Original article

Sex differences in faecal occult blood test screening for colorectal cancer

L. Koskenvuo[1], N. Malila[3], J. Pitkäniemi[3,4], J. Miettinen[3], S. Heikkinen[3] and V. Sallinen[1,2]

Departments of [1]Abdominal Surgery and [2]Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, [3]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, and [4]Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Correspondence to: Dr L. Koskenvuo, Department of Abdominal Surgery, Helsinki University Hospital, PL340, 00029 HUS, Helsinki, Finland (e-mail: laura.koskenvuo@hus.fi)

Background: This analysis of patients in a randomized population-based health services study was done to determine the effects of faecal occult blood test (FOBT) screening of colorectal cancer (CRC) in outcomes beyond mortality, and to obtain explanations for potential sex differences in screening effectiveness.

Methods: In the Finnish FOBT screening programme (2004–2011), people aged 60–69 years were randomized into the screening and control arms. Differences in incidence, symptoms, tumour location, TNM categories, non-vital outcomes and survival in the screening and control arms were analysed.

Results: From 321 311 individuals randomized, 743 patients with screening-detected tumours and 617 control patients with CRC were analysed. CRC was less common in women than in men (0·34 *versus* 0·50 per cent; risk ratio (RR) 0·82, 95 per cent c.i. 0·74 to 0·91) and women were less often asymptomatic (16·7 *versus* 22·0 per cent; RR 0·76, 0·61 to 0·93). Women more often had right-sided tumours (32·0 *versus* 21·3 per cent; RR 1·51, 1·26 to 1·80). Among men with left-sided tumours, those in the screening arm had lower N (RR 1·23, 1·02 to 1·48) and M (RR 1·57, 1·14 to 2·17) categories, as well as a higher overall survival rate than those in the control arm. Furthermore among men with left-sided tumours, non-radical resections (26·2 *versus* 15·7 per cent; RR 1·67, 1·22 to 2·30) and postoperative chemotherapy sessions (61·6 *versus* 48·2 per cent; RR 1·28, 1·10 to 1·48) were more frequent in the control arm. Similar benefits of screening were not detected in men with right-sided tumours or in women.

Conclusion: Biennial FOBT screening seems to be effective in terms of improving several different outcomes in men, but not in women. Differences in incidence, symptoms and tumour location may explain the differences in screening efficacy between sexes.

Paper accepted 5 September 2018

Published online 21 November 2018 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.11011

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world, with 1·4 million new cases diagnosed annually and 0·7 million deaths attributed to the disease[1]. Key factors that improve the prognosis are early diagnosis and complete radical tumour resection. However, CRC is often asymptomatic in its early stages, and is not diagnosed until symptoms manifest at a later stage[2]. Several screening methods have been implemented to detect CRC at early stages. These include faecal occult blood testing (FOBT), endoscopy (flexible sigmoidoscopy or colonoscopy), CT colonography, and combinations thereof[3].

Three population-based prospective randomized controlled studies[4–6] and one volunteer-based trial[7] found that colorectal tumours can be detected at an earlier stage and mortality from CRC reduced with biennial FOBT screening. Biennial FOBT screening reduces CRC mortality by 18 per cent on average[8]. Sigmoidoscopy as a screening method has been found to be more effective than FOBT in reducing CRC mortality[9], but carries a small but significant risk (0·08 per cent) of major complications owing to its invasiveness[10]. Data regarding colonoscopy as a population-based screening method are still lacking, and results of ongoing trials are pending.

In Finland, a prospective randomized population-based health services programme on CRC screening was implemented in 2004[11], with the primary aim of determining whether CRC screening by biennial FOBT in

a population-based programme reduces CRC-specific mortality. The target population was 60–69-year-old men and women, and the study expanded gradually as more regions implemented the programme. By the end of 2011, it covered 41·8 per cent of men and 40·6 per cent of women among all 60–69-year-old individuals living in Finland. The target age limits were chosen based on an earlier study[11] showing that the incidence of CRC and mortality from the disease increase notably in Finland after the age of 60 years. Over 80 per cent of new cases were diagnosed and more than 85 per cent of CRC deaths occurred in people aged over 60 years[11].

