General discussion and future perspectives

SUMMARY

The aims of this thesis were to compare different fecal occult blood tests for colorectal cancer screening and to explore tailored FIT-based screening strategies. We assessed the incidence of interval cancers after a negative guaiac fecal occult blood test and a negative fecal immunochemical test. Second, two different fecal immunochemical test assays were compared with regard to detection of advanced neoplasia, participation rate, and ease of use. Next, tailored screening strategies were explored using fecal immunochemical tests. Finally, requirements for accrediting screening centers as well as individual endoscopists in a colorectal cancer screening program were described.

Colorectal cancer (CRC) is particularly suitable for screening and, in recent years, more CRC screening has been implemented worldwide.[1-3] Currently offered CRC screening programs can be divided in either invasive screening methods, such as colonoscopy or flexible sigmoidoscopy, or non-invasive methods, including fecal occult blood testing (FOBT).

Fecal occult blood testing for colorectal cancer screening

Two types of fecal occult blood testing have been widely available for CRC screening: guaiac fecal occult blood testing (gFOBT) and fecal immunochemical testing (FIT). gFOBT has been the most commonly used stool screening method for years. However, gFOBT has been rapidly replaced by FIT, as FIT has been shown to be more sensitive for the detection of CRC as well as its precursors than gFOBT. FIT also allows for single stool testing, is easier to handle, is associated with higher uptake and may provide quantitative test results.[4-8] The latter characteristic enables to adjust the positivity cut-off to match available resources. However, data on the incidence rate of test-related interval cancers were limited. And, although interval cancer rate is considered a key quality indicator in screening programs, no data were available on how gFOBT and FIT compare with regard to these interval cancers incidence rates. In **Chapter 2** we performed a systematic literature search and meta-analysis to determine and compare the incidence rates of test-related interval colorectal cancers of gFOBT and FIT in population-based CRC screening programs. We found that the incidence of interval cancer after a negative gFOBT was higher than after a negative FIT. We also found that for every FIT interval cancer, 2.6 colorectal cancers were detected; for gFOBT the ratio between interval and detected colorectal cancers was 1:1.2. Although high heterogeneity was shown among studies included in this meta-analysis, and although included FIT studies were generally based on low positivity cut-offs, the study results favor the use of FIT over gFOBT as screening test for CRC. The outcomes further help to adequately inform screenees about the risk of interval cancers after a negative fecal occult blood test.

From January 2014 onwards, a nationwide FIT-based CRC screening program has been gradually rolled out in the Netherlands using the FOB-Gold (Sentinel, Italy). However, previous research in The Netherlands was done using the OC-Sensor (Eiken, Japan). Head-to-head comparisons with enough power to determine if these tests were equivalent in detecting advanced neoplasia were not available. We conducted two large prospective population-based studies within the Dutch CRC screening program to compare these two FIT assays on multiple outcomes. In **Chapter 3**, we demonstrated equivalence between the two FIT assays in detection of advanced neoplasia in a large prospective paired accuracy study at a positivity cut-off level of ≥15 µg Hb/g feces. The paired study also serves as an example for how to assess and possibly improve screening effectiveness within an ongoing program. In **Chapter 4**, we compared participation rates and ease

of use of FOB-Gold and OC-sensor within the Dutch CRC screening program. Screening invitees were asked to complete both OC-sensor and FOB-Gold and assess ease of use and preference of FIT brand by questionnaire. In parallel, we compared participation rates in a randomized trial and assessed the proportions of non-analyzable tests. This study found small, but statistically significant, differences in ease of use in favor of FOB-Gold. Most participants did not express a preference for either FIT. Those that did, preferred FOB-Gold over OC sensor. Despite these differences, our randomized trial showed that participation in the Dutch population based CRC screening program was not influenced by the type of FIT offered. Furthermore, non-analyzable test proportions were small (0.1% versus 0.4%), and we found no differences in non-analyzability between the tests. As these two large prospective population-based studies show that detection rates of advanced neoplasia are equivalent and participation rates similar, other features may guide decision-making for selecting a FIT in a CRC screening program.

We also estimated how these two FIT assays compare in detecting advanced neoplasia at different test positivity cut-offs in **Chapter 5**. FIT assays vary in analytical performance due to a range of factors, including anti-heme antibody characteristics and assay optimization, buffer composition and volume and sample tube design. These differences influence the measured fecal hemoglobin concentration, FIT positivity rate, error rates, and capacity to detect AN.[9, 10] The two widely used FITs had significantly different distributions of reported hemoglobin concentration and yielded different positivity rates at equal thresholds. However, they performed similarly in detecting advanced neoplasia at a similar positivity rate. When comparing and implementing these FIT assays in a screening program, the desired positivity rate that identifies participants to be referred for colonoscopy should first be set, guided by available resources and feasibility.

