New strategy for colorectal cancer screening in Finland

Background

More than 1.2 million people are diagnosed with colorectal cancer (CRC) every year, and more than 600,000 die from the disease (1). In Finland, CRC is the third most common cancer type with more than 3000 annual cases and 1200 annual deaths (2). The number of new CRC cases is predicted to increase almost 40% by 2030 (3).

The increase in CRC incidence is strongly attributable to population aging and also to male gender and lifestyle (extensive alcohol use, smoking, obesity). Despite a familial component, most CRC cases are sporadic and develop slowly over several years through adenoma-carcinoma sequence (1). The survival from CRC is highly dependent on stage; five-year relative survival ranges from greater than 90% with stage I disease to slightly greater than 10% with stage IV disease (4, 5).

Attempts to reduce CRC incidence by primary prevention are limited (1). Screening for adenomas or early cancer provides a secondary prevention means. Results from randomized trials show that screening is effective in reducing CRC mortality in a population aged 50-74 years (6). The range of mortality reduction has, however, been large and major differences by sex have been reported (7).

According to European Union, CRC screening should be offered in an organized manner (8). In Finland, CRC screening was introduced as a randomized, population-based health services program in 2004 (9). The performance estimates of the program have been comparable to those of other European screening programs (10). The interim results on effectiveness showed, however, similar CRC mortality in the screening and the control arms and a non-significant increase in CRC mortality in women (11). Due to these, CRC screening in Finland has been questioned.

The future of well-performing CRC screening must be secured in Finland. However, benefits and harms should be balanced, and gender-specific variation carefully assessed. Here we introduce a new strategy to continuing implementation of CRC screening as a public health policy in Finland.

Existing screening strategies for CRC

A variety of tests are available for CRC screening, but only guaiac-based fecal occult blood testing (gFOBT) and flexible sigmoidoscopy (SIG) have been evaluated by randomized trials. The results of one or two rounds of SIG in a target population aged 50-74 years gained an average of 27% reduction (CI 18-36%) in CRC mortality at 11-12 years of follow-up (6). The results from biennial gFOBT screening trials in a target population aged 45-80 years have shown an average reduction of 12% (CI 10-20%) in CRC mortality after a median follow-up of 14 years (6).

According to several studies, immunochemical fecal test (FIT) offers several advantages over gFOBT by showing increased sensitivity for detection of colorectal neoplasias, and higher compliance (12). Further advantages include non-fixed hemoglobin concentration cutoff, and the specificity to detection of human hemoglobin, which make dietary restrictions unnecessary (13, 1). Compared to endoscopic screening (SIG, colonoscopy), the acceptance of FIT has been much higher and the costs lower (6, 14). The European Union recommends FIT for primary CRC
screening (15). However, effectiveness of CRC screening using a FIT has not been studied. Therefore, FIT should be incorporated into a screening program using a scientific protocol.

Few trials have assessed gender-specific performance and effectiveness of CRC screening. The US gFOBT trial showed significantly different reduction in the CRC mortality between males and females (37% vs. 8%) after 30 years of follow-up (16). In the UK gFOBT trial with 20 years of follow-up, mortality reduction was similar between genders (9% vs. 10%) (17). However, a recent cross-sectional analysis suggests that introduction of gFOBT screening in the UK had a greater impact on male than on female mortality, in spite of lower compliance in men (18). Also the Norwegian SIG trial has reported greater mortality reduction in men than in women (27% vs. 13%), and larger benefit for men has been evident also in the US and the UK SIG trials (19).

There are several explanations for the gender differences. The optimal age for screening initiation has been proposed to be 4 to 8 years higher for women than for men based on differences at cumulative 10-year incidence and mortality of CRC (20). Also, hemoglobin concentrations are, on average, higher among men than among women and women have a slow colonic transit time. As a result, degradation of hemoglobin before defecation may lower fecal hemoglobin concentration to a larger extent among women (21). Additionally, the upper and lower parts of large bowel are derived from two different embryonic tissues, leading to differential sensitivity to sex hormones and variations in carcinogenetic pathways (7). Consequently, more women than men have proximal and sessile serrated lesions, which have been shown to contribute to interval cancers (22, 23).

