GENERAL INTRODUCTION

Opportunities and pitfalls when implementing a FOBT-based CRC screening program in the Netherlands.

Colorectal cancer (CRC) is a major health problem. CRC is the second most common cause of cancer-related death in the industrialized countries. In the Netherlands in 2008, 12,117 new individuals were diagnosed with CRC, ranking it third after prostate and lung cancer in males and second after breast cancer in females (www.ikcnet.nl). Annually, in the Netherlands, more than 4,700 patients die from this disease and costs of CRC patient care amounted to 230 million Euros (1). For demographic reasons the incidence of CRC will increase, as well as the costs of care per CRC patient, mainly due to the use of expensive targeted anti-cancer drugs.

The five year survival rate for CRC depends on tumour stage at time of diagnosis and ranges from over 90% in early stage CRC to as little as 10% in late stage, disseminated disease. Early detection of CRC leads to more successful treatment and better clinical outcome. To date, in the Netherlands most CRCs are detected when they become symptomatic, with a long-term survival of only 55-58% (www.ikcnet.nl). Screening for CRC in the average risk, asymptomatic population can reduce mortality and is cost effective, certainly compared to screening for cervical and breast cancer (2-4).

In 2001 the Health Council of the Netherlands acknowledged that screening for CRC should be investigated for the Dutch situation. A number of research questions were postulated and it was concluded in a National Consensus Development Meeting in 2005 that the Netherlands should investigate how to implement a faecal occult blood test (FOBT)-based screening program for the general Dutch population, while at the same time also looking into other screening modalities (5,6). This intended screening program would contain a two-step approach. At first, offering a biennial FOBT to all asymptomatic, average risk individuals aged 50-74 years. Then, all individuals with a positive FOBT would be offered colonoscopy, which is considered the gold standard for the diagnosis of CRC and its precursors.

Pilot CRC screening studies were carried out to explore the feasibility of different FOBT-based strategies (7,8). Ongoing studies are focusing on patient acceptance of screening tests, adherence to subsequent endoscopic evaluation of the colon and other screening options with potentially better test characteristics (9-11). In parallel to these activities, the studies described in this thesis aimed to focus on several other aspects and pitfalls potentially associated with population-based screening for CRC. This included questions like "Can we manage the increasing endoscopic burden as a consequence of biennial FOBT-based screening? What is the attitude towards CRC screening among gastroenterologists, GI-surgeons and, more importantly, general practitioners (GPs)? What is the spatial distribution of CRC and its precursors in the colo-rectum, how do we deal with incomplete colonoscopies and what significant pathology do we miss after an incomplete colonoscopic procedure in the Netherlands?"

The second part of this thesis focuses on the performance characteristics of FOBTs in a colonoscopy-controlled setting. The biennial use of a guaiac-based FOBT (G-FOBT) in asymptomatic, average-risk populations has been shown to reduce CRC-related mortality (12). However, the success of G-FOBT for CRC screening is hampered by its relatively low sensitivity for advanced adenomas and non-specificity for human haemoglobin (13). The new generation faecal immunochemical tests (FITs), that is specific for human haemoglobin of colonic origin and has a quantitative read out, has better performance characteristics (7,8,14-16). We compared sensitivities and specificities of the two faecal tests that were considered for CRC screening in the Netherlands (OC-sensor and Hemoccult-II). Since screening programs specifically aim to detect early stage, curable lesions, we then evaluated the detection rates of screen relevant neoplasia with the FIT (OC-sensor) at different cut-off levels. We assumed that by adjusting the cut-off level to a higher threshold, pressure on endoscopic capacity could be reduced since less subjects would test positive and consequently less subjects would be referred to colonoscopy. However, it is unknown how detection rates will be affected by these higher cut-off levels. Finally, we evaluated the use of FIT in an asymptomatic high-risk population in order to determine whether elective colonoscopy could be postponed to generate more endoscopic capacity for a future screening program.
OUTLINE OF THIS THESIS

Chapter 1 addresses the issue of colonoscopy capacity in the Netherlands. This chapter shows the results of a national survey dealing with the total endoscopic workload and future manpower concerns with regard to the intended implementation of a CRC screening program.

In chapter 2 attitudes towards CRC screening among GI-specialists and general practitioners (GPs) are presented. This chapter shows the results of preferences for screening and the modality of screening among GI-specialists and GPs.

Chapter 3 shows the spatial distribution of advanced colorectal neoplasms in the colo-rectum in daily clinical practice in Northern Holland. Knowledge of the incidence and distribution of CRC and high-risk, precursor lesions in the colo-rectum in both symptomatic and asymptomatic patients, could tailor endoscopic utilization. It could also inform decisions to choose a future screening modality.

Chapter 4 describes a population-based observational study evaluating diagnostic delay in CRC in daily clinical practice in Northern Holland. In symptomatic patients the yield of reducing time between onset of symptoms and start of therapy in terms of improved survival is controversial. We evaluated the association between diagnostic delay and survival in symptomatic patients with early stage CRC and late stage CRC.

In chapter 5 cecal intubation rate, one of the colonoscopy quality indicators, is addressed. This chapter reviews the reasons for incomplete colonoscopy in Northern Holland and examines the efforts made to achieve complete evaluation of the colon. Additionally, we determined the magnitude of malignant and pre-malignant lesions missed by incomplete colonoscopy.

Chapter 6 focuses on the test characteristics of the two faecal occult blood tests (OC-sensor and Hemoccult-II) that are considered for stool-based CRC screening in the Netherlands. We tested sensitivity and specificity of these two most commonly used faecal tests in a colonoscopy-controlled setting.

Chapter 7 describes the outcomes on test positivity and sensitivity for early stage CRC and all screen relevant neoplasia when adjusting the cut-off level of a FIT (OC-sensor). Implications for the future Dutch screening situation are discussed and issues whether these results of a referral population can be generalized to a screening population are addressed.

In chapter 8 we evaluate whether surveillance of asymptomatic high-risk individuals can be based on FIT sampling (OC Sensor), with colonoscopy referral only in case of a positive FIT result. For this purpose, we have studied the miss rate of advanced neoplasia by using FIT prior to colonoscopy.

In the general discussion we summarize our findings and discuss the implications for clinical practice and the potential consequences for the intended CRC screening program.
References:


