Optimizing screening with faecal immunochemical test for both sexes - Cost-effectiveness analysis from Finland

Heinävaara, Sirpa

2022-04

Heinävaara , S , Gini , A , Sarkeala , T , Anttila , A , de Koning , H & Lansdorp-Vogelaar , I 2022 , ' Optimizing screening with faecal immunochemical test for both sexes - Cost-effectiveness analysis from Finland ' , Preventive Medicine , vol. 157 , 106990 . https://doi.org/10.1016/j.ypmed

http://hdl.handle.net/10138/354806
https://doi.org/10.1016/j.ypmed.2022.106990

Preventive Medicine 157 (2022) 106990

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Optimizing screening with faecal immunochemical test for both sexes - Cost-effectiveness analysis from Finland

Sirpa Heinävaara [a,b,*], Andrea Gini [c], Tytti Sarkeala [a], Ahti Anttila [a], Harry de Koning [c], Iris Lansdorp-Vogelaar [c]

[a] Finnish Cancer Registry, Cancer Society of Finland, Unioninkatu 22, 00130 Helsinki, Finland
[b] Department of Public Health, 00014 University of Helsinki, Finland
[c] Department of Public Health, Erasmus Medical Center, P.O.Box 2040, 3000 CA Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Colorectal cancer screening
Cost-effectiveness
Sex-specific screening
Health policy
Public health

ABSTRACT

A faecal immunochemical test (FIT) screening pilot was introduced in Finland in 2019 with sex-specific screening strategies. This study aims to model cost-effectiveness of sex-specific strategies for the whole population, and to assess whether the current strategies are optimal.

We developed separate MISCAN-Colon models, including different FIT performances, for the Finnish men and women using the first-year data of the FIT screening pilot. We evaluated 180 FIT strategies varying in FIT cut-off, screening interval, age to start, and age to stop screening, and compared them to no-screening by sex. We used incremental cost-effectiveness ratios (ICERs) to identify the optimal strategy after combining all male and female strategies and restricting the analysis by costs and referral rate to diagnostic colonoscopies.

Offering annual FIT screening with a cut-off of 25 μg/g at 50–79 years in men and with a cut-off of 10 μg/g at 55–69 years in women was optimal. This combined strategy prevented 28% of colorectal cancer (CRC) cases and 55% of CRC deaths with acceptable costs (ICER = 9000€/life-years gained). Screening at the current target age of 60–74 years was suboptimal for both sexes. Among strategies with the same target age and interval for both sexes, expected benefits from optimal screening were lower but still reasonable.

Our results support a wider age range of screening in men, and a lower cut-off for a positive test in women when restrictions on colonoscopy capacity and costs are in place. National FIT screening program should start at younger age.

1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer death in Europe (International Agency for Research on Cancer and World Health Organization, 2020). With screening, CRCs or their precursors can be detected early, and part of CRC deaths can be prevented (Winawer et al., 1993; Lauby-Secretan et al., 2018). Currently, screening with faecal immunochemical test (FIT) is widely adopted in Europe. Quantitative FIT has replaced its predecessor, qualitative guaiac faecal occult blood test (gFOBT) due to its better diagnostic performance and higher acceptability (European Commission, 2017; Lee et al., 2014).

Studies suggest that effectiveness of gFOBT screening is larger in men than in women (Shaukat et al., 2013; Pitkäniemi et al., 2015). Similar findings are expected from FIT screening even though conflicting results have been reported (Zorzi et al., 2014). FIT sensitivity and positive predictive value for advanced neoplasia have been shown to be lower among women (Arana-Arri et al., 2017). Consequently, FIT with a lower haemoglobin cut-off in women and a higher cut-off in men might be able to lead comparable relative reductions in CRC mortality between sexes. So far Sweden and Finland are the only countries in Europe implementing sex-specific screening. In their screening programs, FIT cut-offs in women have been set lower than in men, and the positivity rates have been almost equal (Blom et al., 2018; Sarkeala et al., 2021).

CRC screening can be cost-effective (Ran et al., 2019) but there is only limited evidence on cost-effectiveness by sex. A Dutch study showed that sex-specific FIT screening strategies would result in at most

Abbreviations: FIT, faecal Immunochemical test; CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; gFOBT, guaiac faecal occult blood test; LYG, life-years gained; FCR, Finnish Cancer Registry; WTP, willingness-to-pay.

* Corresponding author at: Finnish Cancer Registry, Cancer Society of Finland, Unioninkatu 22, 00130 Helsinki, Finland.
E-mail address: Sirpa.heinavaara@cancer.fi (S. Heinävaara).

https://doi.org/10.1016/j.ypmed.2022.106990
Received 8 July 2021; Received in revised form 30 November 2021; Accepted 6 February 2022
Available online 9 February 2022

7% more quality-adjusted life-years gained than an optimal uniform screening strategy (van der Meulen et al., 2017). A UK study showed sex-specific FIT screening to be more cost-effective with a 61% probability (Thomas et al., 2021). Two modelling studies from the US have supported uniform strategies for both sexes (Meester et al., 2018). These results may be affected by differences in CRC risks, screening protocols, health care systems, and costs between countries. Therefore, optimal FIT strategies need to be assessed separately for each country.

In Finland, a FIT screening pilot was launched in 2019 (Sarkeala et al., 2021). The previous randomized gFOBT screening program since 2004 had been suspended in 2016 due to similar CRC mortality in the screening and control arms and a non-significant increase in women (Pitkäniemi et al., 2015). The FIT pilot aims to attain similar relative reductions in CRC mortality for both sexes. However, first effectiveness results will not be available before 2030's and results on long-term effectiveness decades after that. Until then, modelling provides a means to predict long-term (cost-)effectiveness of FIT screening.

This study analyses cost-effectiveness of various sex-specific FIT screening strategies in the Finnish population using the Finnish FIT pilot and registry data with a well-established micro-simulation model developed within the EU-TOPIA project (Gini et al., 2021).

2. Material and methods

2.1. The Finnish CRC screening program

The biennial FIT screening pilot was launched in April 2019 in nine volunteering Finnish municipalities. The study design and first year results have been discussed in detail elsewhere (Sarkeala et al., 2021). In short, personal invitations with a FIT were sent to everyone in the target population of 60–66-year-old men and women. In 2019, 13,059 men and 14,669 women were invited, of whom 75% and 83%, respectively, returned the test by the end of April 2020. Cut-offs of 70 μg Hb/g faeces in men and 25 μg Hb/g faeces in women indicated a positive test result. These cut-offs resulted in positivity rates of 2.8% in men and 2.4% in women. By September 2020, 73% ($N = 198$) of men and 73% ($N = 216$) of women with positive test result had findings at diagnostic colonoscopy. In men, 16 CRCs and 68 advanced adenomas were detected. In women, the corresponding figures were 17 and 47, respectively.

