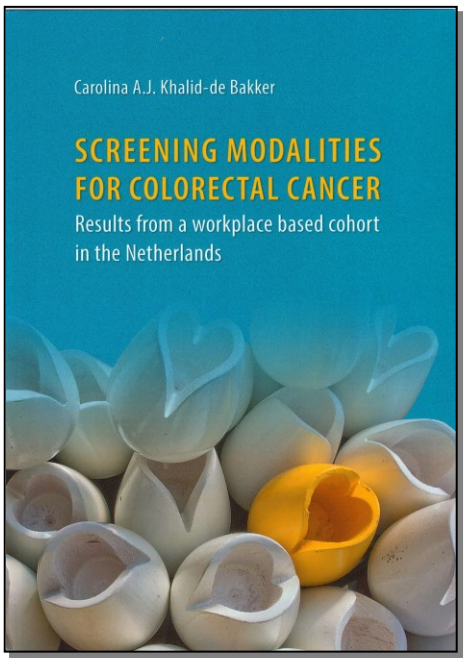

Samenvatting van het proefschrift
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"Screening modalities for colorectal cancer; Results from a workplace based cohort in the Netherlands"

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Colorectal cancer is a significant cause of mortality and morbidity in the Netherlands and the Western world. Screening for colorectal cancer has resulted in a decrease in CRC incidence and mortality by early cancer detection and adenoma removal. Colonoscopy is the current standard in polyp and CRC detection and offers the opportunity of direct polyp removal. On the other hand, in comparison with for example fecal occult blood test (FOBT) screening, it is a relatively invasive method. A Dutch consensus meeting concluded that a national population FOBT CRC screening should be implemented in the Netherlands and alternative screening modalities had to be investigated. Therefore, the aim of the study project resulting in this thesis was to investigate the feasibility and diagnostic yield of opportunistic colonoscopy screening in a small community. In order to evaluate alternative screening modalities, FIT was performed and lifestyle risk factors, stool and blood samples were collected to identify and evaluate non-invasive markers for (advanced) adenomas and CRC. Since the success of a screening method, in terms of health benefit and cost-effectiveness, is influenced by the participation rate, we performed a systematic review on participation rates to CRC screening in Chapter 2. A meta-analysis showed participation to be negatively influenced by the invasiveness of the screening methods, but to be positively affected by several invitation methods. Especially, the addition of the stool test (FOBT) to the information letter, involvement of the General Practitioner, and a more personalized approach resulted in higher participation rates. The feasibility of opportunistic colonoscopy screening was investigated with participation, tolerability and acceptance as endpoints in Chapter 3. After inviting 1090 subjects using an intensive information campaign, the small community (i.e. hospital personnel) in the present project showed a relatively high participation rate of 41%. The majority (i.e. 79%) graded the bowel preparation as uncomfortable, while only a minority

