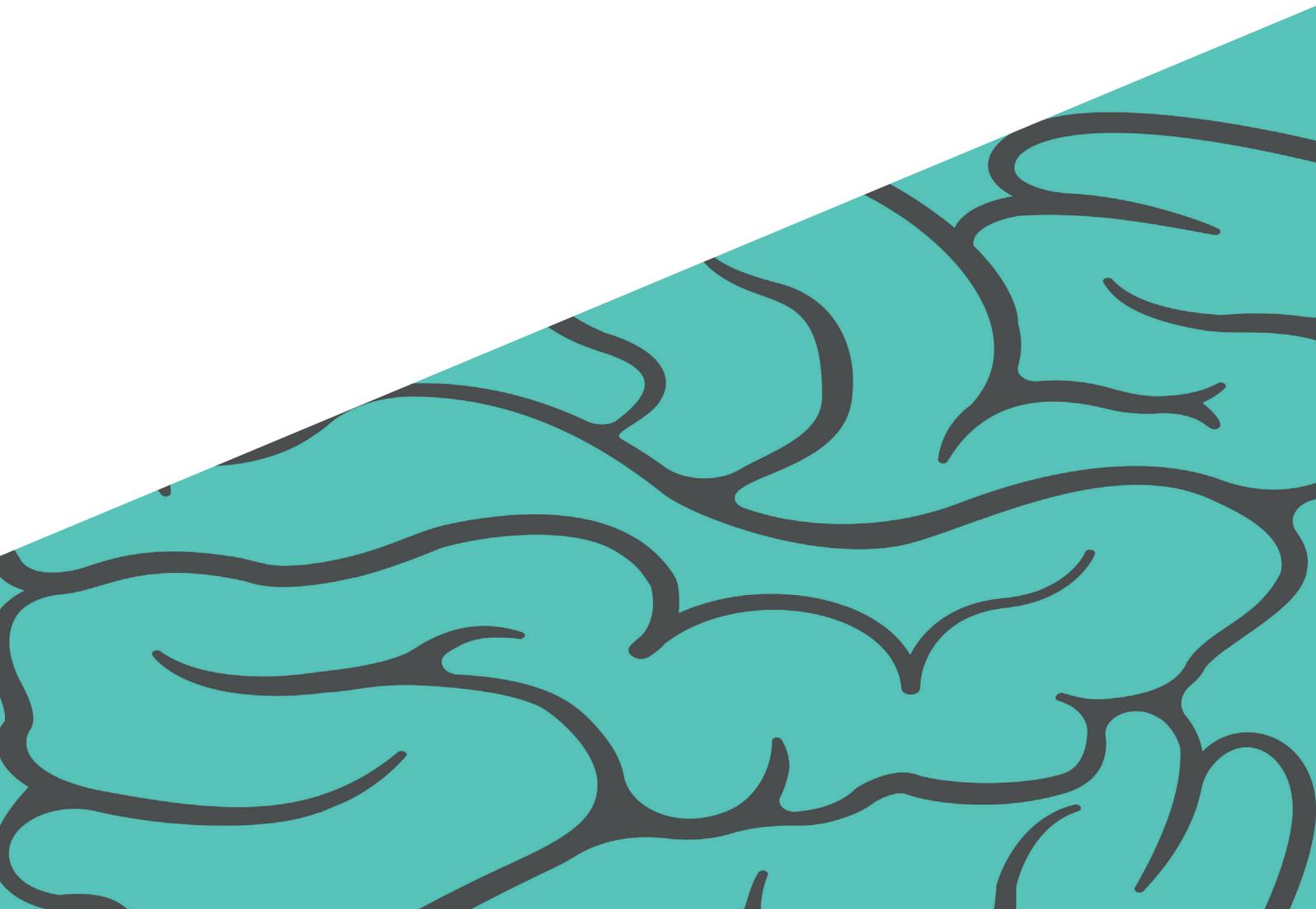


# 7

## Summarizing discussion



The research presented in this thesis aimed to gain insight into the expected impact of the recently implemented Dutch fecal immunochemical test (FIT) -based CRC screening program. To this end, we developed a colorectal cancer (CRC) screening model that included both the adenoma-carcinoma pathway and serrated pathway to CRC. With this model, we assessed the long-term impact of the Dutch screening program on CRC incidence and mortality as well as colonoscopy demand. We also assessed the potential threat of screening fatigue on program effectiveness. Furthermore, we explored opportunities to optimize the Dutch screening program such as alternative screening tests and changes to the surveillance program. This chapter will summarize and discuss the main findings of this thesis. Furthermore, implications of these findings will be addressed and the balance between screening benefit and burden will be discussed. We will end with future perspectives on (CRC) screening.

