Towards optimized colorectal cancer screening in Finland

Background

Colorectal cancer and screening

Colorectal cancer (CRC) is the third most common cancer in Finland subject to over 3300 new cases and 1200 deaths annually (1). The number of new cases is predicted to increase over 30% by 2030 (2). CRC is often diagnosed at an advanced stage with the 5-year relative survival of 40%, and it's one of the most expensive cancers in Finland (3, 4).

Premature CRC deaths can be prevented, if CRCs or their slowly growing precursors, adenomas, are detected at an early stage. Since screening aims to early detection, the EU recommended CRC screening to its member states as a public health policy already in 2003 (5). Recently, screening with fecal immunochemical test (FIT) has shown to decrease CRC mortality (effectiveness) by 10–40% (6).

The new FIT-screening program has started in Finland

CRC screening restarted in spring 2019. Screening test, an inexpensive FIT, is sent with a questionnaire to everyone in target population. Those participating take the specimen and return the test with the questionnaire to the screening laboratory. Participants with a positive test result, fecal blood in stool above the pre-defined cut-off, are referred to colonoscopy. Screening colonoscopies are subject to new criteria, quality assurance guidelines that are introduced with training (7).

This biennial FIT-screening started in nine voluntary municipalities targeted to 60-, 62-, 64- and 66-year old males and females. The screening will enlarge gradually and the whole target age group of 60–74 years will be reached in 2027. Subsequently, first CRC mortality results will be available in 2030's, and long-term effectiveness decades after that.

Towards optimized screening

Several studies have shown that men benefit from CRC screening more than women. In males, positive fecal occult blood test results are more common and may predict advanced adenomas and CRCs in colonoscopy better than in females (8). Given these and the higher incidence of CRC in males (1), it is not surprising that CRC mortality reduction due to screening has been found to be larger in males (33–37%) than in females (8–18%) (9, 10). The gender difference is seen also in costs: CRC screening is cost-effective for both genders but cost saving in men only (11). Despite of that, males and females are screened similarly in European CRC programs (12). Indeed, an optimal CRC screening strategy that would result most benefits, least harms, and equity with reasonable costs for all is not known yet.

Several contradicting approaches have been proposed to improve CRC screening. It may be beneficial to have gender-specific cut-offs but it is uncertain which way: will women benefit from a lower cut-off of a more sensitive FIT-test? Should the cut-off also differ by age, since

test positive rates are known to increase with age? (8). Men could also benefit from a younger starting age, since prevalence of advanced adenoma and CRC increase earlier in males (1, 13). Therefore, in an optimal screening strategy one may need to have test cut-offs by gender and age, and target ages (starting and stopping ages) by gender. It is further to note that screening with colonoscopy might also be a feasible screening strategy.

From equity point of view, everyone should be screened as needed by the risk of disease. In cervical cancer screening, for example, risk groups are invited with shorter intervals. Given limited resources it may be wise to tailor also CRC screening: persons at high CRC risk would be invited with short intervals and those at low risk with long intervals. It has been suggested, but not adequately studied, that information on family history of CRC, screening history, smoking, socioeconomic status and cumulative FIT concentrations can be used in determination of CRC risk levels (14, 15).

In the future, several time consuming and expensive CRC screening strategies cannot be implemented in practice for finding the optimal ones. Fortunately, long-term effectiveness and cost-effectiveness of screening can be predicted with modelling. For example, the previous Finnish screening program over 2004–2012 with a median follow-up time of 4.5 years, resulted in no statistically significant decline in CRC mortality (16). However, after 10-years of follow-up, a 9% reduction in CRC mortality would be expected (17).

Several Markov models have been created for predicting effectiveness and cost-effectiveness of CRC screening (18). Most of these models include parts for an unobservable natural history of the disease and an observable screening program. However, these country-specific and mostly non-transparent models cannot be directly applied to other countries (due to huge variation in underlying CRC risks and screening strategies). Also, recent findings on serrated pathway have not been included in any of these models yet. Serrated adenoma lesions were initially considered benign but they can actually be precursors of up to 1/3 of CRCs (18). This misspecification may affect also on available CRC model predictions.

Our newly started CRC screening program has potential to be effective and cost-effective with optimal test cut-offs, target ages and CRC risk groups by gender. Compared to the previous CRC screening, the new pilot is targeted to a wider age group, flexible screening test is adjustable to various cut-offs, and screening colonoscopies now follow European quality assurance guidelines. It is also of note that the recent government plan for the next four-year period included the implementation of nationwide CRC screening.