The design of the randomized public health programme and initial mortality results were published recently[12]. In contrast with randomized screening trials[4,5,7], no significant difference in CRC-specific mortality between the screening and control arms was found[12]. However, CRC mortality was reduced in men in the screening arm compared with controls, and was increased in women, although the difference between the sexes was not statistically significant[12]. Interestingly, other trials[13,14] have reported a greater reduction in CRC mortality in men undergoing biennial FOBT compared with women, whereas another[15] reported no sex-based difference. It remains unclear why men appear to benefit more than women from CRC screening.

The effects of FOBT CRC screening on many important but non-vital outcomes remain largely unexplored. These include radical surgery, emergency surgery, and the need for chemotherapy and a stoma, which are of paramount interest to healthcare providers and patients alike. The main aims of the present study were to explore reasons for the potential sex difference in FOBT screening effectiveness and to evaluate the effects of screening on non-vital outcomes.

Methods

This study was approved by the Ministry of Social Affairs and Health in 2004 (STM/42/07/2004) on the implementation of CRC screening in Finland, and the approval was updated in 2010 by the official authority, the National Institute of Health and Welfare (THL/619/5.05.00/2010).

The design and details of the randomized public health programme have been reported previously[11]. Briefly, the screening population consisted of 60–69-year-old individuals living in municipalities participating in the organized CRC screening programme. Data from individuals invited to participate were retrieved from the Central Population Registry, and the population was randomized 1 : 1 into the screening or control arm stratified by birth year, sex and residence. The randomized programme commenced in

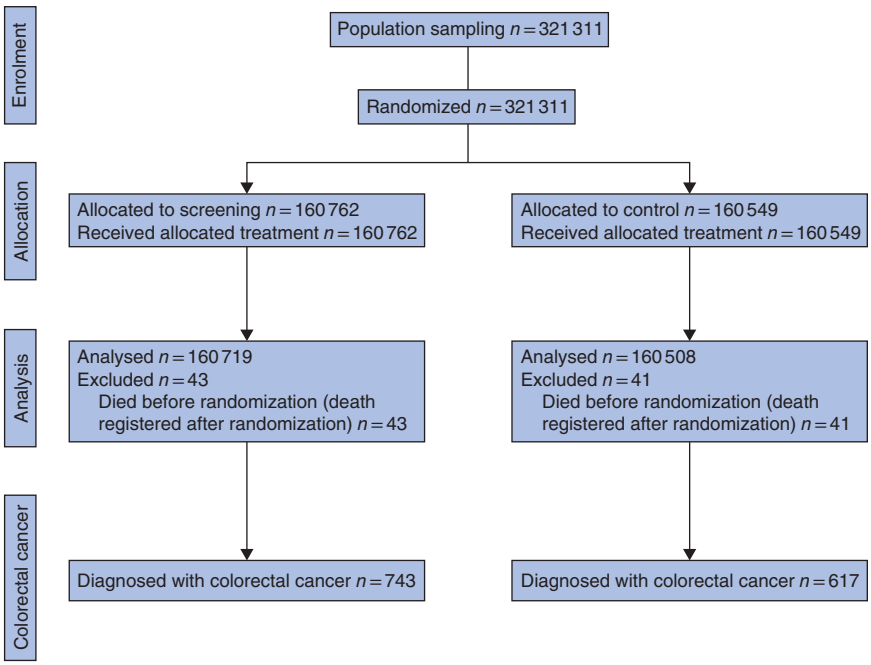


Fig. 1 Flow chart of the original study protocol

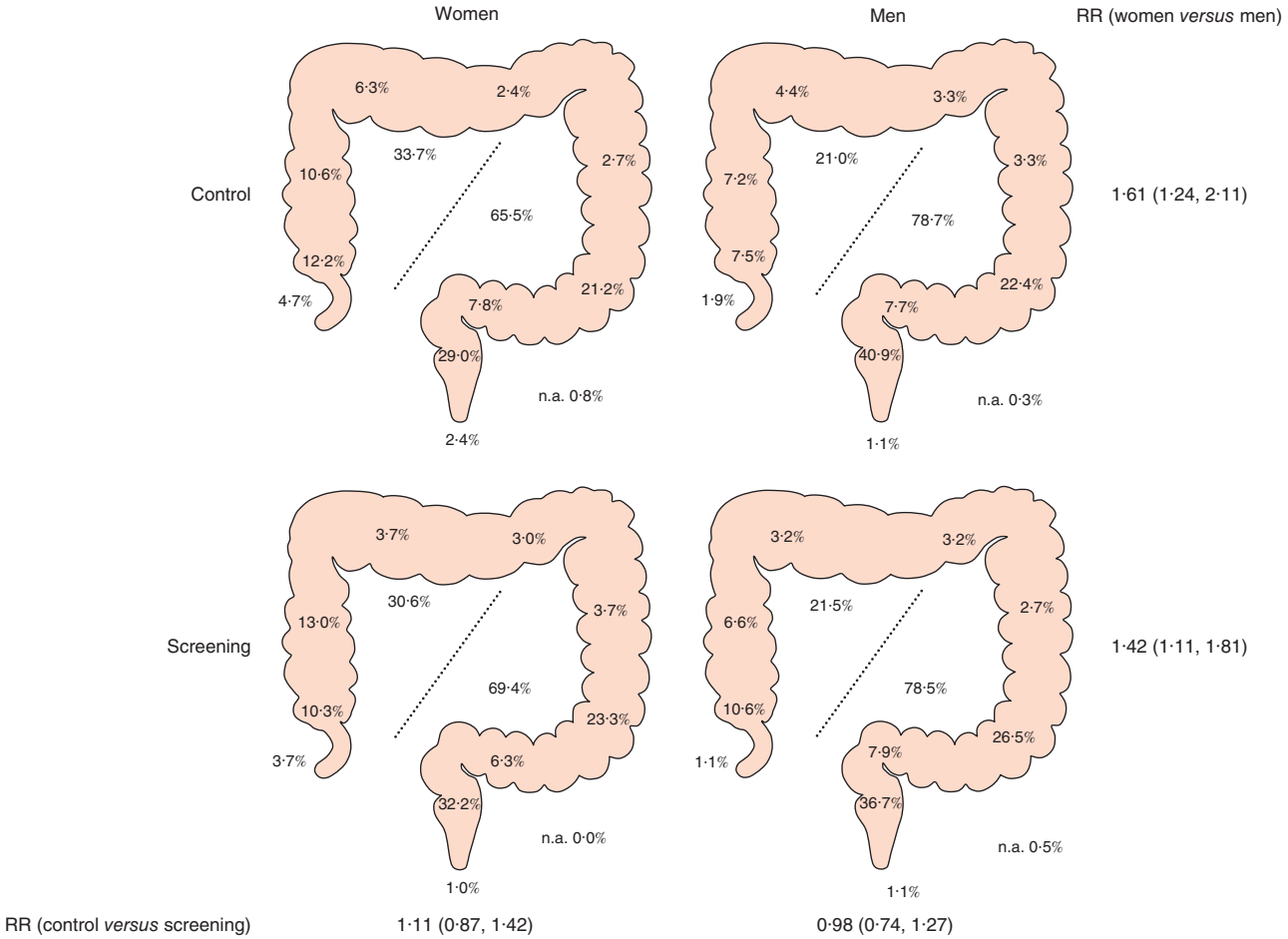


Fig. 2 Distribution of colorectal cancer in women and in men in the screening and control arms. Percentages in the large bowel refer to the following areas: appendix, caecum, ascending colon, right transverse colon, left transverse colon, descending colon, sigmoid colon, rectosigmoid junction, rectum and anus. Percentages in the middle show proportions of right- and left-sided tumours. n.a., Not available. Risk ratios (RRs), shown with 95 per cent confidence intervals, relate to the proportion of right-sided cancers

September 2004. Screening was performed with a biennial guaiac FOBT (Hemoccult®; Beckman Coulter, Krefeld, Germany), which was sent by mail to the screening group. If there was any blood in the stool, the person was referred for a full colonoscopy. The screening letter also contained advice to seek medical attention if any symptoms were present. All individuals in the screening group were re-invited every second year until they reached 69 years of age. The control population was not contacted at all.

The present study included patients diagnosed with CRC between the time of randomization and the end of 2011 in both the screening and control groups. Patients diagnosed with CRC from both study arms were identified from the Finnish Cancer Registry. The registry collects population-based data on patients with cancer in Finland with high coverage (97·4 per cent) for CRCs[16]. Patients randomized to the screening arm were included in this group for the analyses regardless of active participation, because all individuals in the screening arm were sent the letter and FOBT test. Patients were also included in their study arms regardless of whether the tumour was found by screening or in spite of it (symptomatic patient undergoing colonoscopy even though the FOBT was negative).

Hospitals treating the patients with CRC were identified, and copies of patients' medical records were requested. The following data were extracted manually: clinical and pathological UICC TNM stage (7th edition)[17]; symptoms; extent of surgery; need for emergency surgery, stoma, or chemotherapy; and histopathological diagnoses. Radical surgery was defined as complete tumour removal with tumour-free margins of more than 1 mm after the

Table 1 Colorectal cancer diagnoses in 2004–2011 in the randomized population of the Finnish colorectal cancer screening programme: overall sex and study arm differences, and sex differences by study arm in incidence, tumour characteristics, prevalence, age at diagnosis and symptoms

	Screening			Control			Overall adjusted analyses‡		
	Men	Women	RR (women *versus* men)†	Men	Women	RR (women *versus* men)†	RR (control *versus* screening)†¶	RR (women *versus* men)†#	*P* (women *versus* men)#
No. randomized	79 871	80 891		79 882	80 667				
Patients with colorectal cancer*	442 (0·55)	301 (0·37)	0·67 (0·58, 0·78)	362 (0·45)	255 (0·32)	0·96 (0·72, 1·28)	0·69 (0·62, 0·77)	0·82 (0·74, 0·91)	–
Right-sided tumour	95 (21·5)	92 (30·6)	1·42 (1·11, 1·81)	76 (21·0)	86 (33·7)	1·61 (1·24, 2·11)	1·05 (0·88, 1·25)	1·51 (1·26, 1·80)	< 0·001**
Missing	2	0		1	2				
Median age at diagnosis (years)§	63·7	63·8	–	64·1	63·8		−0·03 (−0·50, 0·44)§	−0·34 (−0·80, 0·12)§	0·151
Cancer histology									
Adenocarcinoma	387 (89·8)	247 (84·3)	0·94 (0·89, 0·99)	314 (89·0)	209 (83·3)	0·94 (0·87, 1·00)	0·99 (0·95, 1·03)	0·94 (0·90, 0·98)	0·004**
Mucinous adenoma	26 (6·0)	35 (11·9)	1·98 (1·22, 3·25)	25 (7·1)	25 (10·0)	1·41 (0·82, 2·40)	0·97 (0·68, 1·39)	1·70 (1·19, 2·43)	0·004**
Neuroendocrine	10 (2·3)	3 (1·0)	0·44 (0·10, 1·43)	5 (1·4)	8 (3·2)	2·25 (0·76, 7·37)	1·20 (0·55, 2·59)	1·06 (0·48, 2·27)	0·889
Squamous	5 (1·2)	4 (1·4)	1·18 (0·29, 4·41)	4 (1·1)	5 (2·0)	1·76 (0·47, 7·04)	1·19 (0·47, 3·04)	1·44 (0·57, 3·66)	0·437
Other	3 (0·7)	4 (1·4)	1·96 (0·44, 9·90)	5 (1·4)	4 (1·6)	1·13 (0·28, 4·21)	1·53 (0·57, 4·27)	1·43 (0·53, 3·87)	0·469
Missing	11	8		9	4				
Symptoms									
Intestinal bleeding	106 (24·3)	84 (28·0)	1·15 (0·90, 1·47)	156 (43·3)	90 (36·0)	0·83 (0·67, 1·01)	1·57 (1·34, 1·83)	0·94 (0·81, 1·10)	0·467
Change in bowel habit	104 (23·9)	68 (22·7)	0·95 (0·72, 1·24)	132 (36·7)	95 (38·0)	1·04 (0·84, 1·27)	1·59 (1·35, 1·88)	1·00 (0·85, 1·18)	0·974
Total occlusion	6 (1·4)	8 (2·7)	1·94 (0·68, 5·83)	11 (3·1)	4 (1·6)	0·52 (0·15, 1·51)	1·29 (0·63, 2·69)	1·02 (0·48, 2·10)	0·959
Anaemia	61 (14)	36 (12·0)	0·86 (0·58, 1·25)	73 (20·3)	54 (21·6)	1·07 (0·78, 1·45)	1·58 (1·24, 2·02)	0·98 (0·76, 1·24)	0·842
Abdominal pain	60 (13·8)	68 (22·7)	1·65 (1·20, 2·26)	91 (25·3)	76 (30·4)	1·20 (0·93, 1·56)	1·56 (1·28, 1·92)	1·36 (1·12, 1·67)	0·002**
Other	65 (14·9)	44 (14·7)	0·98 (0·69, 1·40)	75 (20·8)	50 (20·0)	0·96 (0·69, 1·32)	1·38 (1·10, 1·75)	0·97 (0·76, 1·23)	0·805
No symptoms	163 (37·4)	84 (28·0)	0·75 (0·60, 0·93)	12 (3·3)	8 (3·2)	0·96 (0·38, 2·29)	0·10 (0·06, 0·15)	0·76 (0·61, 0·93)	0·011**
Missing	6	1		2	5				