### **KEY MESSAGES OF THIS THESIS**

In order to evaluate the impact of the Dutch CRC screening program, we developed a mathematical model that simulates the natural history of CRC. In **Chapter 2** we described the structure, parameterization and calibration of the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model. This model includes both the adenoma-carcinoma pathway as well as the serrated pathway to CRC. As this is the first model to acknowledge the malignant potential of serrated lesions, it provides the unique opportunity to assess the impact of assumptions regarding the serrated pathway on model predictions of screening benefit and burden.

### **Long-term impact and possible threats**

In **Chapter 3**, we evaluated the long-term impact of the Dutch CRC screening program on CRC incidence and mortality as well as colonoscopy demand using the ASCCA model. Thirty years of screening in an aging population is predicted to reduce CRC incidence and mortality rates with respectively 35% and 47% compared to no screening. To achieve these reductions, considerable colonoscopy resources are required. Due to the phased implementation, the colonoscopy demand will rise gradually. When the programme is fully implemented and a more or less stable situation is achieved, the number of yearly colonoscopies is predicted to have increased by 60% compared to the situation before implementation of the screening program. In addition, we assessed the impact of including the serrated pathway to CRC on these predictions. If serrated lesions are neither detected nor treated at colonoscopy, and/or if CRCs arising from serrated lesions have substantially lower survival rates than those arising from adenomas, model-predicted screening effectiveness would be substantially lower compared to predictions based on the adenoma-carcinoma pathway only. Since the malignant potential of serrated lesions is acknowledged in clinical practice and as a consequence, serrated lesions are normally removed upon detection, model predictions based on the adenoma-carcinoma pathway only are likely to be comparable to those including both pathways. Nevertheless, predictions of screening effectiveness are preferably based on both the adenoma-carcinoma pathway and the serrated pathway to transparently describe the impact of uncertainties regarding the serrated pathway on model predictions.

Our long-term predictions of screening effectiveness were based on realistic FIT participation rates, derived from a Dutch pilot concerning three screening rounds.<sup>1</sup> Since no studies have assessed FIT participation in four or more screening rounds, we extrapolated participation rates as reported for this three-round study to an 11-round screening program. However, such a large number of screening invitations may lead to screening fatigue, i.e. a loss of motivation to participate in

screening because of a false perception of decreased CRC risk after several negative test outcomes.<sup>2</sup> Especially in FIT screening, this could affect program effectiveness since repeated participation is required to achieve reasonable FIT sensitivity for CRC and its precursor lesions. In **Chapter 4**, we assessed the potential threat of screening fatigue, i.e. a decrease in participation after several negative test outcomes, on long-term screening program effectiveness. We explored several scenarios differing in participation pattern, number of negative screens after which screening fatigue occurs and decrease in participation rate due to screening fatigue. We demonstrated that screening fatigue can seriously compromise screening effectiveness. If individuals refrain from further screening after three negative screens, the potential CRC incidence reduction of 39% that could be achieved by the screening program assuming repeated participation, may be halved. Since data on individual participation patterns is not reported in CRC screening programs nor in screening programs for other cancers, it is unclear if screening fatigue will occur. Considering the potentially substantial impact of screening fatigue on screening effectiveness, careful monitoring of individual screening behavior is warranted. Availability of such data could also allow for making more accurate model predictions of screening impact. Depending on the occurrence of screening fatigue, targeted invitation and reminder systems for individuals who have (repeatedly) missed screening rounds may be considered.

#### **Opportunities for optimization**

In **Chapter 5**, we assessed the potential value of alternative screening tests that have a high sensitivity for CRC and its precursor lesions. Such tests allow for a longer screening interval and thus, less screening rounds are required. In a program consisting of few screening rounds, the probability that screening fatigue will occur is likely to be smaller. We focused especially on the potential of imaging tests because these tests have comparable test characteristics as colonoscopy, but are less invasive. We considered several computed tomographic colonography (CTC) and magnetic resonance colonography (MRC) strategies and compared those to no screening, ten-yearly colonoscopy screening and biennial FIT screening. Like colonoscopy and FIT screening, screening by CTC and MRC would be more effective and less costly, and thus considered cost-effective compared to no screening. Imaging is also a cost-effective alternative to three rounds of colonoscopy screening. Compared to this colonoscopy screening strategy, CTC and MRC screening is more effective and may considerably decrease screening burden in terms of negative colonoscopies and colonoscopies required to prevent one CRC death. However, screening by imaging cannot compete with FIT screening; it is less effective and more costly.