(i.e. 22%) regarded colonoscopy itself as uncomfortable. Discomfort caused by colonoscopy itself, was found to be significantly more frequent in participants with symptoms before colonoscopy such as abdominal pain, flatulence and diarrhea. These findings offer the opportunity of providing more targeted information on potential discomfort caused by colonoscopy in this subgroup. Furthermore, the use of more effective sedation strategies may further improve patient satisfaction, since having symptoms during colonoscopy was found to be associated with a lower tolerability. Colonoscopy itself has a risk of complications, but is generally regarded as an invasive but rather safe procedure. The study described in Chapter 4 investigated the occurrence of (cardiopulmonary) complications. No major complications occurred in the present study, partly as the number of examinations performed was rather low. However, minor cardiopulmonary events occurred relatively frequently (hypoxia in 56%, hypotension in 9% and bradycardia in 6%) and were mainly associated with procedure- and not patient-related factors (e.g. sedation, and procedure time). These results point towards an important role of sedation in the occurrence of such events in this relatively healthy screening population. The clinical relevance of these minor cardiopulmonary events remains unclear for screening in the general population, but may have a significant clinical relevance in screenees with more pronounced cardiovascular risk factors. This stresses the importance of for per- and post-colonoscopic surveillance when implementing colorectal cancer screening programs. The ultimate health benefit reached by different screening methods depends on their diagnostic accuracy, especially for the individual screenee. The study described in Chapter 4 investigated the diagnostic yield of colonoscopy screening compared to the immunological FOBT (FIT) and sigmoidoscopy screening. In total, colonoscopy screening detected any adenoma in 26% and advanced adenomas in 11% of 447 screenees. One time FIT was found to have a lower sensitivity (16%) for advanced adenomas than a hypothetical screening sigmoidoscopy (74%) when compared to colonoscopy as current standard. Furthermore, FIT showed especially a low performance in women, younger subjects, and those with proximal lesions. Test performance could be improved by lowering the cut-off values of 50 towards 27.5 ng/ml in these subgroups. Considering that adenoma detection is an important screening target, the low sensitivity of FIT for advanced adenomas and adenomas, makes its usefulness questionable.
If colonoscopy screening is not available, sigmoidoscopy seems a more effective alternative with a 74% sensitivity for the detection of advanced adenomas in the current study. The results on the diagnostic yield of the various methods and the low FIT performance in subgroups, point towards the need for customized screening strategies combining knowledge on test performance and the personal preference of the screenee. In Chapter 6 a review on the Cpg Island Methylator Phenotype (CIMP), characterized by promoter CpG island hypermethylation of multiple genes, compared studies reporting on this phenotype. CIMP has been reported to be associated with a distinct subgroup of CRCs, being more frequently located in the proximal colon, with a higher prevalence in female patients, and a different therapeutic response. The review showed that comparing findings between studies

is hampered by the numerous variations in methods and definitions used to quantify CIMP status resulting in a wide variation in study results. In chapter 7 we investigated the molecular features of adenomas and their association with histologically advanced features. CIMP, or at least one defined chromosomal gain or loss were found in 38% and 15%, respectively, of 113 subjects with adenomas detected during the colonoscopy screening study. In total, 4% of the 75 advanced adenomas analyzed contained carcinoma associated events. In general, the prevalence of molecular events was similar in non-advanced and advanced adenomas. These results indicate that the histopathological features that define an adenoma to be advanced, do not represent all lesions with molecular alterations and that molecular alterations and histology seem to be complementary. FIT detected 6 of 30 (20%) subjects with a CIMP adenoma, 3 of 13 (23%) subjects with adenoma showing chromosomal gains and/or losses and 2 of 4 (50%) with adenomas containing any CAEs. Apart from fecal occult blood testing, another potential non-invasive screening strategy is the use of risk prediction tools, based on individual risk factor analyses. In Chapter 8, we explored risk factors for adenomas in the present screening population. A gender specific risk score showed a sensitivity and specificity for adenomas of 23 and 97% in men, and of 9 and 96% in women, respectively. In our small explorative study, we observed that it is relevant to take into account gender-differences not only in the risk factors for various adenoma subgroups but also for secondary prevention by implementing life style modifications. It has to be taken into account that numbers were small and findings should be interpreted with care. Nevertheless, our preliminary findings represent an interesting trend that needs confirmation in larger trials. In summary, this thesis has shown that colonoscopic screening is feasible in terms of participation, acceptance, cardiopulmonary safety and diagnostic yield in this 'closed community' of hospital staff. For the method FIT, however, the sensitivity to detect adenomas with advanced features and/or molecular alterations is very low. Furthermore, it is important to realize that certain subgroups (e.g. women and subjects with proximal lesions) need different cut off levels in order to reach comparable test sensitivities to those of other groups. The same tendency was found for risk factors, indicating that life style education and also risk prediction tools should be developed in a gender and adenoma subtype specific manner. In future, non-invasive screening methods with a good test performance for the detection of CRC as well as high-risk adenomas are warranted and may be improved by combining different strategies. The accurate definition of 'true' high risk adenoma and therefore screening target remains unclear. Chromosomal instability and gene promoter methylation were found in advanced, non-advanced as well as in diminutive adenomas. This indicates the need for new and more specific molecular markers for the true high risk adenoma in order to establish a clinically relevant intermediate endpoint for screening. ◄