The nationwide CRC programme will start in 2022 when all 60–68-year-old men and women will be invited to screening (Fig. 1). The gradual implementation will continue until the planned target age of 60–74 years will be reached in 2027.

2.2. MISCAN-Colon model

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model (Erasmus University Medical Center, Rotterdam, The Netherlands) to simulate future outcomes of CRC screening by sex in Finland. The model structure and underlying assumptions are reported by (Gini et al., 2021). Briefly, MISCAN-Colon simulates life histories of individuals from birth to death with and without screening. In each simulated individual, zero, one, or more adenomas may occur, progress in size, and develop into a preclinical cancer. Survival after a cancer diagnosis is modelled according to age, stage, and location of cancer. Screening alters the simulated life histories by detecting cancers at earlier stages or by removing precancerous lesions. The model quantifies the effectiveness and costs of screening comparing all life histories with screening with the corresponding life histories without screening.

2.3. Study population

The model simulated male and female cohorts of 10 million individuals aged 50 without CRC in 2019, and these cohorts were followed until death or age 100. To replicate the situation without screening, the model was developed and calibrated separately for men and women using age-specific CRC incidence and mortality rates from 1999 to 2003 (please see Supplementary Methods). The age-specific CRC incidence and mortality rates as well as the age- and stage-specific relative survival rates were obtained from the Finnish Cancer Registry (FCR). All-cause mortality estimates were retrieved from the 2016 Finnish life tables (Shkolnikov et al., 2020). The main model assumptions on demography and natural history are provided in Table 1 with detailed descriptions in Supplementary Table 2 of (Gini et al., 2021).

2.4. Screening strategies

We used the model to simulate 181 different screening strategies, including a no-screening strategy, both in men and women for a total of 362 strategies. The screening strategies varied by starting age (50, 55, 60, and 65 years), stopping age (69, 74, and 79 years), screening interval (1,2, and 3 years), and FIT positivity cut-off (10, 25, 40, 55, to 70 μg Hb/g faeces). All screening strategies were implemented for the whole country from 2019 onwards.

	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
1967	52	53	54	55	56	57	58	59	60	61
1966	53	54	55	56	57	58	59	60	61	62
1965	54	55	56	57	58	59	60	61	62	63
1964	55	56	57	58	59	60	61	62	63	64
1963	56	57	58	59	60	61	62	63	64	65
1962	57	58	59	60	61	62	63	64	65	66
1961	58	59	60	61	62	63	64	65	66	67
1960	59	60	61	62	63	64	65	66	67	68
1959	60	61	62	63	64	65	66	67	68	69
1958	61	62	63	64	65	66	67	68	69	70
1957	62	63	64	65	66	67	68	69	70	71
1956	63	64	65	66	67	68	69	70	71	72
1955	64	65	66	67	68	69	70	71	72	73
1954	65	66	67	68	69	70	71	72	73	74
1953	66	67	68	69	70	71	72	73	74	75

Fig. 1. Gradual implementation of FIT screening program in Finland by calendar year of invitation (x-axis) and calendar year of birth (y-axis). Shaded areas represent invitational age groups.

Table 1
Key modelling assumptions.

Input parameter	*Model assumptions*				
Demography					
All-cause mortality	Finnish lifetables (Human Mortality Database, 2016)				
Natural history					
Adenoma onset	Age-dependent (non-homogenous Poisson)[1]				
Adenoma localization	Finnish Cancer registry				
Adenoma progression					
State transitions	Age-dependent				
State durations, years (total)	Exp($\lambda = 140$)				
Cancer progression (preclinical)					
Stage transitions	Age-dependent[1]				
Stage durations, years	Exp($\lambda = 2.5$)				
Colorectal cancer survival	Age-/stage−/localization-dependent Finnish Cancer registry				
FIT performance in men[2]	10 µg/g	25 µg/g	40 µg/g	55 µg/g	70 µg/g
Sensitivity, %					
Adenomas 0-5 mm	0	0	0	0	0
Adenomas 6-9 mm	10	9	7	5	4
Adenomas ≥10 mm	27	26	24	18	14
Pre-clinically detectable CRC	60	55	50	35	21
Clinically detectable CRC	90	80	75	70	65
Specificity, %	96	99	99	99	99
FIT performance in women[2]	10 µg/g	25 µg/g	40 µg/g	55 µg/g	70 µg/g
Sensitivity, %					
Adenomas 0-5 mm	0	0	0	0	0
Adenomas 6-9 mm	0	0	0	0	0
Adenomas ≥10 mm	9	9	8	6	3
Pre-clinically detectable CRC	40	35	25	20	15
Clinically detectable CRC	57	50	35	25	19
Specificity, %	97	98	99	99	99
Colonoscopy performance					
Sensitivity[3], %	0				
Adenomas 0-5 mm	75				
Adenomas 6-9 mm	85				
Adenomas ≥10 mm	95				
Malignant neoplasia	99				
Specificity[4], %	86				
Complete colonoscopy examination, %					
Complication rates, % with polypectomy[5]	Age-dependent				
Fatal complications[6]	0.000329				
Costs[8]					
FIT	12.4				
Colonoscopy with or without polypectomy	400				
Colonoscopy complications	3280				
Per life-year with cancer care[7]					
Initial and ongoing years, stage I-IV	2888-5665				
Terminal year, stage I-IV[8]	12,884-32,860				

[1] Model parameters calibrated using data of Finnish Cancer registry in pre-screening era (1999–2003, Figs. 5 and 6 in Supplementary Material);
[2] The first-year FIT performance was assumed for all screening rounds.
[3] The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates seen in tandem colonoscopy studies (van Rijn et al., 2006);
[4] Specificity for colonoscopy is based on an adenoma prevalence study of patients undergoing screening colonoscopy (Schroy 3rd et al., 2013);
[5] Age-specific risks for complications of colonoscopy requiring a hospital admission or emergency department visit were obtained from a study by Warren et al. (Warren et al., 2009);
[6] The mortality rate associated with colonoscopies with a polypectomy was derived by multiplying the risk for a perforation obtained from a study by Warren et al. (Warren et al., 2009) by the risk for death given a perforation obtained from a study by Gatto et al. (Gatto et al., 2003);
[7] Please see CRC screening costs for more details.
[8] The terminal year included costs of CRC death from a published study (Färkkilä et al., 2015), and of death from other causes (10,000€) from an expert opinion.

The sex-specific FIT parameters for sensitivity and specificity were based on the first-year performance results of the pilot between April 2019 and June 2020. These parameters were estimated for all the different cut-offs as described in Supplementary Methods. FIT was predicted to be more sensitive in men than in women (Table 1). Assumptions for colonoscopy performance were based on scientific literature (van Rijn et al., 2006; Schroy 3rd et al., 2013). Adherence to screening, diagnostic colonoscopies and post-colonoscopy surveillance were all assumed to be 100%. The post-colonoscopy surveillance was assumed to follow recommendations of the European Society of Gastrointestinal Endoscopy (Hassan et al., 2013). The whole target population was assumed to be invited to screening except those referred to post-colonoscopy surveillance due to their FIT screening findings.