Given that in the Netherlands CRC screening is done by means of FIT testing, screening by imaging is not an option for the Dutch screening program. Therefore, we explored other options to optimize the Dutch screening program in terms of improved (cost-)effectiveness and decreased burden. In **Chapter 6** we assessed the surveillance part of the Dutch screening program in more detail. According to the Dutch surveillance guideline, individuals who undergo diagnostic colonoscopy and are considered at intermediate- or high risk, are referred to surveillance colonoscopy after respectively five and three years. We modelled a strategy of FIT screening plus colonoscopy surveillance based on the Dutch surveillance guideline and compared this to screening without colonoscopy surveillance. In the latter strategy, all individuals considered at increased risk at diagnostic colonoscopy return to the FIT screening program immediately after polypectomy. We showed that the addition of surveillance to FIT screening decreases CRC burden slightly but is not cost-effective compared to screening without surveillance. Moreover, the colonoscopy demand of

screening plus surveillance is substantial. This demand can be considerably reduced, without substantial loss of effectiveness, if surveillance intervals are prolonged to five years.

### **IMPLICATIONS FOR CRC SCREENING MODELS**

The development of the ASCCA model as well as conducting model-based analyses has led to interesting insights concerning the representation of CRC development by models. The natural history of CRC is described by the ASCCA model as progression from adenomas and serrated lesions to cancer. Since the ASCCA model is the only model that explicitly acknowledges the malignant potential of serrated lesions, this raises the question whether other models should also implement the serrated pathway to CRC. We showed that the impact of screening is overestimated by models that only include the adenoma-carcinoma pathway when serrated lesions are not detected nor removed during colonoscopy and/or if the survival probabilities for CRCs arising from serrated lesions are significantly lower than those for CRCs arising from adenomas (**Chapter 3**). Since current guidelines recommend removal of serrated lesions<sup>3-5</sup> and the evidence that CRCs arising from serrated lesions have a worse prognosis is very limited,<sup>6</sup> models that do not include the serrated pathway will lead to fairly accurate predictions of screening effectiveness.

Although inclusion of the serrated pathway is not pivotal to obtain long-term predictions of screening effectiveness and although the structure of a model should not be more complex than required, we believe in the merit of including the serrated pathway in CRC screening models. First, serrated lesions receive much interest and consequently, our understanding of the differences between the adenoma-carcinoma pathway and the serrated pathway will increase in the coming years. Furthermore, new screening tests are developed that have a higher sensitivity for serrated lesions than FIT.<sup>7</sup> In the light of these developments, it is important to include the serrated pathway in order to reflect the most recent data and insights and to assess the cost-effectiveness of new tests.

Compared to the uncertainties surrounding the serrated pathway, the adenoma-carcinoma pathway is reasonably well understood. Therefore, the structure of this pathway in CRC screening models is fairly comparable although the parameterization, and especially the duration from adenoma to CRC, differs. This adenoma dwell time cannot be observed in clinical practice since adenomas are removed upon detection and therefore, this parameter varies considerably between models.<sup>8</sup> However, it is possible to infer dwell times from cross-sectional data as demonstrated by Vink et al. (2013).<sup>9</sup> This study estimated the time span of progression from cervical precursor lesion to cervical cancer based on cross-sectional registry data. Using statistical modeling, Vink et al. accounted for the censored nature of the cross-sectional data and were able to estimate the duration from cervical precursor lesion to cancer. Since the adenoma dwell time has substantial impact on predicted screening effectiveness,<sup>8</sup> more precise estimates of the adenoma dwell time would improve the validity of CRC model predictions.

