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

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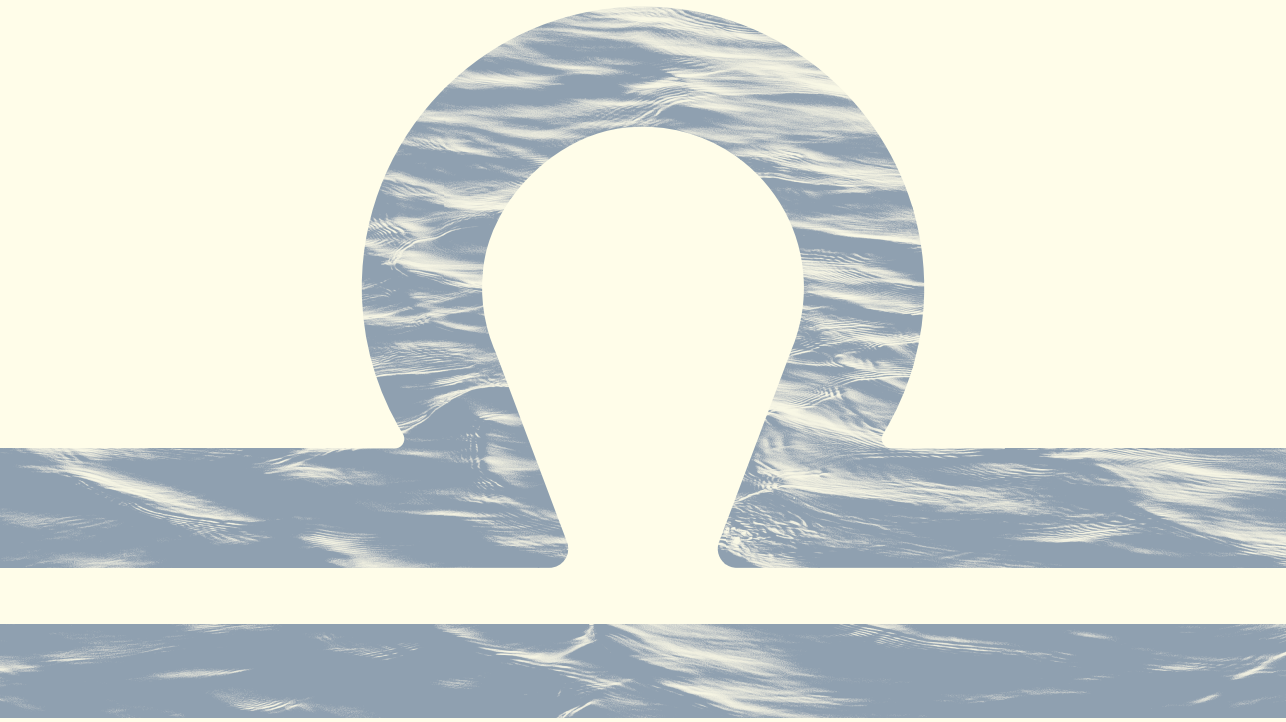

Chapter 1

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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