Introduction and outline of the thesis

INTRODUCTION

Colorectal cancer (CRC) is an important health problem; it is the third most common cancer in men and second in women globally.[1] In Europe, CRC is the most common cause of cancer death after lung cancer.[2] Age is a major risk factor for the development of CRC, with the majority of patients with sporadic cancer being > 50 years of age.[3] Other common risk factors include a first-degree relative with CRC and excess body weight.[4, 5]

The lifetime risk of developing colorectal cancer in many regions is around 5%. Over the past years, treatment modalities have largely improved, but still 40-50% of patients with symptomatic CRC eventually die of metastatic disease.[6] These treatment advancements have been accompanied by increased treatment costs. In the United States, colorectal cancer was estimated to be the second highest cancer site with highest national cost of cancer care in 2010, with approximately 14.14 billion dollar.[7] For patients with non-metastasized CRC, surgery is the main curative treatment, which has been associated with appreciable morbidity and mortality rates.[8] Most CRCs develop from an adenoma, the preclinical precursor of CRC.[9] However, only a minority of adenomas ultimately progress to CRC. The transition from early adenoma to invasive colorectal cancer takes years.[10] These characteristics of CRC make CRC particularly suitable for screening.[11, 12]

Screening for colorectal cancer

In recent years, more than 50 countries have implemented population CRC screening.[13] It has been demonstrated that CRC screening reduces both CRC-related mortality and incidence.[12, 14-20] Screening aims to lower the burden of cancer by detecting the disease at an early, preclinical stage.[12, 14, 17, 21]

There are several CRC screening methods available, which vary in the level of supporting evidence, effectiveness, invasiveness, and uptake. Currently CRC screening programs are either based on direct endoscopic visualization of the colon (colonoscopy or flexible sigmoidoscopy) or use fecal occult blood testing (FOBT) as primary screening method. In the latter form of CRC screening, colonoscopy is offered in case of a positive test.

Fecal occult blood testing

Two types of fecal occult blood testing for CRC screening are available: guaiac fecal occult blood testing (gFOBT) and fecal immunochemical testing (FIT). Randomized controlled trials have shown that screening with gFOBT is associated with a 15%-33% decrease in CRC-related mortality rates.[15, 16, 22] Worldwide, FIT is now rapidly replacing gFOBT, as FIT has been shown to be more sensitive for the detection of both CRCs and it's precursors than gFOBT.[23, 24] Fecal immunochemical tests detect human-specific globin of blood, whereas guaiac fecal occult blood tests react with heme, including consumed non-human

heme. Other advantages of FIT over gFOBT include that these tests are easier to handle, which leads to higher participation and allow for single stool testing.[25, 26] They also allow automated handling and may provide quantitative test results. Consequently, the positivity cut-off is adjustable to match available colonoscopy resources.[25, 26]

Due to these advantages of FIT over gFOBT, the European guidelines recommend the quantitative immunochemical tests as test of choice for population CRC screening.[27] More than 50 FIT brands are widely available.[28] However, only few data are available on differences between FIT-brands in screening effectivity to detect advanced neoplasia (AN). FIT brands vary in sampling tubes and buffer volumes, resulting in different fecal hemoglobin measurements that are incomparable.[29, 30]

Current status in The Netherlands

In the Netherlands, a nationwide FIT-based CRC screening program has been gradually implemented from January 2014 onwards. Individuals, aged 55-75 years, are biannually invited to perform a single test, followed by subsequent colonoscopy in case of a positive test. It was decided to start screening with the FOB-Gold (Sentinel, Italy) through a national tender. To match available colonoscopy resources, the positivity cut-off used was increased from 15 to 47 µg hemoglobin per gram feces halfway 2014.[31]

The European guidelines indicate that a screening program should assess individual device characteristics, including accuracy, ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability.[27]

AIMS OF THE THESIS

The aims of this thesis are to compare different fecal occult blood tests for CRC screening and to explore tailored FIT-based screening strategies.

Outlines of the thesis

Interval cancer rate is a key quality indicator in screening programs. Since data on the incidence rate of interval cancers following negative occult stool tests were limited, we performed a systematic literature search and meta-analysis to determine the pooled incidence rates of interval cancers following a negative gFOBT and FIT in **Chapter 2**. In this chapter, we also assessed how these two types of tests compare with regard to interval cancer incidence. In **Chapter 3**, we assess the accuracy of two FIT assays in detecting advanced neoplasia in the Dutch CRC screening program. For this large population-based study, we use a paired design, in which both tests are compared within the same individual and sampled from the same stool. Such design minimizes the risk of confounding factors and increases the applicability of the study results to CRC screening programs worldwide.

