Tampere University

SANNI HELANDER

Aspects of Lifestyle and Symptoms in Colorectal Cancer Screening

A Population-Based Survey Study in Finland

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Social Sciences
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 5 August 2022, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Social Sciences
Finland
Finnish Cancer Registry
Helsinki, Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-2496-4 (print)
ISBN 978-952-03-2497-1 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2497-1

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2022

ACKNOWLEDGEMENTS

I have worked on my thesis at the Finnish Cancer Registry, which has during my time been led by Timo Hakulinen and later Nea Malila. I thank the Registy and all its current and former personnel for providing me with the facilities to carry out this work.

I owe my deepest graditute to my supervisor, Nea Malila. We first met when I was just a soon-to-be-graduated and her passion for research soon impressed me profoundly. Her vast expertise in epidemiology, endless support and genuine positive attitude has carried me through the whole thesis process.

I thank my other supervisor, Riitta Luoto. I am very grateful for her guidance and expertise during the last part of thesis, the summary writing. Her positive attitude and comments have given me lots of energy to work forward with finalizing the project.

My sincere gratitude goes to professor Marjukka Mäkelä, for kindly agreeing to be my opponent. I admire her commitment and enthusiasm for health care research and screening and deeply thank her for very warm and understanding attitude towards my thesis and flexibility with her timeline, in spite of her undoubtably busy schedule.

I want to acknowledge the contribution of the two official reviewers, professor Tiina Laatikainen and professor emerita Arja Aro. Thank you for agreeing to pre-examine the thesis and for your insightful remarks and feedback that helped me to tremendously improve this summary.

I express my thanks to my co-authors for contributing their valuable criticism and comments. Director of the Mass Screening Registry Tytti Sarkeala is thanked for her firm and persistent way of getting things done and spreading this enabling approach around her as well. I am sincerely grateful for Sirpa Heinävaara who patiently guided me through statistical hot spots and gave numerous comments to my articles. My

warmest thanks go to professor emeritus Matti Hakama for sharing even a scratch of his enormous knowledge in epidemiology and research design, not to mention discussions on ethics we had.

My thanks go to all the wonderful people who worked intensively during the data collection and management of the "Psychosocial consequences of colorectal cancer screening" -study. Liisa Rita, Ralf Simonsson, Jan Magnusson, Nina Simonsson, and Jonna Fredman, thank you for making the study possible.

I extend my thanks to all my co-workers at Finnish Cancer Registry and Finnish Cancer Society of Finland. I feel privileged that I have had such a good company at work. I especially want to thank Maija Jäntti, Lotta Patrikka, Maarit Lamminmäki and Milla Lehtinen for their friendship and sharing not only the high- but also the low moments at work life and outside work.

Although not contributing directly to this thesis, my friends and family have greatly influenced my way of thinking, feeling, and living a life: heartfelt thanks for all of you for always being there, being supportive, and most utterly, giving me lots of fun and meaningful outside the work life. Those I share my dreams with, you matter the most. Oula and Leeni, thank you for being the best ever happened to me.

This study has received financial support from Cancer Foundation of Finland and Doctoral Programs of Public Health which are gratefully acknowledged.

Nummela, April 2022

Sanni Helander

ABSTRACT

An essential part of the overall evaluation of any cancer screening programme is exploring its potential psychosocial effects. Colorectal cancer (CRC) screening may cause changes in health behaviour. In 2010, the Finnish Mass Screening Registry (MSR) began a population study on the lifestyle and quality of life effects of CRC screening. This thesis examines whether there were differential developments in self-reported lifestyle or lower gastrointestinal (LGI) symptom perception at ages 59–61 among CRC screening invitees and non-contacted controls. The role of perceived LGI symptoms in CRC screening attendance and the consequences of a postal survey study on cancer screening attendance were also investigated.

In the Finnish colorectal cancer screening programme, men and women aged 60 were randomized to screening and control groups (1:1). Lifestyle and symptoms were inquired about with a self-administered postal questionnaire one year before and one year after the first-ever CRC screening at age 60 or at a corresponding time for controls. From both survey rounds, 2508 pairs of completed questionnaires were available for analysis from the screening group and 2387 from the control group. The outcome was a 2-year change in the total lifestyle index of CRC risk factors (diet, physical activity, body mass index [BMI], alcohol consumption, and smoking status) (Study I) or a symptom index of eight various LGI symptoms reported as never, occasionally or constantly (Study II). For the association of pre-screening self-reported LGI symptoms and CRC screening attendance, incidence rate ratios were used (Study II). To estimate the potential harm of studying psychosocial consequences via postal survey, we sought to determine whether administering a pre-screening questionnaire affects the subsequent attendance proportion in the first-ever CRC screening and subsequent screenings (Studies III–IV). Furthermore, we investigated whether previous exposure to a lifestyle survey and additional cancer screenings during the same calendar year affected attendance to organized breast and cervical cancer screenings (Study V).

No differences in the CRC-related lifestyle between the screening arms or screening attendance were found. The lifestyle index used in the study changed in the negative direction from the CRC point of view during the two-year follow-up. However, there was no implication that screening status affected this progression. Results show that neither invitation to nor attendance in FOBT-based CRC screening leads to a less healthy lifestyle (Study I). Similarly, the temporal changes in symptom perception were congruent in controls and screening attenders and non-attenders, meaning no effects of screening on LGI symptom perception were presented. Pre-screening symptoms increased attendance to CRC screening in men. In women, symptoms did not affect the attendance (Study II).

In the 60-year-olds who had been sent the survey, the attendance in CRC screening was lower (57%) than in those who had not received the questionnaire (60%) (Study III). The same was observed after the follow-up survey in 2012. The screening attendance rate in 2013 was 58% in the survey population and 64% in those unsurveyed. The attendance pattern created by the initial survey continued even when questionnaires were no longer being sent. On the third screening round in 2015, the attendance rate was 62% among those who had been sent the questionnaires in 2010 and 2012 and 66% in those never surveyed ($P<0.001$) (Study IV). Survey intervention or additional cancer screening invitations did not affect the high attendance of breast and cervical cancer screenings (Study V).

The present study found no unfavourable changes in total lifestyle or LGI symptom perception in the studied age group due to CRC screening. Results are reassuring from the perspective of CRC screening evaluation. LGI symptoms merit attention in population education and information concerning CRC screening because perceived symptoms seem to affect screening attendance, at least among men. Exploring potential psychosocial effects must be carried out in a carefully planned and monitored manner not to harm screening attendance. Introducing a new cancer screening, i.e. CRC screening, resulted in another third cancer screening invitation during the same year for 60-year-old women, who were neither harmed nor benefited from the high attendance of breast and cervical cancer screenings.

TIIVISTELMÄ

Olennainen osa minkä tahansa syöpäseulontaohjelman kokonaisarviointia on sen mahdollisten psykososiaalisten vaikutusten tutkiminen. Suolistosyövän seulonnan on havaittu kansainvälisissä tutkimuksissa voivan aiheuttaa muutoksia terveyskäyttäytymiseen. Suomen Syöpärekisteri käynnisti vuonna 2010 väestötutkimuksen suolistosyövän seulonnan elintapa- ja elämänlaatuvaikutuksista. Tässä väitöstyössä tarkastellaan, vaikuttiko suolistosyövän seulontaan kutsun saaminen tai seulontaan osallistuminen valittuihin elintapoihin tai alemman maha-suolikanavan oireiden havaitsemiseen 59–61-vuotiailla. Lisäksi tutkittiin koettujen vatsaoireiden roolia suolistosyövän seulonnassa sekä postikyselytutkimuksen seurauksia eri syöpäseulontojen osallistumisen näkökulmasta.

Vuosina 2004-2016 käynnissä olleessa suolistosyövän seulontaohjelmassa 60-vuotiaat miehet ja naiset satunnaistettiin seulonta- ja kontrolliryhmiin (1:1). Elintapoja ja oireita tiedusteltiin postikyselyllä ensimmäistä suolistosyövän seulontaa edeltävänä vuonna (59-vuotiaana) ja seulontaa seuraavana vuonna (61-vuotiaana) sekä vastaavaan aikaan seulontaan kutsumattomille kontrolleille. Molemmilta kyselykierroksilta kertyi 2508 paria täytettyjä kyselylomakkeita seulontaryhmästä ja 2387 paria kontrolliryhmästä. Vasteena käytettiin kahden vuoden muutosta suolistosyövän riskitekijöihin kuuluvien elintapojen (ruokavalio, fyysinen aktiivisuus, painoindeksi [BMI], alkoholinkäyttö ja tupakointitila) muodostamassa kokonaiselintapaindeksissä (osatyö I) tai kahdeksan eri maha-suolistokanavan oireen muodostamassa oireindeksissä (osatyö II). Seulontaa edeltävien vatsaoireiden ja suolistosyövän seulontaan osallistumisen analyysiin käytettiin ilmaantuvuussuhteita (osatyö II). Arvioidaksemme seulonnan psykososiaalisten seurausten tutkimisen mahdollisia haittoja pyrimme selvittämään, vaikuttivatko postikyselyt suolistosyövän seulontaan osallistumiseen kolmella ensimmäisellä seulontakierroksella 60-64-vuotiaana (osatyöt III–IV). Lisäksi selvitimme rinta- ja kohdunkaulansyövän seulontojen osalta, vaikuttiko toteutettu elintapatutkimus ja kutsu kolmanteen eri syöpäseulontaan samana vuonna näiden ns. vanhojen syöpäseulontojen osallistumiseen (osatyö V).

Suolistosyöpään liittyvissä elämäntavoissa ei havaittu eroja seulontaryhmien välillä tai seulontaan osallistumisen mukaan. Tutkimuksessa käytetty elintapaindeksi muuttui kahden vuoden seurannan aikana suolistosyövän näkökulmasta lievästi negatiiviseen suuntaan. Seulonnan ei kuitenkaan havaittu vaikuttaneen tähän kehitykseen, vaan muutokset olivat samansuuntaisia eri ryhmillä. Tulokset osoittavat, että kutsu tai osallistuminen ulosteen veritestipohjaiseen suolistosyövän seulontaan eivät johda vähemmän terveellisiin elintapojen omaksumiseen (osatyö I). Samoin ajalliset muutokset alemman mahasuolikanavan oireiden havaitsemisessa olivat yhteneväisiä kontrolliryhmän ja seulontaan osallistuneiden sekä ei-osallistuneiden kutsuttujen joukossa, mikä tarkoittaa, että seulonnan vaikutuksia oireiden havaitsemiseen ei löydetty. Seulontaa edeltävät oireet lisäsivät miesten suolistosyövän seulontaan osallistumista. Naisilla oireet eivät vaikuttaneet osallistumisaktiivisuuteen (osatyö II).

Elintapa- ja elämänlaatukyselyille altistuminen alensi 60-vuotiaiden osallistumista elämänsä ensimmäiseen suolistosyövän seulontaan (osatyö III). Vastaava ilmiö todettiin vuoden 2012 seurantakyselyn jälkeen: vuonna 2013 suolistosyövän seulontaan osallistui 58 % heistä, joille oli lähetetty tutkimuskyselyjä vuonna 2020 ja 2012, ja 64 % heistä, joille kyselyjä ei oltu lähetetty. Ensimmäisellä seulontakierroksella muodostunut osallistumismalli jatkui myös aikaan, jolloin kyselylomakkeita ei enää lähetetty. Kolmannella seulontakierroksella vuonna 2015 (64-vuotiaat) seulontaan osallistui nimittäin 66 % niistä, jotka eivät olleet koskaan saaneet postikyselyjä, ja 62 % niistä, joille kyselyt oli lähetetty vuosina 2010 ja 2012 ($P<0,001$) (osatyö IV). Tutkimuskyselyiden lähettäminen tai kutsu kolmanteen syöpäseulontaan (suolistosyövän seulonta) saman kalenterivuoden aikana eivät kuitenkaan vaikuttaneet rinta- ja kohdunkaulansyövän seulontojen vakiintuneisiin osallistumistasoihin (osatyö V).

Tutkimuksessa ei havaittu suolistosyövän seulonnasta johtuvia epäsuotuisia muutoksia elämäntavoissa tai alemman mahasuolikanavan oireiden havaitsemisessa tutkitussa ikäryhmässä. Tulokset ovat huojentavia suolistosyövän seulonnan vaikutusten arvioinnin näkökulmasta. Erilaiset vatsan alueen oireet tulisi huomioida seulonnan kohdeväestön opastamisessa ja suolistosyövän seulonnasta tiedottamisessa, koska koetut oireet näyttävät vaikuttavan seulontaosallistumiseen ainakin miesten keskuudessa. Syöpäseulontojen piirissä on tärkeä tutkia myös muita seulonnan mahdollisia vaikutuksia kuin seulottavaan syövän sairastuvuuteen ja kuolleisuuteen kohdistuvia vaikutuksia, mutta erityisesti tutkittavilta itseltään vaivannäköä vaativissa tiedonkeruutapoja käytettäessä on se suunniteltava ja

toteutettava huolella, jotta seulontaan osallistuminen ei laske. Tutkimuksen myötä Suomessa on näyttöä, että uuden syöpäseulontaohjelman myötä 60-vuotiaille naisille kohdistuva tilanne kolmesta eri syöpäseulontakutsusta kyseisenä vuonna ei haittaa tai hyödytä heidän rinta- ja kohdunkaulansyövän seulontaosallistumistaan.

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ABBREVIATIONS

AVTK	Health Behaviour and Health among the Finnish Adult Population -study
BMI	Body mass index
CI	Confidence interval
CPR	The Central Population Register
CRC	Colorectal cancer
DNA	Deoxyribonucleic acid
FAP	Familial adenomatous polyposis
FCR	The Finnish Cancer Registry
FFQ	Food frequency questionnaire
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test/testing
FS	Flexible sigmoidoscopy
HNPCC	Hereditary nonpolyposis colorectal cancer
IARC	The International Agency for Research on Cancer
IRR	Incidence rate ratio
LGI	Lower gastrointestinal
MSR	Mass Screening Registry
NA	not applicable/available
NORDCAN	Cancer Statistics by the Association of the Nordic Cancer Registries
OR	Odds ratio
RCT	Randomized controlled trial
THL	The Finnish Institute for Health and Welfare
UC	Ulcerative colitis
UK	The United Kingdom
USA	The United States of America
WHO	The World Health Organization
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals (I-V). The original publications have been reprinted with the kind permission of the copyright holders.

I Helander S, Heinävaara S, Sarkeala T, Malila N. Lifestyle in population-based colorectal cancer screening study over 2-year follow-up. Eur J Public Health 2018:28(2); 333 – 338.

II Helander S, Heinävaara S, Sarkeala T, Malila N. Self-reported lower gastrointestinal symptoms in colorectal cancer screening. submitted

III Helander S, Hakama M, Malila N. Effect of a pre-screening survey on attendance in colorectal cancer screening: A double-randomized study in Finland. J Med Screen 2014:21(2); 82 – 88.

IV Helander S, Sarkeala T, Malila N. Embedded survey study harms colorectal cancer screening attendance: Experiences from Finland 2010 to 2015. J Med Screen 2018: 25(1); 51 – 54.

V Helander S, Heinävaara S, Sarkeala T, Malila N. Effect of a research intervention and additional cancer screening invitations on breast and cervical cancer screening attendance in Finland. submitted

1 INTRODUCTION

Colon and rectal cancer, i.e. colorectal cancer (CRC), is the third most commonly diagnosed cancer (65.7 persons per 100,000) and the second leading cause of cancer death (25.2 persons per 100,000) in Finland, according to the latest numbers published in 2019 (Finnish Cancer Registry 2021a). As a major public health problem, CRC calls for active preventive measures.

Screening and adhering to a healthy lifestyle represent two distinctive approaches to CRC prevention. Firstly, lifestyle choices are suitable for the primary prevention of CRC. Healthy habits such as not smoking, moderate alcohol consumption at most, physical activity, healthy eating, and avoiding obesity are associated with a significantly lower incidence of and mortality from CRC. A substantial proportion (20–70%) of CRC cases are preventable by following a healthy lifestyle emphasizing the role of health behaviours in CRC prevention (e.g. Parkin et al., 2011).

However, primary prevention practices are challenging, and the society and environment may make them even more so. Furthermore, adopting and maintaining a healthy lifestyle may lead to the reported 'health certificate effect' of CRC screening: individuals with negative screening results may perceive themselves as certified healthy and have reduced incentives to focus on a healthy lifestyle (Larsen et al., 2007).

Secondly, CRC can be addressed with the secondary prevention practice: screening. In screening, the purpose is to find cancer early to prevent death. Different screening methods for CRC exist, based on detecting blood in the stool as a potential sign of tumour or on endoscopic procedures in which the bowel is visually examined. Screening´s benefits of are always limited: It is estimated that 20% of CRC cases could be prevented, and mortality could be reduced by 15–20% (Hewitson et al., 2007; Jodal et al., 2019). Screening´s effectiveness of is mainly due to attendance level, test sensitivity and specificity, and functioning of the screening chain. A population-based programme for CRC screening was implemented in Finland in 2004 (Malila et al., 2005) with a target population of 60–69-year-old men and women.

The effectiveness of cancer screening is assessed as the change in screening-specific cancer mortality. Although the evidence on the effectiveness of CRC screening is convincing, other factors must still be investigated. Factors influencing attendance often vary from environment to environment and should be identified on a programme-by-programme basis.

Estimating the harms and benefits of screening for detecting cancer early is vital. Screening may carry various psychosocial consequences, some of which appear different according to the screening results. Since the expected effect of screening on CRC mortality is relatively modest, there should be minimal harm caused concerning the severity of the damage or the number of persons affected. Should screening have adverse side effects, these effects could counterbalance screening´s benefits (reduced CRC incidence and mortality), especially at the population level. Therefore, exploring screening´s potential impact on lifestyle, quality of life, and health behaviour is an integral part of identifying the harms of a screening programme. This thesis investigates the potential harms of Finnish CRC screening.

In CRC screening, concern has been expressed about the possible harms of screening on several lifestyle-related questions, e.g. regarding smoking, physical activity and dietary habits. It has been hypothesized that attending CRC screening might lead to an unhealthier lifestyle than the pre-screening period, known as the 'health certificate' effect due to misinterpreting the negative test result (Berstad et al., 2015; Deutekom et al., 2011). The opposing view argues that cancer screening participation might act as a 'teachable moment' □ a prompt for spontaneous behaviour changes towards a more health-promoting lifestyle or an opportunity to deliver behavioural cancer prevention interventions (Caswell et al., 2009; Senore et al., 2012).

Abdominal and intestinal symptoms are common in the population. These symptoms may affect the uptake of CRC screening through perceived susceptibility and the necessity of the screening (Wools et al., 2016). In turn, participation in the screening, the result of the screening, and the interpretation of the result may affect how individuals interpret and respond to the symptoms post-screening, whether the symptoms previously occurred or are new (Barnett et al., 2017). However, little direct evidence of the role of gastrointestinal symptoms in CRC screening exists.

The EU has recommended CRC screening since 2003, and screening programmes are under-way in several European countries and around the world (Navarro et al., 2017; Schreuders et al., 2015). Thus, screening is present in the lives of millions of people

yearly. Most of those who receive a screening invitation attend the screening, most of whom receive a negative screening result. Screening may not have any major impact on their lives. However, the issue of unintentional screening effects is worth exploring for the size of the potential target group.

In examining these potential effects of screening on, among other things, people's lifestyle habits, behaviours, and perceptions, research cannot rely solely on registry data. The information must be gleaned from the subjects, most typically through interviews and questionnaires. Employing the necessary research methods can damage the screening itself, i.e. participation a key factor in reaching the expected effects of screening. Evidence on the relationships between additional research interventions such as surveys and the willingness to attend cancer screenings are scarce, providing partly contradictory results (Banks et al., 1998; Watson et al., 2013).

Little evidence exists on whether introducing a new cancer screening programme (CRC screening) will affect participation in established female cancer screenings. In Finland, all women receive invitations to breast and cervical cancer screenings during the year they turn 60: half the women living in municipalities involved in a randomized CRC screening programme were also invited also to this third cancer screening. Multiple frequent invitations may impact screening behaviour differently than a corresponding number of invitations across several years.

The thesis aimed to identify the possible indirect harmful effects of CRC screening through the health behaviour of the screening invitees and control group. Such harms would reduce the benefits of an otherwise feasible screening programme, which are important to consider. In this respect, the potential psychosocial consequences of screening are one relevant issue in the overall evaluation of a screening programme. The thesis also aims to determine whether the survey study utilized harmed cancer screening attendance and assess the introduction of a third cancer screening from the perspective of breast and cervical cancer screening attendance.

The survey study used was embedded in the organized screening programme. Hence, the results likely reflect real-life circumstances and are applicable for programme evaluation and development. Moreover, the result can offer valuable insight into other screening programmes in countries where such issues might be of interest.

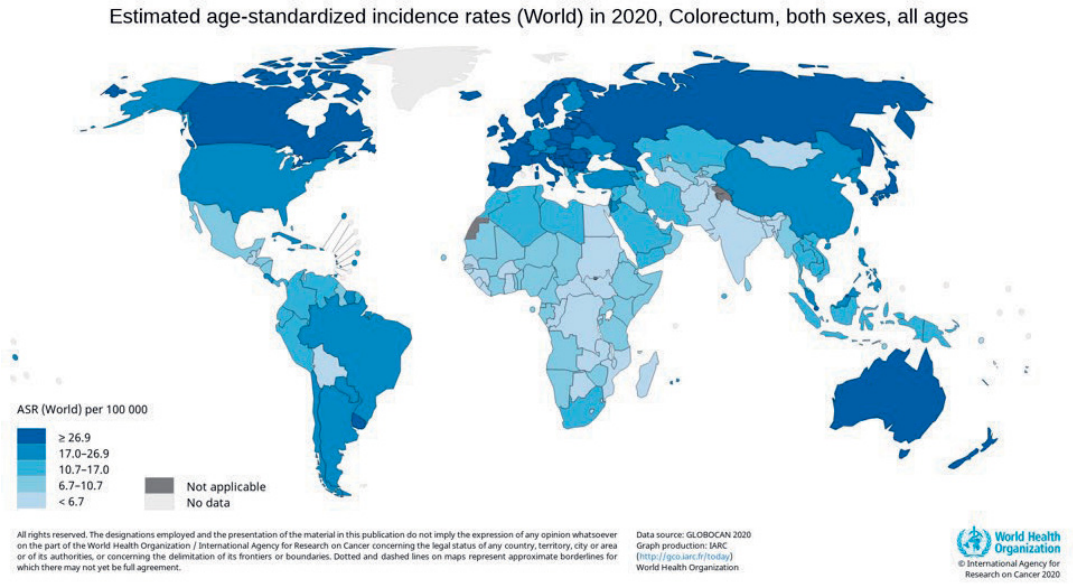
2 REVIEW OF THE LITERATURE

2.1 Colorectal cancer

2.1.1 Epidemiology of colorectal cancer

Colorectal cancer (CRC, also commonly known as bowel cancer) is the third most diagnosed malignancy and the fourth leading cause of cancer death in the world, with an estimated nearly 1.9 million new cases and 916,000 deaths in 2020, corresponding to almost one-tenth of the global cancer burden (Sung et al., 2021). CRC incidence and mortality rates vary widely – up to 10-fold – worldwide, with distinct gradients across human development levels: CRC incidence and mortality rates are rising rapidly in many low- and middle-income countries, whereas stabilizing or decreasing trends tend to be seen in highly developed countries. The incidence rates remain the highest in the world´s most affluent parts, namely Western countries, as shown in **Figure 1** (Arnold et al., 2017).

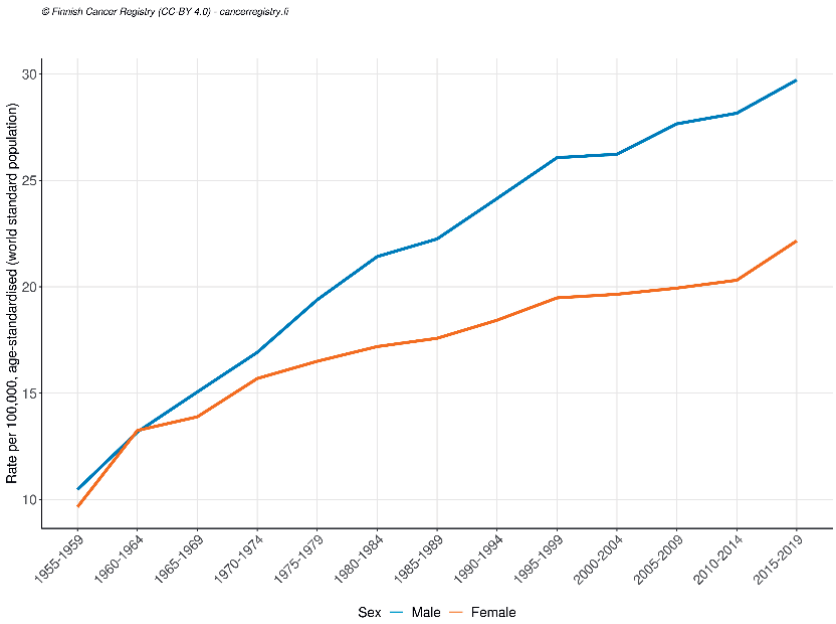
Figure 1. Colorectal cancer incidence globally in 2020, estimation (per 100,000 persons).



Source: GLOBOCAN 2020 (IARC), accessed 20.4.2021 http://gco.iarc.fr/today

Similar to many other Western countries, Finland has a high incidence rate of CRC. The incidence has risen during the past decades (**Figure 2**). In Finland, CRC is the third most common cancer after breast cancer in women and prostate cancer in men. CRC is the most commonly occurring cancer affecting both sexes and the second most common cause of cancer-related death (after lung cancer), with about 3400 new cases and 1300 deaths annually (Finnish Cancer Registry 2021a). Roughly one in 28 Finns will likely develop CRC by age of 80 (the overall lifetime risk of CRC of a Finnish woman by age 80 years is about 3% and about 4% for a man).

Figure 2. Time trend of colorectal cancer incidence in Finland in 1955–2019, age-standardized (World) rates per 100,000 persons.

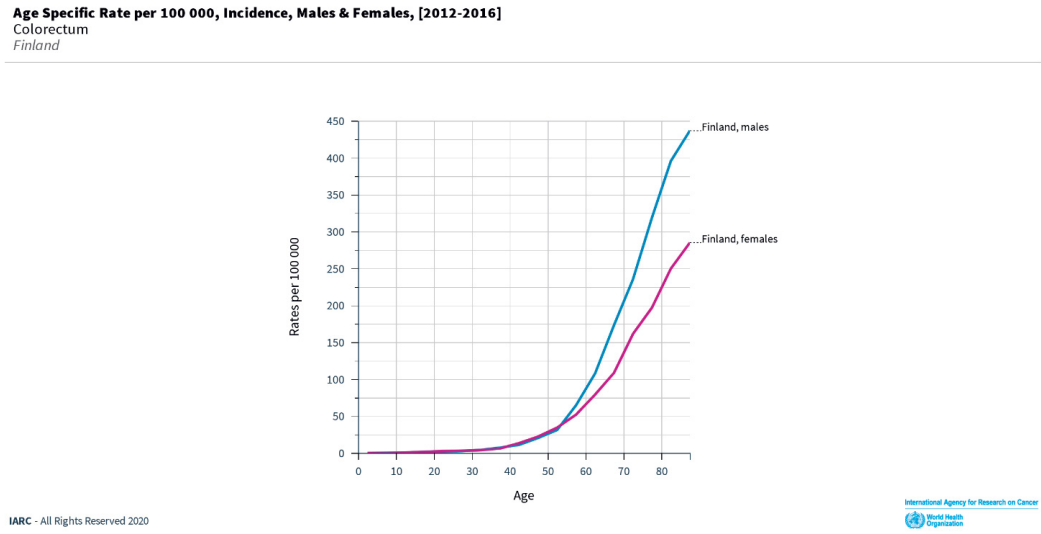


Source: Finnish Cancer Registry, https://tilastot.syoparekisteri.fi/syovat, data as of 7.4.2021, version 2021-04-27-002, accessed 25.7.2021.

The overall five-year relative survival of CRC patients in Finland is 66% (Finnish Cancer Registry 2021a). Survival strongly depends on the stage at diagnosis. It has been estimated that over 90% of early-stage CRC cases can be curatively treated, compared to approximately 10% of those with advanced disease, meaning the disease has spread to parts of the body other than the colorectum at diagnosis.

Like most cancers, CRC risk increases with age. With the incidence beginning to rise from age 40 and sharply after age 50, most new CRC cases are diagnosed after 60 (**Figure 3**).

Figure 3. Age-specific incidence rate of colorectal cancers diagnosed in Finland 2012–2016 by sex.



Source: NORDCAN: Cancer Incidence, Mortality, Prevalence, and Survival in the Nordic Countries. Data as of 26.3.2019, accessed 15.12.2020.

CRC accounts for about 10% of all cancer cases and around 10% of all cancer deaths in Finland (e.g. in 2019, there were 3628 new CRC cases among 35,327 cancers of any site and 1393 deaths due to CRC as compared to a total of 13,085 cancer deaths). In 2019, CRC accounted for 2.6% of all deaths in Finland (Official Statistics of Finland).

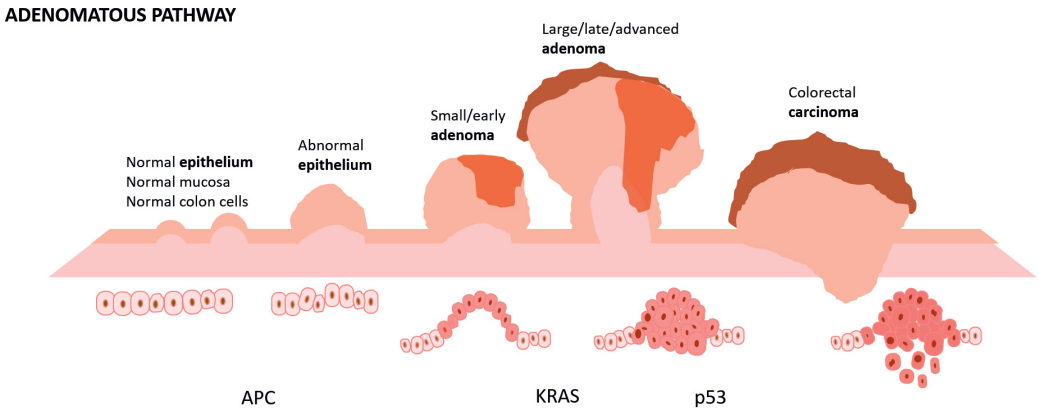
2.1.2 Natural course of colorectal cancer

The precise development of CRC is a multi-step process, the phases of which are not yet all fully understood. However, CRC cancer develops through precancerous stages, i.e. non-malignant polyps in the colon.

In the 1990s', a concept called the adenoma-carcinoma sequence initially suggested decades earlier (Morson, 1974) gained much attention. This sequence describes the gradual progression from normal to dysplastic epithelium to carcinoma associated with accumulating multiple genetic mutations (Leslie et al., 2002). Basically, this concept states that some adenomas in the colorectum begin growing, after which they might become malignant (**Figure 4**), providing a base for one fundamental prerequisite of

screening – that there must be a recognizable latent or early asymptomatic stage – or even preventing CRC by endoscopic removal of these kinds of precursor lesions.

Figure 4. Schematic diagram of traditional adenoma-carcinoma sequence of colorectal cancer.



The transformation occurs for about 10–15 years and is attributable to a set of mutations or deletions of oncogenes (APC, KRAS, p53) accumulating in the cell.

Adenomas are common in the population, though only a tiny fraction of them progress to malignancy. Although adenomas are estimated to be in 20–53% of the US population over age 50, the lifetime risk of developing adenocarcinoma is approximately 2–5% (Strum et al., 2016). Polyps with tubular histological patterns have the least malignant potential, whereas villous adenomatous polyps have the highest (IARC 2019). All CRCs were long believed to develop through adenomas. In recent years, a new route has been found along which CRC can develop: a serrated polyp pathway (or, more simply, a serrated pathway). This mechanism also involves the development of non-malignant polyps. However, unlike adenomas, these polyps are non-neoplastic, and sessile serrated lesions. About 15% of CRC cases are estimated to develop through this pathway. However, the debate over the significance and magnitude of the route´s impact is ongoing (Strum et al., 2016).

2.1.3 Symptoms of colorectal cancer

Symptoms in the CRC context are challenging in several ways. Firstly, CRC symptoms may be minor or nonexistent at the disease´s early stages (Kuipers et al., 2015). If early-stage CRC does cause symptoms, these may include abdominal pain, constipation, diarrhoea, variable bowel habits, and bloody stools. Sometimes tenesmus, mucous and sparse stools, or bloating and cramping are considered possible early warning signs of CRC. Anaemia and its consequences, such as fatigue, dyspnea, and dizziness, can act as symptoms of CRC, especially since rectal tumours often bleed (Hamilton et al., 2005; Majumdar et al., 1999; Rasmussen et al., 2015).

Secondly, interpreting gastrointestinal symptoms may be challenging. Early symptoms commonly do not get much attention. The symptoms often appear gradually, and they may resemble ailments that may have been present for a long time (Majumdar et al., 1999). Conversely, mild initial symptoms can be regarded as normal body functioning or misinterpreted as caused by benign conditions (Astin et al., 2011; Blackmore et al., 2020; Ford et al., 2008; Hall et al., 2015a; McLachlan, et al., 2015). Gastrointestinal symptoms are often benign and transient by nature. Their diagnostic predictive value for CRC is considered low, except for the symptom of 'rectal bleeding' (Adelstein et al., 2011; Astin et al., 2011; Ford et al., 2008; Huggenberger et al., 2015; Schult et al., 2021).

Although gastrointestinal symptoms are widespread in health care, epidemiological data at the population level are sparse. Abdominal and lower gastrointestinal symptoms seem highly prevalent in the population, and women are more likely than men to report symptoms (Avramidou et al., 2018; Rasmussen et al., 2015, Sandler et al., 2000). In a small Swiss survey, one in four females and one in seven males reported at least one symptom during the past year (Avramidou et al., 2018). In a Danish nationwide study with 49,706 respondents aged 20 and older, abdominal pain was the most common specific alarm symptom (20%). A total of 39% of the women and 31% of the men had experienced at least one of the four specific alarm symptoms (abdominal pain, change in stool texture, change in stool frequency, rectal bleeding) in the preceding four weeks. Authors classified some other gastrointestinal symptom non-specific (diarrhoea, constipation, abdominal bloating) as reported by 13–17% of the respondents (Rasmussen et al., 2015). An older US telephone survey found that 42% of the respondents reported at least one digestive symptom during the past month. Women

reported abdominal pain or discomfort and bloating or distension more often than men, but not diarrhoea or loose stools.

In Finland, no detailed epidemiological study on the prevalence of gastrointestinal symptoms was found. However, the annual postal survey "Health Behaviour and Health among the Finnish Adult Population" (AVTK) carried out from 1978 to 2014 also, to some degree, addressed selected general symptoms in section 'Health services and health status'. The questionnaire included a question on the incidence of 15 symptoms and complaints in the past month. According to the spring 2010 survey[1], 24% of 55–64-year-old women reported indigestion and 11% constipation. Of men of the same age group, 18% reported having experienced indigestion and 3% constipation. Corresponding figures in 2012 were 23% and 13% (indigestion and constipation among women) and 18% and 6% in men, respectively (Helakorpi et al., 2011; Helldán et al., 2013).

There is some information available about why or in which circumstances people do or do not seek medical attention for gastrointestinal symptoms that are possibly suggestive of CRC – quantitative (Jarbøl et al., 2018; Mitchell et al., 2007) and qualitative (Blackmore et al., 2020; Hall et al., 2015a; McLachlan et al., 2015). Apparent changes in abdominal and intestinal function should always be sufficient reasoning to seek medical attention. However, because the symptoms associated with CRC are often intermittent, gradual, and similar ailments may have occurred in the past, they are not necessarily considered severe; thus there is a delay in seeking for medical evaluation (Blackthorne et al., 2020; Mitchell et al., 2007). One barrier to seeking help is that some feel the symptoms of the intestinal tract are embarrassing or sensitive; therefore, they delay proactive measures (Hall et al., 2015; Jarbøl et al., 2018). Other reasons for putting off contact with health care may include worrying about wasting the GP's time, fearing of what the GP might find, and being too busy to consult the GP (Jarbøl et al., 2018). Also, seeking medical attention can be influenced by systemic reasons. Access to treatment can be tricky, or trust in accessing more accurate examinations and/or tests may be low.

In the context of CRC screening, symptoms have been researched from multiple viewpoints. Firstly, the role of gastrointestinal symptoms in screening participation is

[1] selected study year due to comparability with "Psychosocial consequencies of colorectal cancer screening" -study

studied. Denters et al. (2015) found that the most frequent reasons for declining home test -based CRC screening were having another disease or being under medical treatment (32%), the absence of symptoms (29%), and the perception that the test is bothersome (18%). They point out that since screening aims to detect disease primarily in asymptomatic persons, it can be considered worrisome that the absence of symptoms is a widely reported reason for declining screening (Denters et al., 2015). Overall, the perception that screening is unnecessary is a common barrier to screening (Honein-AbouHaidar et al., 2016; Wools et al., 2016); a lack of symptoms may be misunderstood to mean that screening is unnecessary. More generally, one established facilitator of CRC screening participation is perceived as susceptibility to CRC (Wools et al., 2016), and experiencing symptoms may understandably reinforce that susceptibility (Robb et al., 2004). Unfortunately, I did not find any original research measuring the explicit association between perceived symptoms and screening participation.

Secondly, research focuses on how many CRC screening attenders experience symptoms (including what symptoms and whether the attender sought medical help for them). A large proportion of those who test positive for faecal occult blood test (FOBT) experience symptoms. Among FIT-positives in Norway, 34% reported at least one symptom (Schult et al., 2021). De Klerk et al. (2018b) found that 47% of screening positive participants reported CRC-related symptoms even though in the Dutch screening programme symptomatic invitees are advised to refrain from screening and instead to directly consult their GP. Likewise, two previous studies assessed symptoms in an FOBT-positive screening population and observed even higher proportions of symptomatic participants: Saldanha et al. (2013) described that 52% of Scottish FOBT-positive screening participants had CRC-related symptoms, and Ahmed et al. (2005) reported as much as 78% FOBT-positive Scottish screening participants symptomatic. The information leaflet used in the Scottish screening programme does not explicitly urge invitees to opt out of screening if they have symptoms but seek medical consultation from their general practitioner for symptoms, which may at least partially explain the higher proportion of participants considered symptomatic.

Thirdly, whether gastrointestinal symptoms have predictive value for adenomas or CRC in CRC screening has been investigated. Most screen-detected CRCs are found in asymptomatic participants (Schult et al., 2021; de Klerk et al., 2018b; Saldanha et al.,

2013). Generally, symptoms other than rectal bleeding do not have much of a predictive value for precursors or carcinoma in the screening context.

2.1.4 Established risk and protective factors of colorectal cancer

A risk factor refers to a single factor increasing person´s likelihood of getting sick with a certain disease; a protective factor decreases likelihood. The exact cause(s) of the CRC are unknown; correspondingly, all risk factors for CRC are not known. No single risk factor accounting for most cases of CRC exists, as is the case for some other cancer sites, e.g. the lungs (smoking) or the skin (ultraviolet radiation). Obviously, environmental and genetic factors play a role. However, several known risks and protective factors for CRC are known and they are grouped in this chapter as modifiable and non-modifiable. The more prominent factors (assessed by population attributable fraction when available and level of evidence) are presented first, followed by the less important. Those risk or protective factors, of which the evidence is at least probable, coupled with the relative magnitudes of their effect, are in **Table 1**. The main source for the risk and protective factors information in this thesis is the latest report from the Continuous Update Project (CUP) led by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018) for its status as a trusted, authoritative scientific resource.

Although the factors categorized here as modifiable are often considered at least partly resulting in individual behavioural choices, one should remember that environment (e.g. practical, sociocultural, economic, and marketing influences) pose serious challenges to achieving and maintaining a healthy lifestyle.

Modifiable risk and protective factors

Dietary factors

Strong evidence exists on several items affecting CRC risk, namely dietary fibre, whole grains, meat, and dairy products (**Table 2**, World Cancer Research Fund/American Institute for Cancer Research [WCRF/AICR] 2018).

Table 1. Established risk and protective factors for CRC and associated relative risk. (Adopted IARC 2019).

Risk factors	Categories	RR (95% CI)	Reference
Processed meat consumption	Per 50 g/day	1.16 (1.08–1.26)	WCRF/AICR 2018
Red meat consumption	Per 100 g/day	1.12 (1.00–1.25)	WCRF/AICR 2018
Alcohol consumption	Per 10 g/day of ethanol	1.07 (1.05–1.07)	WCRF/AICR 2018
Body fatness	Per 5 kg/m2 of BMI	1.05 (1.03–1.07)	WCRF/AICR 2018
Abdominal girth	Per 10 cm of waist circumference	1.02 (1.01–1.03)	WCRF/AICR 2018
Tobacco smoking	Never smokers	1.00	IARC (2012)
	Current smokers	1.15 (1.00–1.32)	
	Former smokers	1.20 (1.04–1.38)	
Attained adult height	Per 5cm	1.05 (1.02–1.07)	WCRF/AICR 2018
Sex	Female	1.00	Ferlay et al., 2018; IARC 2019
	Male	1.47	
Age	45–49 years	1.00	IARC 2019
	50–54 years	1.75	
	55–59 years	2.85	
	60–64 years	4.33	
	65–69 years	6.30	
	≥ 70 years	10.29	
Protective factors			
Dietary fibre	Per 10 mg/day	0.91 (0.88–0.94)	WCRF/AICR 2018
Whole grains consumption	Per 90 g/day	0.83 (0.78–0.89)	WCRF/AICR 2018
Dairy products consumption	Per 400 g/day	0.87 (0.83–0.90)	WCRF/AICR 2018
Milk intake	Per 200 g/day	0.94 (0.92–0.96)	WCRF/AICR 2018
Calcium intake (dietary or supplemented)	Per 300 mg/day	0.92 (0.88–0.94)	Keum et al., 2014
Physical activity (total level)	Low	1.00	WCRF/AICR 2018
	High	0.81 (0.69–0.95)	
ASA use	Never used	1.00	Ye et al., 2013
	Ever used	0.74 (0.64–0.83)	
	Per 325 mg/day	0.80 (0.74–0.88)	
	Per 7 days a week	0.82 (0.78–0.87)	
	Per 10 years of use	0.82 (0.78–0.86)	
HRT use	Never used	1.00	Green et al., 2012
	Ever used	0.84 (0.81–0.88)	
	Current use	0.77 (0.73–0.82)	
	Former use	0.89 (0.84–0.95)	

Possible differences related to subsite or sex-related differences in the magnitude of risk are not considered here.
RR=relative risk, CI=confidence interval, BMI=body mass index, ASA=acetylic-salicylic acid, i.e. aspirin; HRT=hormone replacement therapy

Table 2. Level of evidence on dietary factors, physical activity, and risk of CRC in 2011 and 2018.

Level of evidence		2011		2018	
		Decreases risk	**Increases risk**	**Decreases risk**	Increases risk
Strong evidence	Convincing	Physical activity Dietary fibre	Processed meat Red meat Body fat Abdominal adiposity Adult height	Physical activity	Processed meat Alcoholic drinks Body fat Adult height
	Probable	Milk Calcium Wholegrains Garlic	Alcoholic drinks	Dietary fibre Whole grains Dairy products Calcium supplements	Red meat
Limited evidence	Suggestive	Non-starchy vegetables Fruits Vitamin D	Cheese Foods containing sugar Foods containing haem iron Foods containing animal fats	Foods containing vitamin C Fish Vitamin D Multivitamin supplements	Low intake of non-starchy vegetables Low intake of fruits Foods containing haem iron
	No conclusion	e.g. glycaemic index, fish, folate, vitamin C, vitamin E, selenium, low fat, dietary pattern		e.g. potatoes, animal fat, poultry, fatty acid composition, cholesterol, legumes, garlic, coffee, tea, vitamin A, vitamin B6, vitamin E, selenium, low-fat, energy intake, meal frequency, dietary pattern	

Source for 2018: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. Available at dietandcancerreport.org
Source for 2011: Colorectal cancer 2011 report: food, nutrition, physical activity, and the prevention of colorectal cancer. World Cancer Research Fund / American Institute for Cancer Research 2011. http://www.wcrf.org/int/research-we-fund/continuousupdate-project-findings-reports/colorectal-bowel-cancer

A diet rich in foods containing high levels of dietary fibre decreases CRC risk. The same goes for whole grains, for which there are established dose-response relationships (Aune et al., 2011; WCRF/AICR, 2018). The protective effect appears to be stronger for fibre from grains than from other sources like fruits and vegetables (Hullings et al., 2020). High fibre intake may lower CRC risk by reducing of colonial transit time and increasing faecal bulk, with decreased secondary bile acid production. Moreover, whole grains are a good source of several bioactive compounds such as vitamin E, selenium, zinc, lignans, and phenolic agents, many of which may have anti-carcinogenic properties in the human body (Slavin et al., 1999).

Consuming red and processed meat increases CRC risk. There is also suggestive evidence that consuming foods containing haem iron increases CRC risk (WCRF/AICR

2018). Processing can refer to various acts but often includes cooking at very high temperatures such as grilling or frying, by which heterocyclic amines and polycyclic aromatic hydrocarbons (PAHs) are formed. For preservation purposes, processed meat often contains many carcinogenic N-nitroso compounds. Haem iron promotes colorectal tumorigenesis because it stimulates the formation of N-nitroso compounds.

Dairy consumption (e.g. milk, yoghurt, and cheese,) is protective against CRC, with a clear dose-response relationship (Barrubés et al., 2019). Calcium will likely mediate the effect (Keum et al., 2014), for which evidence of a protective effect is considered probable (WCRF/AICR 2018). Several dietary supplements have been studied, but none have shown a conclusive protective effect for CRC. Meta-analyses of observational studies suggest multivitamins and calcium supplements play a beneficial role in CRC risk, while the association between other supplements and CRC risk is inconsistent (Heine-Bröring et al., 2015).

Evidence also exists that fish might lower CRC risk (Norat et al., 2005). Moreover, diets rich in non-starchy vegetables and fruits appear to protect against CRC, based on suggestive evidence (WCRF/AICR, 2018).

In 2011, the panel of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) in the Continuous Update Project (CUP) judged the available evidence that foods high in dietary fibre protect against developing CRC and that consuming red and processed meat and alcohol (especially in men) increase the risk of CRC as 'convincing'. Milk and calcium have been related to a 'probable ' reduction in CRC risk, whereas evidence is 'limited ' regarding a possible protective effect of folate, selenium and vitamin D (World Cancer Research Fund/American Institute for Cancer Research, 2011).

Compared to the WCRF/AICR report published in 2011, the level of evidence has changed for some foods or nutrients. In 2011, cheese was considered separate from other dairy products, and its use was considered to increase the risk of cancer. The effect of sweets and animal fats on CRC was also estimated as 'likely' to increase the disease. The evidence of the protective effect of garlic was considered 'probable'. See the differences between 2011 and 2018 in **Table 2**.

Body composition

Being overweight or obese increases CRC risk. The association between obesity and colon and rectal cancer risk varies somewhat by sex and cancer site: Overall, increased BMI relates to an increased risk of colon cancer in both sexes (Robshavn et al., 2013). The association is still stronger in men: In men, CRC risk rises by about 8% for every 5 kg/m3 increase in BMI, whereas in women the risk increases about 5% (WCRF/AICR 2018). BMI is positively associated with rectal cancer in men but not necessarily in women. Also, a larger waist circumference elevates CRC risk in both sexes (Larsson & Wolk, 2007). Obesity causes many hormonal, metabolic, and other changes that may affect carcinogenesis, including insulin resistance and hyperinsulinemia, inflammatory responses, promotion of chronic low-level inflammation, altered levels of adipokines like leptin and adiponectin and excess growth factors (Ye et al., 2020).

Being tall increases CRC risk because the reasons for greater attained adult height – genetic, environmental, hormonal, and nutritional factors – are also causative for CRC. The association between adult height and CRC risk is more evident in women than men and for colon cancer than rectal cancer, respectively (WCRF/AICR 2018).

Physical activity and sedentariness

Being physically active decreases CRC risk (Robshavn et al., 2013, WCRF/AICR 2018). Overall, a strong relationship exists between risk reduction and physical activity. Moreover, exercise does not need to be intense or long-lasting to have substantial benefits. This association is plausibly supported by multiple biological mechanisms such as decreased inflammation, reduced intestinal transit time, reduced levels of insulin-like growth factors, reduced hyperinsulinemia, and modulated immune function with physical activity (Wolin et al., 2009).

Sedentary behaviour is associated with elevated colon cancer risk (Schmid & Leitzmann, 2014; Morris et al., 2018). It is defined as "waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture" (Tremblay et al., 2017), meaning the time a person is sitting or lying down, e.g. watching TV, using computer/smart-phone, driving or riding a vehicle, and reading.

Tobacco smoking

Smoking increases the incidence and mortality of CRC (WCRF/AICR 2018). Smoking two packages a day (40 cigarettes) increases CRC risk by about 40% and nearly doubles the risk of CRC death (Liang et al., 2009). Dose-response studies also clearly demonstrate that CRC risk rises with the increasing frequency and duration of smoking. The risk is consistently higher for rectal cancer than colon cancer (Liang et al., 2009). The exact mechanism of how cigarette smoking promotes CRC development remains somewhat unclear. However, smoking probably causes alterations in bowel microbiota and their metabolites, resulting in gut barrier dysfunction and activation of oncogenic and proinflammatory signalling pathways, thus contributing to colorectal tumorigenesis (Bai et al., 2022).

Alcohol

Consuming alcoholic beverages increases CRC risk, with a monotonic dose-dependent relationship above 30 g/day (about two drinks per day) (Shin et al., 2014; WCRF/AICR, 2018). The risk is greater in men than in women and irrespective of the type of alcoholic beverage consumed. The mechanisms of carcinogenesis operating in humans are versatile and well-established, including the carcinogenic nature of acetaldehyde – the main metabolite of ethanol oxidation.

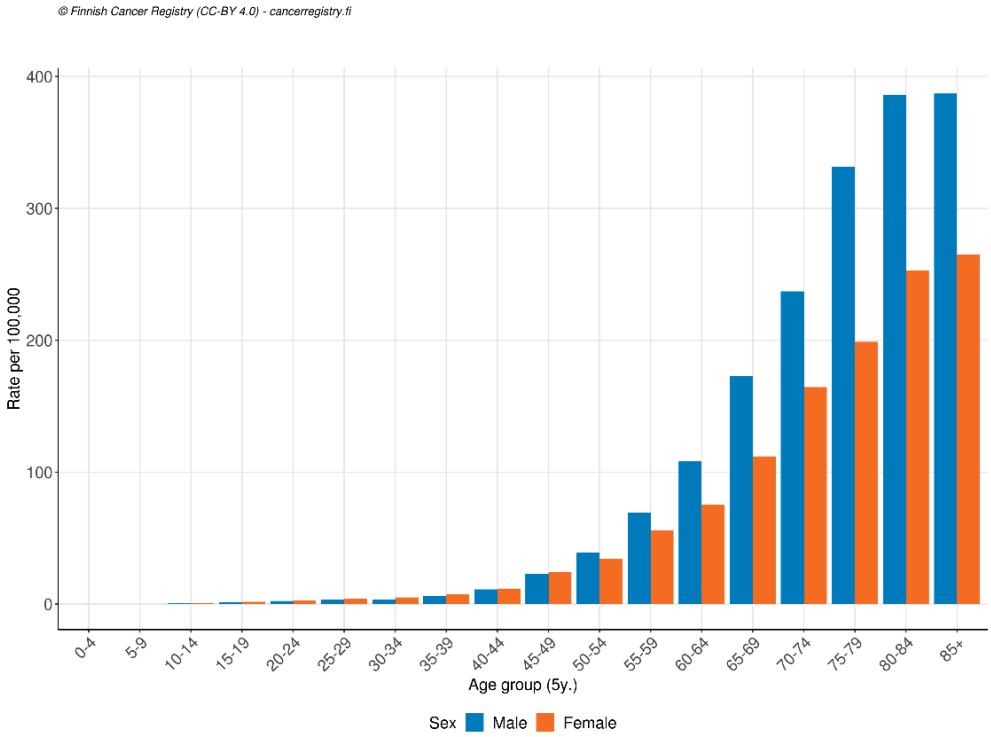
Non-modifiable risk and protective factors

Age

As for cancer overall, age is the biggest single risk factor for CRC. The risk of CRC rapidly increases after age 50; most cases and deaths occur in people over 60. Of the worldwide burden of 1.80 million incident cases in 2018, 0.18 million (10%) were estimated to occur in people younger than 50, 1.07 million (59%) in those aged 50–74, and 0.55 million (31%) in those aged 75 and older (IARC, 2019). In Finland, of the yearly burden of approximately 3400 cases (data based on 2014–2018, Finnish Cancer Registry 2021a), 5.5% were diagnosed younger than 50, 53% occurred in those aged 50–74, and 41.5% in those aged 75 and older (see also **Figure 5**). Corresponding risk ratios by age group were in Finland: 1.56 for 50–54-year-olds, 2.66 for 55–59-year-olds, 3.89

for 60–64-year-olds, and 6.00 for 65–69-year-olds; the 45–49-year-old age group served as reference group with a risk ratio 1.00 (compare with **Table 1**).

Figure 5. Colorectal cancer incidence (per 100,000) for both sexes by 5-year age groups in Finland 2015-2019.



Source: Finnish Cancer Registry, https://tilastot.syoparekisteri.fi/syovat, data as of 7.4.2021, version 2021-04-27-002, accessed 24.7.2021.

Sex

In general, the incidence of CRC is higher in men than in women. The male-female disparity in the age-related risk of CRC is probably due to sex differences in the exposure to and possibly in the effects of lifestyle-related risk factors. Interactions between estrogen exposure, body fat distribution, and the biological features of colorectal tumours also may explain sex-related differences and the higher proportion of proximal colon cancers in women than in men (White et al., 2018).

Also, in Finland, more males develop CRC, with age-standardized (Finland 2014) rates of 71.4 per 100,000 males compared to 49.8 per 100,000 females in Finland in 2014–2018 (equating to, on average, 1800 male and 1600 female new cases annually, and RR of 1.43 for men compared to women) (Finnish Cancer Registry, 2021a). CRC mortality rates are also higher in men (age-standardized rates of 28.3 per 100,000 males and 18.1 per 100,000 females). Mortality rates are higher for males than for females in all age groups from 30 to 34 and over; the gap is widest at the ages of 75–79, when the male to female age-specific mortality rate ratio is around 1.9:1.

Medical conditions

Long-standing inflammatory bowel disease (IBD), i.e. ulcerative colitis (UC) and Crohn's disease increase the risk of colon cancer. IBDs are characterized by chronic inflammation of the gastrointestinal tract, which may lead to the high levels of pro-inflammatory cytokines accumulating within the colon mucosa, leading to dysplastic lesions and cancer. The association is well documented. However, reported risk estimates widely vary. CRC risk is more elevated in patients with longer disease duration, extensive disease, and IBD diagnosis at a young age (Lutgens et al., 2013). A recent sizeable register-based study on the Swedish and Danish populations found that individuals with UC are at increased risk of developing CRC, diagnosed with less advanced CRC, and an increased risk of dying from CRC compared with those without UC. However, these excess risks have markedly declined over the past decades because of developments in UC treatment and surveillance (Olén et al., 2020). A Finnish nationwide study assessing overall and cause-specific mortality in IBD patients found that patients with UC had increased mortality from cancers of the colon, rectum, and biliary tract (Jussila et al., 2014).

Medication

Long-term, low-dose, and regular use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) reduces CRC risk in average-risk individuals (Huang et al., 2015; Rostom et al., 2007; Rothwell et al., 2010). Using cyclooxygenase-2 (COX-2) inhibitors (which cause fewer gastrointestinal side effects than aspirin or other traditional NSAIDs) has reduced the risk of adenomas in randomized controlled trials (Rostom et al., 2007; Thompson et al., 2016). However, since these medications are

associated with important harms (mostly cardiovascular and/or gastrointestinal) the risk-benefit balance does not favor chemoprevention in average-risk individuals.

Hormone replacement therapy (HRT, including different forms and doses of estrogen, alone or combined with progestogen) in postmenopausal women is associated with a reduced risk of CRC according to a meta-analysis of four RCTs and 16 observational studies (Lin et al., 2012). Moreover, HRT usage is associated with lower risks of CRC-specific and overall mortality in patients with CRC (Jang et al., 2019). Yet, since HRT usage is associated with an increased risk of breast, endometrial, and ovarian cancer, HRT cannot be recommended for chemoprevention for CRC.

Metformin, a commonly used tablet-form medication for type 2 diabetes, appears to have a protective effect against CRC in patients with type 2 diabetes, but the risk-benefit balance in a diabetes-free population is unknown (Higurashi & Nagajima, 2018).

Genetic syndromes and family history

While most CRC cases are sporadic, some can be linked to a specific inherited cancer syndrome or other less pronounced genetic factors. Approximately 5% of CRC cases are found in individuals with cancer syndrome. The two major ones are familial adenomatous polyposis (FAP) and Lynch syndrome (also known as hereditary non-polyposis colorectal cancer [HNPCC]). People with FAP have a mutation in the tumour-suppressor gene APC that regulates cell growth developing numerous adenomas at a relatively young age; if left untreated, nearly all will develop CRC by the time they turn 40. On average, people develop HNPCC in their mid-forties; having this form of the disease also increases the risk several other gastrointestinal cancers. Depending on the gene, there is a 15 to 46% risk of developing colon cancer by age of 75. HNPCC involves mutations in DNA repair genes (Mecklin et al.,1995).

People with a positive family history but without an identified cancer syndrome are also at an increased risk for developing the disease; other inherited factors increase CRC risk (Lowery et al., 2016). Although, the cancer is not inherited, the genetic alterations increasing the risk of developing cancer do. Lifestyle, together with other environmental factors, still plays a role in the risk of getting the disease.

2.2 Colorectal cancer screening

The three classical dimensions of prevention include primary, secondary, and tertiary prevention. Primary prevention is often described as preventing a disease, i.e. intervening before health effects occur. From the individual perspective, this means using measures such as getting vaccinated, modifying risky behaviours, and avoiding substances hazardous to health. Secondary prevention refers to detecting the disease early, thus preventing the disease from progressing. Medical screening is a classic example of secondary prevention since it aims to identify disease before the onset of symptoms. Tertiary prevention can be defined as improving one's quality of life and relieving a health problem's consequences – in other words, different acts of treatment and rehabilitation.

CRC is an special type of cancer among all cancers, for it is well-suited for primary and secondary prevention, screening, and has numerous predisposing factors. At least 40% of CRCs are considered preventable (Parkin et al., 2011).

2.2.1 Principles of cancer screening and why colorectal cancer is suitable for screening

The World Health Organization (WHO) defines screening as "the presumptive identification of unrecognized disease in an apparently healthy population using tests, examinations or other procedures that can be applied easily to the target population" (Sagan et al., 2020). More straightforwardly screening can be described as systematically testing in individuals to identify a specific disease or its risk factors.

Screening aims to lower the burden of screened disease in the population achieved by detecting the disease in its preclinical stage when the treatment would be more effective and disease-related deaths could be prevented. Screening is particularly suitable for diseases with a defined preclinical phase, such as cervical cancer or CRC, in which evidence of a benefit in the outcome from early detection and treatment is present.

Screening does not mean just using the screening test in the target population but refers to a cascade of activities that must occur promptly in an organized way for screening's benefits to be realized. Unlike opportunistic screening or case finding, organized programmes can ensure high coverage, equity of access, and enable comprehensive quality assurance (von Karsa et al., 2013). In the organized screening programme target

populations are systematically invited, and follow-up of those with a positive screening test is ensured. The quality of each step in the screening process is measured, reported, and evaluated. In turn, opportunistic screening is delivered on an ad hoc basis, where uptake depends on requests from individuals or recommendations from health care providers. Due to a lack of organization, opportunistic screening is at greater risk of overusing and underusing resources, resulting in a dearth of or suboptimal effectiveness and increasing inequality.

Although screening implemented in an organized manner has many advantages over an unorganized one, any screening programme brings burdens (e.g. primary testing and waiting for the result), harms (e.g. complications of follow-up examinations), and financial costs. Several criteria should be fulfilled before implementing a mass screening programme. One characteristic of screening programmes – typical for population-level health care measures – is that relatively few individuals directly benefit from screening, while many are exposed to minor, adverse effects. Therefore, screening's intended effects (reduced disease-specific mortality) must outweight the unfavourable effects (false positive screening results, physical and psychosocial harms, overdiagnosis) (Sagan et al., 2020).

In 1968, Wilson and Jungner proposed the first set of requirements for population-based screening in a WHO-commissioned report (**Table 3**, Andermann et al., 2008). Their screening principles are still regarded as a gold standard when deciding on the implementation, continuation or discontinuation, and evaluation of screening programmes (Sagan et al., 2020).

Table 3. WHO criteria for screening. Criteria proposed by Wilson and Jungner (1968) according to Andermann et al. (2008)

The condition sought should be an important health problem.
There should be an accepted treatment for patients with a recognized disease.
Resources for diagnosis and treatment should be available.
There should be a recognizable latent or early symptomatic stage.
There should be a suitable test or examination, that is acceptable to the population.
The condition's natural history should be adequately understood, including its development from latent to declared disease.
There should be an agreed policy on whom to treat as patients.
The cost of case-finding (including diagnosing and treating the patients who are diagnosed) should be economically balanced concerning possible expenditures on medical care overall.
Case-finding should be a continuing process, not a "once and for all" project.

Forty years from the original publication and after many screening programmes have been implemented globally, the WHO criteria were updated (**Table 4**, Andermann et al., 2008). Several emerging criteria reflect developments that have influenced Western medicine and society more generally in recent decades, e.g. consumerism, the right to informed decision-making, evidence-based health care, and cost-effectiveness (Andermann et al., 2008). An important new screening criterion is that the effectiveness of screening must be scientifically proven and that screening's overall benefits must outweigh the harms.

Table 4. Revised WHO criteria for screening proposed by Andermann et al. (2008)

The screening programme should respond to a recognized need.
The objectives of screening should be defined at the outset.
There should be a defined target population.
There should be scientific evidence of the screening programme's effectiveness.
The programme should integrate education, testing, clinical services, and programme management.
There should be quality assurance, with mechanisms to minimize screening's potential risks.
The programme should ensure informed choice, confidentiality, and respect for autonomy.
The programme should promote equity and access to screening for the entire target population.
Programme evaluation should be planned from the outset.
The overall benefits of screening should outweigh its harms.

CRC screening has a high potential to meet these criteria since CRC is, in many ways, a specific type of cancer. Due to the cancer burden, CRC is a major public health challenge. CRC has an identifiable precursor, the natural course of the disease process is well-known, and the precursor stage takes a long time to develop into cancer. Furthermore, several possible screening tests exist to find the precursors (see later section on Screening methods), and the treatments for the adenomas and early-stage cancer are effective. Due to its characteristics, CRC is well-suited for screening at the population level.

2.2.2 Screening methods

Several screening modalities suggested for CRC screening can be grouped into four types: stool-based tests, endoscopic examination techniques, radio-imaging techniques, and blood-based biomarker tests. Different methods vary remarkably regarding the level of supporting evidence, effectiveness, invasiveness, and acceptability. According to the International Agency for Research on Cancer (IARC), sufficient evidence exists that screening with currently established stool-based tests for blood (FOBTs) and lower

endoscopy (sigmoidoscopy and colonoscopy) reduces the risk of death from CRC and that the benefits outweigh the harms associated with each type of screening. (Lauby-Secretan et al., 2018). These methods' main features are presented below.

Stool-based tests

The first non-invasive test for occult blood in stool was developed in the late 1960s after it was noticed that CRC patients often suffer from rectal bleeding; even amounts of blood invisible to the naked eye could be found in the stool, indicating the need for further examinations and treatment (Greegor, 1967). Even modern stool-based tests for blood are based on the idea that adenomas and tumours in the colon and rectum tend to bleed, and traces of potential blood can be found in stool.

Stool-based tests include the guaiac-based faecal occult blood test (gFOBT), with or without hydration, and the faecal immunochemical test (referred to most often as FIT but sometimes as iFOBT). Both are widely utilized in organized screening programmes for their low cost and non-invasiveness (Schreuders et al., 2015). RCTs have shown that screening with gFOBT is associated with a 13–33% decrease in CRC-related mortality (Hewitson et al., 2007). Worldwide, FIT has recently replaced gFOBT in several settings, as FIT is more sensitive to detecting CRCs and their precursors (Lee et al., 2014).

Stool-based tests involve screening participants by taking a stool sample themselves and sending it to a laboratory for analysis. Different screening programmes have various practices for whether a test must be ordered or sent directly to the person invited. The returned sample material is analyzed for heme, including consumed non-human heme (gFOBT) or human-specific globin of blood (FIT). Thus, FIT does not require dietary restrictions, as does gFOBT. In contrast with gFOBT, FIT is a quantitative test, meaning the positivity cut-off level can be adjusted, for example, to meet available colonoscopy resources. Other advantages of FIT over gFOBT include that it only requires single stool sample instead of collecting samples from three consecutive defecations, which can lead to higher acceptability.

Because of limited sensitivity, stool-based testing should be repeated annually or biennially. Using FOBTs as the primary screening tool, colonoscopy is provided in the case of a positive test.

Endoscopic methods

The endoscopic techniques for CRC screening use flexible cameras to directly show either part of (flexible sigmoidoscopy FS) or all the colon (colonoscopy) to detect (pre)malignant growth such as adenomas. Adenomas can be removed at the same time thereby preventing their malignant transformation. In four RCTs with up to 17 years of follow-up, sigmoidoscopy screening has reduced CRC mortality by 22– 31% and incidence by 18–26% compared to no screening (Atkin et al., 2017; Holme et al., 2014; Miller et al., 2019; Segnan et al., 2011).

Colonoscopy examines the entire colon, from the rectum to the caecum. During the examination, small and most large polyps can be removed. There are trials under way of screening colonoscopy versus FIT and/or no screening (Robertson et al., 2015). However, no results on CRC incidence or mortality from these trials have been reported yet.

Endoscopy is a more burdensome test than FOBT. Although colonoscopy is more accurate than FOBT, colonoscopy is invasive, carries a risk of complications (bleeding and perforation), requires bowel preparation, and involves much higher costs.

2.3 Attendance in colorectal cancer screening

In this thesis, the term attendance refers to an individual's performance of a screening test induced mainly by invitation. Participation and uptake can be, and possibly even more so than attendance used for practically the same purpose in literature. Yet, when referring to studies in this thesis, participation means taking part in the survey study (i.e. returning the questionnaire), and attendance means participating in the cancer screening. Adherence is another often-used term in the literature for the same situation. However, adherence can be interpreted as stemming from following an order or obedience, which sounds peculiar in times where an individual's active, informed decision about their own actions is emphasized. Furthermore, one can come across the term compliance for the same purpose in screening literature. Nonetheless, adhering and compliance carry potentially negative tones of consenting (giving in or complying). Sometimes, the expression "undergoing a screening/screening test" is used. Yet, some find that this phrase implies having to endure something often burdensome or uncomfortable.

Terms and definitions used to describe the screening usage (the extent to which screening is used) vary among screening settings (Bulliard et al., 2014). Common term coverage usually refers to proportion of the eligible population that has been screened within a defined time, whereas participation and corresponding terms such as uptake and attendance most often mean the proportion of the invited population that has been screened, i.e. taken the screening test (Chubak & Hubbard, 2016).

Achieving an impact of any cancer screening programme on cancer-specific mortality largely depends on the uptake, while, care must be taken to ensure that informed consent and individual autonomy are honoured. Since screening programmes will only make a substantial difference to population health if a sufficient proportion of the eligible population uses them, it is paramount that attendance rates are protected and hampered as little as possible.

Attendance rates of CRC screening are usually suboptimal, meaning too low. For example, in Europe, the attendance varies from Croatia and the Czech Republic approximately 20% to the level of the Netherlands, which is close to 70% (Navarro et al., 2017). There is little evidence of participation developing over time, as screening has been ongoing at length and is needed for this analysis only in a few countries or areas. In the US, where opportunistic screening with several screening modalities began in the 1980s', screening coverage with which-ever modality rose from 1987 to 1998 by approximately 10% (Breen et al., 2001) and by close to 10% in 2005 (Swan et al., 2010). However, these figures must be interpreted with caution due to the non-organized nature of screening and non-centralized registration of screening utilization (information on screening usage is mainly from surveys).

2.3.1 Facilitators and barriers

Much attention has been paid to studying factors affecting the attendance of the at-risk population in CRC screening. Proposed frameworks for analyzing factors related to CRC screening attendance recognize that screening is a multi-level process that occurs at the policy, organizational, provider, and individual levels (IARC 2019). This thesis focuses on the level of the individual, i.e. screened subject. The subject-related factors on screening attendance can be further categorized as socio-demographic factors, environment-related factors, health care utilization, health behavioural/health status characteristics and psychological factors such as beliefs and attitudes towards screening. In **Figure 6** factors identified in reviews on CRC screening attendance (Honein-

AbouHaidar et al. 2016; Subramanian et al. 2004; Vernon, 1997; Wools et al., 2016) are presented according to this categorization. Individual studies on aspects of CRC screening attendance published after the most recent reviews are also included (de Klerk et al., 2018a; Quyn et al., 2018; Wangmar et al., 2021).

The most often utilized method of inquiring about reasons for screening attendance/non-attendance is naturally asking the target population directly by surveys or interviews. It is important to remember the selection, and reporting biases linked to these methods used both by quantitative and qualitative research methodology (who are willing to respond, and that some replies may be considered socially more acceptable than others).

Figure 6. Factors facilitating colorectal cancer screening.

Sociodemographic factors	
Female sex	Quyn et al., 2018; Vernon, 1997; Wools et al., 2016
Older age	Quyn et al., 2018; Vernon, 1997; Wools et al., 2016
Married /having a spouse	Vernon, 1997; Wools et al., 2016
High socioeconomic status/ high education	Quyn et al., 2018; Vernon, 1997; Wools et al., 2016
Belong to ethnic majority	de Klerk et al., 2018; Wools et al., 2016
Environment-related factors	
Urban place of residence	Vernon, 1997; Wools et al., 2016
Lack of insurance	Vernon, 1997; Wools et al., 2016
Healthcare utilization	
Regular healthcare visits	Vernon, 1997; Wools et al., 2016
Engage in other preventive methods like vaccinations	Vernon, 1997 Wools et al., 2016
Attendance in other cancer screenings	Wools et al., 2016
Physician recommendation	Honein-AbouHaidar et al., 2016; Subramanian et al., 2004; Vernon, 1997; Wools et al., 2016

Health status/health behavioural characteristics	
Family/close relative with history of CRC	Honein-AbouHaidar et al., 2016; Vernon, 1997; Wools et al., 2016
Comorbidity, chronic disease(s)	Wools et al., 2016
Never/former smoker	Wools et al., 2016
Physical activity	Wools et al., 2016
Obesity (high BMI)	Wools et al., 2016
Psychological factors	
High risk perception	Wangmar et al., 2016; Wools et al., 2016
Self-efficacy	Vernon, 1997; Wools et al., 2016
Perceived benefits of screening	Wools et al., 2016
Positive attitude toward screening	Honein-AbouHaidar et al., 2016; Subramanian et al., 2004
Motivation for screening	Honein-AbouHaidar et al., 2016
Awareness of CRC, screening, and its purpose	Honein-AbouHaidar et al.,2016; Vernon, 1997; Wangmar et al., 2021; Wools et al., 2016

As a part of studies on screening participation, barriers have also been examined more or less separately from screening facilitators. Here, the term barrier refers to a reason or justification of the screen-invitee for not attending the screening. Therefore, barriers in this context are not only factors related to non-participation (eg. socio-demographic factors).

Considerable research has been conducted to understand the barriers to CRC screening participation. Several barriers have been identified; the most prominent are in **Table 5**. Barriers can be categorized into those arising from the idea of screening (e.g. cancer fatalism), (mis)perceptions of the screened disease (e.g. no family history – not at risk of CRC), or barriers related to the actual performing of the screening test, whether endoscopy or FOBT. Here, barriers concerning endoscopy (e.g. of bowel preparation, or fear of pain/complications) are unaddressed. In a systematic review on CRC screening participation facilitators and barriers, Honein-AbouHaidar et al. (2016) suggest that an individual's awareness of CRC screening is a requisite concept for screening decisions as it is integrated into overcoming other structural and motivational barriers like views of cancer, attitudes towards CRC screening, and motivation for screening.

The dislike of the available tests in the general population is sometimes referred to as a specific barrier to participation in CRC screening compared to other cancer screenings (Lo et al., 2015; IARC, 2019). Participation rates in programmes with stool-based tests for blood are higher in women than men (Klabunde et al., 2015; Basu et al., 2018).

Table 5. Common barriers to CRC screening using stool-based tests for blood.

Barrier	References
Fear of test result and its consequences	Bradley et al., 2015; Chapple et al., 2008; Ekberg et al., 2014; Honein-AbouHaidar et al., 2016; Palmer et al., 2014; Subramanian et al., 2004; Vernon, 1997
Sampling and/or storing faeces found uncomfortable	Chapple et al., 2008; Hall et al., 2015; Honein-AbouHaidar et al., 2016; Palmer et al., 2014; O'Sullivan et al., 2004a; Vernon, 1997
Fatalistic attitude towards cancer	Honein-AbouHaidar et al., 2016; Miles et al., 2011; Subramanian et al., 2004; Vernon, 1997
Misconception that the test is inapplicable if one does not have any apparent symptoms of colorectal cancer	Chapple et al., 2008; Ekberg et al., 2014; Palmer et al., 2014; O'Sullivan et al., 2004a Hall et al., 2015; Vernon, 1997

Low health literacy and numeracy	Gale et al., 2015 Honein-AbouHaidar et al., 2016 Kobayashi, 2014
Test taken at home instead of formal heathcare setting	Bradley et al., 2015 Palmer et al., 2014 Chapple et al., 2008
Lack of motivation	Honein-AbouHaidar et al., 2016; Vernon, 1997
Not feeling that participation is personally necessary	Hall et al., 2015; Wools et al., 2016)

From this dissertation's perspective, perceived gastrointestinal symptoms are the central facilitators and barriers to CRC screening attendance. Previous research suggests that experienced symptoms increase participation, and a lack of symptoms may be a reason for non-participation. It is noteworthy, however, that no study was found in which those invited to screening would have been inquired about their symptom status pre-screening, and the screening behaviour of the same individuals would have been robustly drawn from registry data.

2.3.2 Measures aiming to increase CRC screening attendance

Numerous intervention strategies have been experimented in attempt to increase participation in CRC screening. Several have been identified effective, though it is noteworthy that the potential increases in screening participation from current intervention strategies are considered modest (Goodwin et al., 2019). Below are presented findings from reviews, with an emphasis on those aiming at improving attendance specifically in mail-out FOBT screening programmes. In endoscopy programmes the interventions are partly different due to the different nature of the screening procedure, and they are not dealt here in detail.

An early review (Baron et al., 2008) found that screening by FOBTs increased effectively by use of client reminders and small media such as brochures, or videos. Power et al (2009) concluded that successful intervention strategies include changes at the organizational level, such as increasing access to FOBT kits, providing reminders to healthcare providers and users about screening opportunities, and educational strategies to improve awareness and attitudes towards CRC screening. They stated also that a greater impact is likely to be achieved through multifactoral interventions targeting different levels of the screening process. (Power et al., 2009.) Later on, Myers et al (2020a) approached the issue of combining efforts by investigating whether the

effectiveness of the measures could be increased if specific measures were targeted at different subgroups or if intervention measures were combined. They concluded similarly that simultaneous use of several measures led to a slightly increased participation. On the other hand, the authors argue that because interventions rarely affect very different directions among different subgroups, their limited targeting to a particular subgroup does not appear to be an effective strategy.

Camilloni et al (2013) did not restrict their review on CRC screening but pursued to include all interventions aimed at increasing participation in all cancer screening programmes. They considered letter or phone reminders evidence-based practices, and that advance notification letter and mailing the FOBT kit were effective in CRC screening. GP signature on invitation letter proved effective with modest effect. In this review, evaluations of public information campaigns resulted in contradictory results. If much of information is attached to screening invitation, it it prone to become long, detailed letter which may increase inequalities in screening participation, discouraging those with lower educational level. (Power et al., 2013). Also in a review of RCTs designed to increase individuals' use of CRC screening irrespective of screening method the results indicated that in organized CRC screening programmes, letters of invitation, especially if signed by the person's GP, and reminder letters sent to non-participants showed to be effective in increasing participation. Health care provider reminders were also found to increase participation in screening. (Senore et al., 2015).

Duffy et al., 2017 focused on population-based screening programmes in search for interventions to enhance participation in overall cancer screening services. Across several countries and health systems, a number of interventions were found consistently to improve participation: pre-screening notifications, primary care endorsement, (more personalized) reminders for non-participants, and more acceptable screening tests in CRC and cervical cancer screening. Similarly, in a systematic review specifically on interventions to increase uptake of faecal tests for CRC screening (Rat et al., 2018) participation was increased with use of advance notification letters, postal mailing of the tests, reminders by letter, phone or text message, and possibilities of phone contacts with an advisor. Authors found also limited evidence on the effect of GP involvement (GP-signed invitation letter, communication training or mailing reminders to GPs). Goodwin et al (2019) districted their review and meta-analysis to those interventions aiming at improving attendance in mail-out FOBT screening programmes. They concluded that only interventions involving advance notifications, GP endorsements,

simplified testing procedures, and telephone contact resulted in significant improvements in test uptake.

All in all, IARC handbook on CRC screening states that the primary way to increase participation is to organize screening as population-based organized screening programme. In that way participation in screening is minimally limited by financial or other organizational barriers, and therefore favors the reduction of inequalities. Interventions that have been found to have a modest impact on increasing participation in gFOBT and/or FIT screening include advance notification letters; postal mailing of test kits; written, telephone, and text message reminders; telephone contact with an advisor; invitation letter signed by a GP; communication skills training of GPs; and reminder letters sent to GPs. (IARC 2019.)

2.4 Psychosocial effects of colorectal cancer screening

The psychosocial effects of cancer screening often refer to behavioural or quality of life-related consequences of screening. These can be desirable, undesirable, or neutral. Research on these topics is usually focused on adverse effects, i.e. harm caused by screening – probably because of the classical principle of primum est non nocere – "first, do no harm" in medicine. Screening is urged to have as little harm as possible – why potential negative psychosocial consequences draw more attention than potential positive ones. Here, psychosocial effects are divided into psychological effects and effects on health behaviour regarding lifestyle and symptom perception.

2.4.1 Psychological effects

The possibility of having cancer or perceiving oneself at risk for cancer concerns non-minor concepts related to cancer posing a dire health threat. Thus, attending a cancer screening might trigger psychological effects, most often anxiety and worry (Miles et al., 2009).

Regarding the overall impact of CRC screening, publicity on getting screened seemed reassuring rather than alarming. The group that was sent information about the new CRC screening reported less worry and lower perceived risk than the group that was not sent the information (Wardle et al., 1999).

Little research exists on worry associated with the first phase of screening, i.e. receiving an invitation to attend the screening. One early study found that 10–20% of people reported severe fear about receiving an invitation to FOBT screening (Lindholm et al., 1997). However, the absence of pre-invitation measures of anxiety and the lack of a control group makes assessing the significance of such levels difficult.

Studies assessing the overall psychological impact of screening attendance have shown no effects or minor adverse effects for FOBT screening (Miles et al., 2009). A Norwegian RCT comparing individuals invited to FS, FOBT screening, or non-invited controls showed no clinically relevant psychological harm from receiving a positive CRC screening result or participating in an FS or FIT screening (Kirkøen et al., 2016a; Kirkøen et al., 2016b).

The psychological impact of false-positive FOBT results has been studied to some degree. Vermeer et al. found that some psychological distress remains up to six months after colonoscopy in participants who tested false-positive in the Dutch bowel cancer screening programme (Vermeer et al., 2020). Some studies (Laing et al., 2014; Lindholm et al., 1997) have shown moderate to high anxiety after a positive screening result. However, the tension returned to pre-screening levels in these settings shortly after a subsequent negative screening result (a second gFOBT or a colonoscopy).

Several studies report more anxiety in participants who receive a positive faecal immunochemical test (FIT) or faecal occult blood test (FOBT) result (Parker et al., 2002; Brasso et al., 2010; Denters et al., 2015; Bobridge et al., 2014; Laing et al., 2014). However, this effect seems to diminish (Bobridge et al., 2014) or disappear (Parker et al., 2002; Brasso et al., 2010; Laing et al., 2014) with long-term follow-up. Other studies report no psychological harm from participating in CRC screening (Niv et al., 2012; Robb et al., 2013). Further, some evidence exists for positive effects of CRC screening participation, such as reduced anxiety (Thiis-Evensen et al., 1999; Wardle et al., 2003) and improved health-related quality of life (Taupin et al., 2006; Pizzo et al., 2011). Probable reasons for this inconsistency include the different designs of the studies, such as the lack of baseline measures or control groups and the use of different instruments and time points to measure psychological effects.

2.4.2 Effects on lifestyle and symptom perception

Two suggested approaches exist on why screening could adversely influence various aspects of health-related choices such as lifestyle – unintentionally or as a side effect. Firstly, screening could negatively affect the idea that lifestyle choices matter: Individuals might get the impression that the role of individual behaviour is less important because good health can be maintained by repeated screenings (Marteau et al., 1995; Stewart-Brown & Farmer, 1997). Secondly, people with normal screening results may interpret the test result as allowing them to continue their existing patterns of health behaviour. This attitude might produce lower motivation to change towards more a favourable lifestyle or even maintain the existing one – a phenomenon described as the "health certificate effect," introduced by Tymstra & Bieleman in 1987 (Larsen et al., 2007; van der Aalst et al., 2010; Deutekom et al., 2011).

Most people attending, especially on their first screen, will have a negative result. A negative result's impact on perceived personal risk and complacency about behaviours such as diet, exercise, and smoking has been highlighted as a vital issue. The findings from studies examining these phenomena are broadly reassuring, although scarce in number (Deutekom et al., 2011; van der Aalst et al., 2010). A report from the Telemark study observed poorer improvements in smoking behaviour and a more significant increase in BMI in the group with a negative FS screening result compared to those who had polyps detected. However, neither effect was statistically significant (Hoff et al., 2001). Similarly, no deterioration in practicing several health behaviours was found following negative results in the UK FS Trial (Miles et al., 2003). However, a later Norwegian study found evidence for a certificate of health effect among people invited to FS screening compared to an unscreened control group (Larsen et al., 2007). The screen-invited group reported more weight gain three years later and fewer improvements in smoking, exercise, and fruit and vegetable consumption than the unscreened control group. This same study population was followed further. After 11 years, there were still differences in lifestyle: The improvement in time measured with a lifestyle index was smaller in the "invited-to-screening" arm compared with the control arm. Yet, the authors conclude that the possible unfavourable lifestyle changes after CRC screening are modest (Berstad et al., 2015).

If screening can bring effects, one can try promoting (desired changes) or restraining them (undesired effects). Recently, research on exploring spontaneous behaviour changes following screening attendance and implementing interventions to enable and

direct behaviour changes to the desired direction has also been conducted in the CRC screening context. Two systematic reviews have found little support for spontaneous favourable behavioural change after participation in cancer screening (Slatore et al., 2014; van der Aalst et al., 2010). Similarly, a more recent study of English men receiving their first FOBT invitation from 2008 to 2015 found limited evidence for spontaneous improvement in selected health behaviours following attendance (Stevens et al., 2019).

Another potential harm from screening as an inappropriate reaction to a negative screening result could be ignoring subsequent cancer symptoms, which Miles et al. (2015) studied by inviting CRC patients to complete a questionnaire concerning perceived diagnostic delay, among other issues. After a negative gFOBT result, patients with interval cancer reported greater perceived diagnostic delay than patients with the screen-detected disease. However, no differences in perceived diagnostic delay existed between CRC patients with interval cancers and those not offered a screening (Miles et al., 2015). Similarly, Bouvier et al. (2001) found that interval cancers after a gFOBT screening had a later stage at diagnosis than screen-detected CRC but an earlier stage at diagnosis than CRC detected in unscreened individuals. They also found no increased delay in cancer diagnosis screening non-responders compared to individuals not invited for screening.

2.4.3 Measures to control colorectal cancer screening effects on lifestyle

Population cancer screening has been proposed to provide "teachable moments" for delivering health behaviour advice and interventions (Senore et al., 2012). The term "teachable moment" describes events and circumstances that can lead individuals to alter their health behaviour and facilitate positive behaviour change (Lawson & Flocke, 2009). Comprehensive lifestyle information is not routinely offered alongside any well-established cancer screening programmes. However, the settings provide appealing opportunities to reach many people (Anderson et al., 2013).

Intensive behaviour change interventions in the CRC screening context have predominantly targeted patients with screen-detected adenomas. Trials of such interventions to promote a healthy diet, physical activity, and weight control have been reported to encourage behaviour changes (Caswell et al., 2009; Anderson et al., 2014). Yet, as most people receive a normal screening result, attempts to influence the health behaviour of as many as possible should address all who were invited or at least all who attended.

The acceptability of information delivered at population-based screening has been explored regarding separate cancer screenings. A small study of women attending mammography found that 85% reported interest in receiving information about diet and exercise at breast screening clinics (Fisher et al., 2007), and brief smoking cessation advice given by practice nurses appeared to be accepted when delivered at cervical screening (Hall et al., 2007). Similarly, counselling on smoking cessation is well-accepted in lung cancer screening (Taylor et al., 2007; Steliga & Yang, 2019). However, as lung cancer screening represents a unique cancer screening with target population criteria, including heavy smoking, the experiences may be unsuitable for CRC screening. One early UK trial in FS screening found that the self-reported consumption of fruit and vegetables increased much more in the intervention group (two-page, tailored psycho-educational intervention by post) than in the control group at the six-week follow-up (Baker & Wardle, 2002).

More recently, the readiness to accept lifestyle advice alongside CRC cancer screening was examined in a hypothetical scenario with survey data on screening intentions. Two-thirds of 45–54-year-old screening intenders were willing to receive counsel about diet, weight, and physical activity (Stevens et al., 2018; Stevens et al., 2019). Interest in guidance about smoking and alcohol consumption was lower. Current health behaviour affected the interest in advice on health-promoting behaviour: The desire for advice was stronger in those not adhering to guidelines for weight, physical activity, smoking, and alcohol consumption. The willingness to receive advice increased with a greater awareness of cancer risk factors (Stevens et al., 2018).

Among those disposed to take lifestyle counsel was a strong preference for information to be delivered at the screening appointment (Stevens et al., 2019). Interaction between patients and healthcare professionals has been suggested as necessary in creating the teachable moment (Lawson & Flocke, 2009), challenging the usability of in-home FOBT-based CRC screening with no screening appointment in the test phase.

There is also concern that delivering extra information and interventions alongside screening could compromise attendance. In a hypothetical scenario used in a UK survey to explore the willingness to receive lifestyle advice alongside cancer screening and anticipated future screening behaviour if lifestyle advice were offered, 9% of respondents indicated they might be put off attending future FS screening appointments. Conversely, 21% of respondents stated that receiving lifestyle advice in FS screening would make them more willing to attend (Stevens et al., 2019). In breast

or cervical cancer screenings, lifestyle counselling was much less likely to impact views on future attendance (Fisher et al., 2007; Hall et al., 2007). However, research in breast or cervical cancer screening naturally involves only female respondents.

If lifestyle advice was routinely implemented alongside cancer screening, interventions must be designed to minimize the proportion of people deterred from attending the screening; attendance rates should also be carefully monitored. Evidence would need to be convincing that the health benefits of any intervention offset the harm from any decrease in attendance.

2.5 Gaps identified in research

As the literature contains indications that CRC screening could have an undesirable effect on lifestyle, studying this relevant issue would be necessary, particularly the screening programme environment with an actual screening population and the precise test method the programme used. Regarding qualitative research, ideas have also been put forward that screening – mostly in terms of a negative or positive primary result - could affect future symptom appraisal, even leading to delays in help-seeking behaviour. Little evidence on this novel question exists. Again, the matter should be studied in a real-life context, i.e. alongside the actual screening programme with all its corresponding details.

As much as the factors influencing screening participation have been studied in CRC screening, the experienced gastrointestinal symptoms have received surprisingly little attention. Studying the occurrence, prevalence, and effects in the specific target population and screening protocol is important. There is still a gap in the scientific knowledge about the influences of diverse elements on screening adherence, which deserves further investigations to carry out more focused and effective prevention programmes.

Data must be gathered directly from the screening target population to glean information about these potential effects. It is vital that we do not become detrimental to participation in the screening. There is little research on this topic internationally. The results will presumably depend, to some extent, on the detailed implementation methods (e.g. timing of the surveys or interviews, their content, connection of the

offer/request) – that studying the issues within a study population from the same source population as the screening target population would be preferable.

Although the EU has recommended population-based CRC screening since 2003 and is ongoing in several countries and regions, surprisingly little research exists on the potential impact of introducing a third cancer screening alongside established cancer screenings. A special exception is the screening peak year for a Finnish 60-year-old woman, during which she was invited to three different cancer screenings.

This thesis investigates CRC screening in Finland from two perspectives: It primarily looks at whether screening causes changes in people's lifestyles or in experiencing symptoms. A secondary view is the effects of embedding a survey study in the screening programme: Whether and to what extent queries should be added to the screening invitation process is examined.

This study can help generate information on the unintended effects of screening and achieve a broader understanding of predictors determining screening attendance.

3 AIMS OF THE STUDY

The overall aim of this thesis was to explore the impacts of CRC screening in Finland outside the traditional outcome, i.e. effectiveness of screening based on reducing cancer-specific mortality.

By evaluating changes in lifestyle-related factors and changes in perceived lower gastrointestinal symptoms, the main aim was to study if screening resulted in undesired effects, reducing the potential benefits of an otherwise feasible screening programme.

The information of interest is unavailable from registers and must be inquired directly from the study subjects, which may cause harmful side effects on the screening process. Therefore, an additional aim was to determine whether the survey harmed cancer screening attendance. Another additional aim was to examine the impact of a third cancer screening on attendance to well-established breast and cervical cancer screenings.

The specific aims were:

1. To study the effect of CRC screening on lifestyle by comparing the possible lifestyle changes between those invited for screening and the controls not invited.

2. To study the effect of CRC screening on lower gastrointestinal symptom perception by comparing the possible changes in symptom perception between screening participants or non-participants and the controls not invited to screening.

3. To examine whether pre-screening lower gastrointestinal symptoms affect CRC screening attendance.

4. To explore if a survey study damaged screenings by assessing the impact of receiving a pre-screening survey on CRC screening attendance, breast cancer screening attendance, and cervical cancer screening attendance.

5. To assess whether an additional cancer screening invitation affects breast and cervical cancer screening attendance in the year a woman receives three separate cancer screening invitations.

The results from these studies can be utilized in the overall evaluation of the CRC screening programme.

4 MATERIALS AND METHODS

4.1 Finnish cancer screening programmes

In Finland, health services are the responsibility of local municipalities. From 2022, there are three statutory national cancer screening programmes that municipalities organize for their citizens as a part of preventive health care (Government Decree on Screenings 752/2021): cervical cancer screening every five years for women aged 30–65, breast cancer screening every 20–26 months for women aged 50–69, and CRC screening every second year for both sexes aged 56–74. From 2004 to 2016, CRC screening for 60–69-year-old men and women was voluntary for municipalities to offer their inhabitants.

Screening includes defining the target group, providing individual guidance, performing and analyzing the screening tests, delivering feedback information, granting referrals for further examinations, and organizing the necessary health services. Screening is provided free of charge to those invited by the municipality.

Screen invitees are identified for screening from the Population Information System hosted by Digital and Population Data Services Agency (formerly the Central Population Register [CPR]) based on sex, birth year, and residential municipality. All persons with address information available are invited with no exclusion criteria.

Information on all phases of the screening processes (invitations, tests performed, referrals, further investigations, diagnostic findings) are centrally collected and registered in the Mass Screening Registry (MSR) at the Finnish Cancer Registry (FCR). The MSR maintains national databases for all cancer screening programmes, provides annual statistics, and evaluates the impact of screening and the quality of the programmes. Screening data are used to evaluate and control the programmes and inform public health policy decisions.

Each national cancer screening programme is described in more detail below. A historical perspective illustrates the level of specific screening programmes as part of Finnish healthcare. The participation rate is presented because it is often considered to reflect the acceptability of screening among the population (Bulliard et al., 2014).

4.1.1 The Finnish cervical cancer screening programme

The Finnish screening programme based on cytological screening was initiated during the 1960's, becoming nationwide in the early 1970's. At this time, the Cancer Society of Finland established laboratories and trained personnel for smear taking and reading the samples. Screening activities were based on Public health law 66/1972. However, the screening age range from 30 to 60 was undefined until a bylaw on public health drawn in 1992 (802/1992) (Anttila & Nieminen, 2000). The five-year screening interval was made mandatory by the Governmental Decree on Screening (1339/2006) but had been used from the screening programmes beginning. As well as the obligatory age groups, some municipalities invite women aged 25 and/or aged 65. Furthermore, about 5% of attenders are invited for a follow-up test before the next screening round based on abnormal screening results or anamnestic data (Pankakoski et al., 2017). The primary screening test used in the routine programme is conventional cytology, i.e. the Pap-test, or the human papillomavirus (HPV)-test.

Approximately 240, 000 cervical cancer screening invitations and 170 000 screening visits occur yearly in Finland. The participation rate is around 70%, with a clear difference by age: In young women aged 30–40, the participation barely reaches 60%, whereas in 60-year-olds, participation is around 75% (Finnish Cancer Registry 2021b). Opportunistic screening is also common alongside the organized programme (Salo et al., 2014). Previous opportunistic screening does not exclude women from organized screening invitations.

Since the introduction of the screening programme, cervical cancer incidence and mortality rates in Finland have declined up to 80% (Hristova & Hakama, 1997; Anttila et al., 1999). Inviting 65-year-old women for screening has shown to be effective in reducing cervical cancer mortality, too (Pankakoski et al., 2019). Over 600 cervical intraepithelial lesions are annually diagnosed within the screening programme alone. Screening has been estimated to prevent over 200 cervical cancer deaths every year in Finland.

4.1.2 The Finnish breast cancer screening programme

The nationwide population-based breast cancer screening programme was introduced in Finland in 1987. This mammography screening was started gradually by a group-randomized design, where birth cohorts born in even years were screened, and birth cohorts born in odd years served as controls (Hakama et al., 1997). The randomized implementation period lasted until the end of 1991.

From 1992, the Bylaw on Public Health obligated Finnish municipalities to offer mammography screening every second year for all female inhabitants aged 50–59. Screenings for women aged 60–69 remained optional – some screening centres offered women of this age group screening for a moderate fee (Sarkeala et al., 2004). In 2007, the target age group for screening was extended to 69. Women are invited to screening biannually (a screening interval of 20–26 months). A written invitation letter is posted personally as well as the results of the mammogram.

The Finnish breast cancer screening programme has a long tradition of high attendance. In recent years, within the programme some 370,000–380,000 invitations and over 300,000 screening visits are recorded annually, resulting in an overall participation rate of around 82% (Finnish Cancer Registry 2021b). Achieved attendance rates rank high compared to other European programmes and areas (Lynge et al., 2003, Giordano et al., 2012), indicating that organized mammography screening is well-accepted by Finnish women. Simultaneously, opportunistic mammography before screening age is common: According to two Finnish postal surveys, some 60–67% of respondents reported having had at least one mammography before the screening age (Heikkinen et al., 2016).

Screening's impact on breast cancer mortality has been investigated in Finland since the 1990s. Between 1992 and 2003, mortality among women who had been invited to participate in screening was 22% lower compared to the situation without breast cancer screening (Sarkeala et al., 2008). Breast cancer mortality among those who attended screening was 28% lower than expected without screening. The impact of screening on breast cancer mortality has also been studied with data up to year 2011; the result has remained unchanged (Heinävaara et al., 2016).

4.1.3 The Finnish colorectal cancer screening programme 2004–2016

The Finnish colorectal cancer screening programme 2004–2016 targeted men and women aged 60–69 with a screening interval of two years. This screening was voluntary for municipalities to offer their inhabitants and joining the programme was decided at the level of individual municipalities. Almost half of the Finnish municipalities launched CRC screening covering eventually nearly half the target population. For public health evaluation, an individual level randomization was incorporated into the programme: Half the target population was invited for screening, another half was not contacted. This design was chosen to allow reliable evaluation of the effects of screening by comparing mortality among those offered screening to those in the control group. The programme gradually expanded over regions and age-cohorts during the first six years (Malila et al., 2005). During 2004–2012, some 360,000 men and women were individually randomized to screening or control arms (Pitkäniemi et al., 2015).

The primary screening test was a guaiac faecal occult blood test (gFOBT, Hemoccult®) mailed to the home address of the screen-invitee and returned to the screening laboratory by mail. The test included three test cards for consecutive samples. Test positives, i.e. any blood detected, were referred for a complete colonoscopy (Malila et al., 2005). About 70% of those invited participated in the screening, i.e. sent a faecal sample to the screening laboratory – a very high attendance rate in international comparison (Klabunde et al 2015). About 3% of participants were referred for a colonoscopy. Cancers or severe precursors were found in about one of ten colonoscopies (Malila et al., 2011, Pitkäniemi et al., 2015).

An interim report examining the effect of screening on CRC mortality found no difference between those invited and those not invited for screening after an average follow-up of 4.5 years. CRC mortality among men invited for screening was lower than in their non-screened control group. In contrast CRC mortality among invited women was higher than in the control group (Pitkäniemi et al., 2015). Because of these non-optimal results, the Finnish gFOBT-based screening programme was suspended in 2016. However, screening may have had indirect benefits, as patient survival improved more than expected in the control population, too. Thus, screening seemed to reduce overall CRC mortality in the involving municipalities, taking into account the dissemination of good practice resulting from screening (Miettinen et al., 2018).

In 2019, CRC screening was relaunched in voluntary municipalities. In the new programme, both sexes aged 60–74 are invited to screening every two years with a FIT-

test, requiring only one sample and no dietary restrictions. The first-year results show very high attendance (83% in women and 75% in men), with well-performing test and referral protocols (Sarkeala et al., 2021).

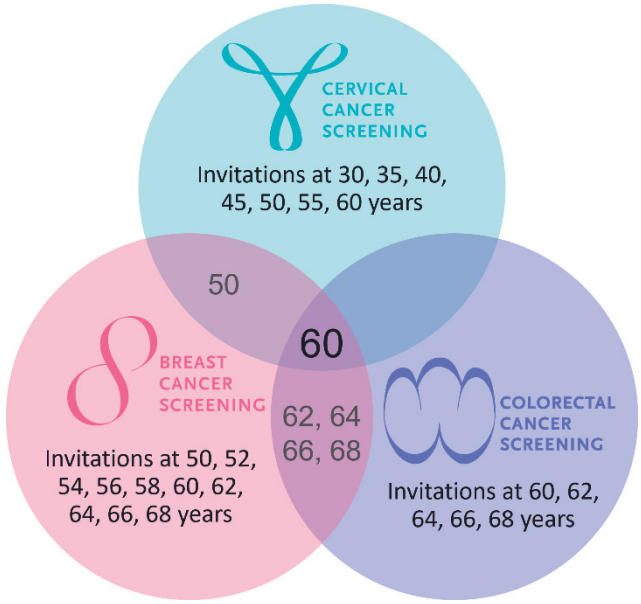
4.1.4 Cancer screening peak year of 60-year-old women

According to the European cancer screening guidelines on target age groups, 60-year-old females are subjected for three cancer screenings: breast, cervical, and colorectal (Arbyn et al., 2010; Perry et al., 2008; von Karsa et al., 2013). In Finland, women aged 60 are eligible for breast and cervical cancer screenings (also referred to as female cancer screenings) as part of nationwide organized cancer screening programmes as described above. Also, half the 60-year-old women living in municipalities involved in randomized CRC screening from 2004 to 2016 were eligible for CRC screening.

Because of the invitational schemas of breast and cervical cancer screenings, the year a woman turns 60 is exceptional: She will receive separate invitations to mammography and cervical cancer screenings in the same calendar year. Women eligible for CRC screening are separately invited to this third cancer screening during the same year. (Figure 6). There is no central governing or systematic monitoring of invitations regarding their order, accumulation, or other temporal distance. The postal invitations women receive do not address other cancer screenings or their occurrence.

At age 60, CRC screening is introduced to women for the first time since it is the youngest age group screened. However, by the time women turn 60, they have encountered several breast and cervical cancer screenings: According to the invitational schemas of screening programmes, a 60-year-old woman receives her sixth lifetime invitation for mammography and seventh invitation – often the last – for cervical cancer screening (**Figure 7**).

Figure 7. Overlapping of cancer screening invitations at age 60.



4.2 Psychosocial consequences of colorectal cancer screening study 2010–2012

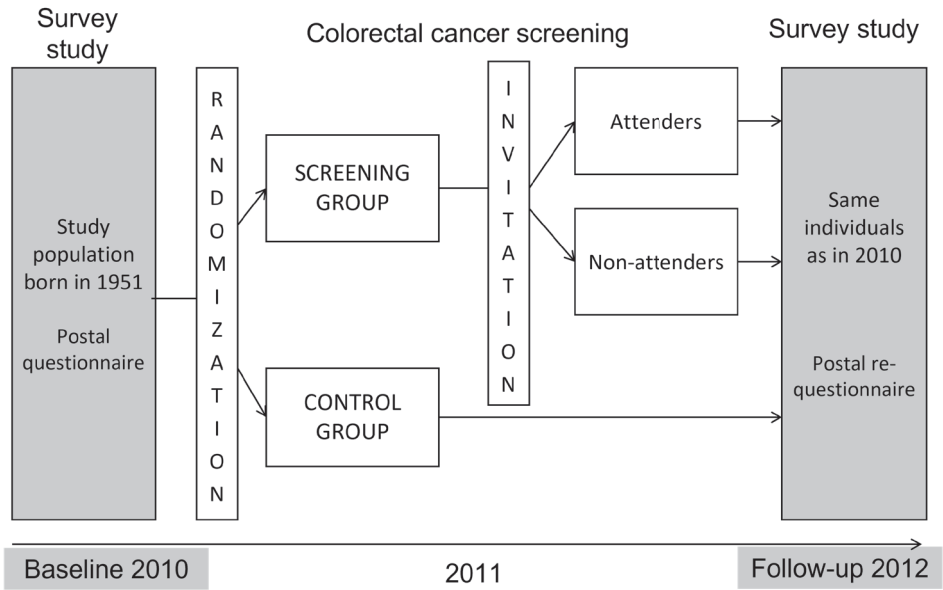
In 2010, the FCR launched a population-based study to evaluate associations among CRC screening, lifestyle, and quality of life. The research aimed to investigate the impact of CRC screening on lifestyle and health-related quality of life. That screening might affect various lifestyle-related factors was considered possible. Data on such would be needed to have a valid basis for decisionmaking when reasoning potential extension of the CRC screening programme to the entire country. This aim was regarded to be achieved best by combining survey study data gathered via questionnaires with screening data obtained from the MSR at FCR. As this survey study (or part of it) has been used as exposure or as a source of exposure or outcome data in all sub-studies (see **Table 6**), it is presented in detail here.

4.2.1 Study design

The study utilized a prospective, randomized, and controlled study design to ensure an unbiased setting. The study material was collected by self-administered postal questionnaire in two phases: at the baseline before potential CRC screening and at the follow-up phase two years later (**Figure 8**). Hence, the baseline questionnaires were mailed before the target population had been randomized to screening or the control group not invited to screening, i.e. not only before the first screening invitation for some, but also before anyone even knew whether to get or not to get invitation to a screening next year. The follow-up phase was carried out on the same individuals after the same time irrespective of the screening status ex post, i.e. whether an individual in question belonged to the screening group or to the control group. This design allows reliably evaluating the effects of screening by comparing potential changes in lifestyle and quality of life among those offered screening to those in the control group.

The study design was reviewed by the Helsinki and Uusimaa hospital district Ethics Committee (420/13/03/00/2009). The National Institute for Health and Welfare provided permission to link the survey data with register data (THL/619/5.05.00/2010).

Figure 8. Study design of psychosocial consequences of colorectal cancer screening study in 2010–2012



4.2.2 Study sample: surveys, screenings, and data collection

When examining the effects of screening in a randomized setting, selecting a population that had never been invited to screening was crucial. The study population of the "Psychosocial consequences of colorectal cancer screening" survey study was a birth cohort born in 1951 who were to enter CRC screening in 2011 for the first time due to their age and lived in municipalities involved in the CRC screening programme (148 out of all 342 Finnish municipalities in 2010).

Individual data on the total population of 31 951 was retrieved from the CPR in March 2010. Random allocation in a ratio of 1:2 resulted in a study sample of 10,648 individuals to whom study questionnaires were mailed in May 2010 (address information obtained from CPR). After four weeks, 3046 (29%) questionnaires were returned, and reminders were sent to the 7602 who had not yet returned theirs. These reminders led to 2029 more questionnaires being returned (27% of those who were reminded, 19% of the original sample). In December 2010, the questionnaires were resent to those 5573 persons who still had not replied after the first mailing and reminder, and 910 (16% and 9%; respectively) new replies were received. Altogether, we collected 5985 responses in 2010. After exclusions (empty questionnaires, respondent other than the one pursued, respondent unconfirmed, respondent denying the use; n=110) the final survey data 2010 comprised of 5875 responses, equalling 55% of the original sample. Women's response rate was 60.5%, while men's response rate was 49.8%.

At the beginning of 2011, the 10,478 from the original study sample who had not died (n=61) or moved to an area uninvolved in CRC screening (n=109) were randomized to be invited to CRC screening (n=5185) or controls who were not invited to the screening (n=5293), according to the CRC screening programme randomization schema (Figure 8). The 60-year-old screening target population in 2011 was 32,072, including the survey study sample. Survey and screening randomizations were independent of each other, and no exclusion criteria, neither in the survey study nor in the screening programme existed. Of the 5185 invited to the CRC screening, 2935 (57%) persons attended screening. The term 'respondent' refers to those who returned their study questionnaire and thus took part in the survey study. 'Attender' refers to those who attended a cancer screening when invited.

During the same year, that is in 2011, the female study population was invited both to breast and cervical cancer screening according to the invitational schemas of these cancer screening programmes. Of the 15,945 women in the original population of

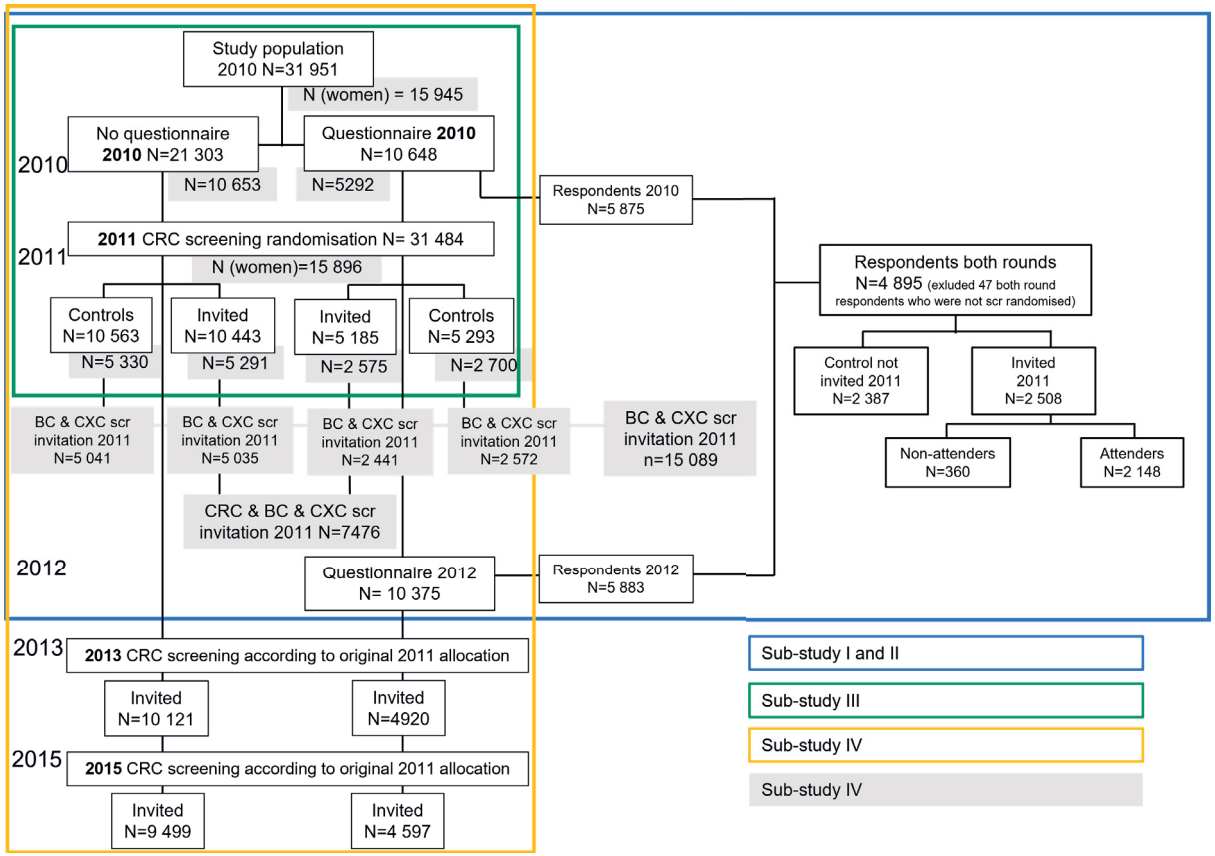
31,951 2, 49 had died or emigrated before the screening invitations in 2011. Accordingly, 755 women were not invited to a breast cancer screening due to varying age-specific invitation policies in seven municipalities. Further, 53 women were not invited to cervical cancer screening due to missing addresses or other reason. Thus, there were 15,141 breast cancer screening invitations and 15,843 cervical cancer screening invitations in the study population, and 15,089 women received invitations to breast and cervical cancer screenings in 2011. Randomly half (n=7866) of the study population was also invited to their first-ever CRC screening; thus, 7476 women received invitations to all three screening programmes in 2011 (**Figure 9**, in grey).

In 2012, a follow-up questionnaire was mailed to the same individuals as at base-line according the study design. The mailings were dispatched roughly at the same time of the year as the previous round – in spring (April – May) 2012 – to 10,375 individuals. After six weeks, 4493 (43%) questionnaires were sent back. Reminders resulted in 966 more questionnaires coming back. Late in 2012, the questionnaires were re-posted to 4916 non-respondents, and 508 extra replies were received. Overall, there were 5883 replies in 2012 after exclusions (n=84) as in previous round; the response rate in 2012 was 57%.

The final survey study population includes those randomized for CRC screening or controls in 2011, sent both the baseline questionnaire in 2010 and follow-up questionnaire in 2012 (n= 10 375), of which the respondents for both rounds were valid for examining screening's potential effects (n= 4895) (**Figure 9**).

[2] The birth cohort born in 1951 who was to enter CRC screening due to their age for the first time in 2011 and lived in municipalities involved in the CRC screening programme (148 out of all 342 Finnish municipalities in 2010): individual data drawn from CPR in 2010.

Figure 9. Flow chart of the "Psychosocial consequences of colorectal cancer screening" study population. Females in the study population are in grey background. CRC=colorectal cancer, BC=breast cancer, CXC=cervical cancer, scr=screening



4.2.3 Questionnaire

The study questionnaires were drawn up by experts in different domains of lifestyle and quality of life research. In most issues, the aim was to utilize question types used in the well-established annual postal survey "Health Behaviour and Health among the Finnish Adult Population" (AVTK, Helakorpi et al., 2011) which has been carried out in Finland since 1978 (since 2015 incorporated to Regional Health and Well-being Study ATH). The primary reason for this principle was to enable comparisons between respondents and respective age groups of AVTK if necessary.

There were two types of questionnaires: the shorter named "The lifestyle questionnaire" entailed 30 questions in seven pages and the wider one named "The lifestyle and quality of life questionnaire" had 45 questions in 10 pages. Since it was anticipated that questionnaire's width could negatively affect the response rate, the extended version was randomly sent to half of the recipients.

The lifestyle questionnaire was divided into seven sections and covered mainly lifestyle factors related to CRC (**Table 6**). The lifestyle and quality of life questionnaire included additionally one section measuring health-related quality of life with a validated, generic Finnish 15D instrument (Sintonen, 2001). The instrument divides the quality of life into 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each of these dimensions appeared as a separate question in the questionnaire with five response levels, from 1 (no problems) to 5 (extreme problems) (Sintonen, 1995).

The questionnaires were sent in Finnish or Swedish according to the respondent´s mother tongue status in the Population Information System data. With the questionnaire, written informed consent was acquired.

Table 6. Study questionnaire contents.

Section	Topics
Sociodemographic background	Sex, marital status, education, profession, height, weight, waist circumference
Smoking	Past and present smoking status
Alcohol	Frequency of alcohol usage, frequency of ≥6 drinks on a single occasion
Physical activity	Light physical activity, vigorous physical activity (exercise), self-assessment of their physical condition
Diet	41-item semi-quantitative food and drink frequency questionnaire, special diet, use of vitamin D supplements, Self-assessment of their diet's overall healthfulness
Health status and use of healthcare services	Perceived bowel symptoms, self-assessment of their overall health status, visits to physician/nurse
CRC-related questions	CRC in relatives, worries concerning CRC, vulnerability for CRC
Additionally in half the questionnaires:	
Health-related quality of life (15D instrument)	Mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, sexual activity

4.3 Sub-study populations and data sources

The survey study "Psychosocial consequences of colorectal cancer screening" or part of it has been used either as an exposure, or as a source of exposure, or outcome data in all sub-studies. Sociodemographic characteristics for the whole study population of 31,951 were obtained from the CPR (information on sex, home municipality, marital status and mother tongue) and Statistics Finland (education level). Screening data were obtained from the database of MSR. Data on cancer and screening history, i.e. previous cancer diagnoses, screening invitations, attendances and results (only in sub-study V) were derived from the FCR/MSR.

Studies I and II on the impact of CRC screening on lifestyle and LGI symptom perception utilized "Psychosocial consequences of CRC screening" survey study data from 2010 and 2012 with CRC screening data from 2011. The sample of respondents in 2010 and 2012 is 4895 persons, of which 2508 were invited to screening in 2011 (and 2148 attended), and 2387 served as controls who were not invited to screening (Figure 9, circled in blue). As for Study II, a total of 4840 respondents were eligible for analyses, i.e. they had the symptom query completed

both in 2010 and in 2012. Study II also explored CRC screening attendance activity by pre-screening self-reported LGI symptoms: Of the 2508 individuals invited to screening in 2011, 2482 were eligible for this analysis with the completed symptom query.

Study III examined CRC screening attendance in 2011 related to questionnaire mailings in 2010 used "Psychosocial consequences of colorectal cancer screening" - study´s first round (baseline questionnaire) mailing information and CRC screening data from 2011: 15,748 men and women were invited for screening, and 5185 of whom had received a questionnaire the previous year (**Figure 9**, circled in green).

Study IV was an extension off Study III in the interest of repeated questionnaires and screening invitations. Of those 15,748 invited to screening in 2011, the survey study sample (n=5091) received the follow-up questionnaire in 2012, and 15,041 were reinvited to CRC screening in 2013. In 2015, 14,096 individuals got a third invitation to CRC screening at age 64 (**Figure 9**, circled in yellow).

Study V on the effect of the survey study in 2010 and the third cancer screening that same year on breast and cervical cancer screening attendance employed only the female study subjects. There were 15,141 breast cancer screening invitations and 15,843 cervical cancer screening invitations in the female study population. Of these, 15,089 women received invitations both to breast and cervical screenings in 2011. Randomly half (n=7866) of the study population was also invited to their first-ever CRC screening; thus, 7476 women received invitations to all three screening programmes in 2011 (**Figure 9**, in grey).

Table 7. Study subjects and data sources in sub-studies.

The shared study source population in all sub-studies is the birth cohort of 1951 residing in municipalities implementing CRC screening in 2010 (n=31,951).

Sub-study	Outcome(s) & source(s)	Exposure(s) & source(s)	Study subjects n
I	2-year change in lifestyle Study[1] response data in 2010 & 2012	CRC screening status 2011 (control/attender/non-attender) MSR screening data	Survey respondents 2010 & 2012 & randomized to CRC screening or control 2011 4895
II	1. 2-year change in symptoms 2. CRC screening attendance in 2011 1. Study[1] response data in 2010 & 2012 2. MSR screening data	1. CRC screening status 2011 (control/attender/non-attender) 2. Perceived symptoms in 2010 1. MSR screening data 2. Study1 response data in 2010	Survey respondents 2010 & 2012 (symptom query completed both rounds) & randomized to CRC screening or control 2011 4840
III	CRC screening attendance in 2011 MSR screening data	Study[1] questionnaire mailing(s) in 2010 Study[1] meta data	60-year-olds invited to CRC screening in 2011 15,748
IV	CRC screening attendance in 2013 & 2015 MSR screening data	Study[1] questionnaire mailing(s) in 2010 & 2012 Study[1] meta data	62-year-olds invited to CRC screening in 2013 15,041, 64-year-olds in 2015 14,096
V	BC & CXC screening attendance in 2011 MSR screening data	1. CRC invitation in 2011 2. Study[1] questionnaire mailing(s) in 2010 1. MSR screening data 2. Study[1] meta data	60-year-old women invited in 2011 to BC screening 15,141, CXC screening 15,843 or both 15,089

[1] Psychosocial consequences of colorectal cancer screening -study

CRC = colorectal cancer , MSR=Mass Screening Registry, BC= breast cancer, CXC=cervical cancer

Regarding the breast and cervical cancer screening data, Finnish municipalities are legally obligated to ensure the collection of individual-level data on all phases of the screening process and the submission of the data to the MSR. MSR collects and records information on all screening invitations (year, municipality, time of invitation), screening visits (screening laboratory, time, screening test result, and possible referral for further examination), and information on further examinations (time of examination, results, histological diagnoses) and treatment. Anamnestic data collected during screening visits are also recorded. The data is stored with unique personal identifiers. Also, for CRC cancer screening in 2004–2016, information on all steps of screening (invitations, FOBTs performed and returned, primary results, referrals, further examinations, diagnostic findings, and treatment information) was collected centrally and registered in MSR at the FCR.

4.4 Lifestyle and symptom measurements

This thesis is based on the hypothesis that CRC screening could affect future lifestyle and/or perceived symptoms. Yet, in the context of CRC screening no single lifestyle-related risk factor accounting for most cases of CRC exists (unlike e.g. smoking in lung cancer), nor is this the case with LGI symptoms, of which only rectal bleeding has some predictive value for CRC (Adelstein et al., 2011; Astin et al., 2011). Consequently it was not expected, that potential effect of screening would manifest specifically in certain single factor (risk factor or symptom). Instead, that small changes in several factors could indicate the phenomenon's existence was considered possible, especially if the changes were in the same direction from a health risk perspective. A further assumption was that potential changes in single factors would be moderate at most. Moreover, lifestyle factors are often interrelated, considering their effect in conjunction is mainly worthwhile (Limpens et al 2022). In general, when assessing lifestyle, particularly changes in lifestyle, single lifestyle factors or combination of multiple factors can be examined (Prochaska et al., 2010). In this thesis, the latter approach was chosen for the aforementioned reasons, and the same approach was applied to symptoms.

4.4.1 Lifestyle index

When compiling a lifestyle index, the purpose should serve as the basis for item inclusion: We aimed for the index to sum up known CRC risk-related lifestyle habits,

even though these are common to several chronic non-communicable diseases. This thesis quantified lifestyle by combining five factors into an overall score: physical activity, weight, smoking status, alcohol use, and diet.

In the "Psychosocial consequences of colorectal cancer screening" -questionnaire respondents reported their height (in cm) and weight (in kg), smoking and alcohol habits, and physical activity and exercise routines. Tobacco smoking was inquired in terms of current smoking (no – irregularly – regularly), and previous regular daily smoking for at least one year (never - ever & number of daily cigarettes). The use of alcohol was asked with questions to determine whether the subject had ever drunk alcohol, and if so, the frequency of consuming alcoholic beverages, and the frequency of having more than six portions on one occasion. Furthermore, the respondents recorded their average consumption of three alcoholic beverages (beer, wine, liquor) in portion sizes corresponding to 10 g of alcohol in five frequency categories ranging from "never" to "several times a day" in the 41-item semi-quantitative food and drink frequency questionnaire (FFQ). There were separate questions for weekly amounts of everyday exercise, such as walking or yardwork, and the frequency of vigorous exercise.

A total lifestyle index was compiled by first deciding the components essential for the purpose of the index. Secondly, it was considered whether some components need weighting, and how this is performed. Thirdly, index scoring was planned, and thresholds were set. The selection of index components was based on current (valid in 2016) epidemiological evidence on risk and protective factors for CRC, mainly on the views of an expert panel of the World Cancer Research Fund/American Institute for Cancer Research 2011. The total lifestyle index included six components: physical activity (PA), body mass index (BMI), and alcohol consumption, with smoking and dietary habits as two separate components (namely, CRC-P and CRC-R, which are detailed more below). Thus, nutrition was given more weight in the overall index.

Each lifestyle component was scored dichotomously by assigning it 1 or 0 points, with 1 point indicating a lifestyle favourable for CRC prevention. Pre-determined limit values were used for physical activity, smoking, alcohol, and body composition. In the physical activity component, defining the limit value was based on Finnish data (Jääskeläinen et al., 2013), where the exercise habits had been asked similarly to our study questionnaires. Being physically active was defined as engaging in regular moderate leisure-time PA and/or vigorous leisure-time PA (**Table 8**). In the tobacco smoking component, being current nonsmoker scored 1 point. In the alcohol consumption component, amounts

not exceeding that which was recommended from the health risk perspective (1 drink/ day in women or 2 drinks/ day in men; Current Care guideline 2015) were applied as limit values for abstaining or moderate drinking (1 point) and excessive drinking (0 points). Sex-specific medians were utilized as limit values on diet indexes: Those scoring above median got 1 point for the total lifestyle index, whereas those at the median and below got 0 point. The overall score was determined by summing up all the points obtained from each lifestyle component. The total score thus ranged from 0 to 6, with higher scores suggesting a lifestyle less prone to CRC than lower scores.

Table 8. Components of the lifestyle score.

Lifestyle score component	Score	Description
Physical activity (PA)	1	≥ 4 h/week of light PA or ≥ 30 min vigorous PA daily/almost daily
	0	< 4 h/week of light intensity PA and no vigorous daily PA
Body mass index (BMI)	1	BMI≤25 kg/m2
	0	BMI>25 kg/m2
Smoking	1	Not currently smoking
	0	Current smoker
Alcohol consumption	1	≤ 1 drink/d for women ≤ 2 drinks/d for men
	0	> 1 drink/d for women > 2 drinks/d for men
CRC-P	1	Above median
	0	Median or below
CRC-R	1	Above median
	0	Median or below

Diet assessment with dietary indexes

The food frequency questionnaire

In the "Psychosocial consequences of colorectal cancer screening" -survey, dietary habits were assessed the baseline and follow-up phases using a 41-item FFQ to measure habitual dietary intake over the preceding 12 months. Respondents completed the FFQ at home as a part of the rest of the questionnaire and posted it back to FCR. In the FFQ, respondents recorded their average consumption of 41 food or drink items commonly consumed in Finland in five frequency categories ranging from "never" to "several times a day". The portion size was fixed for each food/drink item (e.g. glass or slice) to assist in filling out the FFQ.

The CRC-P and CRC-R diet indexes

Two separate dietary indexes were formed based on current epidemiological evidence on protective or causative dietary factors for CRC to characterize the overall diet from the CRC perspective. The first index illustrates eating habits protective for CRC (colorectal cancer protective food index CRC-P). CRC-P included three components (intake of rye bread as an indicator of dietary fibre, intake of milk -irrespective of the type of milk, and including also buttermilk, yoghurt and soured whole milk - and combined intake of vegetables, fruits, and berries, **Table 9**).