This study is based on registry data and was approved by the National Institute of Health and Welfare (reference THL/356/5.05.00/2019).

2.5. Screening costs

We performed a cost-effectiveness analysis from a health care payer perspective. Cost of the screening test including laboratory analyses was obtained from the screening laboratory, and cost of diagnostic colonoscopies from healthcare providers. Costs of common colonoscopy complications were estimated for this study (please see Supplementary Methods). Costs of surveillance were obtained from the National Institute for Health and Welfare (Kapiainen et al., 2014). The pTNM stage-specific costs of CRC care were available only for a short 5-year period in a specialized medical care (Mäklin et al., 2020). All costs were converted to euros for the year 2019 (Table 1).

2.6. Model outcomes

For each simulated strategy, we calculated all outcomes separately for men and women for the whole lifetime and report them per 1000 participants. The benefits are quantified by life-years gained (LYGs) from screening (Martin et al., 2008), and CRCs and CRC deaths prevented (%). The vital health care resources are illustrated by the numbers of diagnostic and total colonoscopies, of which the latter includes post-colonoscopy surveillance. The harms of screening are illustrated by the numbers of colonoscopy complications. The total costs included costs due to screening, post-colonoscopy surveillance and CRC care. The LYGs and the costs were discounted by 3%.

2.7. Specific study questions

The model outcomes were specifically aimed to study whether the current sex-specific screening strategies are cost-effective, and if not, which strategies would be both optimal and feasible with regards to total costs and colonoscopy resources for the whole population (see below). The current strategies refer to biennial screening of 60–74-year-olds with cut-offs 70 µg/g for men and 25 µg/g for women.

2.8. Cost-effectiveness analysis

We determined the cost-effectiveness of sex-specific screening strategies for the Finnish population and compared the results to no-screening. To be able to provide screening and resources optimally for the whole population, sex-specific strategies were combined. We first formed all possible pairwise combinations between 181 male and 181 female strategies (i.e., a total of 32,761 unique combinations), and pooled sex-specific outcomes together as weighted averages of 50-year-old men and women in the population in 2019 (European Commission,

2020). We then restricted these pooled strategies to feasible ones which we determined as total costs maximum of 10% higher than those of the current screening, and as overall referral rate to diagnostic colonoscopy maximum of 5%. The overall referral rate was defined by numbers of diagnostic colonoscopies among those with the FIT in each pooled strategy. The 5%-limit was guided by the clinical expert group of the FCR. Of all screening strategies, only 6% (n = 1981) were infeasible which included strategies with a cut-off of 10 μg/g in men. We then removed the weakly and strongly dominated strategies as described elsewhere (Mark, 2002; Gini et al., 2017). The remaining strategies were considered efficient and constituted the efficient frontier. Finally, we calculated the incremental cost-effectiveness ratio (ICER) of each efficient strategy by comparing its costs and LYGs with those of the next less costly and effective efficient strategy.

In a secondary analysis, we set additional feasibility restrictions to provide support to optimal and easily implementable FIT screening program. We restricted the strategies further to include those with the same target age and interval for both sexes (801 out of 30,780 feasible strategies), and finally to biennial screening (292 out of 801 strategies). We compared efficient biennial strategies closest in cost to the current screening.

Since an official willingness-to-pay (WTP) threshold for the incremental cost-effectiveness ratio has not been defined in Finland, we used a WTP threshold of 10,000€/LYG in this study. All the analyses have been performed on the pooled data, but the results are presented also by sex.

We also performed a budget impact analysis to assess the effect of attendance on the current and the optimal screening strategies. We assumed first-round non-attenders, 25% of men and 17% of women, to be never-attenders in accordance with a previous finding (Jäntti et al., 2021).

2.9. Sensitivity analysis

Several sensitivity analyses were carried out to study the robustness of the primary results for uncertain model assumptions. First, we assumed higher care costs by increasing them by 50% and 100%. Second, we assumed the same FIT sensitivity and specificity for men and women (Supplementary Table 1). Third, we analysed the cost-effectiveness of all strategies assuming no restrictions on total costs and overall referral rate.

3. Results

Without screening, 46/1000 men and 42/1000 women were predicted to be diagnosed with CRC, and 23/1000 men and 22/1000 women to die from it. The current screening strategy prevented 14% of CRCs in men and 10% in women, and 34% of CRC deaths in men and 31% in women (Fig. 2). The current screening was predicted to be quite similar for both sexes in LYGs (29/1000 men vs. 27/1000 women).

Among all 180 sex-specific strategies in comparison to no-screening, men were predicted to gain more from screening than women. In men, prevented CRCs ranged from 5% to 43%, prevented CRC deaths from 13% to 73%, and LYGs from 11 to 76/1000. In women, prevented CRCs ranged from 1% to 27%, prevented CRC deaths from 5% to 59%, LYGs from 4 to 60/1000. (Results not shown.)

Among the feasible strategies in the population, annual screening at 50–79 years with a cut-off of 25 μg/g in men and at 55–69 years with a cut-off of 10 μg/g in women was optimal with acceptable costs (ICER = 9000€/LYG) (Table 2). This strategy prevented 28% of CRCs and 55% of CRC deaths, and resulted in 58 LYGs/1000. Strategies at the current target age of 60–74 years were dominated and thus suboptimal for both sexes (Table 2, Fig. 2).

Among the feasible strategies with the same target age and interval for both sexes, annual screening at 55–74 years with a cut-off of 25 μg/g in men and with a cut-off of 10 μg/g in women was optimal (ICER = 10,000€/LYG, Table 3). This strategy prevented 28% of CRCs and 54% of CRC deaths, and resulted in 55 LYGs/1000 individuals. Biennial strategies with a cut-off of 25 μg/g at 55–69 and 55–74 years for both sexes were closest in costs and superior to the current screening (Table 4, Fig. 3).

Incomplete adherence reduced both LYGs and costs of screening up to 45% and 22% in the current and optimal strategies, respectively (Table 5).