When important decisions such as the implementation of a screening program are based on models, validity of model predictions is essential. Perhaps the most important factor to gain confidence in model predictions is adequate reporting of model structure, assumptions and data on which model parameters are based.<sup>10</sup> Therefore, we provided a detailed description of the ASCCA model (**Chapter 2**). Unfortunately, many models used for decision-making, both in CRC screening as well as in other fields, are more or less 'black boxes'; it remains unclear what happens in the model due to poor model description. In order to increase the quality of model reporting and to facilitate model comparison, the Cancer Intervention and Surveillance Modeling Network (CISNET) has developed standardized forms for model descriptions.<sup>11</sup> Although CISNET is an excellent initiative, up

to now only three CRC screening models have a CISNET model profile. This could be due to the fact that the forms are developed by a small group of modelers. A consensus-based form which is widely supported by all parties involved in CRC screening modeling may have a larger impact on transparent reporting. Such an approach is currently adopted in the field of cervical cancer screening modeling.<sup>12</sup>

However, even with transparent reporting of model structure, parameters and calibration, it remains difficult to fully understand all underlying choices and assumptions of a model and more importantly, the implications of these choices and assumptions on model predictions. This is underpinned by Kuntz et al. (2011) who showed that model predictions can differ considerably, even when models are calibrated to the same data.<sup>8</sup> Therefore, comparative modeling in which several models are set up to conduct the same analyses is important. Such an approach increases the understanding of model assumptions, their impact on predictions and consequently, supports well-informed decision making. Although there are some comparative modeling studies in the field of CRC screening,<sup>8,13–15</sup> we believe that this principle should become common practice in modelling studies, especially when predictions are used to guide policy-making.

### **BALANCING BENEFIT AND BURDEN OF SCREENING**

In screening, only a small proportion of participants will benefit whereas many individuals are invited for screening and consequently, subjected to futile (screening) tests. Therefore, a key principle of screening is that the benefits should outweigh the harms. **Chapter 3** and **Chapter 5** add to the large body of evidence showing that CRC screening is very effective in reducing CRC incidence and mortality and is a cost-effective alternative to treatment only. Thus, the benefits of the Dutch CRC screening program are clear, but do they balance the burden of screening?

The burden of the Dutch CRC screening program mostly consists of the high number of screening invitations, incorrect test results and futile colonoscopies, which are the result of imperfect FIT test characteristics. Due to the low sensitivity for advanced neoplasia,<sup>16–19</sup> repeated testing is required leading to an 11-round screening program. A study on screening experiences reported that roughly 20% of invitees is distressed by receiving an invitation to participate in screening.<sup>20</sup> Such an invitation confronts individuals with their vulnerability to develop CRC. It may therefore be hypothesized that a high number of screening rounds increases the burden of the program. Although receiving a screening invitation causes distress, performing the FIT, i.e. taking a sample of stool using the test kit, is generally not considered as burdensome.<sup>21</sup>

Furthermore, low FIT sensitivity leads to false-negative test results. That is, the FIT can be negative in individuals with colorectal lesions and/or CRC. A study comparing CRC outcomes in patients diagnosed with CRC after a false-negative stool-based test to patients diagnosed after a positive stool-based test suggested that CRC morbidity and mortality may be higher in the former group.<sup>22</sup> A potential explanation for this observation is that individuals with a negative FIT neglect symptoms due to false reassurance. Indeed, there are indications that a small group of individuals with a negative test will not visit a general practitioner when they notice blood in their stool.<sup>20</sup> This raises concerns since the group of individuals with a false-negative test is rather large; our model showed that roughly 25% of participants is false-negative in the first screening round at age 55.

Besides a low sensitivity for advanced neoplasia, FIT also has imperfect specificity. Due to the high number of screening rounds, the cumulative chance of a false-positive FIT is approximately 20% in individuals attending multiple screening rounds (**Chapter 3**). Referral to further diagnostic work-up after a positive screening test has been shown to cause anxiety and decreased health-related quality of life.<sup>23,24</sup> For individuals with a false-positive test, this distress is unnecessary. In addition, these

individuals are subjected to a futile invasive procedure with a chance of complications. This group is substantial; when the Dutch screening program is fully implemented and a more or less stable situation is achieved, over 20,000 individuals will undergo an unnecessary colonoscopy each year (**Chapter 3**).

Colonoscopy is an invasive procedure and especially the required bowel preparation is perceived as burdensome.<sup>25,26</sup> In addition, there is a risk of adverse events such as bleeding, bowel perforation and even death. The risk of serious complications is small; a systematic review on screening colonoscopies reported that serious complications occur in only 0.28% of procedures.<sup>27</sup> Around 85% of these complications occur in colonoscopies during which lesions are removed. Fatal complications are very rare; around 0.007% of procedures lead to death due to colonoscopy.<sup>28</sup> Although the risk of complications is small, the harms of colonoscopy are quite disturbing when considering a fully implemented screening program in which yearly over 110,000 procedures are performed (**Chapter 3**). In that situation, complications are expected to occur yearly in 308 individuals and 8 individuals may die due to colonoscopy.

