up to 40 years after the last cisplatin treatment cycle were measured. This was performed using inductively coupled mass spectrometry (ICP-MS), a highly sensitive technique for measuring total platinum in biological compounds. The results showed that platinum in TCS treated with cisplatin is still measurable in all three tissues long after treatment and was higher than in control samples. Platinum concentrations in all tissues were higher closer to the time of cisplatin treatment. These concentrations were lower after a longer period of time, but almost all measurements, even those at 40 years post-treatment, were above limits of detection. This was the first study to demonstrate platinum retention for such a long period of time and to demonstrate platinum retention in normal colonic mucosa in TCS.

A strong correlation was observed between platinum plasma and urine concentrations (0.78; $p<0.0001$). This was also observed in a previous study, which found a strong correlation between platinum concentrations in plasma and urine up to 16.8 years after cisplatin treatment (108). Brouwers et al. described the phenomenon that approximately 10% of platinum in TCS may still be reactive. It has also been speculated that platinum is gradually released into the bloodstream during tissue regeneration (109). This suggests that platinum has multiple half-lives. In Chapter 11, half-lives of 13 years for plasma and 10 years for urine were observed, indicating that this speculation can indeed be true. A limitation of this study was that no data on renal function in TCS at the time of treatment or at follow-up were available.

It was hypothesized that long-term retention of platinum could lead to cellular senescence in TCS (95), implying that the mechanisms described above can be driven by this retention. I did not observe any trends in the magnitude of platinum concentrations in plasma, urine, and normal colonic mucosa associated with the dose of cisplatin administered in TCS. Besides, no significant differences in the platinum concentrations in plasma and normal colonic mucosa according to findings at colonoscopy were observed. When I performed logistic regression analyses to determine whether platinum concentrations or cisplatin doses were associated with any neoplasia detected at colonoscopy, no significant associations were found [*unpublished data*]. These analyses were performed using multivariable regression analyses, adjusting for age, BMI, alcohol consumption and smoking status.

Clinical implications of these findings remain to be determined, and one caveat must me mentioned here; ICP-MS cannot distinguish between active and inactive platinum compounds. The use of cisplatin may however result in prolonged exposure to low doses of circulating platinum and its accumulation in various patient samples. This accumulation could potentially increase the risk of cancer by causing somatic mutations. This may partly explain the increased risk of SMNs in CCS. Therefore, close monitoring of individuals exposed to cisplatin is critical given the long-term consequences of platinum retention. Future solutions to mitigate these risks may be offered by fourth-generation platinum agents (111).

Future perspectives

Although we have learned the yield of a single screening colonoscopy in TCS treated with platinum-based chemotherapy, still, further research is needed in this area. This research should focus on multiple facets of the process; from translational research on how cisplatin causes the initiation of processes that lead to the development of CRC, to what screening strategies are best for TCS. This could include more advanced techniques to map the genome of cisplatin-treated TCS, such as whole genome sequencing (WGS) of normal colonic mucosa and (advanced) lesions detected in TCS. This will give us insight into the carcinogenesis of CRCs in TCS. WGS allows for looking for specific single base substitutions (SBS), such as those associated with aging or the cisplatin signature, and whether (combinations of) these specific SBS are found on specific genes. We know that with certain algorithms, it is possible to correlate WGS data with the exact time when these changes occurred (112). This could give us more insight into whether

cisplatin leads to somatic genetic changes immediately after administration or later through tissue regeneration and the release of platinum compounds, after which mutations accumulate until a certain threshold is reached. If these findings are combined, we may be able to distinguish between those TCS at low risk and those at high risk of CRC, even in this high-risk group. In addition, the AN prevalence threshold to justify CRC screening for TCS should be determined, which could be supported by cost-effectiveness analyses. CRC screening modalities other than colonoscopy should also be evaluated, including FIT screening at shorter intervals, FIT at a lower cut-off than in the population-based screening program, or more sensitive tests such as the mt-FIT or mt-sDNA test.

Finally, further research on late effects of cisplatin and other alkylating chemotherapeutic agents in CCS may provide more insight in the formation of SMNs in CCS, and how to best provide screening and/or surveillance for these individuals.

KEY FINDINGS

PART I

- After a short increase in CRC incidence after introduction of screening, trend analysis showed a significant decrease in CRC incidence to levels before the introduction of screening.
- Advanced-stage CRC incidence increased slightly until 2015, after which a significant decrease was observed.
- Stage distribution of screen-detected CRCs was more favorable than non-screen-detected CRCs.
- Treatment of screen-detected CRCs was less invasive than that of non-screen-detected CRCs.
- These findings persisted when looking at stage I CRC only, and this could be only partly explained by the higher proportion of T1 CRC within screen-detected CRCs.
- The addition of ASPs to the definition of relevant findings within the screening program led to a modest increase in PPV.

PART II

- The risk of interval CRC increased with increasing f-Hb concentrations below the FIT cut-off.
- A mixed-methods study on personalized screening using these f-Hb concentrations for risk stratification (PERFECT-FIT) was rolled out, with the aim to evaluate the yield, feasibility, acceptability, and (cost)effectiveness of personalized screening compared to uniform screening.
- Information needs on personalized screening of the target population vary widely and therefore a multifaceted approach is needed in information provision.

PART III

- The yield of any colorectal neoplasia and AN by colonoscopy was higher in TCS treated with platinum-based chemotherapy than in an age-matched average-risk cohort consisting of American males; these differences were even larger when applying a propensity score matched analysis.
- The frequency of MMRd of CRC in TCS was higher than that of CRC in a general population cohort; MMRd was more often explained by somatic double or single hits in MMR genes.
- Platinum concentrations in plasma, urine, and normal colonic mucosa were elevated in TCS treated with cisplatin up to 40 years after treatment.