3.1. Sensitivity analyses

The cost-effectiveness results were tested under several assumptions

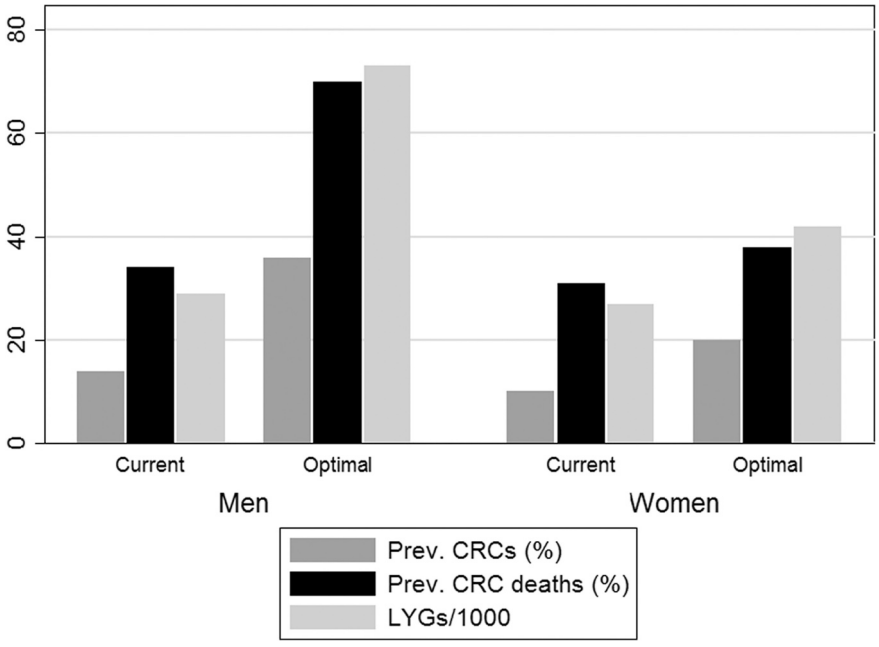

Fig. 2. The current screening and the optimal screening among the feasible screening strategies. Outcome are shown for prevented (prev.) CRCs and CRC deaths (%), and LYGs (/1000) by sex.

Table 2
Efficient FIT (faecal immunochemical test) screening strategies and the current screening in the Finnish population. For each screening strategy outcomes are shown per 1000 individuals assuming 100% adherence to screening, diagnostic colonoscopy, and post-colonoscopy surveillance.

Sex (men/women): Strategy(cut-off, target age, interval)	FITs	Diagnostic COLs	Total COLs[1]	COL compl.	CRCs[2]	CRC deaths[2]	LYGs	Total costs[3](/1000) in €	Net costs[4](/1000) in €	CRC inci. Reduction[3](%)	CRC mort. Reduction[3](%)	ICER (/1000) in €
No Screening	0	22	22	1	44	23	0	946	0	0	0	0
M: FIT70, 65–69, 3 yrs & W: No screening	511	34	46	1	43	21	5	973	26	3	7	2
M: FIT25, 60–69, 1 yr & W: No screening	2637	85	143	2	39	17	22	1003	57	13	24	2
M: FIT25, 55–69, 1 yr & W: No screening	4674	119	153	2	38	17	27	1017	70	14	25	2
M: FIT25, 55–74, 1 yr & W: No screening	5542	134	174	2	37	16	31	1030	84	17	31	4
Current Screening M: FIT70, 60–74, 2 yrs & W: FIT25, 60–74, 2 yrs	4094	105	168	3	39	15	28	1101	155	12	33	Dominated
M: FIT25, 55–74, 1 yr & W: FIT25, 60–69, 1 yr	8452	191	268	3	34	12	45	1117	171	23	45	6
M: FIT25, 50–74, 1 yr & W: FIT25, 60–69, 1 yr	10830	226	298	3	34	12	50	1144	198	24	47	6
M: FIT25, 50–74, 1 yr & W: FIT10, 60–69, 1 yr	10791	270	353	4	33	12	52	1157	211	26	49	8
M: FIT25; 50–79, 1 yr & W: FIT10, 60–69, 1 yr	11396	280	366	4	32	11	53	1169	223	27	53	8
M: FIT25; 50–79, 1 yr & W: FIT25, 55–69, 1 yr	13428	271	336	4	33	11	55	1187	241	26	52	8
Optimal Screening M: FIT25, 50–79, 1 yr & W: FIT10, 55–69, 1 yr	13398	346	420	4	32	10	58	1206	260	28	55	9

M = Men; W = Women; LYG = life years gained; compl. = complications; COLs = colonoscopies; CRC = colorectal cancer; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); inci. = incidence; mort. = mortality.
[1] Total colonoscopies include diagnostic and surveillance colonoscopies.
[2] CRC cases and CRC death were not discounted.
[3] Total costs include costs of CRC screening, surveillance and CRC care costs.
[4] Compared with no-screening.

on CRC care costs and FIT performance. When care costs were increased by 50% or 100%, the optimal screening strategies remained unchanged but were associated with lower costs (ICER = 7000€/LYG, Table 6). When the same FIT performance was assumed for both sexes, optimal strategies no longer differed by sex. Annual screening with a cut-off of 25 μg/g was optimal when offered at 55–74 years in men and at 55–79 years in women (ICER = 10,000€/LYG).

The analysis without restrictions on colonoscopy resources and costs resulted in a more intensive optimal strategy in women. Annual screening was optimal when offered at 50–79 years with a cut-off of 25

Table 3
Efficient FIT (faecal immunochemical test) screening strategies in the Finnish population when the same target age and screening interval was assumed for both sexes. For each screening strategy outcomes are shown per 1000 individuals assuming 100% adherence to screening, diagnostic colonoscopy, and post-colonoscopy surveillance.

Sex (men/women): Strategy (cut-off, target age, interval)	FITs	Diagnostic COLs	Total COLs[1]	COL compl.	CRCs[2]	*CRC deaths*[2]	LYGs	Total costs[3](/1000) in €	Net costs[4](/1000) in €	CRC inci. Reduction[3](%)	CRC mort. Reduction[3](%)	ICER (/1000) in €
No screening	0	22	22	1	44	23	0	946	0	0	0	0
M: FIT70, 65–69, 3 yrs & W: FIT55, 65–69, 3 yrs	1069	43	61	1	43	20	9	995	49	4	10	2
M: FIT25, 60–69, 2 yrs & W: FIT40, 60–69, 2 yrs	2909	86	148	2	39	17	22	1047	101	12	27	3
M: FIT25, 60–69, 1 yr & W: FIT40, 60–69, 1 yr	5563	127	218	3	36	14	35	1080	134	19	37	4
Current Screening M: FIT70, 60–74, 2 yrs & W: FIT25, 60–74, 2 yrs	4094	105	168	3	39	15	28	1101	155	12	33	Dominated
M: FIT25, 55–69, 1 yr & W: FIT25, 55–69, 1 yr	9577	211	272	3	35	13	46	1133	187	21	41	5
M: FIT25, 55–74, 1 yr & W: FIT25, 55–74, 1 yr	11,484	243	317	4	33	11	52	1176	230	25	52	6
Optimal Screening M: FIT25, 55–74, 1 yr & W: FIT10, 55–74, 1 yr	11,427	334	417	4	32	10	55	1199	253	28	54	10

M = Men; W = Women; LYG = life years gained; compl. = complications; COLs = colonoscopies; CRC = colorectal cancer; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); inci. = incidence; mort. = mortality.
[1] Total colonoscopies include diagnostic and surveillance colonoscopies.
[2] CRC cases and CRC death were not discounted.
[3] Total costs include costs of CRC screening, surveillance and CRC care costs.
[4] Compared with no-screening.