Also colonoscopies during which lesions are detected, are not necessarily beneficial. The probability that a diminutive adenoma has characteristics that are associated with increased malignant potential is very small, i.e. 4%.<sup>25</sup> Furthermore, the adenoma prevalence is markedly higher than the prevalence of CRC,<sup>29,30</sup> and therefore it can be concluded that only a small proportion of adenomas will develop into CRC. Limited evidence suggests that only 5% of adenomas will develop into cancer.<sup>31</sup> Thus, many colonoscopies during which colorectal lesions, especially diminutive lesions, are removed by means of polypectomy can also be considered as futile since they do not lead to cancer prevention.

Taking all this into account, the burden of the Dutch FIT screening program is not negligible. A measurement that comprises both survival benefit due to prevention or early detection of cancer as well as distress or complications due to screening procedures is the quality-adjusted life year (QALY). QALYs can be estimated by multiplying the number of life years lived by the quality of life. Subsequently, two strategies can be compared in terms of benefit, burden and costs by calculating the incremental cost utility ratio (ICUR) which is the difference in costs divided by the difference in QALYs. Although the use of the ICUR is common practice in cost-effectiveness research, studies in the field of CRC screening primarily report incremental cost-effectiveness ratios (ICERs), which is the difference in costs divided by the difference in life years. Thus, the burden of screening is not taken into account.

A possible explanation for calculating ICERs instead of ICURs in CRC screening could be that the instrument to measure quality of life, i.e. the EuroQol-5D, can poorly discriminate between the quality of life in the general population and CRC patients.<sup>32</sup> Therefore, new instruments should be developed that accurately assess the quality of life in CRC patients. These estimates can be used to enable more comprehensive evaluations including benefit, burden and costs of CRC screening strategies.

## **FUTURE PERSPECTIVES**

Although the Dutch CRC screening program is expected to be very effective and cost-effective, there is still much room for improvement due to the high burden of FIT screening. In **Chapter 5** and **Chapter 6** we already assessed two options to further optimize the screening program. However, there are many more opportunities to enhance the program in terms of effectiveness and/or cost-effectiveness. We will highlight several other possibilities.

The quantitative nature of the FIT offers the opportunity to adjust the cut-off point. Haug et al. (2016) explored if the interval between subsequent FIT screening rounds could be extended when the positivity threshold of FIT is lowered.<sup>33</sup> The results of this study suggest that strategies in which the FIT cut-off is lowered and the screening interval is extended, reduce the number of screens in the lifetime of an individual while achieving similar diagnostic yield. Thus, the impact on screening benefit is limited while the costs associated with the organization of a screening program as well as the costs of screening tests are reduced due to a lower number of screening rounds. Furthermore, screening with a longer interval reduces the probability that screening fatigue will occur, as described in **Chapter 4**, and screening burden in terms of screening invitations is decreased. Haug et al. also showed that lowering the cut-off point while extending the screening interval led to a similar or slightly higher number of diagnostic colonoscopies compared to the reference strategy, depending on the exact cut-off point used. This indicates that the cut-off point could be chosen such that the decrease in burden due to a reduction in screening invitations is not outweighed by an increase in diagnostic colonoscopies. The findings of this explorative study can serve as a base for future studies on the effects of extending the interval between subsequent FIT screening rounds.

Furthermore, it is possible to implement a more personalized screening regimen in which individuals for colonoscopy referral are not only selected based on FIT results, but on additional risk factors as well. A Dutch study explored the potential benefit of risk-based stratification.<sup>34</sup> The risk model included, besides FIT result, variables that were easy to obtain such as family history, smoking status and age. Selection for colonoscopy based on this risk model led to the detection of more individuals with advanced neoplasia compared to using the FIT result only. Such a personalized approach could reduce the number of futile colonoscopies, thereby decreasing screening burden and costs.