The other index was formed to measure the use of food items that are causative for CRC (colorectal cancer risk food index CRC-R) including four components (intake of processed meat, red meat, cheese and sugary foods, **Table 9**). of Alcohol consumption was excluded from the dietary index because it was considered an independent lifestyle factor.

The components with more compelling evidence on CRC risk were scored depending on the frequency of use from 0–8 (processed meat, red meat, and rye bread) and those with less convincing evidence were scored from 0–4 (milk, vegetables, cheese, and sugary foods). Scores were based on frequency of use so that for example in rye bread intake, those who reported eating rye bread many times a day scored maximum 8 points, daily/almost daily usage scored 6 points, 1-4 times a week usage scored 4 points, 1-3 times a month usage scored 2 points and never/almost never usage of rye bread got 0 points. The scoring of the indexes gave a high value for CRC-P when the diet was rich in colorectal cancer protecting food items and for CRC-R when the diet had only little colorectal cancer-causing food items. The components of the CRC-P thus received scores in ascending order so that the lowest frequency of use resulted in 0 points and the highest frequency in the maximum points (4 or 8). CRC-R, in turn, scored in the opposite order (highest points for the lowest frequency of use and no points for the highest frequency of use). All component scores were summed up to the total score which ranged from 0 (lowest) to 16 in CRC-P or 24 in CRC-R (highest) points. A higher score was considered beneficial, i.e. representing dietary behaviour less prone to CRC than those with a lower score on the dietary index. The diet index score above sex-specific median resulted in 1 point for the total lifestyle index whereas scores at the median and below resulted in 0 point.

Table 9. Composition and scoring of "CRC protect food index" (CRC-P) and "CRC risk food index" (CRC-R).

CRC-P		CRC-R	
Dietary factor	Points	Dietary factor	Points
Rye bread	0–8	Processed meat	0–8
Milk products	0–4	Red meat	0–8
Vegetables, fruits and berries	0–4	Cheese	0–4
		Sugary foods	0–4
Total points	0–16	Total points	0–24

All scores were based on frequency of use

4.4.2 Symptom index

The study questionnaires asked lifestyle, health status, quality of life, and some CRC related questions. Perceived LGI symptoms were inquired about with a symptom query of eight items: "Have you had the following symptoms during the last three months?" The symptoms listed were constipation, diarrhoea, flatulence, abdominal soreness or pain, faecal incontinence, rectal bleeding, hemorrhoids and indigestion. Response options for each symptom were: "no", "occasionally"", and "constantly".

Single missing responses to items were recoded "no" (11.6% of respondents had at least one of the eight items missing). We summarized the symptom query into the total symptom score (**Table 10**). The total symptom score ranged from 0 to 8 points, indicating the number of LGI symptoms the individual reported. For the analysis, we developed a dichotomic symptom index (0, 1) based on the total symptom score (total symptom score 0 = "asymptomatic" and total symptom score ≥1= "symptomatic"). The respondents who skipped the symptom query completely in 2010 or 2012 (n=65), were excluded from the analyses.

Table 10. Composition and scoring of the symptom index.

component	criteria for 0/1-scoring 1 point if:
Constipation	constantly
Diarrhoea	constantly
Flatulence	constantly
Abdominal soreness/ pain	constantly
Faecal incontinence	occasionally
Rectal bleeding	occasionally
Haemorrhoids	constantly
Indigestion	constantly
Total score	0–S8

4.5 Statistical analyses

Statistical analysis software package STATA (versions 11/12/14) was used for data management and statistical analyses. A traditional 0.05 level was used (if not otherwise mentioned) as a level for statistical significance.

Sub-study I: The association of the screening group (invited attenders and invited non-attenders) and a possible change in the CRC-related lifestyle index were assessed using ordered logistic regression with random effects. The study population was classified into screening groups: 1) invited and non-invited controls to study the invitation's effect, and 2) three groups, i.e. those invited were further divided into screening attenders and screening non-attenders to study the effect of screening attendance. Both models used calendar time (before vs after potential screening). Calendar time was used as a within-subject variable and screening group and sex as between-subject variables. Screening group-by-time and screening group-by-sex interactions were estimated. A significant interaction was considered evidentiary for differences in the lifestyle index change by screening group or sex, respectively. Socio-demographic characteristics included marital status (categorized as married, single i.e. never married, divorced and widower), education (categorized as basic education 0–9 years, intermediate education, 9–12 years, and high education > 12 years) and type of residential municipality (urban, rural).

Sub-study II: The association among the screening groups (uninvited controls vs attenders vs non-attenders) and symptom index over follow-up was assessed using Poisson's regression with random effects. Interactions of screening groups-by-time and screening group by-sex and sex-by-time were studied in searching for differential

changes in the symptom index. A 0.2 level was considered statistically significant in testing interactions, leading to a stratified reporting of results. As a sensitivity analysis, the models were analyzed with data that included only participants with all eight symptom responses (complete case analysis).

To assess the effect of screening attendance on post-screening symptoms, screening attenders and non-attenders were compared to control group. Incidence rate ratios (IRRs) and 95% confidence intervals (95% CIs) for screening attendance by symptom index were calculated with Poisson´s regression while correcting the CIs for binary data so that IRRs can be correctly interpreted.

Sub-study III & IV: Two-way tables were used to examine CRC screening attendance related to survey study mailings. Screening attendance proportions were compared between those sent and those not sent the questionnaire(s), and those who received a short versus a lengthy questionnaire. Attendance was also compared by sex, marital status (dichotomized as either married/civil partnership or single/divorced/separated/widow), urbanization level of residential area (dichotomized as urban or rural according to the classification by Statistics Finland) and geographical location of residence (Southern, Western, Middle, Eastern, and Northern Finland). Statistical significance was tested with the χ^2 test (sub-study III) and two sample tests of proportions (z-test, sub-study IV). In sub-study III, the differences in attendance were quantified with 1) absolute attendance difference and 2) relative attendance difference, proportional to the attendance rate of the questionnaire-free group.

Sub-study V: Attendance to cervical and breast cancer screening was assessed by receiving the questionnaire or not and being invited to CRC screening or not. All analyses were adjusted for demographic characteristics and screening history. The statistical method used was Poisson's regression; results are reported by IRRs with 95% CIs. The sociodemographic characteristics applied in the analyses were marital status (categorized as married; single, i.e. never married; divorced; and widow/widower), mother tongue (Finnish, Swedish, other), region (university hospital regions of Helsinki, Turku, Tampere, Kuopio, and Oulu), and education (basic education 0–9 years, intermediate 9–12 years, and high > 12 years). A person with a cancer diagnosis before the screening invitation in 2011 was coded as having a cancer history. Screening history was classified according to the to previous invitation´s response (attender/non-attender) and previous result (sent to any diagnostic follow-up at the previous time of attendance). The dates of breast and cervical screening invitations was based on the

attendance date available in the screening registry data and approximated for the non-attenders as the attenders' median of invitation time by home municipality. The invitational date was available in the register for all women invited for the CRC screening.

5 RESULTS

5.1 Response and basic characteristics of the "Psychosocial consequences of colorectal cancer screening" survey sample

In 2010, the study questionnaire was sent to 10,648 individuals, of whom 5875 (55%) responded. In 2012, the same cohort (10,375 individuals: 273 had died, refused in 2010, or had unknown address) was sent the follow-up questionnaire, and 5883 (57%) responded. A total of 4895 individuals were eligible for analyses (responses from both survey rounds), 2508 in the screening arm and 2387 in the control arm (**Figure 8**).

Characteristics of the "Psychosocial consequences of colorectal cancer screening" study sample are shown in **Table 11**. Survey responders (first round 2010) were self-selected by sex (women responded more actively than men), marital status (married responded more actively than single), education (high education responded more actively than low), socioeconomic status (officials responded more actively than others), and by future CRC screening attendance in 2011 (those to attend screening responded more actively than those who were to non-attend next year).

Table 11. Demographic characteristics of the population sample invited for the lifestyle survey, survey responders 2010, and CRc screening attenders 2011 who replied to the survey

	Population sample		Survey responders		Screening attenders	
	n	%	n	%	n	%
All	10 648	100	5875	100	2280	100
Sex						
Men	5356	50.3	2610	45.3	949	41.6
Women	5292	49.7	3158	54.8	1331	58.4
Marital status						
Married	6547	61.5	3871	67.1	1553	68.1
Divorced	2072	19.5	1050	18.2	406	17.8
Widow	407	3.8	237	4.1	90	4.0
Single	1441	13.5	604	10.5	229	10.0
Missing	181	1.7	6	0.1	2	0.1
Area						
Southern	1974	18.5	1055	18.3	398	17.5
West coast	2070	19.4	1120	19.4	438	19.2

Middle	3586	33.7	1915	33.2	785	34.4
Eastern	1427	13.4	810	14.0	334	14.7
Northern	1591	14.9	868	15.1	325	14.3
Municipality type						
Urban	6428	60.4	3470	60.2	1355	59.4
Semi-urban	2084	19.6	1141	19.8	454	19.9
Rural	2136	20.1	1157	20.1	471	20.7
Mother tongue						
Finnish	9970	93.6	5423	94.0	2167	95.0
Swedish	526	4.9	281	4.9	91	4.0
Other	152	1.4	64	1.1	22	1.0
Education						
Low	3331	31.3	1466	25.4	528	23.2
Intermediate	4468	42.0	2507	43.5	1007	44.2
High	2849	26.8	1795	31.1	745	32.7
Working life status						
Worker/Entrepreneur	3272	30.7	1718	29.8	670	29.4
Official	3379	31.7	2147	37.2	888	39.0
Retired	2187	20.5	1090	18.9	425	18.6
Unemployed	1380	13.0	690	12.0	254	11.1
Missing	430	4.0	123	2.1	43	1.9
Screening group						
Invited	5185	49.5	2874	49.8	na	
Controls	5293	50.5	2894	50.2	na	
Screening attendance						
Yes	2935	56.6	2280	79.3	na	
No	2250	43.4	594	20.7	na	

Table 11. continued

The response rate for the post-screening questionnaire in 2012 was high (94%: 2148 of 2291) among the screening attenders who had completed the pre-screening questionnaire. Among the screening non-attenders and the controls, the corresponding response rates were 60% (360 of 602) and 82% (2387 of 2916), respectively.

5.2 Effect of colorectal cancer screening on lifestyle and symptom perception

5.2.1 Colorectal cancer screening and future lifestyle (I)

Lifestyle at baseline

Almost three out of four respondents were physically active, and 30% of men and 40% of women were of normal weight. One fifth of men and 17% of women reported being current smokers, and alcohol consumption was classified as excessive in 12% of men and 5% of women. The number of lifestyle components scored most often was 4 (31% of men and 34% of women). Women scored high values (4-6) more often and low values (1-3) less often than men. The distributions were similar for the control and screen-invited groups.

Lifestyle changes 2010–2012

Changes in each item of the lifestyle index were minuscule. Smoking became slightly less prevalent from 2010 to 2012 (21% vs 19% of men and 17% vs 16% of women). Excessive alcohol consumption declined during follow-up in men (12% in 2010 vs 9% in 2012). Respondents were more often normal weight (≤25 kg/m2) in 2010 than in 2012 (36% vs 34% of respondents, respectively). In women, subtle changes in diet could be observed, with CRC-P scoring a point in 41% in 2012 vs in 43% at baseline, and CRC-R yielding a point more often in 2012 than in 2010 (43% vs 41%, respectively). These changes are due to decreased rye bread and processed meat intake. Otherwise there were practically no changes from 2010 to 2012 in dietary index component consumption.

The total lifestyle index decreased (OR 0.80, 95% CI 0.74–0.87) from 2010 to 2012, indicating fewer lifestyle components were fulfilled over time. The decrease was evident in men, but suggestive in women (OR 0.68, CI 0.60–0.77 vs OR 0.92, CI 0.82–1.03, respectively).

Changes in lifestyle by screening

The total lifestyle index decreased throughout the follow-up in the screening group (OR=0.80, 95% CI 0.72–0.90) and the control group not invited to screening (OR=0.80, CI 0.71–0.90), meaning both groups had minor temporal changes (fewer points scored from the lifestyle index in 2012 than in 2010). However, there were no differences in lifestyle changes between the compared groups, i.e. invited and controls not invited to screening. There was also no significant difference in screening participation: The changes in scores were similar to those participating in screening (OR 0.81, CI 0.72–0.92) and those invited but not participating (OR 0.75, CI 0.55–1.03).

5.2.2 Colorectal cancer screening and future symptom perception (II)

There were only minor differences in single symptoms between 2010 and 2012 (**Table 12**). The temporal changes in symptom perception were similar in controls, screening attenders and non-attenders.

Screening attendance did not affect symptom perception: The changes in symptom index 2010–2012 did not significantly differ in those attending and those not attending screening when compared to the control group. No pairwise interaction between screening group and sex existed. Women experienced more symptoms than men as such (in women IRR for symptom index 1.23, CI 1.15–1.32 compared to men as the reference group). This sex difference was evident across time and did not differ between screening groups.

Table 12. Single symptoms by sex at baseline 2010 and at follow-up 2012. All survey respondents.

	Men						**Women**					
	2010 n= 2166			**2012** n=2190			**2010** n=2687			**2012** n=2675		
	No	Occasio-nally	Constantly	No	Occasio-nally	Constantly	No	Occasio-nally	Constantly	No	Occasio-nally	Constantly
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Constipation	1596 (79)	391 (19)	27 (1)	1583 (78)	417 (21)	24 (1)	1460 (57)	964 (38)	143 (6)	1501 (59)	920 (36)	122 (5)
Diarrhoea	1363 (67)	642 (32)	31 (2)	1392 (68)	631 (31)	25 (1)	1673 (66)	808 (32)	56 (2)	1692 (67)	783 (31)	49 (2)
Flatulence	525 (25)	1314 (63)	250 (12)	545 (26)	1319 (63)	233 (11)	475 (18)	1726 (65)	454 (17)	499 (19)	1754 (66)	389 (15)
Abdominal soreness/pain	1457 (71)	524 (26)	58 (3)	1503 (74)	500 (24)	41 (2)	1601 (63)	862 (34)	94 (4)	1630 (65)	815 (32)	77 (3)
Faecal incontinence	1873 (93)	136 (7)	8 (0)	1878 (92)	146 (7)	11 (1)	2259 (89)	240 (9)	30 (1)	2221 (89)	248 (10)	29 (1)
Rectal bleeding	1683 (83)	334 (16)	19 (1)	1738 (85)	300 (15)	11 (1)	2102 (83)	430 (17)	13 (1)	2135 (85)	364 (14)	17 (1)
Haemorrhoids	1420 (70)	511 (25)	111 (5)	1499 (73)	471 (23)	92 (4)	1487 (58)	797 (31)	284 (11)	1603 (63)	708 (28)	234 (9)
Indigestion	1340 (65)	657 (32)	50 (2)	1376 (67)	644 (31)	45 (2)	1299 (50)	1158 (45)	139 (5)	1338 (52)	1116 (43)	116 (5)

5.3 Factors affecting cancer screening attendance

5.3.1 Perceived lower gastrointestinal symptoms and colorectal cancer attendance (II)

Symptoms at baseline

Single symptoms were reported at different levels. (**Table 12**) Flatulence was most frequently reported symptom (17% of women and 12% of men responded constantly at baseline) and fecal incontinence most infrequently one (1% and 1%, respectively). Rectal bleeding either occasionally or constantly was reported by 793 persons (16%), in contrast to reporting any other or several other symptoms constantly than rectal bleeding, n= 985 (20%). 37% of respondents scored at least 1 with the symptom index indicating one or more gastrointestinal symptom, and 63% were symptom free at baseline. Women reported symptoms more often than men (symptom index≥1 40% vs 32%, respectively).

There were 2482 individuals who had responded both the surveys in 2010 and 2012 and were invited to screening in 2011. Men having LGI symptoms and women irrespective of symptom status attended more actively than asymptomatic men. In men, 78.9% (594/754) of asymptomatic attended whereas 82.9% (290/350) of symptomatic did the same. Asymptomatic women had an attendance proportion of 90.0% (734/816) and symptomatic women 90.9 % (511/562). Other factors related to higher attendance in screening were marital status (being married), higher education level, current smoking, physical activity, low or moderate alcohol consumption and higher self-rated health (**Table 13**).

Having rectal bleeding symptom compared to those who had other LGI-symptom(s) did not seem to play much of a role in screening attendance in men. Men with rectal bleeding had an attendance proportion of 82.3% (144/175) vs. 83.4% (146/175) attendance proportion among men with some other symptom(s). In women, having rectal bleeding symptom resulted in attendance of 93.5% (202/216) whereas otherwise symptomatic women had attendance of 89.3% (309/346).

Table 13. Colorectal cancer screening attendance (%) 2011 by background, survey data and symptom index. Respondents invited to screening (n=2893).

	Screening attendance (%)					
	Men			Women		
	Invited	Attended%		Invited	Attended%	
	n	n	%	n	n	%
All	1314	952	72.5	1579	1339	84.8
Marital status						
Married	890	662	74.4	1017	897	88.2
Divorced	236	155	65.7	323	254	78.6
Widow/Widower	22	17	77.3	88	73	83.0
Single	166	118	71.1	147	113	76.9
Area						
HUS	225	161	71.6	281	240	85.4
TYKS	242	187	77.3	315	255	81.0
TAYS	432	318	73.6	545	470	86.2
KYS	206	146	70.9	213	189	88.7
OYS	209	140	67.0	225	185	82.2
Municipality type						
Urban	745	539	72.4	983	822	83.6
Semi-urban	278	201	72.3	304	258	84.9
Rural	291	212	72.9	292	259	88.7
Mother tongue						
Finnish	1228	897	73.1	1501	1278	85.1
Swedish	74	46	62.2	57	48	84.2
Other	12	9	75.0	21	13	61.9
Education						
Low (or missing)	351	235	67.0	362	296	81.8
Intermediate	568	412	72.5	700	600	85.7
High	395	305	77.2	517	443	85.7
Working life status						
Worker/entrepreneur	531	388	73.1	343	286	83.4
Official	315	237	75.2	761	656	86.2
Retired	263	190	72.2	283	236	83.4
Unemployed	156	108	69.2	174	147	84.5
Body mass Index						
Normal	394	289	73.4	636	537	84.4
Overweight/obese	907	653	72.0	915	780	85.3
Waist circumference						
Recommended	774	577	74.6	845	732	86.6
Excess	483	339	70.2	656	550	83.8
Current smoking						
No	1008	760	75.4	1244	1090	87.6
Yes	295	185	62.7	313	231	73.8
Physical activity						

Active	943	706	74.9	1134	976	86.1
Inactive	364	239	65.7	437	358	81.9
Alcohol consumption						
Recommended	1121	827	73.8	1437	1231	85.7
Excess	158	104	65.8	94	72	76.6
Self rated health						
Good	639	496	77.6	848	735	86.7
Poor	666	451	67.7	717	594	82.9
Family history of CRC						
No	1147	830	72.4	1392	1179	84.7
Yes	123	91	74.0	141	119	84.4
CRC worry						
No	1020	737	72.3	1168	1000	85.6
Yes	153	111	72.6	241	203	84.2
Symptom index score						
0	905	637	70.4	939	783	83.4
1	401	312	77.8	629	548	87.1

Table 12. continued

5.3.2 Survey study "Psychosocial effects of colorectal cancer screening" (III-V)

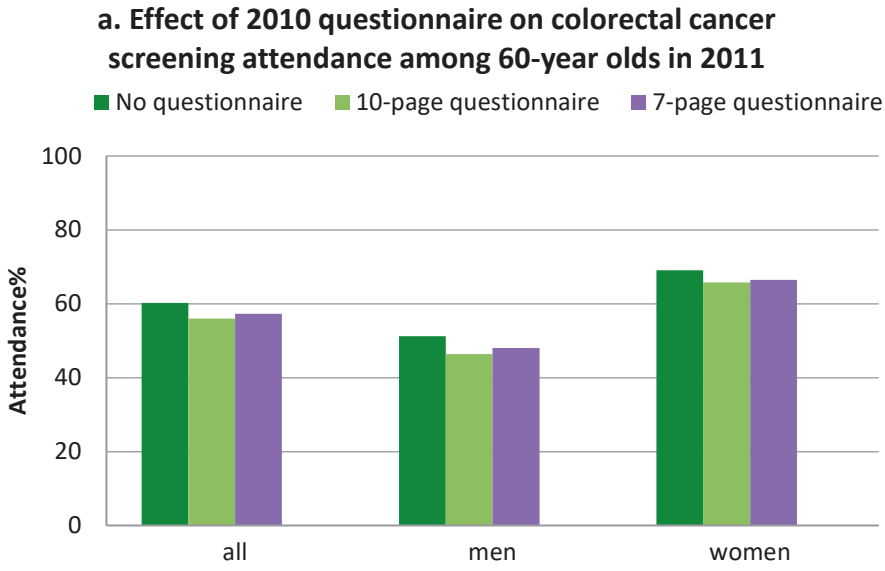
Survey study and colorectal cancer screening attendance 2011-2015 (III, IV)

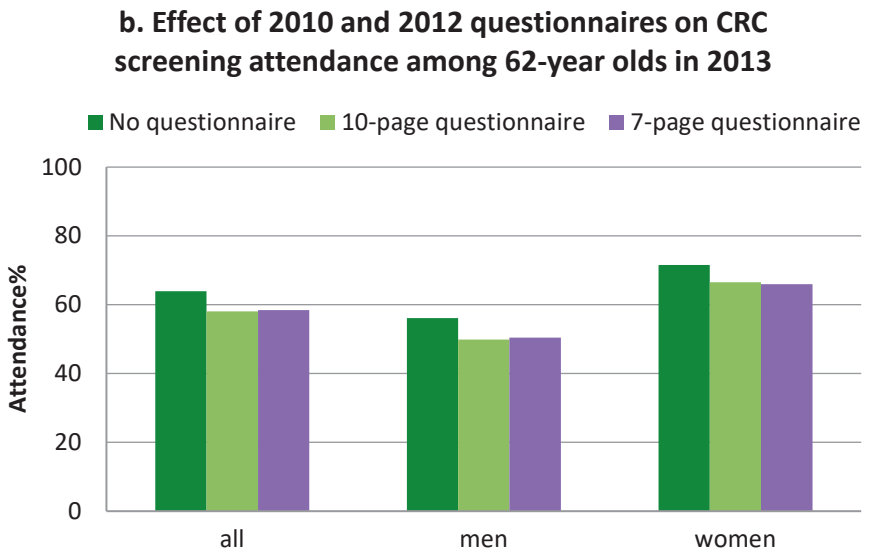
In 2011, the target population of CRC screening born in 1951 were randomized 1:1 into screening or control arms. The number of randomized in the "Psychosocial effects of colorectal cancer screening"-study population was 31 484. Consequently, 15 748 persons (50%) were invited to CRC screening for the first time. Their overall attendance rate was 59.0%. Of the 5185 individuals in the 2010 survey sample invited to CRC screening in 2011, 2935 (56.6%) attended screening whereas 6357 (60.2%) of 10 563 not sent the questionnaire 2010 did the same. Among the recipients of the shorter questionnaire version the attendance rate was 57.3% and among those who received the wider one 56.0% ($p<0.001$) (**Figure 10a**).

The second CRC screening round for age cohort born in 1951 took place in 2013. Following the original screening randomization, and irrespective of their attendance at the first screening round in 2011, 15,041 individuals were invited. The overall attendance in screening was 62.1%. In those who had been sent the surveys in 2010 and

in 2012 the attendance was 58.4% (58.5% for shorter and 58.3% for longer questionnaire) and in those not subjected to survey interventions it was 63.9% (p=0.001) (**Figure 10b**).

In 2015, the age cohort in question had their third CRC screening round. From the "Psychosocial effects of colorectal cancer screening" -study population, 14 096 individuals were invited to screening. No questionnaires had been sent since 2012. The attendance in screening was still significantly lower in people who had received the questionnaires in 2010 and 2012 than among those who had not been sent the questionnaires in the past (**Figure 10c**): the attendance proportions were 61.7% (62.0% for short and 61.4% for long questionnaire) and 66.2%, respectively (p=0.006).





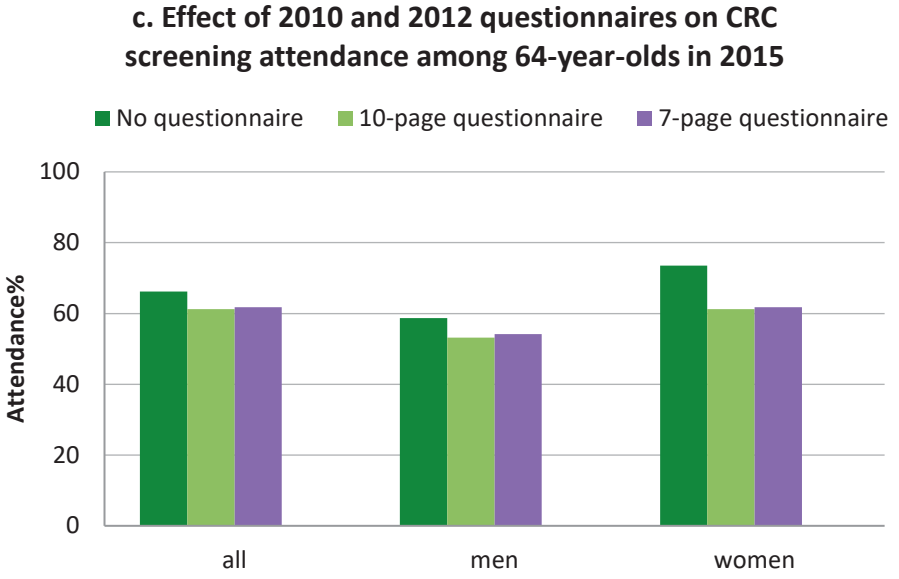


Figure 10. Colorectal cancer screening attendance in the 1st, 2nd and 3rd round in 2011, 2013 and 2015 by survey study status.

Survey study and breast and cervical cancer screening attendance 2011 (V)

Survey intervention 2010 had no effect on the high attendance to breast and cervical cancer screening. Women having received the survey had similar attendance to both breast cancer screening (IRR 1.00, 95% CI 0.96-1.04) and cervical cancer screening (IRR=0.99, 95% CI 0.95-1.03) than those who had not received the survey.

In the whole study population the breast cancer screening attendance in 2011 was 87.0% (15 141 invitations, 13 165 attended). The screening uptake was not affected by the survey study in 2010: among women who were not sent the questionnaire, screening attendance was 87.1%, and in the population receiving the questionnaire, it was 86.7%. Adjusting for demographic factors together with data on screening and cancer history did not alter the result.

In the study population the cervical cancer screening attendance in 2011 was 78.5% (15 843 invitations, 12 437 attended). In survey recipients and non-recipients the attendance rate was 77.9% and 78.8%, respectively.

5.3.3 Colorectal cancer screening invitation and breast and cervical cancer screening attendance (V)

In 2011, there were 341 559 invitations sent nationally in the Finnish breast cancer screening programme to women aged 50-69 years. Total attendance rate was 84.8% (n=289 555). Among all 60-year-olds the attendance rate nationally was 84.1% (31 562 attenders out of 37 539 invited). In our study population the breast cancer screening attendance in 2011 was 87.0% (15 141 invitations, 13 165 attended).

Among women invited for CRC screening before breast cancer screening, the attendance to mammography was 87.0% and among the control group who were not invited to CRC screening (or who were invited to CRC screening after invitation to breast cancer screening) it was at the same level: 86.9%.

Within the Finnish cervical cancer screening programme, there were 246 261 invitations sent to women aged 30–60 years in 2011 with overall attendance rate of 68.2% (n=168 028). In 60-year-olds, the attendance rate reached 76.7% (29 451 attenders out of 38 422 invited) and in our study sample it was 78.5% (15 843 invitations, 12 437 attended).

In the CRC screening invitees, attendance to cervical cancer screening was 77.8% and in the CRC screening non-invitees 79.1%. (**Table 14**.) No effect of CRC screening invitation on breast or cervical cancer screening attendance was observed after adjustment with sociodemographic data.

Table 14. Attendance to breast and cervical cancer screening in 2011 by colorectal cancer (CRC) screening allocation in 2011.

	Breast cancer screening 2011				**Cervical cancer screening 2011**			
	Invited	Attended	%	IRR (95% CI)	Invited	Attended	%	IRR (95% CI)
All	15141	13165	87.0	na	15843	12437	78.5	na
CRC screening invitation in 2011								
No[1]	8494	7382	86.9	1.00 (ref)	8487	6715	79.1	1.00 (ref)
Yes[2]	6647	5783	87.0	1.00 (0.96-1.03)	7356	5722	77.8	0.98 (0.95-1.02)

[1] Control in CRC screening programme or CRC screening invitation sent after the cancer screening invitation in question.

[2] CRC screening invitation sent before the cancer screening invitation in question.

IRR= incidence rate ratio, CI= Confidence Interval

When accounting for both possible interventions – third cancer screening invitation of CRC screening and survey questionnaires the previous year - in terms of "general screening activity", i.e. attendance to both breast and cervical cancer screenings, either of them or neither screening, only minor differences can be found (**Table 15**). The highest screening activity to both the screenings was achieved in group not exposed to either intervention.

Table 15. Screening activity in 2011 by intervention exposures in those who received both breast (BC) and cervical cancer (CXC) screening invitations in 2011 (n=15 089).

	No colorectal cancer screening invitation 2011[1] n=8872 Attendance to BC and CXC screening			**Colorectal cancer screening invitation 2011**[2] n=6217 Attendance to BC and CXC screening		
	Both	Only either	Neither	Both	Only either	Neither
No questionnaire 2010	4324	1099	492	2995	796	370
n=10076	73.1%	18.6%	8.3%	72.0%	19.1%	8.9%
Questionnaire 2010	2098	595	264	1485	389	182
n=5013	71.0%	20.1%	8.9%	72.2%	18.9%	8.9%

[1] control in colorectal cancer screening programme or either breast cancer screening invitation or cervical cancer screening invitation before colorectal cancer screening invitation in 2011

[2] before breast and cervical cancer screening invitations in 2011

6 DISCUSSION

The overall context of this thesis is a comprehensive evaluation of the Finnish CRC screening programme. The primary aim was to clarify if screening brings undesired consequences, damaging the programme's benefit-harm ratio. Secondary purpose were to determine whether the survey instrument used in data collection adversely affected attendance to colorectal, breast, or cervical cancer screenings, and explore the role of novel cancer screening invitations on attendance to breast and cervical cancer screenings when all three screening invitations are sent the same year.

Exploring the potential effects of screening on various aspects of health-related behaviour is an integral part of identifying the harms of a screening programme. Also, predictors for screening attendance are paramount, for adequate attendance is fundamental for population screening success. Although in Finland, good or even excellent participation rates have been achieved in the previous CRC screening programme and the pilot phase of the new CRC screening programme (Malila et al., 2011; Sarkeala et al., 2021), the situation should not be taken for granted. Screening attendance must be monitored, protected, and strengthened continuously.

This questionnaire study embedded in the Finnish CRC screening programme did not show differential changes in the CRC-related lifestyle between the screening arms or attendance. Neither did screening attendance affect future symptom perception in the same setting. To my knowledge, this thesis is the first to investigate the potential harm of differential symptom perception due to screening with the quantitative method. Because no effect of CRC screening on lifestyle or LGI-symptom perception was found, the potential damage of screening on these issues was not present.