μg/g in men and at 55–74 years with a cut-off of 10 μg/g in women (ICER = 10,000€/LYG, Table 6).

4. Discussion

Our study demonstrates that men gain more from FIT screening than women. However, women also benefit from screening at acceptable costs. An annual screening strategy with a cut-off of 25 μg/g at 50–79 years was predicted to be optimal in men, and with a cut-off of 10 μg/g at 55–69 years in women. The current strategies would lead similar relative reductions in CRC mortality among men and women, but they would not be cost-effective. Among strategies with the same target age and interval for both sexes, benefits from optimal screening were reasonable compared to those in the primary analysis. Biennial strategies with a cut-off 25 μg/g at 55–69 and 55–74 years for both sexes are closest in costs and superior to the current screening. Sensitivity analyses indicate that our cost-effectiveness estimates are conservative especially when comparing them to studies where the uniform FIT performance has been assumed.

We studied screening strategies by pooling them over sex and used the current screening as a reference. Unfeasible strategies were ruled out due to their relatively high costs and colonoscopy demand. Due to these constraints, the most extensive strategies were excluded, and even the highest incremental cost-effectiveness ratios were acceptable with regards to WTP thresholds used in European countries/studies (10,000€ in Sweden (Aronsson et al., 2017), 20,000€ in the Netherlands, ~38,000€ in France (Hassan et al., 2011)). The colonoscopy demand was described by the overall referral rate to diagnostic colonoscopy which is expected to decrease with subsequent screening rounds (Crotta et al., 2012). The overall referral rate of max 5% was a minor restriction: only suboptimal screening strategies with the lowest cut-off 10 μg/g were excluded in men. Nonetheless, the overall referral rate will underestimate the short-term demand of colonoscopies which is critical for a CRC screening program. Fortunately, the current FIT screening is being gradually implemented to older ages, and the colonoscopy demand will thus increase gradually.

FIT screening was found to be less effective in women which is in line with previous studies (Shaukat et al., 2013; van der Meulen et al., 2017;

Table 4
The current screening and efficient FIT (faecal immunochemical test) screening strategies in the Finnish population when the same target age and biennial screening interval was assumed for both sexes. For each screening strategy outcomes are shown per 1000 individuals assuming 100% adherence to screening, diagnostic colonoscopy, and post-colonoscopy surveillance.

Sex (men/women): Strategy (cut-off, target age, interval)	FITs	Diagnostic COLs	Total COLs[1]	COL compl.	CRCs[2]	CRC deaths[2]	LYGs	Total costs[3](/1000) in €	Net costs[4](/1000) in €	CRC inci. Reduction[3](%)	CRC mort. Reduction[3](%)	ICER (/1000) in €
No Screening	0	22	22	1	44	23	0	946	0	0	0	0
M: FIT70, 65–69, 2 yrs & W: FIT55, 65–69, 2 yrs	1559	52	77	2	42	19	12	1012	66	5	14	2
M: FIT25, 65–69, 2 yrs & W: FIT55, 65–69, 2 yrs	1549	60	95	2	41	18	16	1023	77	8	20	2
M: FIT25, 60–69, 2 yrs & W: FIT55, 60–69, 2 yrs	2912	84	143	2	39	17	25	1044	98	12	26	2
M: FIT25, 60–69, 2 yrs & W: FIT40, 60–69, 2 yrs	2909	86	148	2	39	17	26	1047	101	12	27	3
M: FIT25, 55–69, 2 yrs & W: FIT40, 55–69, 2 yrs	5161	124	166	2	38	16	34	1080	134	13	30	4
M: FIT25, 55–69, 2 yrs & W: FIT25, 55–69, 2 yrs	5157	137	181	2	38	15	36	1092	145	14	32	5
Current Screening M: FIT70, 60–74, 2 yrs & W: FIT25, 60–74, 2 yrs	4094	105	168	3	39	15	28	1101	155	12	33	Dominated
M: FIT25, 55–74, 2 yrs & W: FIT25, 55–74, 2 yrs	5940	153	206	3	37	14	41	1121	175	16	40	6
M: FIT25, 50–74, 2 yrs & W: FIT25, 50–74, 2 yrs	8482	197	250	3	37	13	48	1167	221	17	43	7
Optimal Screening M: FIT25, 50–74, 2 yrs & W: FIT10, 50–74, 2 yrs	8464	263	323	3	36	12	50	1187	241	19	46	9
M: FIT25, 50–79, 2 yrs & W: FIT25, 50–79, 2 yrs	9058	208	266	3	36	12	50	1193	247	18	49	28

M = Men; W = Women; LYG = life years gained; compl. = complications; COLs = colonoscopies; CRC = colorectal cancer; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); inci. = incidence; mort. = mortality.
[1] Total colonoscopies include diagnostic and surveillance colonoscopies.
[2] CRC cases and CRC death were not discounted.
[3] Total costs include costs of CRC screening, surveillance and CRC care costs.
[4] Compared with no-screening.

Holme et al., 2017). So far only one cost-effectiveness study has compared sex-specific screening to uniform screening with regards to age range, interval, and FIT cut-off (van der Meulen et al., 2017). In that study, efficient strategies and incremental cost-effectiveness ratios were similar for both sexes indicating the uniform strategy to be sufficient. In our analyses with and without restrictions on colonoscopy use and costs, efficient strategies differed by sex. FIT sensitivity is likely to be one of the reasons for the difference between the study results. In women the

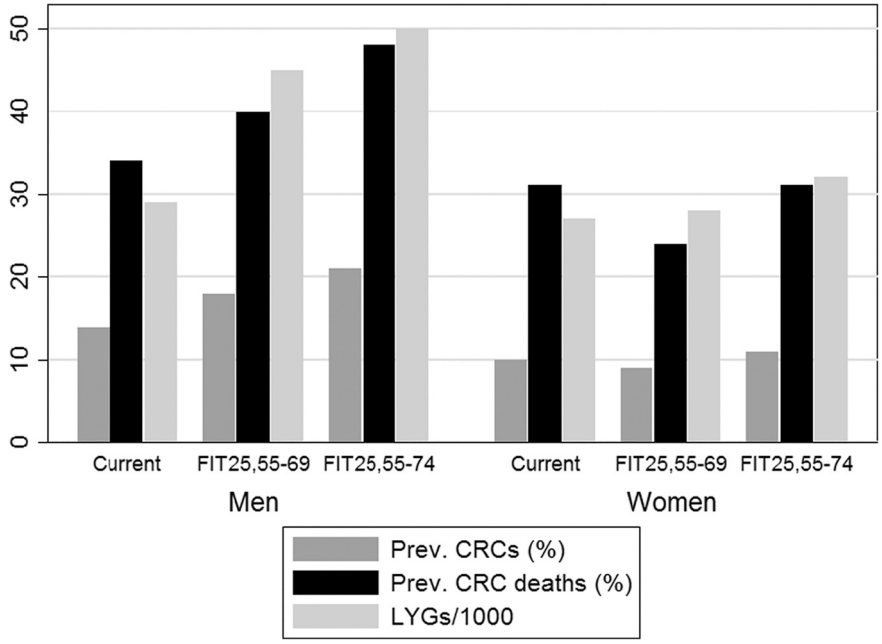

Fig. 3. The current screening (Current) and two efficient biennial screening strategies (FIT25,55–69 & FIT25,55–74) with the same target age for both sexes, and closest in cost to the current screening. Outcomes are shown for prevented (prev.) CRCs and CRC deaths (%), and LYGs (/1000) by sex.

