Opportunities and pitfalls in colorectal cancer screening

Terhaar sive Droste, J.S.

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General discussion and future perspectives

This thesis addresses multiple issues concerning population-based screening for colorectal cancer (CRC), as is currently in preparation in the Netherlands. When starting this research project in January 2005, a number of questions were postulated that remained to be answered by that time. Since then, many of these issues have been addressed, several of which by studies described in this thesis. The first part of this thesis deals with general issues including colonoscopy capacity and manpower planning, attitudes towards CRC screening among gastrointestinal specialists and general practitioners, spatial distribution of advanced colorectal neoplasia in the colon, effects of diagnostic delay on CRC stage and survival in symptomatic patients, cecal intubation rates and the magnitude of (pre-)malignant lesions missed by incomplete colonoscopy. The second part of this thesis addresses the potential of a Faecal Immunochemical Test (FIT) for early detection of colorectal neoplasia in both symptomatic, and asymptomatic high-risk patients. The main findings per chapter will be summarized and these findings will be put in perspective to the recent report on population-based screening for CRC issued by the Dutch Health Council (1).

Part I: General issues related to introduction of a CRC screening program in the Netherlands

Chapter 1

Adequately managing colonoscopy capacity is of prime importance. At present, waiting times for colonoscopy can already be substantial in certain areas in the Netherlands. When introducing a CRC screening program, special care should be taken to avoid an unacceptable increase in waiting times for colonoscopy in the context of regular healthcare. Our data indicate that a biennial FOBT-based screening strategy seemed feasible in 2005 without greatly interfering with regular health care. However, these calculations were carried out assuming a G-FOBT positivity rate of 2% in line with other studies (1-4). In 2009, the Dutch Health Council has advised to start screening with FIT since this test has been proven to be superior to G-FOBT in detecting advanced adenomas and CRC (1). The positivity rates of FIT range from 5.3-8.4%, depending on the cut-off

level (1). This will result in a much higher colonoscopic workload. Against this background, any plans for introducing CRC screening should anticipate on national and regional endoscopic capacity and manpower in order to allow for a successful implementation. Over the next few years, a substantial number of endoscopists will retire. In the less populated provinces in particular, (smaller) hospitals have difficulties in recruiting certified endoscopists. Although the structure of the screening organisation has not yet been determined completely, geographic dissimilarities may affect a nationwide introduction of a screening program. In 2010, the national survey on endoscopic capacity and manpower planning was repeated and these results are expected soon. Trends in endoscopic practice and manpower issues can then be compared to the estimations postulated in the report on population-based screening for CRC issued by the Dutch Health Council (1).

Chapter 2

A high participation level of the target population is essential for the success of a screening program. The role of the general practitioner (GP) is important for a nationwide screening program, particularly in the Netherlands where GPs are the gatekeepers of the healthcare system. GPs recommendations on CRC screening is a major predictor for attending CRC screening (5-8).

We showed that in 2005 Dutch gastroenterologists and GI-surgeons favoured the implementation of CRC screening and that colonoscopy was the preferred screening modality at that time. GPs, however, were more reluctant to population-based screening (only 51% in favour) and did not have a clear preference for a screening test. Lack of support for a CRC screening program by GPs may have a negative effect on screening uptake. Informing GPs on all aspects of CRC screening could help changing this attitude towards CRC screening and will be part of the educational campaign preceding the introduction of the CRC screening program (1,9). Contradictory results have been published on the benefit of personalized invitation of screenees by the GP for CRC screening (6, 10-13). Therefore, a central invitation system might be more appropriate and will not overlook subjects in the target population without a GP (14). However, a

Dutch study recently showed that involving GPs in the process of informing screenees on a positive test result and the subsequent hospital referral did considerably increase the uptake of a follow-up colonoscopy (15). More data are expected addressing the GPs perception to screening, willingness to participate in screening, effects of increasing CRC awareness and insights in additional workload for GPs (1).