Male individuals with more symptoms were more likely to attend screening than counterparts who reported no or only infrequent symptoms. Sending a 7- or 10-paged pre-screening survey reduced attendance in subsequent CRC screenings. The detrimental effect of questionnaires on screening attendance was long-term over two

consecutive screening rounds. However, exposure to the questionnaire did not affect subsequent breast or cervical cancer screening participation. Invitation to CRC screening with a home stool test did not change aforementioned participation levels either. These findings contribute to existing knowledge on the harms of screening and provide opportunities to better understand the nature of FOBT-based CRC screening.

6.1 Colorectal cancer screening on future lifestyle and symptom perception

Although CRC screening positively impacts CRC mortality, it may have adverse effects, such as, lifestyle choices or symptom vigilance. Our results imply that screening for CRC with FOBT had no long-term (two-year) effect on studied issues – positive or negative.

Invitation to CRC screening did not affect a lifestyle measured with a 6-item lifestyle index in two-year follow-up. The direction or volume of changes in the total lifestyle index did not significantly differ between those attending and those not attending the screening. Results provide some evidence that neither invitation to nor attendance in FOBT-based CRC screening leads to a less healthy lifestyle.

Some European studies have investigated the effect of CRC screening on diet and lifestyle (Berstad et al., 2015; Knudsen et al., 2018a; Larsen et al., 2007; Miles et al., 2003; Stevens et al., 2019). However, the findings have been inconclusive. Some of the studies are limited by a relatively small sample size, short follow-up, non-detailed diet and lifestyle information, and the lack of a control group and/or randomized setting. These studies are based on faecal occult blood test (FOBT) (Stevens et al., 2019) or sigmoidoscopy (Berstad et al., 2015; Larsen et al., 2007; Miles et al., 2003), or either (Knudsen et al., 2018a) as the primary screening tests.

A recent FOBT-based CRC screening study from the UK found that vigorous physical activity increased for screened participants (Stevens et al., 2019). In the cohort of 774 screening-naïve men, no other spontaneous lifestyle changes following the first FOBT participation regarding smoking, alcohol consumption, fruit and vegetable intake, or modest physical activity were found. Similarly, in the Bowel Cancer Screening in Norway pilot study, no changes in lifestyle were observed at

one-year follow-up between controls and screened negative (either the first round of FIT or FS) (Knudsen et al., 2018a). Our results align with these findings, except for the tentative increase in physical activity in men, which remained stable in our data.

The Norwegian Colorectal Cancer Prevention (NORCCAP) study using sigmoidoscopy screening from 2001 to 2004 found an unfavourable change in physical activity after screening at three and eleven years of follow-up (Berstad et al., 2015; Larsen et al., 2007). Only at three-year follow-up, an increase in smoking and weight and a decrease in fruit and vegetable consumption were observed after screening (Larsen et al., 2007). The difference between our results to NORCCAP's may stem from the different age groups of the study populations, time of the study screening, and dissimilarities in study designs. Above all, FOBT as a screening test clearly differs from sigmoidoscopy: FOBT is sent by post, completed at home, and returned by mail without directly encountering a healthcare provider. Instead, performing sigmoidoscopy as the screening test is a medical procedure requiring a visit to the screening site and face-to-face contact with the personnel. People may interpret the result of self-performed versus professional-performed tests differently, or the test procedure per se may affect the person being screened differently. Endoscopy examination might thus be more reassuring than a FOBT. Interestingly, a recent US study investigating lifestyle changes after the endoscopic screening found that endoscopy screening was associated with a modest improvement in healthy lifestyles, especially in individuals with more severe findings (Knudsen et al., 2021). However, the study results should be interpreted with caution because they are based on self-reported data both on lifestyle and endoscopy, the inability to reliably differentiate between screening and diagnostic endoscopy, and a non-population based study population.

Furthermore, an early questionnaire study in the UK did not find FS-based CRC screening leading to a less healthy lifestyle during a three-month follow-up (Miles et al., 2003). The same study also observed positive changes in smoking behaviour and fruit and vegetable consumption. Our study, which included a non-invited comparison group, demonstrated that smoking slightly decreased among FOBT attendees and controls (1.0 % and 1.3%, respectively) suggesting that although smoking appears to reduce rather than increase over time, screening is unlikely to be the catalyst for change. Also, in the UK study, the study participants had consented participate in a screening trial before the pre-screening questionnaire, which may positively affect the results.

Screening attendance did not affect symptom perception in a two-year follow-up. The overall improvement in symptom index in time (being asymptomatic became more frequent in all groups irrespective of CRC screening) in the two-year follow-up aligns with the finding from Finnish CRC programme that general health status regarding self-rated health improved over time (Jäntti et al., 2018). Research on the effect of screening on symptom perception came from qualitative studies (Barnett et al., 2017; Hall et al. 2015a), and comparisons to these are very limited. Yet, based on our study results with one age group, no effect of screening on LGI-symptom perception on any direction was found. Hence the potential harm of screening in terms of impact on symptom perception was not present. I could not find any other published research with quantitative methodology on this question.

6.2 Symptoms and cancer screening attendance

Lower gastrointestinal symptoms were common among the screening population. Over a third (37%) of the study population could be deemed symptomatic. This finding is in line with other research (Helakorpi et al., 2011; Helldán et al., 2013; Schult et al., 2021). The prevalence of symptoms among those invited for screening should be properly addressed in screening communication: informing the public that symptoms are not a prerequisite for participating in screening, is vital. Nor are they a reason to opt out of screening. Population-based screening is and should be aimed at certain age group of the whole population. However, screening is often seen as reserved for an asymptomatic population at average risk only. Those experiencing symptoms are advised to seek healthcare instead of waiting for a screening, or even attending one. While urging symptomatic people to prompt help-seeking and vastly educating population about early signs of cancer is crucial, potentially denying screening potentially from a quite extensive group of the target population may seem unfeasible.

Lower gastrointestinal symptoms merit attention in population education and information concerning CRC screening because perceived symptoms seem to affect screening attendance among Finnish men. Generally, symptoms are considered to increase attendance rather than decreasing it (Wools et al., 2016), supporting our result. Nonetheless, no accurate information from other screening programmes or research was found regarding the issue by sex. The finding suggests that perceived symptoms are important in understanding sex-specific screening behaviour. Insights

the study provides can also be utilized in tailoring and targeting the screening information material.

Perceived GI symptoms increased attendance in CRC screening, especially in men. Men also have positive test results more often than women. One explanation could be that some men "attend for a reason", i.e. they already suspect some health issue. Instead of seeking personal medical contact, they resort to screening. Conversely, women in Finland with a decades-long tradition of cervical and breast cancer screenings are so used to screening invitations that attendance remains high whether factors are interpreted as predisposing or not. Cultural expectations (male role expectations in health care) affect how men are encouraged to interpret, allow, and intervene in one's own symptoms. Women are assumed and expected to monitor, report, and treat their symptoms, but on a speculation, men are historically and culturally discouraged from detecting or treating theirs.

6.3 Pre-screening survey and cancer screening attendance

Being subjected to a study questionnaire before the CRC screening invitation reduced CRC screening attendance. A pre-screening survey in 2010 reduced screening attendance in 2011 from 60.2% to 56.6% among the survey recipients. The decrease in women with higher original attendance, was from 69.1% to 66.2%, and from 51.2% to 47.2% in men. These results are parallel with findings from the NHS Bowel Cancer Screening Programme in 2008–2010, where the screening uptake was significantly lower in those receiving an additional research study questionnaire, consent form and study information with their FOBt kit than in those who did not (53.5% vs 48.6%). The reduced uptake was similar in both sexes. When the study documents were sent by separate mailing two or three days after the FOBT kit, no effect on screening uptake was found (Watson et al., 2013).

Other similar European studies – albeit conducted well earlier – have found no evidence of an effect of self-administered research studies on the uptake of mammography screening. In a study conducted in the NHS Breast Screening Programme, 6,400 women invited for breast screening were randomized to receive or not receive an adjunct research questionnaire with their standard invitation to screening. The questionnaire requested personal information regarding lifestyle, past and current health, reproductive factors, family history of breast cancer, and

hormone replacement therapy. Screening attendance rates were similar in women who did and did not receive a questionnaire (71% in each group) (Banks et al., 1998). Two further studies investigated the effect on mammography screening attendance by sending mailed invitations to participate in adjunct research projects around the time breast screening invitations were conducted in the Netherlands (Peeters et al., 1994) and Norway (Gram & Lund, 2008). Neither study found an association between receiving adjunct research invitations and breast screening attendance.

One previous study of the effect on screening uptake of adjunct research in a CRC screening setting was located, conducted by O'Sullivan and colleagues within the setting of the pilot for the NHS Bowel Cancer Screening Programme (O´Sullivan et al., 2004b). Individuals who were sent an FOBt kit received or did not receive a self-administered questionnaire addressing their attitudes to participating in FOBt screening. The questionnaires were mailed two working days after the FOBt kits. No significant difference in overall screening uptake between the two groups was present. The notable difference between this study and ours was the timing of the survey: it was sent only after the screening invitation.

There seems to be no obvious reason why sending and receiving a lifestyle (and quality of life in half) questionnaire reduces future screening uptake in Finland. Though the questionnaires were mostly about general lifestyle largely comparable to the forms generally used in population health surveys, the accompanying covering letter referred to the study "Psychosocial effects of colorectal cancer screening" as a whole. In addition, the questionnaire contained some CRC-specific questions (and space for answering open question of "what kind of thoughts does CRC raise in you?"). In this way, the questionnaire was linked, if not directly to CRC screening but to CRC as a disease. Even though it was emphasized that part taking in the survey was completely voluntary and it would not affect screening randomization, the screening invitation next year may have been perceived by the recipients as burdensome when dealing with the same matter again. It is also conceivable that some thought there is no need for screening anymore once they had already answered the year before when this matter had been investigated, Overall, we suggest that the nature of the pre-screening contact, not the contact per se, is pivotal. Requesting effort on the part of the recipient may be harmful for future screening willingness.

The survey study ”Psychosocial consequences of colorectal cancer screening” employed two questionnaire types. “The lifestyle questionnaire” was 7 pages wide and the “The lifestyle and quality of life questionnaire” had questions on 10 pages. The longer questionnaire had a greater detrimental effect on screening attendance than the shorter one. It would be easy to conclude, that the longer the questionnaire, the worse it is on future screening attendance. However, in addition to the length of the questionnaires, it is also worth considering the content. The extra content in our study was due to generic health-related quality of life measure 15D, which consists of 15 single item questions on functional capacity like hearing, eating, distress and so on. Perhaps some felt that instrument items on e.g. mental health or sexuality very sensitive or annoying in which case the content may have played more of a role in harm than the extra pages on questionnaire. Indeed, in a published literature review aiming to compile and systematically evaluate evidence of a possible relationship between questionnaire length and respondent burden, Rolstad et al (2011) concluded that since the comparison of questionnaires of different lengths is inherently problematic, it is better to make decisions about the use of tools based on content rather than length only.

Advance notification letters are among few interventions of which there is evidence to have a modest effect on increasing participation (Camilloni et al., 2013; Duffy et al., 2017; Goodwin et al., 2019; Rat et al., 2017). These are in use in several national screening programmes, e.g. in Australia (Brown et al., 2020), Scotland (Quyn et al., 2018), and Netherlands (Toes-Zoutendijk et al., 2017). Advance notification letters have not been introduced in Finland. This is mainly due to the fact that high participation rates are achieved in cancer screening in Finland without prenotifications, thanks to reminder letters addressed to non-participants. The effect of reminder letters on screening attendance is far from marginal: in two separate studies embedded in Finnish cervical cancer screening, reminder letters increased attendance by 7-9 percentage points (Virtanen et al., 2011a; Virtanen et al., 2011b), and in the recent CRC screening pilot two reminder rounds together improved the overall attendance from 54% to 79% (first reminder increased attendance from 54% to 74%, Sarkeala et al., 2021). Advance notifications are probably a more expensive way to reach the presumably corresponding level of attendance because they are sent to everyone. For this reason, however, there is no Finnish habit of pre-screening contact, which is not yet a screening invitation itself.

The harmful effect of questionnaires on screening attendance appeared to be long-term. The effect augmented with repeated surveys: the reduction in screening attendance in those subjected to questionnaires was greater in the second (2013) than in the first screening round (2011). Furthermore, the effect seemed to continue so that in the subsequent third screening round (2015) with no questionnaires the previous year, the attendance still did not reach the level of group never exposed to questionnaires. Results were similar for men and women, by marital status, and by area. The long-term effect could be due to attendance pattern, i.e. previous screening behaviour (especially participation in the first invitation round) predicts future attendance. This has been observed earlier in the context of breast (Drossaert et al., 2003; Lagerlund et al., 2000, Larsen et al., 2021), cervical (Conry et al., 1993) and CRC screening (Cole et al., 2012; Lo et al., 2015; Moss et al., 2012, Steele et al., 2016). Various attendance patterns in cancer screening include people who attend whenever they receive a screening invitation (regular participants); those who never attend (constant non-participants); or those who are inconsistently involved. The last group includes those who participate subsequent round(s) after rejecting the first ones (late participants), those who participate at first but then "drop out" and those who participate in screening in varying degrees (Cole et al., 2012; Osborne et al., 2017). We believe, that those disturbed by the original study questionnaires in 2010 established a pattern of non-participation which did not ease-off later (constant non-participants). Unfortunately, the 2015 screening round at the age of 64 remained the last one for this age group because randomized CRC screening programme was abolished in Finland in 2016. It would have been interesting to verify the phenomenon of constant non-participation on fourth screening round at the age of 66 (year 2017) and on fifth screening round at the age of 68 (year 2019).

After the notion that exposure to the "Psychosocial consequences of colorectal cancer screening" -study questionnaire harmed attendance to subsequent CRC screening a question was raised whether the survey could affect breast or cervical cancer screening participation, too. After all, female subjects of the questionnaire study had entered the "peak year of cancer screening" following year of survey study. No sign of survey affecting breast or cervical cancer screening participation was found in sample of 15 089 women: attendance rates to both breast and cervical cancer screenings remained at the same level irrespective of questionnaire exposure.

One obvious reason for this reassuring finding may be that the survey intervention material 2010 was not associated with breast or cervical cancer screening in any way, but with CRC screening because of the accompanying information letter.

Furthermore, the three cancer screenings differ from each other by characteristics and status which may explain why one is affected by additional research load and others are not. Firstly, "attendance" means different things in different cancer screenings from the point of view of the attendee effort: CRC screening uses a test sent by post, completed at home, and returned by mail without direct encounter with a health care provider. Instead, both in mammography and in cervical cancer screening the screening test involves face-to-face contact with a health care personnel. People may perceive a test more worthy when it requires a professional to perform the test. Moreover, it is perhaps easier not to engage in unscheduled home test, than to miss a pre-booked appointment (use of which is recommended in cancer screening invitations). Secondly, in the study setting the CRC screening was introduced to women for the first time whereas breast and cervical cancer screenings can be considered almost routine procedures. It is possible that a solid behavioural pattern is not affected by outside factors as easily as a more novel behaviour. Thirdly, breast and cervical cancer screenings in Finland enjoy a long history, compelling evidence of effectiveness and a established practice. Especially in breast cancer screening, high attendance in international comparison is reached (Giardano et al., 2012): though approximately half of European mammography programmes achieved the European Union benchmark of acceptable participation (>70%), only few achieved the desirable level (>75%). In Finland, the participation has been 82–87% throughout the 2000s (Finnish Cancer Registry 2021b). Attendance enthusiasm based on these factors may not get undermined as easily as the attendance to CRC screening with quite short history (earliest from year 2004) and only partial geographical diffusion.

Probably due to the exceptional setting of three separate cancer screening invitations within a short time period no research fully comparable was found. More generally, two early studies found that asking women to attend to an adjunct research besides routine screening did not affect the attendance to the breast cancer screening programme (Gram & Lund, 2008; Peeters et al., 1994). Though it is noteworthy, that recruitment letters instead of actual survey study questionnaires may carry sense of "being offered" instead of "being asked for extra effort" the results are in line with ours. In addition, inclusion of a questionnaire on lifestyle and health issues

accompanying the invitation to routine breast cancer screening did not affect the screening uptake in 1994–1996 in southern England (Banks et al., 1998). In the context of cervical screening, questionnaires on screening-related intentions and attitudes attached to the invitation letter increased the attendance (Sandberg & Conner, 2009).

6.4 The third cancer screening on the attendance in established cancer screenings

We studied whether additional cancer screening invitations in the same calendar year changes screening attendance of well-established breast and cervical cancer screenings. Invitation to colorectal cancer screening with home stool test did not change attendance rates of mammography or cervical cancer screening. We believe this is due to the entrenched screening attendance behaviour of 60-year-old Finnish women.

In our study setting the colorectal cancer screening was introduced to women for the first time. Breast and cervical cancer screenings were instead routine procedures (according to the programme schemas a 60-year old woman receives her 6th lifetime invitation for breast cancer screening and 7th invitation for cervical cancer screening). It is possible that a solid behavioural pattern is not affected by outside factors as easily as a more novel behaviour. Previous screening behaviour has been found to predict future attendance both in breast and in cervical cancer screening (Conry et al., 1993; Drossaert et al., 2003; Lagerlund et al., 2000; Larsen et al., 2021). Unfortunately, I did not find any other studies in a similar setting in which the research question was specifically about the effect of (new) CRC screening invitation on participation in other cancer screenings. Generally speaking, cancer screenings are interrelated, meaning that participants in one or two screenings are more likely to participate in other cancer screenings as well (Venturelli et al., 2019; Ishii et al., 2021). There is some findings for why participation on CRC screening is typically lower than on breast and cervical cancer screenings (Kotzur et al., 2020. Lo et al., 2013): for CRC screening, typical reasons for non-participation in relation to other cancer screenings have included dislike of the self-taken home test; worry about completing the test incorrectly; idea that treatment for colorectal cancer is more severe than for breast or cervical cancer; understanding that intestinal symptoms are

easier to self-detect than breast or cervical symptoms; and that the home test for CRC is be more easily delayed or forgotten than breast/cervical screening.

The higher breast and cervical screening participation rates observed in our study population than in all 60-year-old women in Finland are due to the fact that only municipalities with voluntary CRC screening are included in the data. These municipalities lack several large cities, especially the metropolitan area. Large cities traditionally have lower participation in both screenings for women, probably because there is also a supply of non-screening testing in their area. (Finnish Cancer Registry 2021b).

All in all, the results can be considered rather reassuring. An invitation to three distinct cancer screening during one calendar year is of course an exception. On the other hand, the recent update of screening legislation now states, that cervical screening must extend to cover all 65-year-olds beginning in 2022. This means one more screening invitation for the females over 60 years of age, and just begun with CRC screening. Yet, no other single year than the one a woman turns 60 years, will she receive all three cancer screening invitations during the same calendar year.

6.5 Implications for research and practice

6.5.1 Implications for research

How to incorporate surveys into screening with minimum harm

Large-scale, well-organized screening programmes with centralized electronic databases have huge potential as research resources. If and when research studies involve direct contact with programme participants it should not be assumed that they will not have an impact on screening behaviour.

From efficiency and ethical point of view, it is important to ensure both that research is enabled and conducted in a way that is least detrimental to screening participation. While the purpose of an additional survey is high-minded, it can do more harm than good if it damages attendance. Because attendance is so central to the effectiveness of screening, it needs to be carefully monitored and protected.

This risk of lowering participation should be taken into account when planning to exploit the screening context in conducting epidemiological surveys or other intervening studies. Simultaneous mailing in the same envelope is the standard method to incorporate an extra survey into routine health research activity. It is reasonable to assume that such extra effort could reduce the willingness to participate even more than was observed in our study with a one year lag between these two activities (survey and screening invitation mailings) and thus it cannot be unreservedly recommended.

To minimize survey or other research initiative hampering the future screening participation it is encouraged to emphasize in the survey study participant recruitment material that when individual´s screening invitation is due, he/she should not mind the survey effort at hand anymore. In other words, the independency of questionnaire study and screening should be strongly underlined. Correspondingly, some kind of mention in screening invitation with a core message of "though you may have responded a questionnaire on this topic in the past, screening is still relevant for you" should be considered. It may not be impossible that some screen invitees have had an understanding of already taking part on preventive measure if they have provided the information asked in the research questionnaire. Yet, it is possible that these kinds of extra information in the invitation act as extra burden, too.

Areas in need for further research

More insight is needed into the association between symptoms and screening attendance. Future research could focus on identifying factors such as health literacy, attitudes towards screening and broader cancer prevention, use of health care services, and family history of colorectal cancer in relation to symptom interpretation, all of which might deepen the issue of perceived gastrointestinal symptoms and CRC screening attendance. In addition, studying the difference in demographic background factors such as gender, age and socio-economic status between symptomatic and asymptomatic screen-invitees might help us to understand the association more broadly.

For some, receiving a research questionnaire may raise feelings of burden, irritability and uncertainty. The prevalence, intensity and effects of these reactions should be studied in more depth. Requesting effort on the part of the recipient appears harmful for future screening willingness in the light of the results of this thesis. Other possible

consequences for example on health care engagement, trust and motivation should also be addressed. One point to consider is also the non-awareness that issues related to health choices and behaviour – those asked in questionnaires - are not available on health registers, though they may have been discussed upon with a public health nurse or a doctor on an appointment. For this matter, more open communication on research opportunities and constraints to the public is needed.

The issue of multiple cancer screening invitation within a short period of time deserves more research from various perspectives. Since the target age group of cervical cancer screening has been extended to 65-year-olds throughout the country, females aged 60-65 years of age are subjected to three cancer screenings: cervical cancer screening at the age of 60 and 65, breast cancer screening at 60, 62, and 64 years, and colorectal cancer at 60, 62, and 64 years, too. Research could aim at exploring versatile attendance patterns between programmes from conscientious and regular uptake to flexible selective uptake or persistent non-attendance and exploring the reasonings for these with potentially qualitative methods.

6.5.2 Implications for practice

The findings of sub-study II on the association of LGI symptoms and CRC screening attendance suggests that perceived symptoms are important in understanding screening behaviour. The study insights can be utilized in tailoring and targeting the screening information material e.g. by gender. One important issue to address in the future is how to optimally use information on symptoms in the CRC screening programme. Raising awareness of potential cancer symptoms and prompt help-seeking more generally are also warranted. Of equal importance is the inclusion of all men and women in the target age groups in screening and not to encourage self-exclude those with symptoms.

6.6 Strengths and limitations

The studies in this thesis are based on data from two primary sources: a survey study designed and carried out for this specific purpose and data from the national mass screening register. The questionnaire used in the survey study was designed by experts from various relevant fields and it utilized the conventional questionnaire forms in the Finnish health surveys of the adult population. We aimed to make the

questionnaires as effortless as possible for the respondent to complete with clarity and guidance. Finnish health and administrative registers are high quality (Gissler & Haukka, 2004; Sund, 2012; Pukkala et al., 2018) and have a unique personal identity code, enabling the reliable linking of information. The coverage and completeness of the mass screening register as part of the Finnish cancer register is exceptionally high.

The study's main strength is the population-based, double-randomized, and controlled design. The "Psychosocial consequences of colorectal cancer screening" -study is population-based with no exclusion criteria. Double-randomization refers to the randomization at two separate time points independent of each other. Firstly, the study population was randomized to the survey study (to receive the questionnaire or not), and secondly, to CRC screening (to receive invitation or not). Those not contacted served as a natural control group. The screening controls represent a genuinely unscreened reference group since opportunistic FOBT screening was not a common practice in Finland during the study data collection. With a baseline measurement before the potential exposure and a two-year follow-up measurement occurring in corresponding calendar time well after the screening, reliably assessing the effect of CRC screening on changes over time in issues studied was possible. This kind of well-planned and executed prospective, randomized, and controlled design minimizes reporting bias, e.g. recall bias.

A screening-naïve study population offers the least biased sample to investigate screening's effects on behaviour. It was a case of first invitation to whichever cancer screening for men, but for women, it was the first invitation to CRC screening. In the context of cardiovascular screening, one's first participation in health screening is the most effective at prompting behaviour change (Stevens et al., 2019). Previous research has not always distinguished between participants with and without prior cancer screening experience.

The response proportion of the survey study (5 % at baseline, 84% of baseline respondents at follow-up) can be considered moderate. In addition, respondents were self-selected by certain demographic factors. We could look at the selection for survey participation and screening attendance according to certain background factors - sex, residential area, marital status, education - obtained from national registers (CPR and Statistics Finland) for the whole study population. Women, married, and more highly educated responded more often than men, single, and less

educated (Jäntti et al., 2016), naturally limiting the generalizability of the results. Respondents to the surveys tend to be selective in many ways, including lifestyle (Van Loon et al., 2003). The uptake of FOBT screening in Finland is also selective by sex, marital status, and at least some lifestyle aspects: non-attenders are more often men, non-married, obese (BMI>30), smokers and physically inactive (Artama et al., 2017).

However, these few background factors will unlikely reach most of the reasons or meanings behind non-participation. Also, non-responding and non-participating individuals are a heterogenous group likely consisting of different sub-groups. Some of them (as a group) may react differently to a screening invitation or outcome or whose lifestyle differs from the respondents. Conversely, individuals adhering to both interventions (84% of baseline respondents at follow-up) can be considered remarkably stronger (albeit parallel) selected. One could argue that this highly motivated group is somehow more resistant to screening's effects due to, e.g. health-consciousness, meaning although we do not notice spontaneous effects of screening in this group, effects could theoretically manifest in non-respondents.

It is noteworthy that the general screening attendance proportion in 60-year-old men in 2011 was 51% and in women 69%, in contrast to 80% and 90%, respectively, in the study population, highlighting the strong self-selection of this population active in research participation and preventive healthcare attendance. Above all, the respondents were self-selected by future screening attendance: Of those 2874 screen-invited persons who responded to the questionnaire in 2010, 2286 (79%) attended the screening in 2011, whereas only 644 (28%) of the 2292 survey non-respondents attended. Examining the change of health behaviour suffers from a small number of non-attenders, because in this highly self-selected group of study participants (respondents at baseline 2010 and follow-up 2012), non-attendance in screening is quite rare.

One limitation of the study concerns including only one age cohort due to the study question on the effect of first ever CRC screening, which may limit the generalizability of the results. Also, the study population was not representative of the capital area since CRC screening was not ongoing in Helsinki, Espoo, or Vantaa at the time of study data collection. National cultural factors may also limit translating of experiences from one national context to another.

A follow-up span of two years arose from screening intervals in the Finnish CRC screening programme. The follow-up measurement was regarded as essential to occur before potential re-exposure. Screening may introduce short-term effects on lifestyle or symptom perception undetected under our follow-up of two years. Time-points for measurements may fail to capture transient changes in health behaviours, which might be made following cancer screening. On the other hand, short-term changes seldom have large-scale health effects, especially typical for lifestyle choices whose health-related effects accumulate over a long time.

Our study examined the outcome of lifestyle changes with an index combining several lifestyle factors, capturing the influence of multiple health behaviours. With a total CRC-related lifestyle index approach, we formulated an overview of CRC-related lifestyles instead of examining single lifestyle factors, whose relevance and interplay for lifestyle changes can be difficult to assess (Limpens, 2022). Moreover, a CRC risk-related broad lifestyle approach within the screening target population may reveal developments influencing the CRC screening's overall effectiveness. The limitation of this approach is interpreting the non-validated, self-regenerated instrument. The selection of lifestyle components (i.e. promoted/discouraged behaviours), the quantification of cut-off points for each component, and the weighting of components related to the total score are all more or less subjective. Research using objective measures of health behaviours is needed to explore whether the changes observed in other studies are reliable.

For the analysis, each lifestyle component was scored dichotomously by assigning 1 or 0 points, with 1 point indicating a lifestyle favourable for CRC prevention. Also for the symptoms, a dichotomic symptom index (0, 1) based on total symptom score (total symptom score 0 = "asymptomatic" & total symptom score ≥1= "symptomatic") was developed and applied. In general, dichotomizing of variables affects analysis and results. Dichotomizing variables is often justified by the notion of simplifying phenomena into a more explorable form (Altman & Royston., 2006). Much information is lost in the process, and the statistical power to detect a genuine relation between the variable and outcome suffers. Dichotomization may also increase the risk of a positive result being a false positive (type I error). Moreover, dichotomization reduces variation and using only two groups conceals any non-linearity in the relationship between the variable and outcome. Since only one of the six components utilized in lifestyle index (BMI) was originally continuous (others were categorical), the amount of information lost can be considered moderate.

6.7 Ethics

The choice of research topic can be viewed as a statement that this phenomenon or issue is considered worthy of research and must be explained. The ethical reflection of the topic also involves who chose the topic and why the research will be undertaken. The subject of this thesis research is ethically justified as it aims to ensure the population possibly targeted for a health care intervention of cancer screening is harmed as little as possible. The issue of potential psychosocial effects of CRC screening became relevant – at least when there was preliminary evidence on other screening studies or pilots that screening could carry undesirable lifestyle effects.

The intended benefit of the study, i.e. information on the potential impact of screening on health behaviour, should also be assessed concerning the suspected harm, i.e. the reduced proportion of participants in screening (resulting in potentially missed adenomas and cancers). When initiating the survey study no explicit knowledge existed on how the questionnaires would affect attendance – or if they would have any effect. Questionnaires were pursued to be as least burdensome as possible to follow the principle of minimum harm; the wider version was restricted to only a random sample.

The research was conducted following the standard ethical principles of scientific research ethics, especially regarding the treatment of study subjects. The CRC screening programme was launched in 2004 as a public health policy among volunteering municipalities. The registration follows the permission from the Ministry of Social Affairs and Health (2003). The study protocol received a favourable opinion from the coordinating ethics committee on the Helsinki and Uusimaa Hospital District (decision number 420/13/03/00/09) before conducting the study. Those participating in the survey study gave their informed consent: A written consent form requesting the respondent's informed consent accompanied the postal questionnaires. The study's objectives and the need to link the survey data to the screening data were described in the form. Study subjects returned their signed consent by mail along with their questionnaire response.

The research group worked according to the data protection principles and ethical rules.

7 CONCLUSIONS

This thesis evaluated the unintentional effects of the Finnish colorectal cancer screening programme. The following conclusions can be drawn:

1. No support for the suggested undesirable effect of CRC screening concerning lifestyle was found. Invitation to, or attendance in FOBT screening did not harm total CRC-related lifestyle in a 2-year follow-up of 59–61-year-old Finnish men and women. Conversely, the CRC-related lifestyle did not show spontaneous improvements towards a more favourable lifestyle due to CRC screening. The idea and implementation of the screening context in promoting of cancer-preventive lifestyle choices must be carefully considered.

2. There was no support for the suggested undesirable effect of CRC screening regarding symptom perception. Attendance in FOBT screening did not influence symptom perception. No harm of CRC screening concerning the impact on lower gastrointestinal symptom perception was discovered.

3. Perceived symptoms may provide a novel, less explored dimension for understanding screening behaviour and sex differences in CRC screening. Perceived lower gastrointestinal symptoms increased CRC screening attendance in men.

4. Exploring the potential effects of lifestyle and quality of life may harm screening attendance. A relatively wide postal survey sent the previous year of the first-ever CRC screening invitation reduced the corresponding screening attendance proportion. This CRC screening attendance-reducing effect of the original survey study appeared to be long-term while it was present on subsequent screening rounds even when no more questionnaires were sent. Attendance among those exposed to questionnaires initially did not reach the attendance level of those unexposed, i.e. those who were never surveyed. However, the survey intervention in question did not harm other cancer screenings regarding the female breast and cervical cancer screening attendance.