RECOMMENDATIONS AND IMPLICATIONS

PART I

- The ultimate outcome of screening, CRC-related mortality, should be evaluated in the coming years, to determine the effectiveness of FIT-based screening in the Netherlands.
- This thesis demonstrates the importance of monitoring and evaluation to assess the (positive) impact of CRC screening in the Netherlands; future laws and regulations should (continue to) enable monitoring and evaluation to ensure that screening programs keep delivering a favourable balance between harms and benefits.
- Given the positive impact of the Dutch CRC screening program, it is critical to keep the target population engaged in the program. Efforts should therefore be made to investigate and counter the downward trend in participation.
- Long-term recurrence rates of locally excised screen-detected and non-screen-detected T1 cancers should be evaluated to assess whether the more frequent choice for local excision in screen-detected T1 cancers was justified.
- The detection of ASPs should be automatically recorded as relevant findings within the screening IT systems.

PART II

- Implementation of personalized screening based on f-Hb concentrations should be considered.
- In view of the promising performance of risk stratification and the expected results of the PERFECT-FIT study, focus should be on how to set up organizational frameworks for personalized screening.
- Given the need for a multifaceted approach to information provision, the specific ways in which this can best be communicated to the target population need to be further explored.
- The predictive value of f-Hb concentration for post-colonoscopy CRC in FIT-positive individuals without relevant findings at colonoscopy should be investigated to assess whether risk stratification could also be applied to this group.

PART III

- The AN prevalence threshold to justify CRC screening or surveillance (and what screening modality to use) for TCS should be determined, which could be aided by cost-effectiveness analyses.
- Determining if and how cisplatin leaves a signature in the colorectum that leads to carcinogenesis in TCS is necessary to determine the best way to prevent or early detect CRC, which could be investigated through whole genome sequencing of normal colon mucosa and (advanced) lesions.
- Treating physicians should make TCS aware of the risk of CRC and other SMNs early in follow-up, and uniform guidelines should be developed for surveillance of SMNs in TCS.
- Further research on late effects of cisplatin and other alkylating chemotherapeutic agents in CCS may provide further insights in the formation of SMNs in CCS, and how to best provide surveillance for these individuals.

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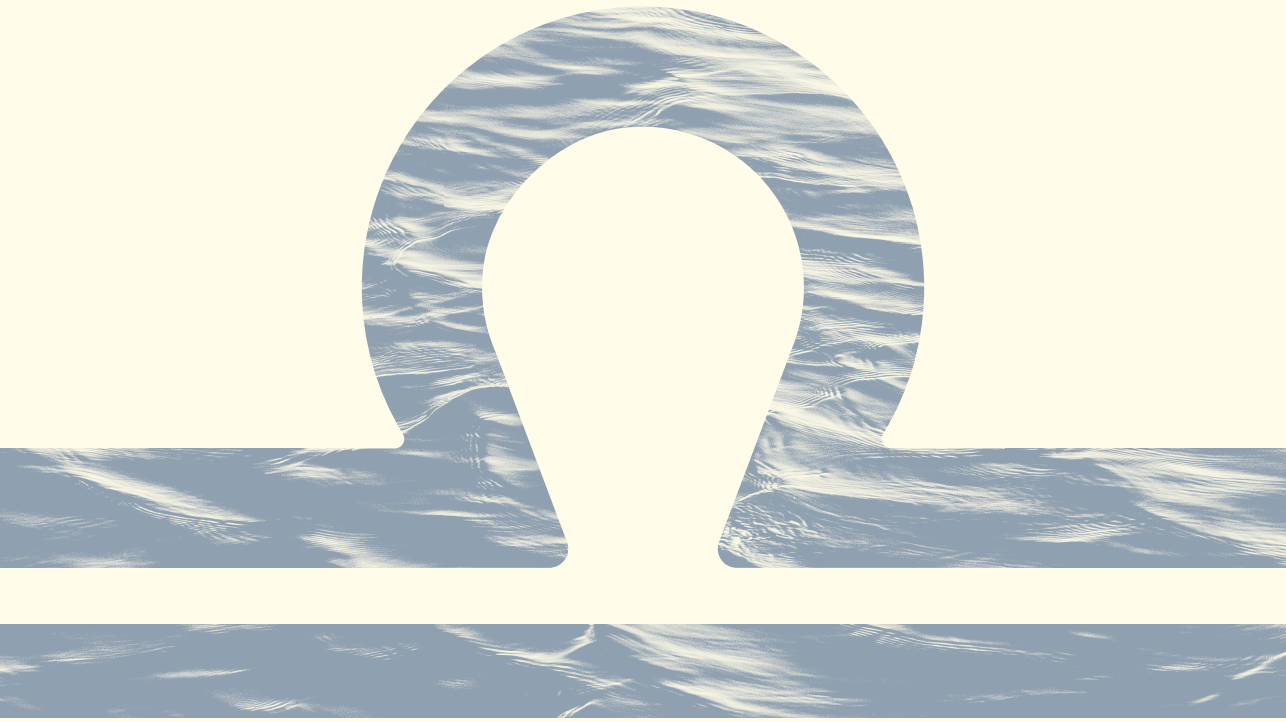
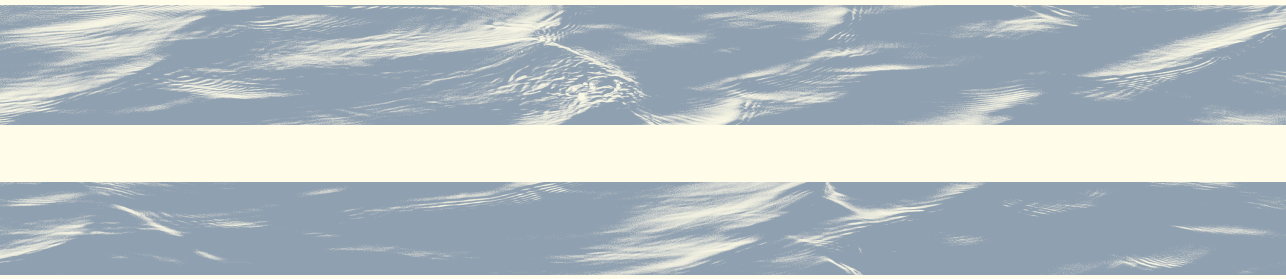


Appendices



SUMMARY

Colorectal cancer (CRC) was diagnosed in nearly two million new cases and caused nearly one million deaths in 2020, making it the third most diagnosed cancer worldwide and the second leading cause of cancer-related deaths. Worldwide, many countries have implemented CRC screening programs, aimed at the prevention of development of CRC through removal of precursor lesions, as well as the detection of CRC at an early stage (stage I and II), with the ultimate goal to reduce the (late-stage; stage III and IV) CRC incidence and CRC-related mortality.