Chapter 3

One of the outcomes of the Dutch National Consensus Development Meeting in 2005 was that additional studies were needed that would focus on other screening modalities besides FOBT (16). One of the suggested modalities is the use of endoscopy to screen for CRC. Besides Dutch screening trials that are evaluating the use of endoscopy (15,17), we have studied the spatial distribution of CRC and the high-risk precursor lesions within the large bowel in daily practice. International data are scarce regarding real life incidence figures of colorectal neoplasia found in routine endoscopy programs, evaluating both symptomatic and asymptomatic patients. We have studied a large cohort of patients undergoing colonoscopy or sigmoidoscopy in Northern Holland over a three months period. All colonoscopies and sigmoidoscopies were evaluated, representing a large unselected sample of the population of the Netherlands. These data accurately represent the entire (lower gastrointestinal) endoscopic practice in Northern Holland, which we regard to be representative for the whole of the Netherlands. In this series, 33% of advanced neoplasia were located proximal to the splenic flexure. Furthermore, 51% of all patients with proximally located advanced neoplasia did not have any distal lesions that would have warranted a total colonoscopic evaluation. The facts that right-sided advanced neoplasia are found frequently, and that absence of distal lesions that would trigger a total colonoscopy is common, may help to decide on the appropriate screening modality when considering endoscopic screening. In comparison to other countries, we observed an overall higher yield of advanced neoplasia in clinical practice than in Asian countries (13,5% versus 9,4%) (18). This finding underlines the higher incidence of CRC in Western countries. Similar percentages of isolated proximal advanced neoplasia have been observed in the US and Asia (18,19). Although the mixed referral population used in our study will have a higher pre-test likelihood for colorectal neoplasia compared to a

screening population, the distribution of these lesions throughout the large bowel is likely to be the same. This led us to conclude that colonoscopy is warranted for the evaluation of both symptomatic and asymptomatic patients, since substantial numbers of right-sided advanced neoplasia are found in both patient groups. In a population screening setting, however, also other factors have to be taken into account such as patient acceptance of the screening test, endoscopic capacity and potential procedure-related complications, all of which affect the ultimate decision on the most appropriate screening test.

Another result of monitoring daily endoscopic practice is the relatively high percentage of colonoscopies performed in asymptomatic patients. CRC awareness accounts for an increasing number of colonoscopies performed in asymptomatic patients with a screening request or (poorly defined) family history of CRC in The Netherlands. Ten percent of all colonoscopies in routine endoscopy programs were performed in asymptomatic patients. When implementation of a screening program will be postponed, the proportion of asymptomatic patients with a screening request may further increase. This so called opportunistic screening without appropriate screening infrastructure, quality assurance and quality control will create potential overuse of endoscopy resources, and major difficulties in logistics and assessment of effects of screening once a screening program would be implemented. On the other hand, the yield of advanced neoplasia in asymptomatic patients is substantial (7%) and right-sided lesions were common findings. This may encourage clinicians to stimulate opportunistic screening.

Largely based on these data, the Health Council has estimated that 9-10% of all colonoscopies in routine endoscopy practice are performed for opportunistic screening. It is anticipated that this percentage will decrease when population based screening is implemented.

Chapter 4

In the same population-based cohort, the diagnostic delay was studied in all symptomatic patients that were ultimately diagnosed with CRC. In the absence of a screening program, CRC is usually detected as a result of symptoms and 46% of all newly diagnosed CRC patients present with late stage disease (AJCC stage III or IV) (www.ikcnet.nl). Awaiting implementation of a screening program in which a shift towards diagnosis of CRCs in

