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

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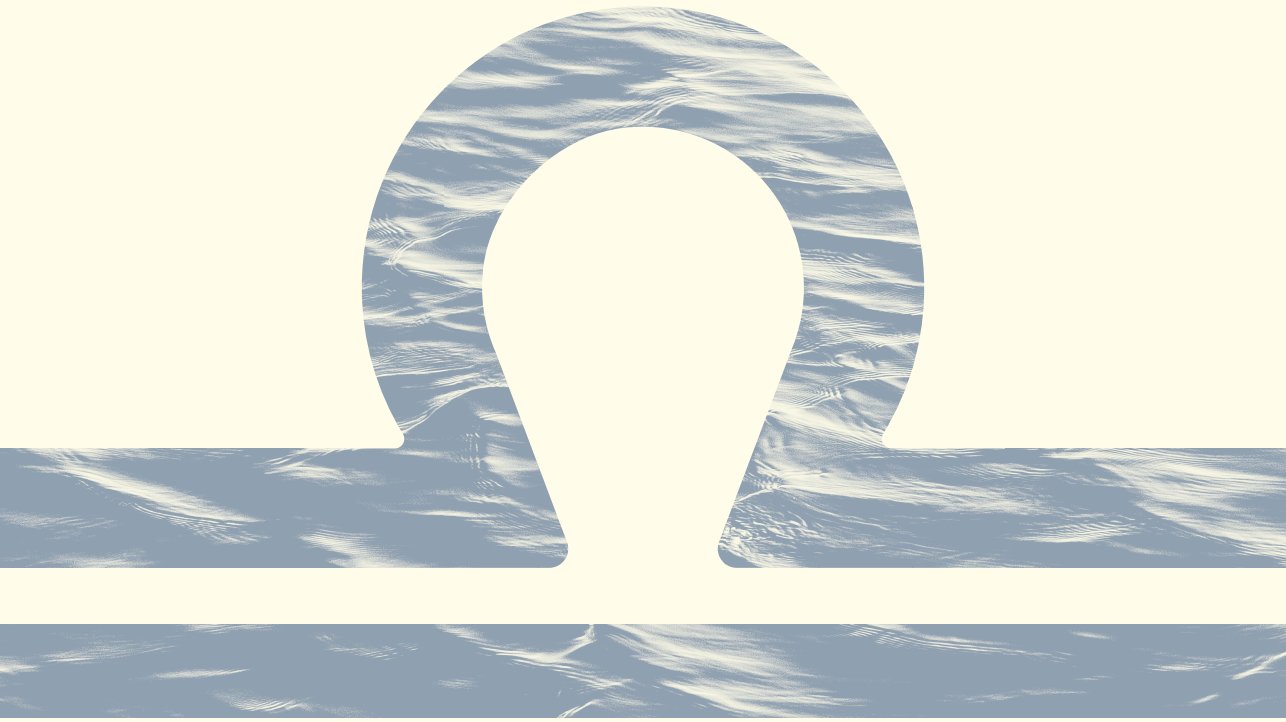
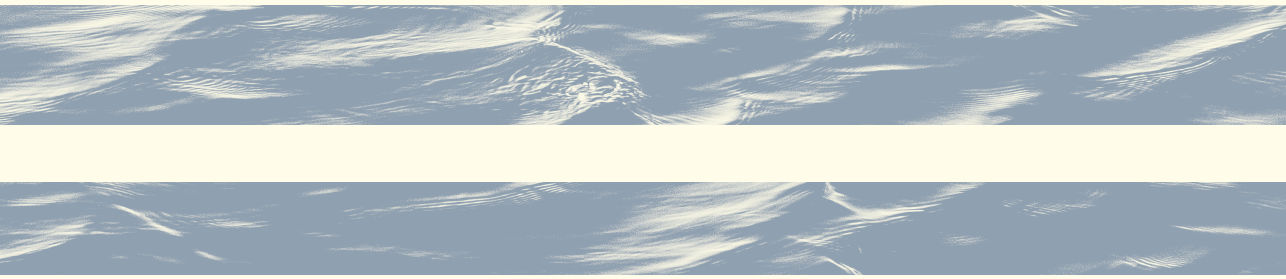


Appendices



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.