To facilitate further informed decision-making on implementing one of both tests for a CRC screening program, we assessed participation rates and ease of use of the tests in **Chapter 4.**

Furthermore, we compare the accuracy of the two FIT assays in detecting advanced neoplasia across various test positivity cut-offs in **Chapter 5**.

Second, we explore tailored CRC screening strategies with FIT. Potential factors of use for tailored or personalized screening may include sex, age, family history, genetic and environmental factors, lifestyle, fecal hemoglobin levels detected (over time) and multiple sample screening. In **Chapter 6**, we assess the diagnostic yield of two-sample screening and provide information for the decision-making on how to deal with two discordant FIT results. We further analyze positivity rates and detection rates of advanced neoplasia across age categories in **Chapter 7**, and assess how these relate to the positive predictive values and colonoscopy demand at multiple test positivity cut-offs. Finally, we illustrate the effect of gender-tailored FIT screening in **Chapter 8.**

The impact of CRC screening as well as the balance between screening burden and benefits strongly depends on the quality of colonoscopy. Besides quality, safety of the endoscopic procedure and patient satisfaction are important outcome parameters for a screening program. In the final chapter of the thesis, **Chapter 9,** we describe the requirements for accrediting screening centers as well as individual endoscopists in a CRC screening program.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.
2. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
3. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. Nat Rev Dis Primers. 2015;1:15065.
4. Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. BMJ. 2012;345:e8076.
5. Brandstedt J, Wangefjord S, Nodin B, Gaber A, Manjer J, Jirstrom K. Gender, anthropometric factors and risk of colorectal cancer with particular reference to tumour location and TNM stage: a cohort study. Biol Sex Differ. 2012;3(1):23.
6. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917.
7. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103(2):117-28.
8. Rabeneck L, Paszat LF, Hilsden RJ, Saskin R, Leddin D, Grunfeld E, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology. 2008;135(6):1899-906, 906 e1.
9. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. Gastroenterology. 1987;93(5):1009-13.
10. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. Gut. 2007;56(11):1585-89.
11. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease] Principios y metodos del examen colectivo para identificar enfermedades. Bol Oficina Sanit Panam. 1968;65(4):281-393.
12. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977-81.
13. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637–49.
14. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366(8):687-96.
15. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472-77.
16. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365-71.
17. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007(1):CD001216.

18. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut. 2002;50(1):29-32.
19. Zorzi M, Fedeli U, Schievano E, Bovo E, Guzzinati S, Baracco S, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 2015;64(5):784-90.
20. Holme O, Loberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. 2014;312(6):606-15.
21. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624-33.
22. Kronborg O, Fenger C, Olsen J, Jørgensen OD. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467-71.
23. Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JC, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer. 2009;100(7):1103-10.
24. Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. Gut. 2015;64(8):1327-37.
25. Kuipers EJ, Spaander MC. Colorectal Cancer Screening by Colonoscopy, CT-Colonography, or Fecal Immunochemical Test. J Natl Cancer Inst. 2016;108(2):djv383.
26. Kuipers EJ, Rosch T, Bretthauer M. Colorectal cancer screening--optimizing current strategies and new directions. Nat Rev Clin Oncol. 2013;10(3):130-42.
27. Halloran SP, Launoy G, Zappa M, International Agency for Research on C. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Faecal occult blood testing. Endoscopy. 2012;44 Suppl 3:SE65-87.
28. Daly JM, Xu Y, Levy BT. Which Fecal Immunochemical Test Should I Choose? J Prim Care Community Health. 2017;8(4):264-77.
29. Grobbee EJ, van der Vlugt M, van Vuuren AJ, Stroobants AK, Mundt MW, Spijker WJ, et al. A randomised comparison of two faecal immunochemical tests in population-based colorectal cancer screening. Gut. 2017;66(11):1975-82.
30. Chiang TH, Chuang SL, Chen SL, Chiu HM, Yen AM, Chiu SY, et al. Difference in performance of fecal immunochemical tests with the same hemoglobin cutoff concentration in a nationwide colorectal cancer screening program. Gastroenterology. 2014;147(6):1317-26.
31. Toes-Zoutendijk E, van Leerdam ME, Dekker E, van Hees F, Penning C, Nagtegaal I, et al. Real-Time Monitoring of Results During First Year of Dutch Colorectal Cancer Screening Program and Optimization by Altering Fecal Immunochemical Test Cut-off Levels. Gastroenterology. 2017;152(4):767-75.e2.