5. Introducing a new cancer screening, i.e. colorectal cancer screening resulting in a third cancer screening invitation during the same year for 60-year-old women did not harm or benefit the high attendance to breast and cervical cancer screenings.

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PUBLICATION 1

Lifestyle in population-based colorectal cancer screening study over 2-year follow-up

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European Journal Public Health 2018; 28(2): 333–338.
doi: 10.1093/eurpub/ckx139

The European Journal of Public Health, Vol. 28, No. 2, 333–338

doi:10.1093/eurpub/ckx139 Advance Access published on 15 September 2017

Lifestyle in population-based colorectal cancer screening over 2-year follow-up

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Background: Colorectal cancer (CRC) screening may cause changes in health-related lifestyle. In 2010, Finnish Mass Screening Registry began a study on psychosocial effects of CRC screening. This article examines whether there are differential developments in self-reported lifestyle at ages 59–61 years among CRC screening invitees and non-contacted controls. **Methods:** A population-based random sample of 10 648 Finnish adults born in 1951 and living in the municipalities voluntary involved in the CRC screening programme were sent a lifestyle questionnaire in 2010. In 2011, the cohort was randomised (1 : 1) for their first ever CRC screening at age 60 or for controls. The questionnaires were repeated in 2012 for all. From both survey rounds, 2508 pairs of completed questionnaires were available for analysis from the screening group and 2387 from the control group. The outcome was 2-year change in total lifestyle index of CRC risk factors (diet, physical activity, body mass index, alcohol consumption and smoking). **Results:** Total lifestyle index decreased throughout the follow-up in both the screening group [odds ratio (OR) = 0.80, 95% confidence interval (CI) 0.72–0.90] and in the control group (OR = 0.80, CI 0.71–0.90) indicating no difference in lifestyle changes between groups. There was also no significant difference by screening participation: the change in score was similar in those participating screening (OR 0.81, CI 0.72–0.92) and in those invited, but not participating (OR 0.75, CI 0.55–1.03). **Conclusion:** Present study found no unfavourable changes in total lifestyle in the studied age group due to CRC screening. Results are reassuring from the point of view of CRC screening evaluation.

Introduction

Ideally, colorectal cancer (CRC) is suitable for prevention both by lifestyle choices and by screening. In terms of research evidence, CRC incidence and mortality can be reduced by repeated faecal occult blood (FOB) testing followed by colonoscopy for test positives.[1] A national population-based programme for CRC screening was implemented in Finland in 2004. In the Finnish programme targeting men and women aged 60–69, the eligible subjects were randomised into invitees and controls when entering the programme as described in more detail earlier.[2]

Potential downside of screening is that it might have a negative effect on various lifestyle-related factors.[3–6] Screening could adversely influence health behaviour–unintentionally or as a side effect–either by the misinterpretation that good health can be maintained by repeated screening tests diminishing the importance of lifestyle choices,[3] or through 'certificate of health effect' suggesting that people who have received a normal screening result may have lower motivation for lifestyle improvements.[3–6]

According to the World Health Organization, non-communicable diseases (NCDs)–mainly cancers, cardiovascular diseases, respiratory diseases and diabetes–are responsible for almost 70% of all deaths worldwide.[7] In the origin and progression of most NCDs including CRC, lifestyle in terms of physical inactivity, nutrition, obesity, tobacco use and alcohol consumption is essential. Bearing this in mind, even a mild deterioration in lifestyle at population level–even if caused unintentionally by health care or research activities–can have major influence in human and economic burden.[8]

There are a number of individual modifiable lifestyle factors that are related to risk of developing CRC. These include diet,[9,10] physical activity,[9,11] smoking,[12,13] alcohol drinking[14,15] and body composition.[16,17] There is also accumulating evidence associating combined lifestyle factors, or patterns of behaviour, with overall cancer risk[18] or site-specifically with colorectal cancer risk.[19,20] Indeed, as behavioural factors are often correlated with one another in everyday life, it is informative from a public health point of view to examine simultaneously a set of lifestyle factors in relation to CRC, and also in relation to CRC screening.

In this study, the psychosocial effects of CRC screening are explored by comparing the possible changes in self-reported lifestyle among those invited to screening with the control population not invited to screening. In addition, comparisons are drawn between those attended the screening and those not attended. The main aim is thus to clarify, if screening is introducing harmful effects and consequently reducing the potential benefit of an otherwise feasible screening programme.

Methods

Study design and study population

The study design has been described in detail elsewhere.[21,22] Briefly, the Finnish Cancer Registry launched a population-based study to evaluate associations between CRC screening, lifestyle and quality of life in 2010. The study questionnaires with information letters and forms for informed consents were mailed to 1 : 2 random sample ($n = 10\,648$) of the future screening target population (men and women born in 1951 living in the municipalities involved in CRC screening in 2010, $n = 31\,951$) the previous year of the randomisation to CRC screening at the age of 60 years. The same material was mailed again to the same individuals in 2012, a year after the first screening

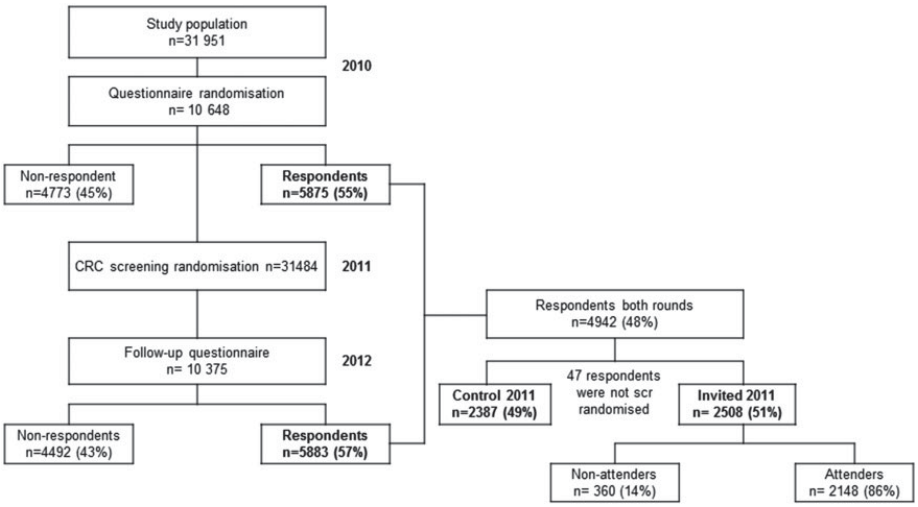

Figure 1 Flow chart on survey participation and screening participation

invitation for those randomised to screening and at the same time for controls (Figure 1).

The study questionnaire focused on lifestyle-related risk factors and lifestyle indicators, such as smoking, alcohol consumption, physical activity and dietary habits. A reminder was sent to non-respondents after 4 weeks and the questionnaires were resent once to those still non-respondents after few months.

The sample of respondents both in 2010 and in 2012 ($n = 4895$) was overrepresented by females, (Supplementary Appendix S1 for baseline sociodemographic characteristics of respondents compared to study population), married and people of higher socioeconomic status. Generally, 68% respondents were currently married and 10% had never been married (12% of men and 8% of women). About one in four of respondents had only basic education (max. 9 years of education) whereas almost every third had high education. Approximately, two thirds of respondents were working in the age of 59 (65% of men and 72% of women).

In 2011, a randomly selected half of the target population was invited for the first ever CRC screening. The Finnish programme was an individually randomised community-based CRC screening programme (a randomised health services study) nested as part of the routine health services.[23,24]

The main outcome of the current study was a 2-year change in CRC risk-related lifestyle factors. To better illustrate the phenomenon of total lifestyle change we formed a lifestyle index for CRC specific modifiable lifestyle factors (diet, physical activity, body composition, alcohol consumption and smoking).

Total lifestyle index

A total lifestyle index was compiled based on current epidemiological evidence on risk and protective factors for CRC, mainly on views of expert panel of World Cancer Research Fund/American Institute for Cancer Research.[9] The total lifestyle index included six components: physical activity, body mass index (BMI), alcohol consumption, smoking and two diet indexes as markers for quality of diet (namely CRC-P and CRC-R, see below). Each lifestyle component was scored dichotomously by assigning 1 or 0 points, 1 point indicating lifestyle favourable for CRC prevention. The cut-offs were defined as being physically active (≥ 4 h/week of light or moderate intensity physical activity or vigorous physical activity ≥ 30 min daily/almost daily), normal weight (BMI $\leq 25\,kg/m^2$), consuming no or moderate amount of alcohol (≤ 1 drink/d for women, ≤ 2 drinks/d for men), being non-smoker and having diet rich in CRC protective foods and poor in CRC causative foods (Table 1). The overall score was determined by summing all the points obtained from each lifestyle factor. The total lifestyle index ranged thus from 0 to 6, high scores indicating CRC protecting lifestyle.

Diet indexes

Diet was examined with a 41-item semi-quantitative food and drink frequency questionnaire (FFQ). In order to characterise quality of diet from the CRC point of view, two separate indexes were created based on current evidence on protective or causative food for CRC.[10,11] The colorectal cancer protective food index (CRC-P) included three components (intake of rye bread as an indicator of dietary fibre, intake of milk and combined intake of vegetables, fruits and berries). The colorectal cancer risk food index (CRC-R) included four components (intake of processed meat, intake of red meat, intake of cheese and intake of sugary foods). Those components that have more compelling evidence on CRC risk were scored from 0–8 (processed meat, red meat and rye bread) and those with less convincing evidence were scored from 0–4 (milk, vegetables, cheese and sugary foods) based on frequency of use (Supplementary Appendix S1). The components of the CRC-P received scores in ascending order so that the lowest frequency of use resulted in 0 points and the highest frequency in maximum points (4 or 8 points). CRC-R was scored in the opposite order (highest points for the lowest frequency of use and no points for the highest frequency of use). All component scores were summed to the total score which ranged from 0 (lowest) to 16 in CRC-P or 24 in CRC-R (highest) points. A higher score was considered to be beneficial, i.e. to represent dietary behaviour less prone to CRC compared to those who had a lower score on the dietary index. Diet index score above sex-specific median resulted in 1 point for the total lifestyle index whereas scores at median and below resulted in 0 point.

Statistical analysis

The study population was classified into screening groups in two ways. First, to study the effect of invitation, the study population was divided into screening invited and non-invited controls. Secondly, to study the effect of screening attendance, the study population was divided into three groups, i.e. those invited were further divided into screening attenders and screening non-attenders.

Table 1 Components of the lifestyle score and distribution of points in study population (responses from both rounds 2010 and 2012)

Lifestyle score component	Score	Description	Study population ($n = 4895$)		Men ($n = 2171$)		Women ($n = 2724$)	
			2010 *n* (%)	2012 *n* (%)	2010 *n* (%)	2012 *n* (%)	2010 *n* (%)	2012 *n* (%)
Physical activity (PA)	1	Plenty[a] of PA	3588 (73)	3550 (73)	1593 (73)	1593 (73)	1995 (73)	1957 (72)
	0	Little[b] or no PA	1287 (26)	1330 (27)	570 (26)	574 (26)	717 (26)	756 (28)
		Missing	20 (0)	15 (0)	8 (0)	4 (0)	12 (0)	11 (0)
Body mass Index	1	BMI $\leq 25\,kg/m^2$	1743 (36)	1670 (34)	658 (30)	639 (29)	1085 (40)	1031 (38)
	0	BMI $> 25\,kg/m^2$	3095 (63)	3147 (64)	1494 (69)	1508 (70)	1601 (59)	1639 (60)
		Missing	57 (1)	78 (2)	19 (1)	24 (1)	38 (1)	54 (2)
Smoking	1	No current smoking	3961 (81)	4032 (82)	1705 (79)	1745 (80)	2256 (83)	2287 (84)
	0	Current smoker	911 (19)	849 (17)	457 (21)	422 (19)	454 (17)	427 (16)
		Missing	23 (1)	14 (0)	9 (0)	4 (0)	14 (1)	10 (0)
Alcohol consumption	1	$\leq$ 1 drink/d for women, $\leq$ 2 drinks/d for men	4455 (91)	4553 (93)	1893 (87)	1964 (91)	2562 (94)	2589 (95)
	0	> 1 drink/d for women, > 2 drinks/d for men	404 (8)	332 (7)	264 (12)	205 (9)	140 (5)	127 (5)
		Missing	36 (1)	10 (0)	14 (1)	2 (0)	22 (1)	8 (0)
CRC-P	1	Above median	1975 (40)	1908 (39)	808 (37)	789 (36)	1167 (43)	1119 (41)
	0	Median or below	2834 (58)	2898 (59)	1326 (61)	1346 (62)	1508 (55)	1552 (57)
		Missing	86 (2)	89 (2)	37 (2)	36 (2)	49 (2)	53 (2)
CRC-R	1	Above median	1937 (40)	2012 (41)	832 (38)	852 (39)	1105 (41)	1160 (43)
	0	Median or below	2853 (58)	2775 (57)	1296 (60)	1270 (59)	1557 (57)	1505 (55)
		Missing	105 (2)	108 (2)	43 (2)	49 (2)	62 (2)	59 (2)

a: $\geq$ 4 h/week of light or moderate intensity PA or vigorous PA $\geq$ 30 min daily/almost daily.
b: < 4 h/week light or moderate intensity PA and no daily vigorous PA.

The association of screening group (invited attenders and invited non-attenders) and possible change in CRC-related lifestyle index was assessed using ordered logistic regression with random effects. In both models, calendar time (before vs. after potential screening) was used as a within-subject variable, and screening group and gender as between-subject variables. We estimated the screening group-by-time and screening group-by-gender interactions and considered a significant interaction as an evidence for differences in lifestyle index change by screening group or gender, respectively. Socio-demographic characteristics included marital status (from Central Population Register), education and type of residential municipality (from Statistics Finland). Statistical analysis software package STATA 14 was used for data management and statistical analyses.

The study design was approved by the Helsinki and Uusimaa hospital district Ethics Committee (15.12.2009, 420/13/03/00/2009).

Results

In 2010, the study questionnaire was sent to 10 648 individuals, of whom 5875 (55%) responded. In 2012, the same cohort (10 375 individuals; 273 had died, refused in 2010 or had unknown address) were sent the follow-up questionnaire, and 5883 (57%) of them responded. A total of 4895 individuals were eligible for analyses (response from both survey rounds), 2508 in the screening arm and 2387 in the control arm (Figure 1). The response rate for the post-screening questionnaire was high (94%, 2148 of 2291) among the screening attenders who had completed the pre-screening questionnaire. Among the screening non-attenders and the controls, the corresponding response rates were 60%, (360 of 602) and 82% (2387 of 2916).

Lifestyle at baseline

Scoring of single lifestyle index components at baseline is presented in Table 1. Almost three out of four respondents were physically active, and 30% of men and 40% of women were of normal weight. One fifth of men and 17% of women reported current smoking, and alcohol consumption was classified as excessive in 12% of men and 5% of women. Supplementary Appendixes S2a–3 present how respondents scored in different components of diet indexes CRC-P and CRC-R. Best points were most often from consumption of vegetables, fruits and berries and also from consumption of rye bread while consumption of processed meat most often yielded low points.

The distributions of lifestyle index at baseline are shown in Figure 2. The most often scored number of lifestyle components fulfilled was 4 (31% of men and 34% of women).

Changes in lifestyle overall

Changes in each item of lifestyle index were very small (Table 1). Smoking became slightly less prevalent from 2010 to 2012 (21% vs.19% of men and 17% vs. 16% of women). Excessive use of alcohol got less frequent during follow-up in men (12% in 2010 vs. 9% in 2012). Respondents were more often normal weight ($\leq 25\,kg/m^2$) in 2010 than in 2012 (36% vs. 34% of respondents, respectively). In women, subtle changes in diet could be observed with CRC-P scoring a point in 41% in 2012 vs. in 43% at baseline, and CRC-R yielding a point more often in 2012 than in 2010 (43% vs. 41%, respectively). These changes are due to decreased consumption of rye bread and processed meat (Supplementary Appendix S3). Otherwise there were practically no changes from 2010 to 2012 in dietary index component consumption.

The total lifestyle index decreased [odds ratio (OR) 0.80, 95% confidence interval (CI) 0.74–0.87] over time. In men the decrease was more evident than in women (OR 0.68, CI 0.60–0.77 vs. OR 0.92, CI 0.82–1.03, respectively).

Changes in lifestyle index by screening allocation

Invitation to CRC screening had no effect on lifestyle (in men controls OR 0.66, CI 0.55–0.78 vs. screen-invited OR 0.70, CI 0.59–0.84 and in women controls OR 0.94, CI 0.80–1.11 vs. screen-invited 0.90, CI 0.77–1.05, Table 2). Interaction between screening invitation status and calendar time or adjusting for socio-demographic characteristics (marital status, education and type of residential municipality) or including only respondents with low education did not affect the results (data not shown).

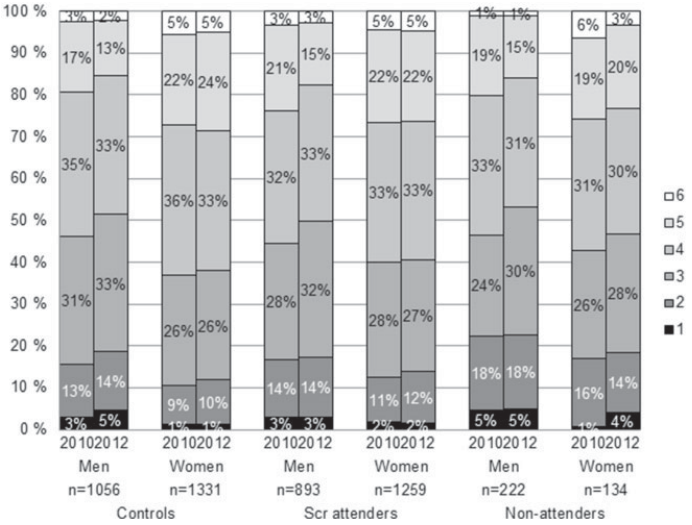

Figure 2 Lifestyle index at baseline (2010) and follow-up (2012) by sex and screening group. High scores indicate more CRC protecting lifestyle. 12 respondents (7 men, 5 women) scored 0 points in the lifestyle index in 2010 and 17 (11 men, 6 women) in 2012. These few observations were combined with the group of the second lowest score 1

Table 2 Lifestyle index change 2010–12 by screening allocation, attendance and gender

	Controls ($n = 2387$)		Scr invited ($n = 2508$)		Scr attenders ($n = 2152$)		Scr non-attenders ($n = 356$)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All	0.80	0.71–0.90	0.80	0.72–0.90	0.81	0.72–0.92	0.75	0.55–1.03
Men	0.66	0.55–0.78	0.70	0.59–0.84	0.69	0.57–0.83	0.77	0.52–1.14
Women	0.94	0.80–1.11	0.90	0.77–1.05	0.92	0.78–1.08	0.73	0.43–1.23

Changes in lifestyle index by screening attendance

The direction or volume of changes in total lifestyle index did not differ significantly between those attending and those not attending screening (Table 2, Figure 2). In men the OR for lifestyle index change from 2010 to 2012 was 0.69 (CI 0.57–0.83) in attenders vs. 0.77 (CI 0.52–1.14) in non-attenders, and in women 0.92 (CI 0.78–1.08) vs. 0.73 (0.43–1.23), respectively. No interactions of attendance status and time were found. Due to reasonably small number of non-attenders (222 men, 134 women) the estimates of the group did not reach statistical significance.

Discussion

This questionnaire study embedded in the Finnish CRC screening programme did not show differences in the CRC-related lifestyle between the screening arms or by screening attendance. Lifestyle index used in the study changed towards negative direction from CRC point of view in 2-year follow-up, but there was no implication that screening status affected this progression. Results provide at least some evidence that neither invitation to nor attendance in FOBT-based CRC screening leads to a less healthy lifestyle.

All analyses were carried out by sex since lifestyle habits vary between Finnish men and women.[25] Gender-specific variation has frequently been reported also in the CRC screening participation[26–29] and in the screening outcome.[30,31]

The main strength of the study lies in its population-based, randomised controlled design. With a baseline measurement truly before the exposure we were able to reliably assess the effect of CRC screening invitation on lifestyle score changes. The controls represent a genuinely unscreened reference group since opportunistic FOBT screening is not a common practice in Finland. Our study examined the outcome of change in lifestyle with an index combining several lifestyle factors, which captures the influence of multiple health behaviours.

Our response proportion (55% at baseline, 84% of baseline respondents at follow-up) can be considered as moderate. Additionally, respondents were self-selected by certain demographic factors.[22] Women, married and more highly educated responded more often than men, single and less educated (Supplementary Appendix S1). This, naturally, limits generalisability of the results. Among non-respondents there may be sub-groups who either respond differently to screening invitation or to screening outcome or whose lifestyle differs from that of the respondents. The uptake of FOBT screening in Finland is also selective by sex, marital status and lifestyle[28,29,32]: non- attenders are more often men, non-married, obese (BMI > 30), smokers and physically inactive.

One limitation of the study concerns the inclusion of only one age cohort. This was due to the study question of effect of first ever CRC screening, and may also limit the generalisability of the results. Follow-up span of 2 years arose from screening interval in Finnish CRC screening programme. We wanted to carry out the follow-up measurement before potential re-exposure. It is possible that screening is introducing short-term effects on lifestyle which are not detected under our follow-up though there is no evidence for such a phenomenon in the literature. On the other hand, such changes barely would have major public health relevance.

With a total CRC-related lifestyle index approach we formulated an overview of CRC-related lifestyle instead of examining single lifestyle factors, whose relevance and interplay for lifestyle changes

can be difficult to assess. Moreover, CRC risk-related broad lifestyle approach within the screening target population may reveal developments influencing the overall effectiveness of CRC screening. The limitation of this approach is the interpretation of non-validated, self-regenerated instrument. The selection of lifestyle components (i.e. promoted/discouraged behaviours), the quantification of cut-off points for each component and the weighting of components in relation to the total score are all more or less subjective.

Previous studies on effects of CRC screening on lifestyle choices are few. A questionnaire study in the UK did not find flexible sigmoidoscopy CRC screening leading to less healthy lifestyle in a 3-month follow-up.[33] However, the study did not have an unscreened control group and the study participants had consented to take part in a screening trial before the prescreening questionnaire. A Norwegian study in 2001–04 found undesirable lifestyle changes associated with flexible sigmoidoscopy CRC screening: the screening group gained more weight, had poorer quitting rates for smoking and increased the intake of fruit, berries and vegetables less than the control group.[4] With extended follow-up it was observed that even long-term (11-year) changes in lifestyle were still poorer in screen-invited population compared to the control population.[34] The difference between our results compared to these results may partly due to different age groups of study populations, time and also to dissimilarities in study designs. Furthermore, FOBT as a screening test is different than sigmoidoscopy: FOBT is sent by post, completed at home and returned by mail without direct encounter with a health care provider. Instead, performing sigmoidoscopy as the screening test is a medical procedure requiring visit to screening site and face-to-face contact with the personnel. People may interpret the result of self-performed vs. professional-performed test differently, or the test procedure *per se* may have different effects on screened individual. Moreover, our findings are similar to a more recent Norwegian study which indicated no differences in health behaviour changes at 1-year follow-up between controls and screened negative (either a first round of fecal immunochemical test or flexible sigmoidoscopy) at screening.[35]

According to meta-analyses[1,30] the effect of FOBT-based CRC screening on CRC mortality is quite modest, 12–16%. It is estimated that with reasonable modification of multiple diet and lifestyle factors 20–30% of CRC cases could be prevented.[36] As we observed that CRC-related lifestyle changed rather to negative than to positive direction in our study population during study period, one could see a need for lifestyle counselling for this population. Screening programme with a mailed material could serve as a context in which to promote healthy behaviour–also for screening non-attenders. For example, in Scotland a lifestyle intervention delivered through CRC screening programme has yielded desired results.[37]

Studying psychosocial effects in terms of health behaviour is part of the overall evaluation of a screening programme. Lifestyle deterioration after screening can be seen as a harm of screening, while improvements as a benefit. Since there were no changes in lifestyle due to screening to either direction, there is no impact of lifestyle choices on the benefit–harm ratio of Finnish CRC screening programme.

In conclusion, we found no effect of FOBT screening on CRC-related lifestyle in 2-year follow-up of 59–61-year old Finnish men and women. The CRC-related lifestyle showed, however, a downward trend with changes towards unfavourable lifestyle. Results do not support the suggested undesirable psychosocial effects of CRC screening. Nonetheless, the results hold a challenge for using the screening context in promotion of cancer-preventive lifestyle choices.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgement

The authors would like to thank PhD Clarissa Bingham for expertise in generating the dietary indexes.

Conflicts of interest: None declared.

Key points

- A lifestyle index of colorectal cancer risk factors was produced using data on self-reported diet, physical activity, body mass index, alcohol consumption and smoking in a population-based survey study.
- We found no changes in lifestyle index due to screening: there was no difference in lifestyle changes between groups invited to screening and controls or by screening participation.
- Lifestyle effects do not affect the cost-benefit ratio of the colorectal cancer screening programme in Finland.

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The European Journal of Public Health, Vol. 28, No. 2, 338–343

doi:10.1093/eurpub/ckx170 Advance Access published on 4 October 2017

Brain cancer cluster investigation around a factory emitting dichloromethane

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Background: The health risks associated with dichloromethane (DCM) for the general population living near industrial activities have not yet been quantified, primarily due to lack of epidemiological datasets. In the absence of such human data, we undertook a cancer cluster investigation in Cyprus around a historically using DCM plant producing shoe soles that were globally exported. We designed the methodology to investigate the possible existence of a cancer cluster in the area around the factory (point zero) and within a radius of 500 meters. **Methods:** A retrospective comparative population study was designed using a group of cancer patients living or working in the chosen geographical area around the factory. **Results:** Mean stack emissions of DCM of 88 mg/Nm^3 and flow rates of 850 g/h exceeded the permissible DCM limits established for industrial zones. Brain and central nervous system (CNS) cancer incidence rates showed significant ($P < 0.001$) increase in the study area around the plant when compared with those observed in other areas of Cyprus. Calculated standardized incidence ratios for brain/CNS after adjusting for the age at diagnosis ranged from 11.3–25.7 [mean 6.5 (3.02 : 12.3)] for the study area. **Conclusions:** We showed the association between chronic, unintentional DCM exposures and brain/CNS cancer cases for the general population located in a residential area being in close proximity with a plant historically emitting DCM.

Introduction

Dichloromethane (DCM) or methylene chloride (CASRN, Chemical Abstract Services Registry Number, 75-09-2) is a chlorinated organic solvent that has been widely used in the industry.[1] DCM finds use as paint stripper, in sprays/aerosols as propellant/solvent, in chemical processing, metal cleaning and degreasing, printer ink removal.[1] It is ubiquitous in the

PUBLICATION 2

Self-reported lower gastrointestinal symptoms in colorectal cancer screening

Sanni Helander, Sirpa Heinävaara, Tytti Sarkeala, Nea Malila

submitted manuscript

PUBLICATION 3

Effect of a pre-screening survey on attendance in colorectal cancer screening: A double-randomized study in Finland.

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Journal of Medical Screening 2014; 21(2): 82–88

doi: 10.1177/0969141314534229

J Med Screen
2014, Vol. 21(2) 82–88

DOI: 10.1177/0969141314534229
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Effect of a pre-screening survey on attendance in colorectal cancer screening: A double-randomized study in Finland

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Abstract

Objectives: To explore effects of a pre-screening life style survey on the subsequent attendance proportion in colorectal cancer screening.

Setting: Finnish colorectal cancer screening programme in 2011.

Design: Double randomized and controlled follow-up design.

Methods: The study population comprised of 31,951 individuals born in 1951. In 2010 to a random sample of every sixth (n = 5,312) person we sent a 7-paged life style questionnaire, and to another random sample of every sixth person (n = 5,336) a 10-paged life style and quality of life questionnaire. One year later, in 2011, 31,484 individuals of the original cohort were independently randomized (1:1) for colorectal cancer screening (n = 15,748) or control group (n = 15,736). Of those who were invited for screening, 5185 had received a questionnaire during the previous year.

Results: 5870 individuals (55.1 %) responded to the questionnaire in 2010. The overall attendance at screening in 2011 was 59.0 % in those born in 1951 (i.e. the 60-year-olds). In those who had been sent the survey the attendance in screening was 56.6% (57.3% for the short and 56.0% for the long questionnaire) and in those who had not received the questionnaire it was 60.2% ($P < 0.001$).

Conclusions: We believe that the observed reduction in attendance in those who had been sent a questionnaire earlier is generally true. Thus, if any survey is enclosed in the screening invitation, this finding should be taken into account when planning the programme. Any extra effort requested may reduce the attendance proportion for screening, reducing the population level impact of screening.

Keywords

colorectal cancer screening, health surveys, participation, questionnaires, life-style, quality of life

Date received: 24 November 2014; accepted: 14 April 2014

Introduction

Colon and rectum cancers together are the third most common cancer site by incidence among Finnish men and women combined, with over 2500 new cases annually.[1] Colorectal cancer (CRC) incidence and mortality can be reduced by repeated faecal occult blood testing, followed by colonoscopy for test positives.[2,3] A population-based programme for CRC screening by biennial faecal occult blood testing for 60–69 year olds has been running in Finland since 2004. The screening is voluntary for the municipalities to organize. An experimental design has been incorporated for public health evaluation, using individual level randomization of the target population into screening and control groups.[4]

For a cancer screening programme to be effective from the mortality-lowering aspect, a high participation rate is crucial. The Finnish CRC screening has achieved high attendance: from 2004 to 2007, overall attendance was 71%. Participation was better in women (78%) than in men (62%)[5,6] and in older age groups than in younger people.

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Screening programmes provide a useful setting in which to conduct epidemiological surveys, but there is a risk of lowering attendance if participants are asked to submit to extra investigations. In evaluating the effects of CRC screening, information on life style, quality of life, and costs is also needed. In Finland, the ''Psychosocial effects of colorectal cancer screening study'' was incorporated into the CRC screening programme in 2010. The study utilizes a prospective, randomized and controlled study design to ensure an unbiased setting. Life style and quality of life are assessed through a self-administered postal questionnaire at two stages, at baseline one year before the first possible screening invitation, and a similar questionnaire one year after the first invitation (Figure 1). A comparison can then be made on how different life style related factors change among the invited and the control population, and the possible effect of screening on health habits can be evaluated.

We here attempt to determine whether sending a short (7-paged) or long (10-paged) questionnaire on life style and quality of life one year before the first ever screening invitation has an effect on uptake of screening. We also investigate whether this effect varies between different groups according to background demographic factors.

The study design was approved by the Helsinki and Uusimaa hospital district Ethics Committee (15.12.2009, 420/13/03/00/2009).

Methods

Study population

The study population was comprised of those born in 1951 and living in municipalities involved in the CRC screening programme (148 out of total 342 in 2010). These individuals were to turn 60 in the calendar year 2011, when the first invitation to CRC screening was due. Individual data on the target population (n = 31,951) was provided by the Central Population Register (CPR) in March 2010. Random allocation of 1:2 resulted in 10,648 individuals to whom questionnaires were mailed in May 2010. Of these, a random 5312 received a 7-paged questionnaire and 5336 a 10-paged questionnaire.