earlier stages is expected, it could be beneficial to reduce diagnostic delay to improve survival. We have studied the association between diagnostic delay and survival in symptomatic patients with early stage CRC and late stage CRC. No significant overall difference in diagnostic delay was found between early and late stage cancers. In addition, we found no relation between diagnostic delay and survival in early stage cancers after 3.5 years of follow up. However, in late stage cancers, with Dukes D tumors as the culprit, a shorter delay was associated with poor prognosis. This latter finding is usually referred to as the 'waiting time paradox' and has also been reported for other types of cancer (20). The most common explanation for the paradox is the aggressiveness of the tumor, which is said to act as a hidden confounder, influencing both patients' and doctors' ability to detect cancer, while at the same time being a predictor of mortality. An alternative explanation of the paradox is the impact of differentiated clinical triage, i.e. the doctor's ability to organize investigation on the basis of his/her interpretation of symptoms (21). Patients presenting with specific high-risk symptoms warrant rapid investigation while at the same time having an inherent poorer prognosis at presentation. This effect is referred to as 'confounding by indication' and is considered one of the most important weaknesses in observational studies of exposure effects (22). However, alternative study designs for exploring the relationship between diagnostic delay and survival are not easily at hand. These observations do not rule out a beneficial effect of expediting diagnosis, since observational studies do not test the hypothesis that expediting diagnosis provides a mortality benefit. The diagnostic interval is a highly complex variable reflecting tumor biology, patient behavior, the clinical pathway, and the functioning of the healthcare system.

Chapter 5

Quality assurance is of utmost importance when a screening program is implemented. This topic has gained more attention by reports on lack of mortality reduction due to proximal cancers after colonoscopy at long term follow-up periods (23,24-26). Explanations for these worrisome findings include inadequate compliance with quality guidelines resulting in low caecal intubation rates and poor bowel cleansing. Recently, adenoma detection rates and withdrawal times after reaching the caecum have been

adopted as new quality measures for colonoscopy as it has been shown that a high adenoma detection rate (>20%) and more than 6 minutes withdrawal time were associated with less interval cancers. (27,28). In the present series, 9.7% of colonoscopies performed in daily clinical practice were incomplete. This >90% caecal intubation rate meets the target set by the U.S. Multi-Society Task Force on Colorectal Cancer. As such, it satisfies one of the indicators of colonoscopic quality control (29). The predominant reasons for the inability to intubate the caecum were looping of the scope or redundant colon, patient's discomfort, obstructing tumours, insufficient bowel preparation and adhesions due to previous abdominal/pelvic surgery.

Only 54% of incomplete colonoscopies was followed up by additional imaging, which revealed advanced neoplasia in 4.3% of patients in the segment that had not been inspected due to incomplete colonoscopy. Putting these findings into perspective, even lower percentages of follow up examinations were seen in other studies (30,31). This study was the first to address the proportion of missed lesions in the non-visualized part of the colon in a population-based study. In the report issued by the Health Council, the importance of quality assurance for colonoscopy is underlined since it is essential for the effectiveness and acceptability of the screening program. Consequently, a quality system for colonoscopy including both quality assurance and quality control will have to be in place before a screening program starts (1).

Part II: The potential of faecal occult blood tests for early detection of colorectal neoplasia

Chapters 6 & 7

In the last chapters the potential of FOBTs for early detection of colorectal neoplasia was evaluated. It was shown that FIT is superior to G-FOBT in terms of sensitivity for advanced adenomas, CRC, screen relevant neoplasia and all advanced neoplasia (**chapter 6**). Specificity, however, was higher in G-FOBT compared to the FIT at a cut-off level of 100ng/ml; the cut-off level that was initially recommended by the manufacturer. These findings are in keeping with other studies reporting a lower specificity for FIT using a cut-off level of 50-100 ng/ml (32-34). Once this test, with these low cut-off levels, is applied in a CRC screening program, the lower specificity will result in more futile

colonoscopies. Although a cut-off level of 50 ng/ml has been shown to be cost effective, constrains on colonoscopy resources may lead to the choice of a higher cut-off level (1). A higher cut-off level, however, might also be associated with more curable CRCs remaining undetected. The study described in **chapter 7** showed that increasing the cut-off level to 200 ng/ml resulted in a substantial increase in specificity, whereas the effects on detection rates of curable, early stage CRCs were rather limited.

Using a colonoscopy-controlled referral population, like in this thesis, both has its advantages and drawbacks compared to studying a screening population. Studies in screening populations, consisting of individuals with average-risk for CRC, best reflect the true target population. However, in most of these studies, only subjects who test positive on FIT are referred for colonoscopy, which means that specificity can not be determined directly and sensitivity can not be determined at all (33). In addition, the number of cases, particularly cancers, is usually low. The important advantage of our study design with a referral population is that colonoscopy is performed in all patients allowing for calculation of direct sensitivity and specificity. In addition, these studies often yield more cases, allowing for stratification by stage of the disease. More precise data on sensitivity and specificity, i.e. with smaller confidence intervals than data from screening studies can be calculated.