CRC screening can be tailored to meet the needs of a specific target population (i.e., average- or high-risk). When deciding on the optimal screening strategy in these populations, several choices can be made in terms of primary screening modality (non-invasive stool tests or endoscopy including sigmoidoscopy or colonoscopy), availability of resources, organizational framework, invitation intervals, age range, etc. Balancing the benefits and harms of screening in the context of the above factors is key in selecting a particular screening strategy for specific populations.

For average-risk individuals in the Netherlands, a population-based CRC screening program was implemented in 2014 by age cohort, eventually inviting all individuals aged 55-75 to perform biennial fecal immunochemical testing (FIT) at a cutoff of 47 µg hemoglobin (Hb)/gram (g) feces. Participants with a positive FIT are referred for colonoscopy. In 2019, the screening program was fully implemented and the whole target population was at least invited once. Part I of this thesis evaluated the short- and long-term outcomes of the CRC screening program in the Netherlands between 2014 and 2019.

To further improve the balance of benefits and harms of CRC screening programs, risk stratification may be the way forward. Improving this balance can be achieved by targeting individuals at high risk and offering them more intensive screening, thereby increasing benefits, while reducing harms for those at low risk by offering less intensive screening. Risk stratification can be based on multiple individual risk factors. Challenges remain in determining the most appropriate risk factors for personalized CRC screening. Part II of this thesis discusses risk stratification of CRC screening based on fecal Hb (f-Hb) concentrations after negative FIT and information needs of the target population for personalized CRC screening strategies.

While population-based CRC screening may be (cost-)effective for average-risk individuals, high-risk populations (based on for example familial CRC risk, inflammatory bowel disease, and other genetic syndromes) have at least twice the risk of developing CRC during their lifetime, highlighting the importance of potential intensified CRC screening and surveillance for these individuals. Gaining further knowledge on CRC carcinogenesis is of importance to provide recommendations on how to best prevent CRC in these populations. An example of a high-risk population is testicular cancer survivors (TCS). Various retrospective cohort studies have highlighted that TCS, particularly those treated with platinum-based chemotherapy, are at higher risk of developing second malignant neoplasms, including CRC. Part III of this thesis investigated the prevalence and carcinogenesis of (advanced) colorectal neoplasia in TCS, as well as the yield of colonoscopy screening in these high-risk individuals.

Part 1 - Evaluation of the Dutch colorectal cancer screening program

Several indicators can be used to evaluate the effectiveness of CRC screening programs. These include changes in stage distribution, reductions in overall, early-stage, and late-stage CRC incidence, less invasive treatment of screen-detected CRC, and ultimately reductions in CRC-related mortality. Chapter 2 explored the effects of the implementation of a population-based CRC screening program in the Netherlands on these indicators. It was concluded that the FIT-based CRC screening program in the Netherlands resulted in a more favorable stage distribution (stage I and II) of screen-detected CRC than clinically detected CRC (67% vs. 46%), as also observed in several other European countries. Furthermore, after introduction of the program in 2014, a significant decrease in overall and late-stage CRC incidence was observed. Chapter 3 examined trends in late-stage CRC incidence following the gradual implementation of the CRC screening program by birth cohort. An increase in the incidence of late-stage CRC was observed when these birth cohorts were invited to screening. This was followed by a decline to levels below those observed prior to the introduction of screening. The distinct "wave" pattern where later invited birth cohorts experience this trend later in time than earlier invited birth cohorts supports a causal relationship between the introduction of screening and the reduction in late-stage CRC incidence. The observed reduction in CRC incidence, particularly in late-stage disease, and the shift in stage distribution are promising. Theoretically, these changes would contribute to a decrease in CRC-related mortality

following the introduction of screening. Chapter 2 did not observe changes in CRC-related mortality following the introduction of screening yet. However, one would not expect this decrease in trend until at least 7 years after introduction of CRC screening, given the lead time bringing diagnosis forward with an estimated 2 years, and the average overall survival of patients with CRC exceeding 5 years.

In chapter 2, it was found that treatment of screen-detected CRC was less invasive than that of clinically detected CRC, and this pattern was observed for colon cancers (17% vs. 5%) as well as rectal cancers (22% vs. 9%). This finding was persistent when only considering stage I CRCs. Therefore, in chapter 4, the reasons for the higher frequency of local excisions of stage I screen-detected CRCs in comparison with clinically detected CRCs were evaluated. This chapter concluded that the higher proportion of T1 cancers within screen-detected stage I cancers may be part of the explanation for the higher frequency of local excisions of screen-detected stage I cancers compared to clinically detected stage I cancers. In addition, these screen-detected T1 stage I CRCs were more likely to undergo local excision than their clinically detected counterparts, even after adjusting for risk factors such as lymphovascular invasion and tumor differentiation. Although explanations for the higher proportion of local excisions for screen-detected stage I CRCs are unknown, these findings may be related to unknown cancer-related factors or the competence of the endoscopists identifying these early cancers suitable for local excision within the CRC screening program. Finally, Part I assessed short-term performance indicators of the Dutch CRC screening program. In Chapter 5, the focus was on investigating the detection rate and positive predictive value by incorporating advanced serrated polyps into the definition of relevant findings in the Dutch CRC screening program. In ~3% of all FIT-positive individuals, at least one advanced serrated polyp was present in the absence of AA or CRC. This increased the positive predictive value of the screening program from 41% to 44%. Although these numbers do not indicate that the yield of the screening program with the current definition is greatly underestimated, it might indicate that the sensitivity of FIT for advanced serrated polyps is low. As advanced serrated polyps account for a considerable proportion (~10%-30%) of precursor lesions of CRC, further research into new stool tests with a higher sensitivity for these lesions is warranted, and inclusion of these lesions in the current definition of relevant lesions in the future is needed. Last, chapter 6 explored the incidence of interval CRCs within the CRC screening program. Interval CRC is defined as CRC diagnosed after a negative FIT

and before invitation to the next screening round. A low incidence of interval CRC was observed in both the first and second screening round (both around 10 per 10,000). The interval CRC rate is closely correlated with the FIT-sensitivity, which was high in both the first (76%) and second (79%) screening round.