FIT sensitivity was consistently lower for all screening outcomes compared to the Dutch study (van der Meulen et al., 2017). In men, however, there was no such consistent pattern in the FIT sensitivity between the studies. Thus, even with best available data, FIT sensitivity may not have been properly estimated for the Finnish women. Nevertheless, FIT screening is cost-effective in women compared to no-screening.

Our study results support younger starting age and larger age range of FIT screening in men. This finding is line with one cost-effectiveness study which compared biennial sex-specific screening to uniform screening with regards to age in three fixed FIT cut-offs for a resource-constraint setting (Thomas et al., 2021).

Based on a recent review, cost-effectiveness ratios of biennial FIT screening compared to no-screening ranged in Europe from 2400€/LYGs in Sweden to 4000€/LYGs in France (in 2016) (Ran et al., 2019; Aronsson et al., 2017; Hassan et al., 2011). Our estimate for biennial screening with a cut-off of 25 μg/g at 55–69 and 55–74 years corresponds with the upper limit, 4000€/LYGs. Low CRC incidence and low care costs are known to increase the cost-effectiveness ratios (Ran et al., 2019). The Finnish incidence rates are only slightly lower than in Sweden (Danckert et al., 2020). Therefore, the uniform FIT performance assumed and the high care costs in the Swedish study are likely to explain the difference between the estimates.

Our study has several strengths. We used the well-established microsimulation model MISCAN-Colon which has previously been used to inform public makers in Western countries (van Hees et al., 2015; Knudsen et al., 2016; Cenin et al., 2014). Model predictions were externally validated to several different screening trials and studies (Gini et al., 2021). Sex-specific colon models were calibrated to replicate the situation without screening using nationwide cancer registry data which is known to be accurate (Leinonen et al., 2017). Sex-specific models were calibrated also using the first-year data which were almost complete. The FIT screening pilot is run within the routine health care in municipalities which have been shown to be representative for the whole country. Therefore, the cost-effectiveness results can be regarded representable for the population-based screening in Finland.

As for limitations of the study, the first-year pilot data were rather uncertain due to the narrow age range and small numbers of screening outcomes: even a few CRCs by sex could have changed detection rates notably. The positivity rate was surprisingly low among women, and the predicted FIT sensitivity was very low as mentioned above. It is yet to be seen whether the FIT performance will remain the same in the first and subsequent rounds when based on more comprehensive data. Nevertheless, the predicted FIT performance will remain uncertain especially in low cut-offs among men. At the time of data delivery in June 2020, 11% of screening outcomes were still missing and their distribution by sex was assumed to be same to those reported so far. This assumption held perfectly for the CRCs and almost so for advanced adenomas as confirmed in September 2020 (Sarkeala et al., 2021). We also assumed that the FIT positivity rates were from the first screening round even though 6% of individuals had been invited to the gFOBT screening. Further, to assure comparability between strategies and to avoid hypothetical implementation plans, we assumed that screening was immediately implemented from 2019 onwards. We also assumed full adherence to screening, diagnostic, and post-colonoscopy surveillance. If imperfect adherence had been assumed, strategies with short intervals and larger target age could have compensated suboptimal adherence in the population. However, this would have implied over-screening of individuals who adhere recommendations. All in all, our results can provide useful insights in the benefits and costs of FIT screening in Finland.

The study results support a wider age range of screening in men, and a lower FIT cut-off in women when restrictions on colonoscopy capacity and costs are in place. We showed strategies with the same target age and interval for both sexes to lead lower benefits but only to some extent. This is reassuring since it can be difficult to justify and implement a truly sex-specific screening programme. Public acceptance of sex-specific FIT cut-offs is also needed to contribute high adherence to screening. Altogether, efficient strategy for both sexes is a logical aim of a screening programme. Men are then predicted to gain more from screening than women. However, since adherence to screening is likely to be higher in women, actual difference in effectiveness will be smaller than predicted.

In conclusion, this study suggests that optimal strategies may differ by sex with regards to target age and FIT cut-off. Therefore, our results provide support for other countries to consider sex-specific CRC screening.

Table 5
Impact of adherence on the current and the optimal FIT (faecal immunochemical test) screening strategies in the Finnish population. For each screening strategy outcomes are shown per 1000 individuals.

Sex (men/women): Strategy (cut-off, target age, interval) Adherence assumption	FITs	Diagnostic COLs	Total COLs[1]	COL compl.	CRCs[2]	CRC deaths[2]	LYGs	Total costs[3] (/1,000) in €	Net costs[4] (/1,000) in €	CRC inci. reduction[3] (%)	CRC mort. reduction[3] (%)
No screening	0	22	22	1	44	23	0	946	0	0	0
Current screening											
M: FIT70, 60–74, 2 yrs & W: FIT25, 60–74, 2 yrs											
100% adherence	4094	105	168	3	39	15	28	1101	155	12	33
Incomplete adherence[+]	2319	70	109	2	41	19	17	1031	85	7	18
Reduction[+] (%, incomplete vs 100% adherence)							39		45		
Optimal screening[p]											
M: FIT25, 50–79, 1 yr & W: FIT10, 55–69, 1 yr											
100% adherence[*]	13398	346	420	4	32	10	58	1206	260	28	55
Incomplete adherence[+]	10444	279	337	3	35	13	45	1152	206	22	42
Reduction[α] (%, incomplete vs 100% adherence)							22		21		
Optimal screening[s]											
M: FIT25, 55–74, 1 yr & W: FIT10, 55–74, 1 yr											
100% adherence[*]	11427	334	417	4	32	10	55	1199	253	28	54
Incomplete adherence[+]	9046	272	338	4	35	13	43	1149	203	22	43
Reduction[α] (%, incomplete vs 100% adherence)							22		20		

M = Men; W = Women; LYG = life years gained; compl. = complications; COLs = colonoscopies; CRC = colorectal cancer; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy); inci. = incidence; mort. = mortality.
[1] Total colonoscopies include diagnostic and surveillance colonoscopies.
[2] CRC cases and CRC death were not discounted.
[3] Total costs include costs of CRC screening, surveillance and CRC care costs.
[4] Compared with no-screening.
[p] Optimal screening in the primary analysis (Table 2).
[s] Optimal screening in the secondary analysis (Table 3).
[*] Assuming 100% adherence to screening, diagnostic colonoscopy, and post-colonoscopy surveillance;
[+] Incomplete adherence: Assuming 75% of males and 83% of females attended each screening round, i.e., 25% of men and 17% of women, were assumed to be never-attenders. Among those who attended to screening, 100% adherence to diagnostic colonoscopy, and post-colonoscopy surveillance was assumed;
[α] Calculated only for LYGs and net costs.