It has been suggested that conclusions from studies that use a referral population cannot be extrapolated to the screening setting (35,36). Due to the higher pre-test likelihood and presence of symptomatic individuals included in referral populations, the risk of spectrum bias exists limiting translation to population based screening. Spectrum bias refers to the situation that the spectrum of the disease phenotype differs from that in the population in which the test ultimately will be applied (37). This might lead to overestimation of sensitivity. The ultimate answer whether spectrum bias is relevant to our studies can only come from a colonoscopy-controlled screening population. To accrue a similar number of cancers in such a study design as in our study would require over 30,000 screenees with a high compliance to sample the FIT and a high adherence to colonoscopy. This very large sample size affects the feasibility of such a study. The three arguments that have been addressed in **chapter 7** show that the effect of spectrum bias in a referral population may be limited. Spectrum bias could be explained by a different tumour stage distribution in

the referral population compared to those in a screening population. Indeed, referral populations have a higher prevalence of late stage cancers and stage distribution is likely to have a large influence on FIT results (38). However, the most compelling argument against significant spectrum bias is that after stratifying for T-stage, no differences in FIT results were found between a screening and referral population (39). Although the most solid study design for investigating the performance of a screening test like FIT indeed is a prospective screening study, the use of referral populations can be useful, provided that the results are stratified by tumor stage. This particularly goes for research questions that either require large numbers of cases, colonoscopy confirmation in all individuals, and do not seek predictive values as outcome.

Chapter 8

The referral population that was studied contains a high percentage of asymptomatic patients that are at increased risk of colonic neoplasia. A substantial part of colonoscopic workload is caused by the surveillance of these asymptomatic high-risk patients with a personal or family history of colonic neoplasia. Given the increasing burden on colonoscopy capacity, the use of FIT has been suggested to triage asymptomatic high-risk individuals for immediate colonoscopy referral versus repeated FIT testing and postponed colonoscopy surveillance (40,41). This strategy, if proven successful, could result in a more efficient use of endoscopic capacity to accommodate the increased colonoscopic demand when CRC screening is implemented. Promising sensitivities of 100% and 65% for the detection of CRC and all advanced neoplasia, respectively, have been presented recently using a three day FIT sampling regimen (40). Unfortunately, we were unable to confirm these promising data. It was shown that the majority of all advanced neoplasia are not detected by single or double FIT sampling before elective colonoscopy using the lowest cut-off level of 50 ng/ml. Therefore, a once-only FIT strategy is unsafe to decide to increase surveillance intervals in these individuals. However, it is debatable whether missing advanced adenomas is clinically relevant since they could be detected in subsequent surveillance rounds while still being in a curable stage. We have also adapted a previously described model for the calculation of cumulative sensitivity if repeated FIT sampling is applied (42). Although these computed sensitivities should be interpreted

with caution, it indicates that 81% of advanced adenomas could be detected after five FIT screening rounds. Such a strategy of repeated FIT sampling in selected individuals may hold potential to postpone invasive colonoscopy and create more colonoscopic capacity. Particularly in patients with only a few small tubular adenomas in the past or a non-significant family history of CRC, multiple rounds of FIT sampling may be a good alternative to colonoscopic surveillance.

The ultimate goal would be to utilize endoscopic capacity in a more efficient manner without affecting detection rates of advanced adenomas or early stage cancers. The Health Council has also acknowledged that the surveillance guidelines should be revisited after the introduction of a screening program in order to accommodate the increased colonoscopic needs (1).

In conclusion, since the start of the studies that have led to this thesis, many issues related to CRC screening have been clarified, in part by work presented in this thesis. These studies contribute to evidence based strategies for implementing colorectal cancer screening in the Netherlands, something that is urgently needed because it can save many lives.

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