Aim and hypotheses

The **primary aim** is to obtain an optimal, effective and cost-effective CRC screening strategy by gender and age using new predictive models. Secondarily, we aim to assess whether CRC screening can be improved further by risk-based screening. Available registry data will be utilized for the study aims.

<u>Steps needed for optimal screening strategy:</u>

1 Develop new simulation model for CRC screening that is accurate, also by gender
2 Via simulation model, find optimal CRC screening strategy by gender and age with respect to effectiveness and cost-effectiveness
3 Explore possibility of risk-based improvement in CRC screening

Predictive models will first be developed by extending Markov based model to include FIT-screening with gender- and age-specific cut-offs. The optimally performing FIT-screening program will then be searched among feasible models with respect to effectiveness and cost-effectiveness. Colonoscopy will also be explored as an alternative screening test.
For risk-based screening we start by assessing the high CRC risk level, and other CRC risk levels will be studied when longer term screening data are available. If high CRC risk levels can be reliably estimated in the target population, we will then optimize FIT-screening strategy further with respect to screening intervals.

Study questions will be answered in scientific, peer reviewed articles. Program codes of the final predictive models will made freely available.

Material and methods

Data of the newly started CRC screening pilot, the previous CRC screening study, and cancer registry data are stored at individual level at the Finnish Cancer Registry. The new CRC screening pilot includes the questionnaire items on CRC risk factors on such as smoking and alcohol use.

Data on socioeconomic status and cause of death from Statistics Finland will be linked with these data and used for the high CRC risk assessment. For predictive models, other aggregate level data, such as population forecasts from Statistics Finland, will also be used. For cost-effectiveness analyses, costs and utilities will be gathered from published data.

A Markov model describing the adenoma-CRC sequence is implemented which allows gender- and age-specific features of CRC screening to interfere the natural history. Feasible alternative scenarios of biannual FIT-screening with gender- (and age-) specific cut-offs and target ages will be implemented. In colonoscopy screening, alternative target ages and screening intervals will be implemented. To verify the accuracy of the models, they will be subject to extensive validation and calibration including internal training and prediction sets. When possible, model predictions will also be externally validated with the well-established but non-transparent microsimulation model which is being developed for Finland within EU-TOPIA-project (https://eu-topia.org/). This microsimulation model is too inflexible as such to answer the study aims.

Persons diagnosed with advanced adenoma or CRC in screening colonoscopy are regarded as those at the high CRC risk. Random forest technique will be used to identify cut-offs for risk factors most separable in terms of CRC risk.

Time frame 2020–2022

The project will recruit one PhD student whose main task will be the programming of the predictive models. Writing of such models requires vast expertise on programming and mathematics. Therefore, a part-time senior expert will be hired in the study group. Our collaborators will provide clinical, methodological and epidemiological expertise. The first version of the model will be finalized within a year. Scientific articles for answering the study aims above are due on the second and third year.

Collaborative partners

The study is collaborative project between the Finnish Cancer Registry, Helsinki University Hospital (HUS), University of Helsinki, Jyväskylä Central Hospital, Oulu University Hospital, Tampere University Hospital, University of Tampere, Turku University Hospital, University of Turku and Aalto University School of Science, Department of Mathematics and System Analysis, Espoo. Docent Nea Malila (PI), Docent Ahti Anttila, Docent Sirpa Heinävaara, Professor Janne Pitkäniemi, PhD Karri Seppä and PhD Tytti Sarkeala are responsible for in-house advice and supervising the PhD student. Professor Martti Färkkilä, Professor Markku Voutilainen, Docent Matti Kairaluoma, MD Marja Hyöty, and Docent Tero Rautio will provide their clinical expertise on colorectal cancer diagnosis, care and surveillance needed for modelling. Assistant professor Pauliina Ilmonen will provide her strong theoretical and methodological expertise for modelling and novel approaches.

Ethical considerations

The study utilizes only registry data, most of which are stored at the Finnish Cancer Registry. Individuals in the screening target population will not be contacted. Research permission for this registry-based study will be updated (THL/179/5.05.00/2015) from the National Institute for Health and Welfare, and Statistics Finland concerning causes of death and socioeconomic data.

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