Table 6
Optimal FIT (faecal immunochemical test) screening strategies and their associated incremental cost-effectiveness ratios (ICER) per life-years gained (LYG) under specific sensitivity analyses.

	Screening strategy (sex (men/women): Cut-off, target age, interval)	ICER (/1000) in €
Primary analyses:	M: FIT25, 50–79, 1 yr & W: FIT10, 55–69, 1 yr	9
Sensitivity analyses[1]:		
50% higher CRC care costs	M: FIT25, 50–79, 1 yr & W: FIT10, 55–69, 1 yr	7
100% higher CRC care costs	M: FIT25, 50–79, 1 yr & W: FIT10, 55–69, 1 yr	7
Uniform FIT sensitivity and specificity	M: FIT25, 55–74, 1 yr & W: FIT25, 55–79, 1 yr	10
No restrictions on colonoscopy resources and total costs	M: FIT25, 50–79, 1 yr & W: FIT10, 55–74, 1 yr	10

M = Men; W = Women; ICER = Incremental cost-effectiveness ratio (Δcosts/ΔLYs gained compared to the previous less costly efficient strategy).
[1] Detailed data on efficient screening strategies and uniform FIT performance are shown in Supplementary Tables 1–5.

Funding

This modelling study is part of the EU-TOPIA project, funded by the EU-Framework Programme (Horizon 2020) of the European Commission, project reference 643753. The funding body has not involved with the study design, data collection, analysis and interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication.

CRediT authorship contribution statement

Sirpa Heinävaara: Conceptualization, Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. **Andrea Gini:** Data curation, Formal analysis, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Tytti Sarkeala:** Conceptualization, Writing – review & editing. **Ahti Anttila:** Conceptualization, Writing – review & editing. **Harry de Koning:** Funding acquisition. **Iris Lansdorp-Vogelaar:** Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

T.S. is a member of the National Screening Board.

Acknowledgments

We thank Docent Marja Hyöty, M.D. for her expertise and Mrs. Lotta Patrikka for her assistance in colonoscopy complications.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2022.106990.

References

Arana-Arri, E., Idigoras, I., Uranga, B., Pérez, R., Irurzun, A., Gutiérrez-Ibarluzea, I., et al., 2017. Population-based colorectal cancer screening programmes using a faecal immunochemical test: should faecal haemoglobin cut-offs differ by age and sex? BMC Cancer 17 (1), 577. https://doi.org/10.1186/s12885-017-3555-3.

Aronsson, M., Carlsson, P., Levin, L.Å., Häger, J., Hultcranz, R., 2017. Cost-effectiveness of high-sensitivity faecal immunochemical test and colonoscopy screening for colorectal cancer. Br. J. Surg. 104 (8), 1078–1086. https://doi.org/10.1002/bjs.10536.

Blom, J., Löwbeer, C., Elfström, K.M., Sventelius, M., Öhman, D., Saraste, D., et al., 2018. Gender-specific cut-offs in colorectal cancer screening with FIT: increased compliance and equal positivity rate. J. Med. Screen. 26 (2), 92–97. https://doi.org/10.1177/0969141318804843.

Cenin, D.R., St John, D.J., Ledger, M.J., Slevin, T., Lansdorp-Vogelaar, I., 2014. Optimising the expansion of the national bowel cancer screening program. Med. J. Aust. 201 (8), 456–461. https://doi.org/10.5694/mja13.00112.

Crotta, S., Segnan, N., Paganin, S., Dagnes, B., Rosset, R., Senore, C., 2012. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin. Gastroenterol. Hepatol. 10 (6), 633–638. https://doi.org/10.1016/j.cgh.2012.02.030.

Danckert, B., Ferlay, J., Engholm, G., Hansen, H.L., Johannesen, T.B., Khan, S., et al., 2020. NORDCAN: Cancer Incidence, Mortality, Prevalence, and Survival in the Nordic Countries, Version 8.2 (26.03.2019). Association of the Nordic Cancer Registries. Danish Cancer Society. [Internet]. [cited 2020 Sep 28]. Available from: http://www.ancr.nu.

European Commission, 2017. Cancer screening in the European Union (2017). In: 2nd Report on the Implementation of the Council Recommendation on Cancer Screening. IACR, Lyon.

European Commission, 2020. EUROSTAT [Internet]. [cited 2020 Nov 3]. Available from: https://ec.europa.eu/eurostat/data/database.

Färkkilä, N., Torvinen, S., Sintonen, H., Saarto, T., Järvinen, H., Hänninen, J., et al., 2015. Costs of colorectal cancer in different states of the disease. Acta Oncol. 54 (4), 454–462. https://doi.org/10.3109/0284186X.2014.985797.

Gatto, N.M., Frucht, H., Sundararajan, V., Jacobson, J.S., Grann, V.R., Neugat, A.I., 2003. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J. Natl. Cancer Inst. 95 (3), 230–236. https://doi.org/10.1093/jnci/95.3.230.

Gini, A., Zauber, A.G., Cenin, D.R., Omidvari, A.H., Hempstead, S.E., Fink, A.K., et al., 2017. Cost effectiveness of screening individuals with cystic fibrosis for colorectal cancer. Gastroenterology 154 (3), 556–567. https://doi.org/10.1053/j.gastro.2017.10.03627.

Gini, A., Buskermolen, M., Senore, C., Anttila, A., Novak Mlakar, D., Veerus, P., et al., 2021. Development and validation of three regional microsimulation models for predicting colorectal cancer screening benefits in Europe. Med. Decis. Mak. Policy Pract. 6 (1) https://doi.org/10.1177/2381468320984974, 2381468320984974.

Hassan, C., Benamouzig, R., Spada, C., Ponchon, T., Zullo, A., Saurin, J.C., et al., 2011. Cost effectiveness and projected national impact of colorectal cancer screening in France. Endoscopy. 43 (9), 780–793. https://doi.org/10.1055/s-0030-1256409.

Hassan, C., Quintero, E., Dumonceau, J.M., Regular, J., Brandão, C., Chaussade, S., et al., 2013. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 45 (10), 842–851. https://doi.org/10.1055/s-0033-1344548.

Holme, Ø., Schoen, R.E., Senore, C., Segnan, N., Hoff, G., Løberg, M., et al., 2017. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. Br. Med. J. 356, i6673 https://doi.org/10.1136/bmj.i6673.

International Agency for Research on Cancer, World Health Organization, 2020. Cancer Today [Internet]. Global Cancer Observatory. [cited 2020 Sep 28]. Available from: https://gco.iarc.fr/.