**Current strategy in Finland**

Organized, biennial CRC screening using gFOBT was launched gradually in 2004 in Finland using an individual randomization (1:1) to those invited and not invited (9). The target group included men and women aged 60-69 years. In 2014, the program covered approximately 50% of the target population. In 2004-2014, altogether 466 000 men and women had been individually randomized either to screening or to control arms (Malila, personal communication).

The effectiveness of the Finnish program was assessed in 2015, ten years after the launch of the program (11). Due to gradual expansion, the median follow-up time was 4.5 years (maximum 8.3 years). There was no difference in CRC mortality between the screening and control arms. However, CRC mortality among men had reduced by 12%. Among women, CRC mortality had increased by 33% (11). Both results were statistically non-significant but the difference between men and women was nearly significant (p 0.06).

A recent study covering municipalities within the Finnish CRC program concluded that screening had increased the need of hospital resources only slightly (24). Another study on CRC survival among the non-invitees in municipalities launching the CRC screening early (2004-2008) or late (2009-2013) found a spillover effect on mortality reduction (12% in men, 7% in women) in both municipality groups indicating an indirect benefit from CRC screening for both men and women (Miettinen, personal communication).
Compliance within the randomized CRC screening program in Finland has been considerably high and other performance parameters comparable to those of the European trials (25, 26). The program has also improved CRC diagnostics and treatment among the non-invited population. Nonetheless, the observed increase in CRC mortality in women and the evolution in the analytical capacity of screening tests induce a need to find a new screening strategy for both genders in Finland (7, 13).

**Aims and hypotheses**

The primary aim of the study is to implement a cost-effective strategy for CRC screening in Finland with a special focus on gender differences. Secondary aim is to improve further the uptake and performance of CRC screening.

Based on previous studies, we hypothesize that biennially offered immunochemical fecal occult blood testing (FIT) is a well-accepted, feasible, and valid CRC screening method for a long-term mortality reduction of 12-15% in a population aged 60-74 years. We also hypothesize than non-organized screening cannot deliver services uniformly to all members of the eligible population and cannot thus compete with an organized program in the early detection of colorectal neoplasias.

**Data and methods**

European Commission recommends CRC screening as a public health policy and thus it should be included in the National Act of Screening by the Ministry of Social Affairs and Health. The CRC screening program is to be coordinated centrally and implemented gradually to balance the benefits of detection with the harms and the burden of service provision.

The target population will be invited to biennial FIT test at ages 60-74 years with a gradually expanding scheme (implementation period of ten years, 2017-2026). Due to gender-specific differences in the cumulative incidence of CRC, there will be a special focus in the age of initiation. A centralized tendering process will be organized to acquire a valid, quantitative test with an adjustable cutoff for the preferred sensitivity/specificity level. To assess further the interrelations between gender-specific CRC incidence and screening, a questionnaire concerning risk factors of CRC, such as family history, symptoms and major lifestyle-related measures (alcohol use, smoking, BMI) will be created and sent to all screening invitees.

The outcome, detection of high grade adenomas and CRCs at screening and between the screening rounds (interval carcinomas), will be followed regularly. To validate the usefulness of the risk assessment, a random sample of high risk screen negatives will be invited to early colonoscopy in research settings (23).

The analyzing of FITs is to be centralized to maximally five areas, e.g. to the university hospital regions. Colonoscopies are organized regionally using a common quality assurance protocol. Data will be collected centrally to the Mass Screening Registry for monitoring and quality assurance.
Collaborative partners

The study is a collaborative venture between the Finnish Cancer Registry, the Helsinki University Hospital (HUS), the University of Helsinki, the Jyväskylä Central Hospital, the University of Oulu, the Tampere University Hospital and the University of Tampere. Professor Nea Malila (PI), Docent Ahti Anttila, Docent Sirpa Heintaaara, MSc Sanni Helander, MSc Suvi Mäkilä, Docent Janne Pitkäniemi, PhD Karri Seppä and PhD Tytti Sarkeala are responsible for planning and evaluation of the CRC screening implementation study. Professor Martti Färkkilä, Docent Matti Kairaluoma and Docent Marja Hyötty provide clinical expertise on colorectal cancer diagnostics, and are responsible for the regional coordination of CRC care and treatment.

Ethical considerations

The FIT program will be run as service screening. The risk based colonoscopy add-on will be conducted with ethical permission from the HUS Coordinating Ethical Committee and with informed consent from the participants. The data will be registered with permission from the authorities (National Institute for Health and Welfare).

References