In 2011, a randomly selected half of the target population received their initial Finnish CRC screening programme invitation. This programme randomizes (1:1) to screening or control groups in men and women aged 60 and eligible for screening for the first time.[4] Survey randomization and screening randomization were independent of each other. There were no exclusion criteria in either the survey study population or in the screening programme.

Questionnaire

The self-administered postal questionnaires were designed in collaboration with experts in life style and quality of life research, and as far as possible incorporated questions of the type used in the ''Health Behaviour and Health among the Finnish Adult Population'' validated annual postal survey carried out since 1978.[7] The main reason for this was to enable comparisons between respondents and respective age groups within our study and those in the annual survey.

The two questionnaires were the short (7-paged) ''lifestyle questionnaire'' and the longer (10-paged) ''life style and quality of life questionnaire''. The short questionnaire included 30 questions divided into seven sections: sociodemographic background data of the respondents,

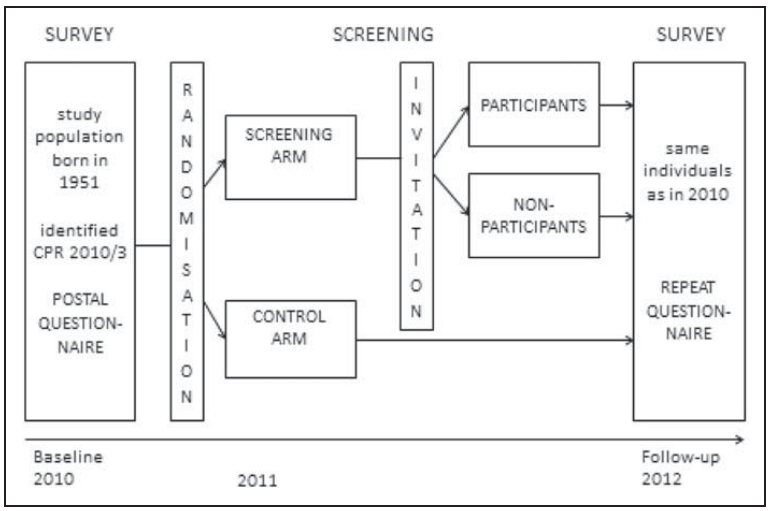

Figure 1. Study design of Psychosocial effects of colorectal cancer screening study.

smoking, alcohol consumption, exercise, diet, health status and CRC related questions. The longer version included an additional section measuring health related quality of life with the Finnish 15D instrument.[8] Two different questionnaires were used in order to build a dose-response relationship on any potential effect. The questionnaire type was also randomly allocated in a 1:1 ratio. The questionnaires were sent in Finnish or in Swedish as determined by the respondents' CPR data, and a form for written informed consent was also included.

Analysis

To assess the association between CRC screening attendance and inclusion in the survey study, two-way tables were used. Statistical significance was tested with χ^2 test. CPR data on background characteristics that included gender, marital status, mother tongue, habitation, and geographical area were available for all participants, and were linked with data on CRC screening for invitations and participation. Marital status was categorized from CPR data as either having a partner (married or civil partnership) or not (single, divorced, separated or widow/er). Place of residence was categorized as urban or rural according to the classification by Statistics Finland, which has been in use since 1989. Geographical area was by place of residence in the five areas: Southern, Western, Middle, Eastern, and Northern Finland.

Screening attendance proportions were compared between those who received a questionnaire and those who did not, and between those who received a short versus a long questionnaire. The differences in attendance were quantified with 1) absolute attendance difference and 2) relative attendance difference, which takes into account the attendance rate for screening in those who did not receive any questionnaire. The absolute difference is the difference in attendance between those who had received a short or long questionnaire, and those who had not received any questionnaire, before their screening invitation. The relative attendance difference is the absolute difference divided by the attendance percent in the referent population not receiving any questionnaire. Response to the questionnaire was designated as "participation" and response to screening as "attendance".

Statistical analysis was performed using software package STATA 11.0.

Results

In May 2010, 10,648 randomly selected individuals from the study population were mailed the study questionnaires. The rest (n = 21,303) were not contacted (Figure 2). A reminder letter was sent to non-responders after four weeks in June 2010. In December 2010, the questionnaires were resent to those who still had not responded. After exclusions (empty return forms, wrong person responded, returned refusals, same person

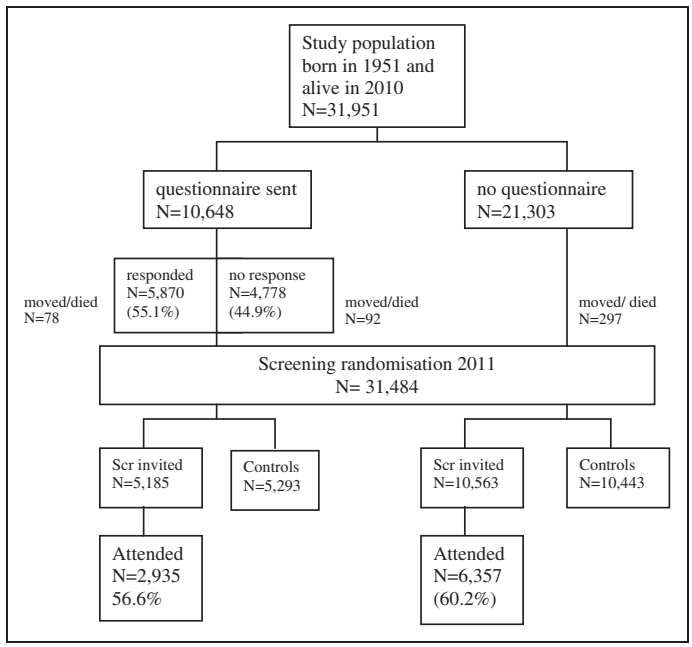

Figure 2. Flow chart on survey and screening attendance of the survey population.

responded twice) the final survey response rate was 55.1% (n = 5,870) (Figure 2). The response rate in women was higher than that in men (60.5% and 49.8%, respectively).

In January 2011, the target population of CRC screening born in 1951 (n = 32,072) was randomized 1:1 into screening arm (n = 16,037) or control arm (n = 16,035). Of the 2010 survey study population 467 individuals had either died or moved to a municipality not involved in colorectal cancer screening programme or abroad, and were no longer in the target population. There were 31,484 individuals randomized twice, first for the survey and later for screening, of whom 15,748 were invited for screening (Figure 2). The overall attendance rate for screening in the 60 year-olds in 2011 was 59.0% (n = 9,292). The attendance rate of 60-year-olds had shown a downward trend in the course of CRC screening in Finland (Figure 3).

Of the 5185 individuals who had received the survey in 2010 and were invited for CRC screening in 2011, 2,935 (56.6%) attended screening. Of the 10,563 individuals who had not received the questionnaire in 2010, 6,357 (60.2%) attended screening (Figure 2). Screening attendance for those who had received the shorter questionnaire was 57.3%, and for the longer one 56.0% (Table 1).

Table 2 shows the absolute (difference in percent of attendance between the groups) and relative decrease (the absolute difference divided by attendance in those with no previous questionnaire) in screening attendance, by length of the questionnaire and demographic factors. Willingness to attend screening, especially among men, was reduced among those who had received a survey (the relative decrease in attendance was 7.8% in men and 4.2% in women). Marital status or habitation appeared not to have any major effect on screening adherence. In the Swedish speaking minority, the pre-screen questionnaire decreased consecutive screening attendance more than in the Finnish speaking group (relative decrease of 10.7% vs. 6.1%). There were some differences in the decrease of screening attendance by geographical area: in Eastern Finland, having received the survey questionnaire reduced future screening attendance only slightly (2.6%), but in Northern Finland the decrease was considerable (10.5%).

The longer questionnaire was more detrimental for the future screening attendance than the shorter one. This was most obvious in Northern Finland, where the short questionnaire did not affect screening uptake much, but the longer one lowered uptake considerably (19.5%) (Table 2).

Discussion

There were two important considerations in our study design: firstly, the value of a valid control group, and secondly, the necessity for all conclusions to be made based on a randomized design.

For several reasons, organized screening with personal invitations may be an ideal setting for incorporating different kinds of survey initiatives. Population-based screening has the advantage of reaching the total population of a

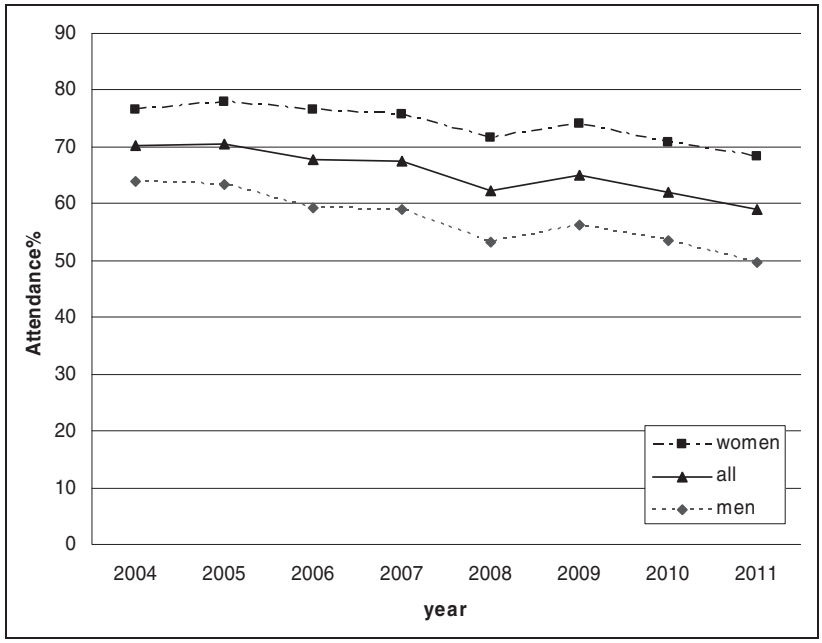

Figure 3. Attendance of 60-year-olds in Finnish colorectal cancer screening programme 2004–2010 by sex.

Table 1. Number of individuals invited, attending and attendance proportions for colorectal cancer screening 2011 in Finland among those who had been sent a survey study questionnaire in 2010 and those with no preceeding questionnaire.

	short questionnaire			long questionnaire			no questionnaire			
	invited	attenders	Attendance rate (%)	invited	attenders	Attendance rate (%)	invited	attenders	Attendance rate (%)	*P*-value
sex										<0.001
man	1288	618	48.0	1322	613	46.4	5272	2700	51.2	
woman	1285	855	66.5	1290	849	65.8	5291	3657	69.1	
marital status[1]										<0.001
partner	1596	993	62.2	1605	977	60.9	6630	4308	65.0	
no partner	968	477	49.3	1001	484	48.4	3922	2047	52.2	
mother tongue[2]										0.211
Finnish	2429	1399	57.3	2438	1373	56.2	9856	5951	60.4	
Swedish	109	61	56.0	132	68	51.1	563	336	59.7	
residence										0.008
urban	1569	866	55.2	1540	866	56.2	6355	3763	59.2	
rural	1004	607	60.5	1072	596	55.6	4208	2594	61.6	
area										0.017
South	480	259	54.0	455	252	55.4	1939	1163	60.0	
Middle	889	516	58.0	878	522	59.5	3639	2211	60.8	
West	522	297	56.9	491	268	54.6	2005	1190	59.4	
East	314	185	58.9	373	223	59.8	1388	851	61.3	
North	368	216	58.7	415	197	47.5	1592	942	59.2	
total	2573	1473	57.3	2612	1462	56.0	10563	6357	60.2	<0.001

[1]Data on marital status was missing for 26 in CPR data.
[2]221 had other mother tongue than Finnish or Swedish (144 with "no Q" had screening attendance rate of 48.6%, 35 with "short Q" had screening attendance rate of 37.1% and 42 with "long Q" had screening attendance rate of 50.0%)

pre-defined target group. Well-established screening may already have gained support within the population, which could also help to diminish the barriers to participation in studies embedded within the screening setting. It is important, however, that combining any extra research into routine medical practice should not have a detrimental effect on screening participation, as this is vital in achieving the primary aim of screening - in this instance, cancer-specific mortality reduction. Two reviews on the determinants of participation in CRC screening[9,10] have suggested that participation patterns depend on local circumstances, highlighting the need to acquire information on programme participation.

Our results suggest that sending a 7- or 10-paged questionnaire to potential participants one year prior to the first screening invitation had an effect on screening uptake. Screening attendance rate was 60.2 % among those who were not sent the questionnaire, and 56.6% among questionnaire-receivers. In addition, the longer questionnaire had a more detrimental effect on screening attendance than the shorter one. Sending a questionnaire may adversely affect future screening attendance, and the longer the questionnaire, the greater this effect.

The strengths of our study include the randomized and controlled design, with no exclusions in the invited population-based sample.

Inclusion of a self-administered questionnaire accompanying the invitation to routine breast cancer screening did not affect the screening uptake in a randomized setting in the Netherlands in 1992, nor in southern England in 1994–1996.[11,12] It is noteworthy that these studies only contacted target individuals once, whereas in our study target individuals were contacted 1–3 times (questionnaire, reminder, resending of questionnaire). In the Dutch and UK studies, conducted over a decade ago, target groups consisted only of women aged 50–70[11] or 50–64.[12] Our study included only one age cohort of 60-year-olds.

In general, women and married individuals tend to participate in surveys more actively than men and single or divorced people. The same pattern can be observed in screening attendance, and has been evident since the launch of the Finnish CRC screening programme in 2004.[13] The youngest age group has the lowest attendance in Finland, and there has been a downward trend for many years. Compared with 2010, attendance rates in 2011 were worse, even without the extra lowering effect of survey (60.2% vs. 62.1% in 2010; men 51.2% vs. 53.4%, women 69.1% vs. 70.8%). It could be argued that the survey manifested a strengthening of an existing trend.

The absolute differences in attendance rates by various background factors were mostly modest. For example, the

Table 2. Attendance to colorectal cancer screening in those with no previous questionnaire (No Q-group) and absolute and relative difference between those who had been sent a short (short Q), long questionnaire (long Q), or any questionnaire (any Q) before.

	Attendance rate (%)	Absolute attendance difference (%)			Relative attendance difference (%)		
	No Q-group	short Q	long Q	any Q	short Q	long Q	any Q
total	60.2	−2.9	−4.2	−3.6	−4.8	−7.0	−6.0
sex							
man	51.2	−3.2	−4.8	−4	−6.3	−9.4	−7.8
woman	69.1	−2.6	−3.3	−2.9	−3.8	−4.8	−4.2
marital status							
partner	65	−2.8	−4.1	−3.5	−4.3	−6.3	−5.4
no partner	52.2	−2.9	−3.8	−3.4	−5.6	−7.3	−6.5
mother tongue							
Finnish	60.4	−3.1	−4.2	−3.7	−5.1	−7.0	−6.1
Swedish	59.7	−3.7	−8.6	−6.4	−6.2	−14.4	−10.7
residence							
urban	59.2	−4.0	−3.0	−3.5	−6.8	−5.1	−5.9
rural	61.7	−1.2	−6.1	−3.7	−1.9	−9.9	−6.0
area							
South	57.6	−3.6	−2.2	−2.9	−6.3	−3.8	−5.0
Middle	61.7	−3.7	−2.2	−3.0	−6.0	−3.6	−4.9
West	59.4	−2.5	−4.8	−3.6	−4.2	−8.1	−6.1
East	61.0	−2.1	−1.2	−1.6	−3.4	−2.0	−2.6
North	59.0	−0.3	−11.5	−6.2	−0.5	−19.5	−10.5

absolute difference in attendance rates by marital status was 2.9% in women and 4% in men. After correcting for attendance relative to those who had not received a survey, these rates changed to 4.2% and 7.8%. Overall, the absolute differences in screening attendance rates were not large, but after correcting for attendance relative to those with no survey, the relative differences were larger and had more variability. Using the same method to assess the effect of marital status showed that sending a questionnaire decreased attendance at screening more in those without a partner than in those with a partner (6.5% vs. 5.4%).

In 2011 the Finnish CRC screening programme carried out 9,462 primary tests in 60-year-olds, resulting in 343 positive results, equating to 3.6% of participants. We estimate that, if there had been no survey in 2010, the overall screening attendance rate would have been similar to that among those who did not receive the pre-screening questionnaire, ie. 60.2%. This would mean that 192 more individuals would have attended screening (60.2% out of 16,037 invited, instead of 59.0% now reached in the 60-year old population). We therefore calculated that, because of the survey, an estimated seven positive test results were not produced (3.6% x 192). Out of 343 test positives in 2011, 86 (25%) were diagnosed as having an adenoma (n = 76) or CRC (n = 10) in the follow-up colonoscopy. With seven test positives, there would have been two more expected adenomas. However, if we had sent a questionnaire to all of the cohort and gained an overall attendance rate of 56.6% (attendance in those who were actually sent the questionnaire in 2010), the loss of people attending would have been close to 577 individuals (56.6% out of 16,037 invited instead of 60.2%). Especially in the subgroups where the relative decrease in attendance was most marked (eg. in Northern Finland), this could also affect screening results, as non-attendance may be selective. Even if no substantial harm was caused, on this occasion, to our target population, we do not generally recommend a policy of combining surveys with screening programmes.

We will monitor the future CRC screening behaviour of this study group. The same invited individuals were re-invited to CRC screening in 2013, after a two year interval. In the previous year (2012) the study group had been subjected to the follow-up questionnaire of ''Psychosocial effects of colorectal cancer screening''. Extending monitoring until 2015 (when there will no longer be any further pre-screening questionnaire) will ultimately disclose whether or not the effect of questionnaires on screening attendance is long-term.

Why does sending and receiving a questionnaire lower future screening uptake? Though the questionnaires were mostly about general life style in terms of diet, physical activity, smoking and alcohol use, the accompanying covering letter referred to the study ''Psychosocial effects of colorectal cancer screening'' as a whole. In this way, the questionnaire was linked to screening. The screening invitation may then have been perceived by the recipients as

burdensome when dealing with the same matter again, even though it was clearly stated that participation in the survey was completely voluntary and it would not affect screening randomization. In previous studies on colorectal cancer screening participation, sending a pre-screening notification two weeks prior the screening invitation has had a positive effect on screening participation.[14,15] We therefore suggest that the nature of the pre-screening contact, not the contact *per se*, is pivotal. Requesting effort on the part of the recipient may be harmful for future screening willingness.

Simultaneous mailing in the same envelope is the standard method to incorporate an extra survey into routine health activity. It is reasonable to assume that such extra effort reduces the willingness to participate even more than was observed in our study with a one year lag between these two activities (survey and screening). Therefore, in a real life situation, the observed effect may be sufficient to preclude incorporating any extra material in an activity like a screening invitation.

In conclusion, sending a pre-screening survey reduced attendance in colorectal cancer screening. This risk of lowering participation should be taken into account when planning to exploit the screening context in conducting epidemiological surveys or other intervention studies.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The Finnish Cancer Organisations are thanked for issuing psychosocial cancer research grants for the project.

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PUBLICATION 4

Embedded survey study harms colorectal cancer screening attendance: Experiences from Finland 2010 to 2015

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Journal of Medical Screening 2018; 25(1): 51–54

doi: 10.1177/0969141317698177

Research Letter

Embedded survey study harms colorectal cancer screening attendance: Experiences from Finland 2010 to 2015

J Med Screen
2018, Vol. 25(1) 51–54

DOI: 10.1177/0969141317698177
journals.sagepub.com/home/msc
SAGE

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Abstract

Objective: We previously found that administering a pre-screening lifestyle questionnaire lowered the subsequent attendance proportion in the first-ever colorectal cancer screening. We sought to determine whether the effect continued in subsequent screening rounds.

Methods: The eligible survey cohort ($n = 10,375$) received a follow-up questionnaire in 2012, and in 2013, they were invited for colorectal cancer screening for the second time. For the third screening round, in 2015, no questionnaires were sent in the previous year. Screening attendance in 2013 and in 2015 was examined in relation to survey mailings.

Results: The colorectal cancer screening attendance rate in 2013 was 58.4% in the survey population, and 63.9% in those not surveyed ($P < 0.001$). In 2015, the screening attendance rate was 61.7% among those who had been sent the questionnaires in 2010 and in 2012, and 66.2% in those not surveyed ($P < 0.001$). The reduction in screening attendance was greater at the second (2013) round than at the first (2011).

Conclusion: The effect of the initial survey seemed to continue even when no questionnaires were being sent. Attendance among those who had been sent questionnaires earlier did not reach the level of the group that was never surveyed.

Keywords

Colorectal cancer screening, attendance, questionnaires, research intervention, mass screening

Date received: 15 December 2016; accepted: 15 February 2017

Organized screening programmes provide appealing settings for epidemiological surveys, but such additional investigations may reduce willingness of the target population to participate in screening. A population-based colorectal cancer (CRC) screening programme using biennial fecal occult blood testing (FOBt) for 60–69 year olds has been running in Finland since 2004.[1] The 'Psychosocial effects of colorectal cancer screening study' was incorporated into the CRC screening programme in 2010–2012. Lifestyle and quality of life were assessed through a self-administered postal questionnaire at baseline one year before the first screening invitation, and again after two years.[2,3] We previously reported that participation after the first screening invitation was lower among those surveyed (56.6% vs. 60.2%).[2] A similar baseline phenomenon has been reported from England, where CRC screening uptake was significantly lower in those who received a questionnaire with their FOBt kit than in those who did not (48.6% vs. 53.5%).[4] The purpose of this study was to examine CRC screening behaviour after subsequent invitations, to determine if the effect of surveys on screening attendance is long term.

The study population consisted of individuals born in 1951, residing in municipalities involved in the CRC screening programme and, therefore, eligible to be invited to CRC screening in 2011 ($n = 31,951$). In 2010 (i.e. in advance of screening), we sent a random sample of every sixth subject ($n = 5312$) a 7-paged lifestyle questionnaire, and to another random sample of every sixth subject ($n = 5336$) a 10-paged lifestyle and quality of life questionnaire (Figure 1). In 2011, 31,484 individuals of the original cohort (467 had moved to a non-screening municipality, or died) were independently randomized (1:1) to be invited for CRC screening ($n = 15,748$) or to the control group ($n = 15,736$), according to the invitation schema of Finnish CRC screening programme.[1] In 2012,

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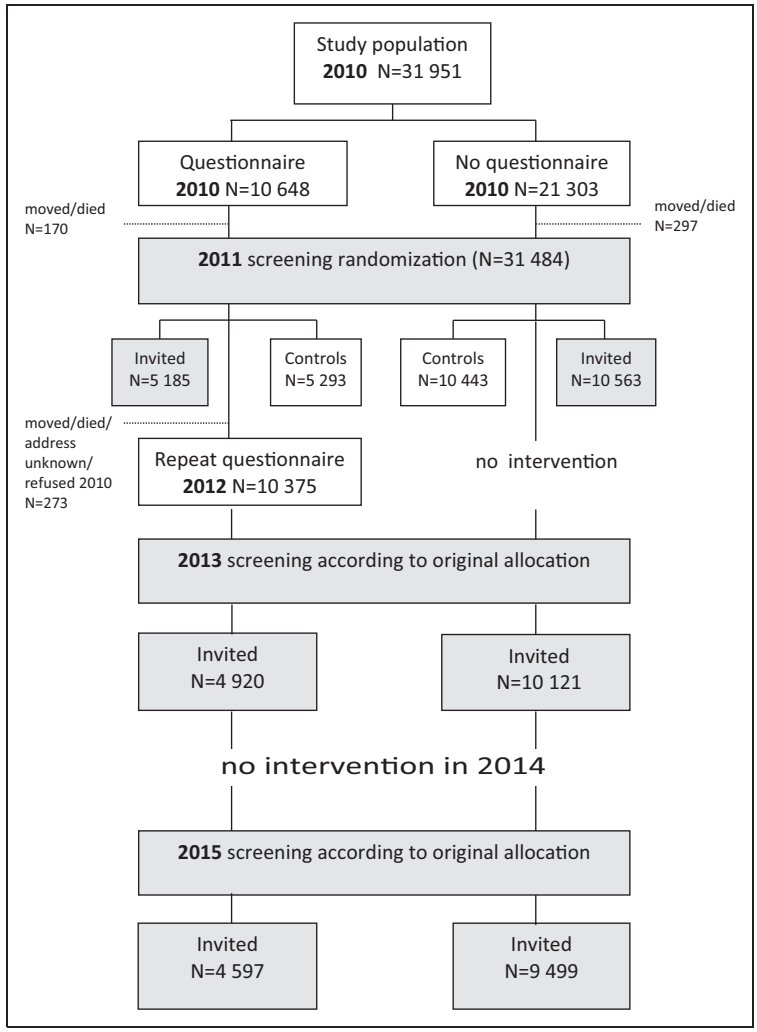

Figure 1. Flow chart of study population of 'Psychosocial effects of colorectal cancer screening' study.

the survey cohort ($n = 10{,}375$; 273 had either died, refused 2010, or had unknown address) received a follow-up questionnaire with the same contents as in 2010. In 2013, 15,041 individuals were invited to CRC screening for the second time, following the original screening randomization, irrespective of their attendance at the previous screening round. The third screening round was in 2015 (14,096 individuals invited), with no questionnaires sent the previous year.

To assess the association between CRC screening attendance and inclusion in the survey study, two-way tables were used. Screening attendance proportions were compared between those who were and were not sent the questionnaires, using a two sample test of proportions (z-test) with a 5% significance level. Attendance was also compared by sex, marital status, urbanization level of residential area and geographical area of residence. The study received ethical approval from the Helsinki and Uusimaa Hospital District Ethics Committee (15 December 2009, 420/13/03/00/2009).

In our sample, the overall CRC screening attendance was 62.1% in 2013. In those who had been sent the surveys earlier (in 2010, and again in 2012), the attendance was 58.4% (58.5% for short and 58.3% for long questionnaire), and in those not subjected to survey interventions it was 63.9% ($p = 0.001$) (see Table 1). Surveys were associated with significantly reduced attendance in both men and women, in married and non-married, and in urban and rural areas.

In 2015, screening attendance was still significantly lower in those who had received the questionnaires in 2010 and 2012 than among those who had not. Attendance was 61.7% (62.0% for short and 61.4% for long questionnaire) and 66.2%, respectively ($p = 0.006$).

Table 1. Colorectal cancer screening attendance 2013 and 2015 in those sent and not sent study questionnaires 2010 and 2012.

	Screening 2013						Screening 2015					
	No Q		Q 2010 and 2012		Difference		No Q		Q 2010 and 2012		Difference	
	inv *n*	att %	inv *n*	att %	%	*p*	inv *n*	att %	inv *n*	att %	%	*p*
All	10,121	63.9	4920	58.4	−5.5	0.001	9499	66.2	4597	61.7	−4.5	0.006
Sex												
Men	5013	56.1	2439	50.3	−5.8	0.009	4680	58.7	2258	53.8	−5.0	0.027
Women	5108	71.6	2481	66.4	−5.2	0.017	4819	73.5	2339	69.4	−4.2	0.050
Marital status[a]												
Married	6369	68.1	3067	62.3	−5.7	0.005	5997	70.3	2869	66.2	−4.2	0.033
Divorced/single/widow	3741	57.0	1840	52.0	−5.0	0.039	3461	59.6	1709	54.4	−5.2	0.041
Municipality type												
Urban	6026	62.8	2925	57.5	−5.3	0.009	5624	65.2	2758	61.2	−4.0	0.043
Rural	4095	65.5	1995	59.8	−5.8	0.017	3842	68.0	1839	62.3	−5.6	0.024
Area												
Southern	1858	63.8	886	56.1	−7.7	0.030	1710	65.9	816	60.7	−5.2	0.109
Central	3553	63.9	1735	60.3	−3.6	0.109	3195	66.2	1546	62.5	−3.7	0.117
West-coastal	1957	64.2	951	56.9	−7.3	0.032	1889	66.9	925	61.2	−5.7	0.077
Eastern	1539	64.8	761	58.9	−5.9	0.091	1493	67.0	735	61.6	−5.3	0.118
Northern	1214	62.5	587	58.1	−4.4	0.189	1179	65.7	568	62.2	−3.6	0.241
CRC screening attendance on previous round[b]												
Yes	6168	91.8	2828	89.1	−2.7	0.120	6121	94.0	2715	93.7	−3.2	0.444
No	3940	20.4	2079	16.6	−3.8	0.080	3345	15.8	1875	15.5	−2.9	0.460
Result of CRC screening on previous round												
Negative	5947	92.5	2737	89.6	−2.9	0.104	5946	94.3	2643	94.3	0	0.475
Positive	221	71.5	91	73.6	2.1	0.568	175	82.9	72	70.8	−12.0	0.195

Q: study questionnaire; inv: invited; att: attended; CRC: colorectal cancer.
[a]Marital status was missing in Population Register Centre data for 24 persons in 2013 and in 20 persons in 2015.
[b]Twenty-six persons in 2013 were not invited in 2011, and 40 persons in 2015 were not invited in 2013.

Being subjected to a questionnaire study before screening invitation resulted in reduction in CRC screening attendance. We found that the detrimental effect of questionnaires on screening attendance was long term. The effect augmented with repeated surveys; the reduction in screening attendance in those subjected to questionnaires was greater in the second (2013) than in the first screening round (2011). The effect seemed to continue so that in the subsequent third screening round with no questionnaires the previous year, the attendance still did not reach the level of the group never exposed to questionnaires. Results were similar for men and women, by marital status, and by area. Unlike in 2011, the length of the questionnaire did not have an effect on screening attendance, except in Northern Finland, where screening attendance was decreased only among the long (10-paged) questionnaire recipients.

Screening attendance for CRC screening in the survey study population remained low in 2015, even though one could imagine that the detrimental effect of burdensome questionnaires would dilute after not receiving the questionnaires anymore. We believe that the long-term effect is partly due to *attendance pattern*, i.e. previous screening behaviour (especially participation in the first invitation round) is a predictor of subsequent participation. This has been observed previously in the context of breast cancer screening[5–7] and CRC screening.[8–10] Those disturbed by the original study questionnaires in 2010 established a pattern of non-participation, which did not abate with time.

Jäntti et al.[3] examined, in this same population, whether screening allocation in 2011 had any impact on follow-up survey response. Among CRC screening invitees in 2011 response to the survey increased in 2012 compared with that in 2010, whereas among controls (not invited for screening) the response to the survey decreased slightly. These results support the idea that it is the nature of the contact, not just the contact, which is essential. The screening invitation can be perceived as a service or offer, which could make the attitude towards the subsequent survey more positive. Rather laborious surveys, instead, can be seen as a burden, and the rejection of this burden also affects future screening.

Adequate attendance is fundamental for successful population screening, and careful monitoring and optimization of attendance must be ensured in any screening

programme. Surveys are necessary to obtain information that health care or other registers cannot provide. When embedding surveys in cancer screening, questionnaire design should aim to include only relevant issues, in a compact form, and to present the questionnaire as advantageous for the recipient. There is an ethical issue in employing a research intervention endangering engagement; the benefit gained should outweigh the harm caused by reduced attendance.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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PUBLICATION 5

Effect of a research intervention and additional cancer screening invitations on breast and cervical cancer screening attendance in Finland

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submitted manuscript