Values in parentheses are percentage of people with colorectal cancer, except *percentage of people randomized and †95 per cent confidence intervals. RR, risk ratio. ‡Binomial regression with log-link function, except §difference in medians analysed by quantile regression; adjusted for ¶sex and #study arm. **Significant at 5 per cent false discovery rate based on Benjamini–Hochberg criterion.

primary surgery. Emergency surgery was defined as a colorectal operation during an emergency admission. Stomas included both loop and end stomas as well as permanent or temporary stomas. Chemotherapy included both adjuvant therapy administered after curative surgery and therapy administered for metastatic CRC. Dates of death were collected from the Central Population Registry until the end of 2015. This observational analysis was planned after the original trial had been completed.

Statistical analysis

Sex differences in incidence, histology, treatments, symptoms and laterality were estimated by risk ratios (RRs) using log-link binomial regression, and in median age at diagnosis using quantile regression. These sex differences were adjusted for study arm. Study arm differences in non-vital outcomes were also estimated using RRs for all patients, by sex, and by both sex and tumour laterality (right-sided *versus* left-sided). Overall study arm differences in non-vital

Table 2 Differences between randomization arms in T, N, and M categories by both laterality and sex, by laterality and overall

	Right				Left			
	Men		Women		Men		Women	
	Screening ($n = 95$)	Control ($n = 76$)	Screening ($n = 92$)	Control ($n = 86$)	Screening ($n = 345$)	Control ($n = 285$)	Screening ($n = 209$)	Control ($n = 167$)
T category								
T ≤ 2	22 (26)	9 (13)	20 (23)	10 (14)	140 (43·1)	73 (27·2)	71 (39·4)	36 (23·5)
T > 2	63 (74)	59 (87)	66 (77)	61 (86)	185 (56·9)	195 (72·8)	109 (60·6)	117 (76·5)
Missing	10	8	6	15	20	17	29	14
RR (control *versus* screening)*								
Sex and laterality stratum†	1·17 (1·00, 1·38)		1·11 (0·95, 1·30)		1·28 (1·13, 1·44)		1·33 (1·15, 1·56)	
Laterality stratum‡	1·14 (1·02, 1·28)				1·30 (1·18, 1·43)			
Overall§	1·23 (1·15, 1·33)							
N category								
N0	48 (59)	38 (58)	43 (52)	32 (46)	194 (61·0)	138 (52·1)	94 (54·0)	82 (55·4)
N ≥ 1	33 (41)	28 (42)	39 (48)	37 (54)	124 (39·0)	127 (47·9)	80 (46·0)	66 (44·6)
Missing	14	10	10	17	27	20	35	19
RR (control *versus* screening)*								
Sex and laterality stratum†	1·04 (0·70, 1·53)		1·11 (0·80, 1·53)		1·23 (1·02, 1·48)		1·05 (0·82, 1·35)	
Laterality stratum‡	1·08 (0·84, 1·38)				1·16 (1·00, 1·35)			
Overall§	1·14 (1·00, 1·29)							
M category								
M0	70 (76)	57 (75)	64 (70)	60 (71)	289 (84·5)	215 (75·7)	173 (82·8)	123 (74·5)
M1	22 (24)	19 (25)	28 (30)	25 (29)	53 (15·5)	69 (24·3)	36 (17·2)	42 (25·5)
Missing	3	0	0	1	3	1	0	2
RR (control *versus* screening)*								
Sex and laterality stratum†	1·05 (0·61, 1·78)		0·97 (0·61, 1·52)		1·57 (1·14, 2·17)		1·48 (1·00, 2·21)	
Laterality stratum‡	1·00 (0·70, 1·41)				1·53 (1·19, 1·97)			
Overall§	1·33 (1·08, 1·62)							

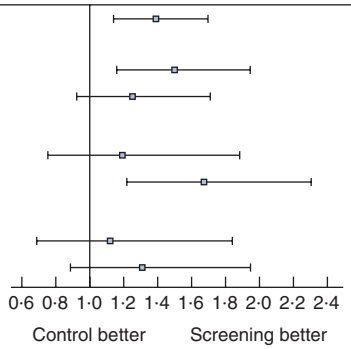
Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Risk ratio (RR) estimated separately by sex and laterality for each stage category. ‡RR adjusted for sex and estimated separately by laterality for each stage category. §RR adjusted for sex and laterality, and estimated separately for each stage category response. A RR above 1 indicates a greater prevalence of the higher T, N or M category in control *versus* screening group.

outcomes were estimated with adjustment for T category (T0–2 or T3–4).

Differences between the sexes in variables described above were also estimated separately by study arm. Prevalence differences between study arms were estimated with regard to histology, symptoms, laterality and TNM categories. TNM category analysis was also stratified by sex, and both sex and laterality. These estimates were adjusted for sex, laterality, or both where they were not stratified by these variables. Simple proportions of tumour locations were computed by sex and study arm. Stratifying by both sex and laterality, survival was estimated for the study arms using the Kaplan–Meier method, and differences in patient survival between the study arms were estimated by means of hazard ratios (HRs) derived using Cox regression. Follow-up commenced at the time of diagnosis of CRC and ended upon death, emigration or on 31 December 2015, whichever was earliest.

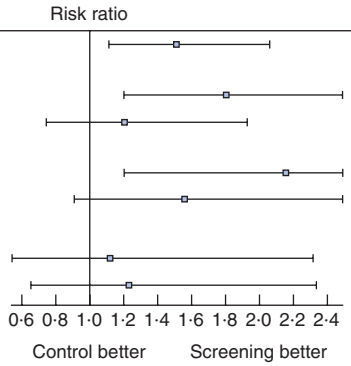
Confidence intervals were estimated for all RRs and HRs at the 95 per cent confidence level. No estimate was adjusted for age because age adjustment had no effect. *P* values were estimated using two-sided tests for the main results, unstratified sex differences and all study arm differences in non-vital outcomes. In addition, multiple

	Non-radical surgery		Risk ratio	*P*
	Screening	Control		
All	141 of 733	162 of 605	1·39 (1·14, 1·70)	0·001*
Sex				
Men	80 of 433	98 of 354	1·50 (1·16, 1·95)	0·002*
Women	61 of 300	64 of 251	1·25 (0·92, 1·71)	0·150
Men				
Right-sided tumours	26 of 93	25 of 75	1·19 (0·75, 1·89)	0·451
Left-sided tumours	53 of 338	73 of 279	1·67 (1·22, 2·30)	0·002*
Women				
Right-sided tumours	23 of 92	24 of 86	1·12 (0·68, 1·84)	0·660
Left-sided tumours	38 of 208	39 of 163	1·31 (0·88, 1·95)	0·183



