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

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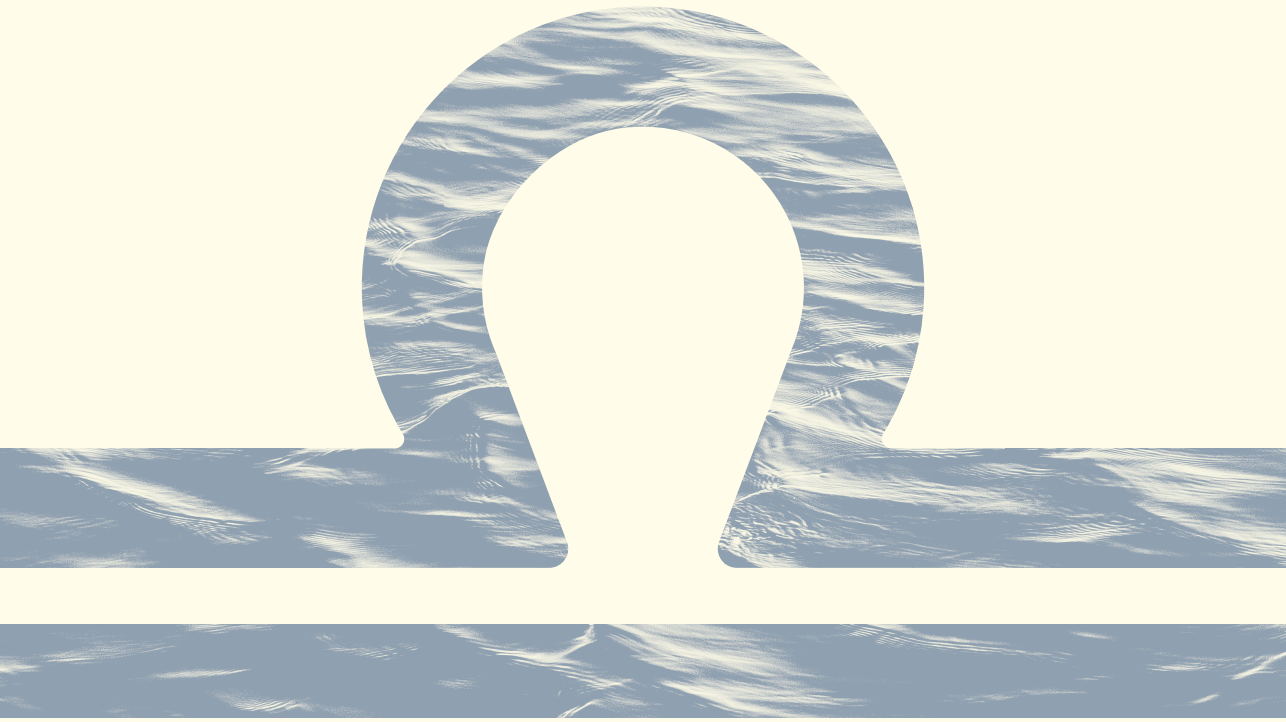

Chapter 12

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.

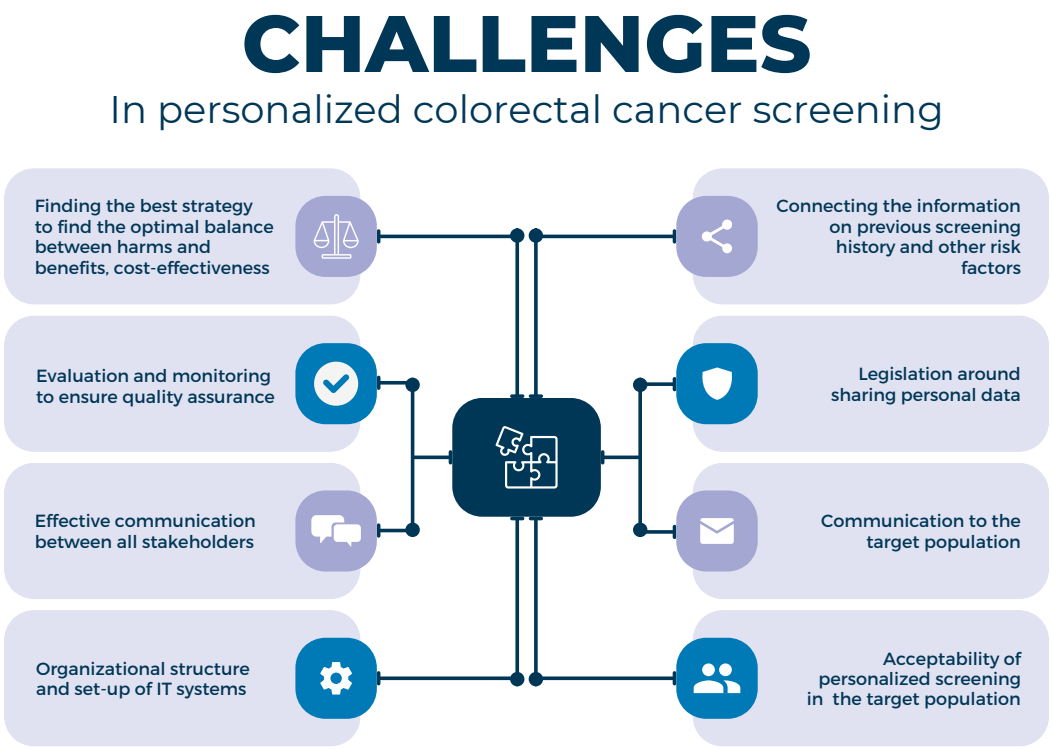

Figure 1 - Challenges in the implementation of personalized colorectal cancer screening

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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