Jäntti, M., Heinävaara, S., Malila, N., Sarkeala, T., 2021. Sociodemographic features and patterns of non-participation in colorectal cancer screening in Finland. Eur. J. Pub. Health 31 (4), 890–894. https://doi.org/10.1093/eurpub/ckab074.

Kapiainen, S., Väisänen, A., Haula, T., 2014. Unit Costs of Health and Social Care in Finland in 2011 (in Finnish, Terveyden- ja Sosiaalihuollon Yksikkökustannukset Suomessa Vuonna 2011) [Internet]. 2014 [cited 2020 Nov 13]. Report No.: 3/2014. Available from: http://urn.fi/URN:ISBN:978-952-302-079-5.

Knudsen, A.B., Zauber, A.G., Rutter, C.M., Naber, S.K., Doria-Rose, V.P., Pabiniak, C.K., et al., 2016. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US preventive services task force. J. Am. Med. Assoc. 315 (23), 2595–2609. https://doi.org/10.1001/jama.2016.6828.

Lauby-Secretan, B., Vilahur, N., Bianchini, F., Guha, N., Straif, K., 2018. The IARC on cancer handbook working group. The IARC perspective on colorectal cancer screening. N. Engl. J. Med. 378 (18), 1734–1740. https://doi.org/10.1056/NEJMsr1714643.

Lee, J.K., Liles, E.G., Bent, S., Levin, T.R., Corley, D.A., 2014. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann. Intern. Med. 160 (3), 171. https://doi.org/10.7326/M13-1484.

Leinonen, M.K., Miettinen, J., Heikkinen, S., Pitkäniemi, J., Malila, N., 2017. Quality measures of the population-based Finnish Cancer registry indicate sound data quality for solid malignant tumours. Eur. J. Cancer 77, 31–39. https://doi.org/10.1016/j.ejca.2017.02.017.

Mäklin, S., Koskenvuo, L., Heikkinen, S., Sallinen, V., Malila, N., 2020. Five-Year Hospital Costs of Colorectal Cancer in a Randomized Health Services Study on Colorectal Cancer Screening. Unpublished Manuscript.

Mark, D.H., 2002. Visualizing cost-effectiveness analysis. J. Am. Med. Assoc. 287 (18), 2428–2429. https://doi.org/10.1001/jama.287.18.2428.

Martin, S., Rice, N., Smith, P.C., 2008. The Link Between Health Care Spending and Health Outcomes for the New English Primary Care Trusts. Centre for Health Economics, York (Report No.: CHE Research Paper 42).

Meester, R.G.S., Peterse, E.F.P., Knudsen, A.B., de Weerdt, A.C., Chen, J.C., Lietz, A.P., et al., 2018. Optimizing colorectal cancer screening by race and sex: microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. Cancer. 124 (14), 2974–2985. https://doi.org/10.1002/cncr.31542.

Pitkäniemi, J., Seppä, K., Hakama, M., Malminiemi, O., Palva, T., Vuoristo, M.S., et al., 2015. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterol. 2 (1), e000034 https://doi.org/10.1136/bmjgast-2015-000034.

Ran, T., Cheng, C.Y., Misselwitz, B., Brenner, H., Ubels, J., Schlander, M., 2019. Cost-effectiveness of colorectal cancer screening strategies - a systematic review. Clin. Gastroenterol. Hepatol. 17 (10), 1969–1981. https://doi.org/10.1016/j.cgh.2019.01.014.

Sarkeala, T., Färkkilä, M., Anttila, A., Hyöty, M., Kairaluoma, M., Rautio, T., et al., 2021. Piloting gender-oriented colorectal cancer screening with a faecal immunochemical test: population-based registry study from Finland. BMJ Open 11 (2), e046667. https://doi.org/10.1136/bmjopen-2020-046667.

Schroy 3rd, P.C., Coe, A., Chen, C.A., O'Brien, M.J., Heeren, T.C., 2013. Prevalence of advanced colorectal Neoplasia in whites and blacks undergoing screening colonoscopy in a safety net hospital. Ann. Intern. Med. 159 (1), 13–20. https://doi.org/10.7326/0003-4819-159-1-201307020-00004.

Shaukat, A., Mongin, S.J., Geisser, M.S., Lederle, F.A., Bond, J.H., Mandel, J.S., et al., 2013. Long-term mortality after screening for colorectal cancer. N. Engl. J. Med. 369 (12), 1106–1114. https://doi.org/10.1056/NEJMoa1300720.

Shkolnikov, V., Barbieri, M., Wilmoth, J., 2020. Human Mortality Database [Internet]. [cited 2020 Nov 13]. Available from: https://www.mortality.org/.

Thomas, C., Mandrik, O., Whyte, S., Saunders, C.L., Griffin, S.J., Usher-Smith, J.A., 2021. Should colorectal cancer screening start at different ages for men and women? Cost-effectiveness analysis for a resource-constrained service. Cancer Rep. (Hoboken) 4 (4), e1344. https://doi.org/10.1002/cnr2.1344.

van der Meulen, M., Kapidzic, A., van Leerdam, M.E., van den Steen, A., Kuipers, E.J., Spaander, M.C.W., et al., 2017. Do men and women need to be screened differently with fecal immunochemical testing: a cost-effectiveness analysis. Cancer Epidemiol. Biomark. Prev. 26 (8), 1328–1336 (DOI: 1158/1055-9965.EPI-16-0786).

van Hees, F., Zauber, A.G., van Veldhuizen, H., Heijnen, M.L.A., Penning, C., de Koning, H., et al., 2015. The value of models in informing resource allocation in colorectal cancer screening: the case of the Netherlands. Gut. 64 (12), 1985–1997. https://doi.org/10.1136/gutjnl-2015-309316.

van Rijn, J.C., Reitsma, J.B., Stoker, J., Bossuyt, P.M., van Deventer, S.J., Dekker, E., 2006. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am. J. Gastroenterol. 101 (2), 343–350. https://doi.org/10.1111/j.1572-0241.2006.00390.x.

Warren, J.L., Klabunde, C.N., Mariotto, A.B., Meekins, A., Topor, M., Brown, M.L., et al., 2009. Adverse events after outpatient colonoscopy in the Medicare population. Ann. Intern. Med. 150 (12), 849–857. https://doi.org/10.7326/0003-4819-150-12-200906160-00008.

Winawer, S.J., Zauber, A., Ho, M.N., O'Brien, M.J., Gottlieb, L.S., Sternberg, S.S., et al., 1993. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N. Engl. J. Med. 329 (27), 1977–1981. https://doi.org/10.1056/NEJM199312303292701.

Zorzi, M., Fedeli, U., Schievano, E., Bovo, E., Guzzinati, S., Baracco, S., et al., 2014. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 64, 784–790. https://doi.org/10.1136/gutjnl-2014-307508.