Part II. Towards personalized colorectal cancer screening for average-risk individuals in the Netherlands

In population-based CRC screening programs, uniform screening is offered to the whole target population, while their CRC risk differs. Risk factors include variables such as sex, age, family history, lifestyle, genetic variation and screening history (particularly the f-Hb concentration). The cumulative effect of these factors can be used to calculate personalized risk estimates for individuals and offer them a personalized screening strategy. The overall goal of this personalized approach, as opposed to one-size-fits-all screening, is to optimize the balance between the benefits and harms of screening. Although numerous risk prediction models have been applied to investigate the mentioned risk factors, their diagnostic accuracy has been moderately satisfactory. Inclusion of f-Hb concentrations in these prediction models was shown to be the most effective in improving the accuracy of risk prediction. This is corroborated by the results presented in Chapter 6 of this thesis, which indicate an increased risk of interval CRC following negative FIT results with increasing f-Hb concentrations. Individuals with f-Hb concentrations just below the cut-off of 47 µg Hb/g feces had a 17-fold increased likelihood of developing interval CRC compared to those with undetectable f-Hb concentrations in the first screening round; this was a 12-fold increased likelihood in the second screening round. Considering the predictive performance of previous f-Hb concentrations for CRC risk, a mixed-methods study was launched to investigate the effectiveness, feasibility, acceptability, and cost-effectiveness of personalized CRC screening. Chapter 7 outlines the study protocol of this study, called PERFECT-FIT, which is a study comprising a randomized controlled trial (RCT), focus group studies, and a cost-effectiveness analysis. The RCT involves the recruitment of 20,000 individuals, with 10,000 assigned to the intervention arm and 10,000 to the control arm. Participants in the intervention arm receive personalized screening intervals based on their prior f-Hb concentration. Enrollment began in October 2022, and as of August 2023, 20,000 participants have been successfully enrolled. If the results of the RCT show that personalized screening is effective, its acceptance by the target population is an

incredibly important component of its eventual implementation. Therefore, in Chapter 8, individuals' views on personalized CRC screening were explored in a focus group study. This study highlighted varied preferences for information on individual risk and the need for diverse communication strategies when implementing personalized screening programs. In conclusion, while personalized CRC screening seems very promising in terms of improving the balance between benefits and harms of CRC screening, challenges remain. These include, but are not limited to, effective communication between stakeholders, communication to the target population, and acceptability of these strategies in the target population.

Part III. Colorectal cancer in testicular cancer survivors treated with platinum-based chemotherapy

The personalized approach described above may be applicable to high-risk individuals as well, as these have a higher risk of developing CRC than average-risk individuals. Among these high-risk groups are TCS, as a large epidemiologic study found that the hazard rate of colorectal second malignant neoplasms is 4 in TCS treated with platinum-based chemotherapy compared to TCS not treated with platinum-based chemotherapy. It may be argued that TCS should be offered CRC screening at an earlier age, rather than waiting until they are invited to the population-based CRC screening program at age 55, in line with practices for other high-risk groups. Furthermore, understanding CRC carcinogenesis in this high-risk group of TCS is important to further develop guidelines for follow-up and diagnostics in these individuals. In Chapter 10, the yield of colonoscopy in TCS treated with platinum-based chemotherapy was assessed. The prevalence of advanced neoplasia and any neoplasia, including non-advanced adenomas/serrated polyps, was notably higher when compared to an age-matched control group of average-risk American males. The propensity score matched analysis revealed a significant difference in advanced neoplasia prevalence in TCS (9%) as opposed to the control cohort (2%). While the prevalence of advanced neoplasia was significantly higher in TCS than in the average-risk cohort, no CRCs were detected in TCS, and additional cost-effectiveness studies are needed to determine whether the increase in AN prevalence justifies offering (colonoscopy) screening to TCS, and at what age. In Chapter 9, it was found that in secondary CRCs in TCS, somatic double or single hits in mismatch repair genes were significantly more prevalent in compared to primary CRCs detected in an average-risk male cohort from the general population. Exposure to

anticancer treatment appears to be associated with the occurrence of these rare somatic double-hit mismatch repair deficient CRCs in cancer survivors. Finally, in Chapter 11, platinum concentrations were measured in plasma, urine, and normal colon mucosa up to 40 years after the last cisplatin treatment cycle using highly sensitive inductively coupled mass spectrometry. The results showed detectable levels of platinum in cisplatin-treated TCS in all tissues, persisting even 40 years after treatment. Platinum concentrations were consistently higher than in control samples. Concentrations were highest near the time of treatment and decreased over time, but remained above detection limits. This platinum retention may increase second cancer risk through somatic mutations, potentially contributing to the increased risk of second malignant neoplasms in TCS. Monitoring the long-term effects of platinum retention is critical to understanding carcinogenesis and establishing guidelines for early detection of (gastrointestinal) second malignant neoplasms.