Tailored colorectal cancer screening strategies

Next, we explored tailored CRC screening strategies with FIT. Tailored screening strategies that we explored included two-sample FIT screening, the use of different positivity cut-offs, and tailored screening based on age categories and gender.

In **Chapter 6**, we assessed the number of advanced neoplasia detected by two-sample screening with FIT assays taken from the same bowel movement. We found that the proportion of participants with discordant FIT results almost equaled the proportion of those with two positive tests, while a generally low positivity cut-off was used. Given the high rate of advanced neoplasia detection in this group with two discordant test results (27%), colonoscopy should strongly be considered in case a screenee has one positive FIT. The findings did however not particularly favor two-sample over one-sample FIT

screening. When screening strategies are considered that improve advanced neoplasia detection rates, drop in specificity should be taken into account.

When facing limited colonoscopy resources, various FIT-based screening strategies are optional. We calculated if increasing the positivity cut-off and screening age affects colonoscopy yield, missed lesions, and colonoscopy demand in **Chapter 7**. In a population-based CRC screening cohort, we found that FIT positivity rates, detection rates and the positive predictive value to detect advanced neoplasia all increase with age. Both increasing the screening starting age and increasing the positivity cut-off resulted in a substantial reduction in colonoscopy demand, at the cost of a similar number of advanced neoplasia missed.

We illustrated the effects of gender-tailored screening in **Chapter 8** and assessed the effects on miss rates of advanced neoplasia. We showed that in absolute numbers more advanced neoplasia are detected and missed in men than in women at all positivity cut-offs. Gender based positivity cut-offs could level sensitivity for both men and women by using a lower cut-off in women, or level the amount of lesions missed when using a lower cut-off in men.

Depending on the desired aim of CRC screening policy-makers, tailored screening strategies are optional. When colonoscopy resources are limited, tailored screening based on age categories, gender and FIT positivity cut-off are all considerable options.

Screening endoscopists and the endoscopy service

Population-based screening for CRC and precursor lesions can be effective provided that services and colonoscopy are of high quality.[11] Therefore, the European Union recommends to use evidence-based methods with quality assurance of the entire screening process.[12] Screening enables known finite health gains, but also potential harms. Therefore, quality assurance of screening services and endoscopists is of utmost importance. The review of **Chapter 9** describes the requirements for accrediting screening centers as well as individual endoscopists in a CRC screening program.

Future Perspectives

Worldwide, CRC screening programs have been implemented over the past years.[3] However, improvements regarding the quality and accuracy of CRC screening programs and optimization of screening strategies can still be made. Besides, the optimal screening strategy may not be similar for different demographic areas, due to differences in the screening population, insurance systems and access to health care systems. Also, these aspects may change over time. Therefore, continuous evaluation of new strategies

to optimize screening program effectiveness and reduce possible harms is crucial to guarantee screening quality, and should be performed on a routine basis.[13]

In Europe, the quantitative immunochemical tests are recommended as test of choice for population CRC screening.[6] However, more than 50 FIT brands are widely available.[14] In this thesis, we compared two FIT brands and their ability to detect advanced neoplasia, participation rates, and ease of use. Although literature is available on other FIT brands, more research is required. Also, many other features should be compared including cost-effectivity, ease of use for laboratory staff or other stakeholders involved in FIT analysis, suitability for transport, keeping quality of the tubes, analyzer features, capacity, speed, analytical performance, sample stability, easy of handling, safety during postage and labeling. Depending on context and setting, more studies are warranted to evaluate these other aspects of FIT.

One should realize that CRC screening using FIT is far from optimal. A meta-analysis showed that, at generally used test positivity cut-offs, the pooled sensitivity and specificity of FIT for CRC were 0.79 and 0.94, respectively. The perfect screening test has a sensitivity and specificity of 1.0. In addition, we found in our meta-analysis that for every CRC missed by FIT, 2.6 CRCs were detected. Potential new screening targets include CRC-specific proteins, fecal deoxyribonucleic acid (DNA) or detection by odor material.[11, 15, 16] However, none of these alternative screening tests have proven to be superior to FIT or direct colonoscopy so far.

An important feature in screening is uptake of the test. A screening test or series of tests must be acceptable for the population.[1] As others have stated, "the best screening test, is the test that gets done, and gets done well".[17] Still much can be improved with regard to reaching high-risk groups for CRC screening. A recent study even argued that greater benefit, at lower cost, could be achieved by increasing participation rates for unscreened older and higher-risk persons than lowering the screening starting age to 45 years.[18]

Finally, future research can focus on surveillance strategies for patients after polyp removal. Current guidelines recommend frequent surveillance colonoscopies for patients after polyp removal, which contributes to a significant burden of colonoscopy demand.[19-22] Currently, there is a lack in evidence of clinical trials on optimal surveillance colonoscopy strategies. The upcoming European Polyp Surveillance (EPoS) study results may contribute to more evidence-based knowledge on this topic.[23]

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