Besides changes to the manner in which the FIT result is used, there is also the possibility of replacing the FIT by another primary screening test. Due to the high acceptability of stool-based testing, the focus has been on developing non-invasive tests such as stool-based DNA testing. This test detects genetic mutations that are associated with CRC and its precursor lesions in stool. The U.S. Food and Drug Administration already approved a stool-based DNA test.<sup>35</sup> A study comparing this stool-based DNA test to FIT showed that the former had a significantly higher sensitivity for CRC than FIT, i.e. 92% versus 74%.<sup>7</sup> Also the sensitivity for advanced adenomas and large serrated lesions was considerably higher. In contrast, the specificity of the DNA test was 90% compared to 97% for FIT. In screening, a high specificity is required because a screening population consists of mostly healthy individuals. A test with a suboptimal specificity would lead to many futile diagnostic colonoscopies and thus, a considerable screening burden. In addition, the DNA test is currently performed on whole stool samples whereas a small sample is sufficient for FIT. Although the results for stool-based DNA testing seem promising, the test needs further development to increase the specificity and user friendliness before DNA testing will be considered in the Dutch screening setting. Subsequently, studies should evaluate the performance of stool-based DNA testing compared to the FIT used in the Dutch screening program since a different type of FIT was used in the comparator study. Finally, cost-effectiveness analyses should be conducted to determine whether stool-based DNA testing is a feasible alternative to the current FIT screening program. Since this DNA test misses significantly less large serrated lesions compared to FIT, it is important that the model used for these analyses includes the serrated pathway to CRC to accurately assess the potential of DNA testing.

Follow-up by colonoscopy after a positive FIT test could also be improved. An example is the implementation of a resect and discard strategy. Currently, all colorectal lesions are removed upon

detection with the exception of small hyperplastic polyps in the rectosigmoid.<sup>3</sup> All removed lesions are subsequently evaluated by a pathologist. However, diminutive adenomas seldomly harbor malignant characteristics.<sup>36</sup> Therefore, histopathological analysis of these lesions might be unnecessary. A modeling study showed that a resect and discard strategy in which diminutive adenomas are not subjected to histopathological evaluation could lead to substantial cost-savings without markedly affecting screening effectiveness.<sup>37</sup>

Besides possibilities to improve the Dutch CRC screening program, there are also ongoing efforts to develop a screening test that is able to detect multiple diseases. Examples of such tests are the blood-based liquid biopsy and the total body scan. The blood-based liquid biopsy focuses on the detection of six different types of cancer. One drop of blood is sufficient to assess whether platelets contain tumor RNA, which indicates the presence of a tumor in the body. Furthermore, the test is able to pinpoint the tumor location and can differentiate between primary tumors and metastases. Besides early cancer detection, results of this test can also be used to guide cancer treatment based on certain mutations in the RNA. A recent study including 55 healthy individuals and 228 individuals with cancer showed promising results; blood-based liquid biopsy correctly identified 96% of cancer cases.<sup>38</sup> Since the majority of individuals included in this study had cancer whereas in a screening population, the majority is healthy, the test needs further research to assess the potential in a screening setting.

The total body scan does not only detect tumors, but can also detect other abnormalities such as, amongst others, aneurysms and osteoporosis. With the total body scan, the whole body is examined using MRI and CT scanners, exposing individuals to ionizing radiation. Currently, there is no evidence that a total body scan leads to health benefits for average-risk, asymptomatic individuals.<sup>39</sup> In contrast, there is a high chance that this test will lead to unnecessary distress due to the detection of abnormalities that are deemed benign at further, possibly invasive, follow-up tests or to the detection of a disease for which no cure or treatment is available. In addition, total body scans will require considerable health care resources. Because it is not established that the benefit outweighs the burden, this test is prohibited in the Netherlands.

Currently, the Netherlands have organized screening programs for breast cancer, cervical cancer and colorectal cancer. The focus of these cancer screening programs is the early detection of cancer, thereby increasing survival probabilities.<sup>30,40</sup> In CRC and cervical cancer screening, also prevention of cancer is possible due to the detection and removal of precursor lesions. However, screening is not the only method to decrease the burden of cancer. Approximately 20% of cancers is caused by overweight and obesity.<sup>41</sup> Policy-makers could also focus on decreasing overweight and obesity in the population to reduce cancer burden, in addition to screening. Since excess weight is also a risk factor for many other diseases, e.g. diabetes and cardiovascular disease, such an approach could lead to a considerable health benefit.<sup>42</sup>

## **CONCLUDING REMARKS**

This thesis extends our knowledge of the benefit and burden of CRC screening. It clearly shows that the Dutch FIT screening program is likely to lead to a considerable reduction in CRC incidence and mortality. However, the burden of screening is non-negligible. We discussed opportunities to optimize the Dutch CRC screening program, thereby increasing the effectiveness while decreasing the burden. This research will serve as a base for future (modeling) studies.

## Chapter 7 - Summarizing discussion

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