SAMENVATTING

Dikke darmkanker werd in 2020 bijna twee miljoen keer gediagnosticeerd en veroorzaakte bijna een miljoen sterfgevallen, waarmee het wereldwijd de op twee na meest vastgestelde kanker is en de op één na belangrijkste oorzaak van kanker-gerelateerde sterfte. Veel landen wereldwijd hebben screeningsprogramma's geïmplementeerd, gericht op het voorkomen van de ontwikkeling van darmkanker (door het verwijderen van voorloperstadia), evenals het opsporen van darmkanker in een vroeg stadium (stadium I en II). Het uiteindelijke doel van deze screeningsprogramma's is het verlagen van de (laat-stadium; stadium III en IV) incidentie van darmkanker en darmkanker-gerelateerde sterfte.

Darmkankerscreening kan worden afgestemd op een specifieke doelgroep (d.w.z., gemiddeld- of hoog-risico populaties). Bij het kiezen van de optimale screeningsstrategie voor deze populaties moeten verschillende afwegingen worden gemaakt. De keuze voor de primaire screeningstest (niet-invasieve ontlastingstesten of een kijkonderzoek van (een deel van) de darm; sigmoïdoscopie of coloscopie), beschikbaarheid van middelen, organisatorische uitdagingen, uitnodigingsintervallen, en doelgroep zijn allen van belang. Het afwegen van de voor- en nadelen van screening, waarbij bovengenoemde factoren moeten worden meegenomen, is cruciaal bij het selecteren van een screeningsstrategie voor verschillende populaties.

In Nederland werd het bevolkingsonderzoek darmkanker in 2014 ingevoerd, waarbij alle mannen en vrouwen van 55-75 jaar tweejaarlijks worden uitgenodigd om een fecaal immunochemische test (FIT) uit te voeren met een grenswaarde van 47 µg hemoglobine (Hb)/gram (g) ontlasting. Deelnemers met een positieve FIT worden doorverwezen voor een coloscopie. In 2019 kwam er een einde aan de implementatiefase van het screeningsprogramma, welke per geboortecohort gefaseerd werd ingevoerd. Vanaf 2019 wordt de gehele doelgroep elke twee jaar uitgenodigd. In Deel I van dit proefschrift werden de korte- en langetermijnresultaten van het bevolkingsonderzoek darmkanker van 2014-2019 geëvalueerd.

Om het evenwicht tussen voor- en nadelen van darmkankerscreeningsprogramma's verder te verbeteren, kan gebruik worden gemaakt van risicostratificatie. Hierbij krijgen hoog-risico individuen intensievere screening, waardoor de voordelen toenemen (bijvoorbeeld eerdere diagnose van darmkanker), terwijl de nadelen voor laag-risico individuen worden verminderd door minder intensieve screening.

Risicostratificatie kan worden gebaseerd op meerdere individuele risicofactoren. Deel II van dit proefschrift bespreekt risicostratificatie van darmkankerscreening op basis van fecale hemoglobine (f-Hb) concentraties na een negatieve FIT en informatiebehoeften van de doelgroep voor gepersonaliseerde darmkankerscreening.

Hoewel georganiseerde bevolkingsonderzoeken (kosten-)effectief kunnen zijn voor individuen met een gemiddeld risico, hebben individuen met een hoog risico (bijvoorbeeld familiaire darmkanker, inflammatoire darmziekten en andere genetische syndromen) minstens tweemaal zoveel risico op het ontwikkelen van darmkanker tijdens hun leven, wat het belang benadrukt van potentieel geïntensiveerde darmkankerscreening en/of surveillance voor deze individuen. Ook is het vergaren van meer kennis over de ontstaanswijze van darmkanker in deze individuen van groot belang, om aanbevelingen te kunnen doen over de beste manier om darmkanker te voorkomen. Een voorbeeld van hoog-risico individuen zijn overlevenden van teelbalkanker. Diverse retrospectieve cohortstudies hebben aangetoond dat overlevenden van teelbalkanker, met name degenen behandeld met platinum-bevattende chemotherapie (cisplatin), een hoger risico lopen op het ontwikkelen van een secundaire maligniteit later in hun leven, waaronder darmkanker. Deel III van deze scriptie onderzocht de opbrengst van darmkankerscreening in teelbalkanker-overlevenden, evenals de ontstaanswijze van darmkanker in deze hoog-risico individuen.

Deel I – Evaluatie van het bevolkingsonderzoek darmkanker in Nederland

Om de effectiviteit van darmkankerscreeningsprogramma's te beoordelen, worden verschillende indicatoren gebruikt. Deze omvatten verschuiving in de stadiumverdeling, een afname in de darmkanker incidentie, minder invasieve behandeling van screen-gedetecteerde darmkanker, en uiteindelijk een afname in het aantal darmkanker-gerelateerde sterfgevallen. Hoofdstuk 2 onderzocht de effecten van de invoering van het bevolkingsonderzoek darmkanker in Nederland op deze indicatoren. De stadiumverdeling van screen-detecteerde darmkanker was gunstiger (meer stadium I en II) in vergelijking met niet-screen-gedetecteerde darmkanker (67% vs. 46%). Dit wordt ook gezien in verschillende andere Europese landen. Bovendien was er na de introductie van het bevolkingsonderzoek in 2014 een significante afname van de totale en laat-stadium incidentie van darmkanker. Hoofdstuk 3 onderzocht trends in de incidentie van laat-stadium darmkanker na de

gefaseerde invoering van het screeningsprogramma op basis van geboortecohorten. De laat-stadium darmkanker incidentie nam toe in de jaren waarin deze geboortecohorten werden uitgenodigd om deel te nemen aan het bevolkingsonderzoek. Uiteindelijk was in 2019 de laat-stadium darmkanker incidentie lager dan de trend die je zou verwachten als de incidentie van vóór de invoering van screening zich had doorgezet. Dit duidelijke 'golf'-patroon, waarbij later uitgenodigde geboortecohorten deze verandering later in de tijd doormaken dan eerder uitgenodigde geboortecohorten, versterkt het bewijs voor een causaal verband tussen de invoering van het bevolkingsonderzoek darmkanker en de afname van de laat-stadium darmkanker incidentie.

De afname van de darmkanker incidentie, en dan met name de laat-stadium darmkankers en de verschuiving in stadiumverdeling zijn veelbelovend. Theoretisch gezien kunnen deze veranderingen bijdragen aan een afname van het aantal darmkanker-gerelateerde sterfgevallen na de invoering van het bevolkingsonderzoek. Hoofdstuk 2 liet echter nog geen verandering in trend in darmkanker-gerelateerde sterfte zien na de invoering van het bevolkingsonderzoek. Deze afname in trend zou men echter ook niet verwachten tot minstens zeven jaar na de introductie van darmkankerscreening, gezien de doorlooptijd van het naar voren brengen van de diagnose ongeveer twee jaar is, en de gemiddelde overleving van darmkanker minstens vijf jaar is.

Hoofdstuk 2 toonde aan dat de behandeling van screen-gedetecteerde darmkanker minder invasief was dan die van klinisch gedetecteerde darmkanker, en dit patroon gold voor zowel dikke darmkankers (17% vs. 5%) als endeldarmkankers (22% vs. 9%). Zelfs wanneer alleen werd gekeken naar stadium I darmkankers, bleef deze bevinding staan. Daarom werden in hoofdstuk 4 de redenen onderzocht voor het vaker lokaal verwijderen van screen-gedetecteerde stadium I darmkankers in vergelijking met klinisch gedetecteerde stadium I darmkankers. Het hogere percentage T1 kankers binnen de screen-gedetecteerde stadium I kankers is mogelijk een deel van de verklaring voor het vaker lokaal verwijderen van screen-gedetecteerde stadium I kankers in vergelijking met klinisch gedetecteerde stadium I kankers. Bovendien werden screen-gedetecteerde T1 kankers vaker lokaal verwijderd dan niet-screen-gedetecteerde T1 kankers, zelfs na correctie voor risicofactoren zoals lymfovasculaire invasie en tumordifferentiatie. Hoewel de redenen voor het vaker lokaal verwijderen van screen-gedetecteerde stadium I darmkankers (nog) onbekend zijn, kan dit gerelateerd zijn aan kanker-specifieke

factoren of aan de bekwaamheid van de endoscopisten die deze vroege kankers identificeren als geschikt voor lokale verwijdering binnen het bevolkingsonderzoek.

Ten slotte beschrijven hoofdstuk 5 en 6 de korte termijn prestatie-indicatoren van het bevolkingsonderzoek. Hoofdstuk 5 onderzocht het detectiecijfer en de positief voorspellende waarde van het Nederlands bevolkingsonderzoek, waarbij advanced serrated poliepen werden toegevoegd aan de huidige definitie van relevante bevindingen. Bij ongeveer 3% van alle personen met een positieve FIT was ten minste één advanced serrated poliep aanwezig, zonder dat een advanced adenoom of darmkanker werd gevonden. Dit verhoogde de positieve voorspellende waarde van het screeningsprogramma van 41% naar 44%. Hoewel deze cijfers er niet op wijzen dat de opbrengst van het bevolkingsonderzoek met de huidige definitie sterk wordt onderschat, zou het er wel op kunnen wijzen dat de sensitiviteit van FIT voor advanced serrated poliepen laag is. Aangezien advanced serrated poliepen een aanzienlijk deel (~10%-30%) van de voorlopers van darmkanker uitmaken, is verder onderzoek naar nieuwe ontlastingstesten met een hogere sensitiviteit voor deze voorlopers nodig, en zouden advanced serrated poliepen toegevoegd moeten worden aan de huidige definitie van relevante bevindingen. Ten slotte werd in hoofdstuk 6 de intervalkanker incidentie in het bevolkingsonderzoek onderzocht. Een intervalkanker wordt gedefinieerd als darmkanker die wordt vastgesteld na een negatieve FIT en vóór de uitnodiging voor de volgende screeningsronde. De intervalkanker incidentie was laag in zowel de eerste als de tweede screeningronde (beide rond de 10 per 10.000). De intervalkanker incidentie hangt nauw samen met de FIT sensitiviteit, welke hoog was in zowel de eerste (76%) als tweede (79%) ronde.

Deel II – De weg naar gepersonaliseerde darmkankerscreening voor gemiddeld-risico individuen in Nederland

In het bevolkingsonderzoek wordt uniforme screening aangeboden aan de gehele doelgroep, terwijl het risico op darmkanker per individu verschilt. Risicofactoren omvatten onder andere geslacht, leeftijd, familiaire voorgeschiedenis, leefstijl, genetische variatie en screeningsgeschiedenis (met name de f-Hb concentratie). Het gecombineerde effect van deze factoren kan worden gebruikt om gepersonaliseerde risicoschattingen voor individuen te maken en hen een op maat gemaakte screeningsstrategie aan te bieden. Het overkoepelende doel van deze gepersonaliseerde aanpak, in tegenstelling tot een one-size-fits-all aanpak, is om de balans tussen de voor- en nadelen van screening te optimaliseren. Hoewel talrijke

risicovoorspellingsmodellen zijn onderzocht waarin de voorgenoemde risicofactoren zijn meegenomen, is hun diagnostische nauwkeurigheid beperkt. Het opnemen van f-Hb-concentraties in deze voorspellingsmodellen bleek het meest effectief te zijn bij het verbeteren van de nauwkeurigheid van de risicovoorspelling. Dit wordt bevestigd door de resultaten gepresenteerd in hoofdstuk 6, waarbij het risico op intervalkanker na een negatieve FIT groter wordt naarmate de f-Hb-concentratie toeneemt. Individuen met f-Hb-concentraties net onder de grenswaarde van 47 µg Hb/g ontlasting hadden een 17 keer verhoogde kans op het ontwikkelen van een intervalkanker vergeleken met degenen met niet-detecteerbare f-Hb-concentraties in de eerste screeningsronde; dit was een 12 keer verhoogde kans in de tweede screeningsronde. Gezien het goede voorspellend vermogen van eerdere f-Hb-concentraties voor het risico op darmkanker, werd een mixed-methods studie gelanceerd om de effectiviteit, haalbaarheid, aanvaardbaarheid en kosteneffectiviteit van gepersonaliseerde darmkankerscreening op basis van de f-Hb concentratie te onderzoeken. Hoofdstuk 7 van dit proefschrift beschrijft het onderzoeksprotocol van deze studie, genaamd PERFECT-FIT, welke een randomized controlled trial (RCT), focusgroep studies en een kosteneffectiviteitsanalyse inhoudt. De RCT omvatte de werving van 20.000 individuen, waarbij 10.000 werden toegewezen aan de interventiegroep en 10.000 aan de controlegroep. Deelnemers in de interventiegroep krijgen gepersonaliseerde screeningsintervallen toegewezen op basis van hun eerdere f-Hb-concentratie. De RCT is gestart in oktober 2022, en in augustus 2023 zijn alle 20.000 deelnemers succesvol geïncludeerd. Als de resultaten van de RCT aantonen dat gepersonaliseerde screening effectief is, is de acceptatie ervan door de doelgroep een ongelooflijk belangrijk onderdeel van de uiteindelijke implementatie ervan. Daarom verkende hoofdstuk 8 de informatiebehoefte van individuen op gepersonaliseerde darmkankerscreening in een focusgroep studie. Deze studie toonde aan dat personen verschillende informatievoorkeuren hebben als het gaat om het communiceren van een individueel risico op basis van f-Hb-concentraties. Ook was er een verschil in behoefte aan communicatiestrategieën bij de implementatie van gepersonaliseerde screeningsprogramma's. Kortom, hoewel gepersonaliseerde darmkankerscreening zeer veelbelovend lijkt voor het verder verbeteren van de balans tussen de voor- en nadelen van darmkankerscreening, blijven er uitdagingen. Deze omvatten onder andere effectieve communicatie tussen alle belanghebbenden, communicatie naar de doelgroep, en de aanvaardbaarheid van deze strategieën in de doelgroep.

Deel III – Darmkanker bij teelbalkanker-overlevenden behandeld met platinum-bevattende chemotherapie

De gepersonaliseerde aanpak voor darmkankerscreening zoals hierboven beschreven kan ook worden toegepast bij hoog-risico individuen. Onder deze hoog-risicogroepen vallen onder andere teelbalkanker-overlevenden. Uit een grootschalige epidemiologische studie blijkt namelijk dat het risico op het ontwikkelen van darmkanker bij teelbalkanker-overlevenden behandeld met platinum-bevattende chemotherapie (o.a. cisplatin) vier keer hoger is dan bij ex-patiënten die niet met deze chemotherapie zijn behandeld. Hieruit kan worden afgeleid dat teelbalkanker-overlevenden misschien eerder darmkankerscreening aangeboden zouden moeten krijgen, in plaats van te wachten tot ze op 55-jarige leeftijd worden uitgenodigd voor het bevolkingsonderzoek. Daarnaast is het vergaren van kennis over hoe darmkanker zich ontwikkelt bij teelbalkanker-overlevenden belangrijk voor het verder ontwikkelen van richtlijnen voor follow-up en diagnostiek bij deze individuen.

In hoofdstuk 10 werd de opbrengst van coloscopie bij teelbalkanker-overlevenden behandeld met platinum-bevattende chemotherapie onderzocht. De prevalentie van (advanced) neoplasie bij teelbalkanker-overlevenden was hoger dan bij een controlegroep van Amerikaanse mannen van dezelfde leeftijd met een gemiddeld risico op darmkanker. De propensity score matching analyse toonde een significant verschil in prevalentie van advanced neoplasie bij teelbalkanker-overlevenden (9%) in vergelijking met de controlegroep (2%). Hoewel de prevalentie van advanced neoplasie significant hoger was bij teelbalkanker-overlevenden dan in de controlegroep, zijn er geen darmkankers gevonden in deze studie. Daarom zijn aanvullende kosteneffectiviteitsstudies nodig om te bepalen of de hogere opbrengst van advanced neoplasie bij teelbalkanker-overlevenden het aanbieden van (coloscopie) screening rechtvaardigt, en op welke leeftijd deze zou moeten beginnen. Hoofdstuk 9 toonde aan dat darmkanker met fouten in het reparatiesysteem (mismatch repair deficiëntie) bij teelbalkanker-overlevenden vaker voorkomt dan in een cohort van mannen met een gemiddeld risico op primaire darmkanker uit de algemene bevolking. Blootstelling aan kankerbehandelingen lijkt verband te houden met het voorkomen van deze zeldzame somatische dubbel-hit mismatch repair deficiënte darmkankers bij teelbalkanker-overlevenden. Ten slotte onderzocht hoofdstuk 11 gemeten platinum-concentraties in het bloedplasma, urine, en normaal darmslijmvlies van teelbalkanker-overlevenden behandeld met

cisplatin. De resultaten lieten aantoonbare concentraties van platinum zien bij met cisplatin behandelde teelbalkanker-overlevenden in alle weefsels, zelfs 40 jaar na behandeling; de concentraties waren significant hoger dan in weefsels van de controlemonsters. De concentraties waren hoger kort na de behandeling en namen af in de loop van de tijd, maar bleven boven de detectielimieten. De retentie van platinum kan het risico op secundaire maligniteiten bij kankeroverlevenden verhogen door het induceren van somatische mutaties. Dit mechanisme kan mogelijk bijdragen aan het verhoogde risico op secundaire maligniteiten en darmkanker bij teelbalkanker-overlevenden. Het monitoren van de lange termijn effecten van de retentie van platinum is cruciaal voor het begrijpen van de ontstaanswijze van tweede (darm)kankers en het opstellen van richtlijnen voor vroege detectie van (gastro-intestinale) secundaire maligniteiten bij kankeroverlevenden.

LIST OF PUBLICATIONS

Publications related to this thesis

ECH Breekveldt, I Lansdorp-Vogelaar, E Toes-Zoutendijk, MCW Spaander, AJ van Vuuren, FJ van Kemenade, CRB Ramakers, E Dekker, ID Nagtegaal, MF Krul, NFM Kok, KFD Kuhlmann, GR Vink, ME van Leerdam, MAG Elferink, on behalf of the Dutch National Colorectal Cancer Screening Working Group. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. *Lancet Gastroenterol Hepatol*. 2022;7(1):60-68.

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DEFWM van Toledo, **ECH Breekveldt,** JEG IJspeert, AJ van Vuuren, FJ van Kemenade, CRB Ramakers, ID Nagtegaal, ME van Leerdam, MCW Spaander, I Lansdorp-Vogelaar, E Toes-Zoutendijk, and E Dekker. Advanced serrated polyps as a target of screening: detection rate and positive predictive value within a fecal immunochemical test-based colorectal cancer screening population. *Endoscopy*. 2023;55(6):526-534.

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RGS Meester, HJ van de Schootbrugge-Vandermeer, **ECH Breekveldt**, L de Jonge, E Toes-Zoutendijk, A Kooyker, D Nieboer, CR Ramakers, MCW Spaander, AJ van Vuuren, EJ Kuipers, FJ van Kemenade, ID Nagtegaal, E Dekker, ME van Leerdam, I and Lansdorp-Vogelaar; Dutch colorectal cancer screening working group. Faecal occult blood loss accurately predicts future detection of colorectal cancer. A prognostic model. *Gut*. 2023;72(1):101-108.

L van der Schee L, KJC Haasnoot, SG Elias, KM Gijsbers, YA Alderlieste, Y Backes, AM van Berkel, F Boersma, F Ter Borg, **ECH Breekveldt**, K Kessels, M Koopman, I Lansdorp-Vogelaar, ME van Leerdam, G Rasschaert, RM Schreuder, RWM Schrauwen, TCJ Seerden, MBW Spanier, JS Terhaar Sive Droste, E Toes-Zoutendijk, JB Tuynman, GR Vink, WH de Vos Tot Nederveen Cappel, FP Vleggaar, MM Laclé, and LMG Moons. Oncologic outcomes of screen-detected and non-screen-detected T1 colorectal cancers. *Endoscopy*. Published online March 13, 2024.

PHD PORTFOLIO

COURSES, SEMINARS, WORKSHOPS AND MASTER CLASSES	YEAR	ECTS
Biostatistical methods I	2020	5.7
Ethics and integrity in science	2021	2
Planning and evaluation of screening	2021	1.4
Systematic literature retrieval	2021	
Scientific writing course	2021	
Medical statistics with R	2021	1.5
Basiscursus regelgeving en organisatie voor klinisch onderzoekers	2021	2
How to write research papers	2021	1
Basic oncology course	2022	2
Being able to influence yourself positively	2022	0.3
Histopathology of human tumors	2022	0.6
Knowledge gaps in intestinal cancer	2022	1.5

PRESENTATIONS	YEAR	ECTS
Oral presentation, Digestive Disease Week, online	2021	0.5
Oral presentation, European Society of Gastrointestinal Endoscopy Days, online	2021	0.5
Poster presentation, United European Gastroenterology Week, online	2021	0.5
Oral presentation, Digestive Disease Week, San Diego	2022	0.5
Poster presentation, OOA retreat, Amstelveen	2022	
Oral presentation, chirurgendagen, Antoni van Leeuwenhoek Ziekenhuis	2022	0.5
Oral presentation, Digestive Disease Days, online	2022	0.5
E-poster, United European Gastroenterology Week, Copenhagen	2023	0.25

(INTER)NATIONAL CONFERENCES	YEAR	ECTS
World Endoscopy Organization, online	2020-2022	0.5
Oncology graduate school retreat, Amstelveen	2022	2
Digestive disease days, Veldhoven	2022	0.25
World Endoscopy Organization, San Diego	2022	0.1
United European Gastroenterology Week, Copenhagen	2023	0.1
World Endoscopy Organization, Copenhagen	2023	0.1

OTHER MEETINGS	YEAR	ECTS
OOA annual supervisory committee meeting (2x)	2020-2022	1
Research meetings/journal clubs/seminars	2020-2023	5
Landelijke Evaluatie team voor Colorectaal kanker bevolkingsonderzoek meetings	2020-2023	0.5
Screen section meetings	2020-2023	0.5

OTHER RELEVANT ACTIVITIES	YEAR	ECTS
Commissielid/bestuurslid De Jonge Dokter	2021-2023	5
Supervision community project BSc Medicine students	2021	1
Revising bachelor essays BSc Medicine students	2021	0.7

DANKWOORD

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CURRICULUM VITAE

Emilie Christine Henriëtte Breekveldt was born in Santpoort-Noord, the Netherlands, on December 30, 1993. After completing her secondary education the Stedelijk Gymnasium Haarlem, she started her medical education at the Vrije Universiteit Amsterdam in 2012. Emilie completed her bachelor's degree in medicine in 2017, during which she employed several extracurricular activities in the students' sailing association A.S.Z.V. Orionis, including one year as president of the board. During her master's degree, she did a research internship at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Ziekenhuis on prognostic factors in gastroenteropancreatic neuroendocrine tumors, where her fascination with gastrointestinal oncology originated. Emilie received her medical degree in 2020 during the COVID pandemic. After her graduation, she started her PhD trajectory at the Department of Public Health at Erasmus MC University Medical Center and at the Department of Gastrointestinal Oncology at the Netherlands Cancer Institute, under supervision of prof. dr. Monique van Leerdam, prof. dr. Iris Lansdorp-Vogelaar, and dr. Esther Toes-Zoutendijk. This trajectory allowed her to combine working with large national databases, maintaining patient contact, and exploring translational research. Her research focused on colorectal cancer screening for average- and high-risk individuals. In November 2023, she started as resident not in training at the department of Internal Medicine at the Meander Medisch Centrum in Amersfoort.