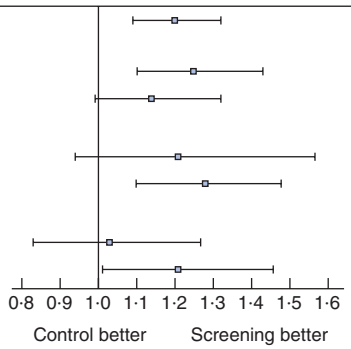
a Non-radical surgery

	Emergency surgery		Risk ratio	*P*
	Screening	Control		
All	65 of 698	80 of 568	1·51 (1·11, 2·06)	0·008*
Sex				
Men	34 of 407	50 of 333	1·80 (1·20, 2·73)	0·005*
Women	31 of 291	30 of 235	1·20 (0·74, 1·93)	0·452
Men				
Right-sided tumours	13 of 85	23 of 70	2·15 (1·20, 4·07)	0·013*
Left-sided tumours	21 of 320	27 of 263	1·56 (0·91, 2·73)	0·108
Women				
Right-sided tumours	13 of 91	13 of 81	1·12 (0·55, 2·31)	0·747
Left-sided tumours	18 of 200	17 of 153	1·23 (0·65, 2·33)	0·511



b Emergency surgery

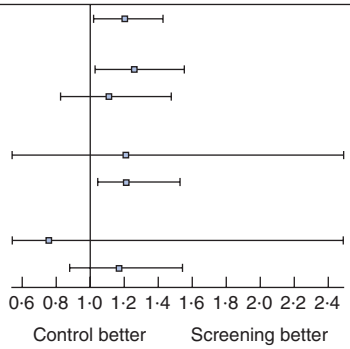
	Chemotherapy		Risk ratio	*P*
	Screening	Control		
All	357 of 685	364 of 580	1·20 (1·09, 1·32)	< 0·001*
Sex				
Men	200 of 402	212 of 340	1·25 (1·10, 1·43)	< 0·001*
Women	157 of 283	152 of 240	1·14 (0·99, 1·32)	0·068
Men				
Right-sided tumours	48 of 89	47 of 72	1·21 (0·94, 1·57)	0·143
Left-sided tumours	150 of 311	165 of 268	1·28 (1·10, 1·48)	0·001*
Women				
Right-sided tumours	58 of 87	54 of 79	1·03 (0·83, 1·27)	0·816
Left-sided tumours	99 of 196	98 of 160	1·21 (1·01, 1·46)	0·042



c Chemotherapy

Fig. 3 Effect of faecal occult blood test screening on non-vital outcomes, overall, by sex, and by both sex and laterality: **a** non-radical surgery, **b** emergency surgery, **c** chemotherapy and **d** stoma. Risk ratios are shown with 95 per cent confidence intervals for the control *versus* screening arms (log-link binominal regression); *significant at 5 per cent false discovery rate based on Benjamini–Hochberg criterion

	Stoma				
	Screening	Control	Risk ratio	Risk ratio	*P*
All	190 of 697	189 of 576		1·21 (1·02, 1·43)	0·028
Sex					
Men	120 of 411	125 of 340		1·26 (1·03, 1·55)	0·028
Women	70 of 286	64 of 236		1·11 (0·83, 1·48)	0·491
Men					
Right-sided tumours	2 of 82	2 of 68		1·21 (0·15, 9·84)	0·849
Left-sided tumours	118 of 327	123 of 271		1·26 (1·04, 1·53)	0·021
Women					
Right-sided tumours	3 of 87	2 of 76		0·76 (0·10, 4·49)	0·764
Left-sided tumours	67 of 199	62 of 158		1·17 (0·88, 1·54)	0·275



d Stoma

Fig. 3 Continued

comparisons were taken into account by considering significant only the results that were accepted at a 5 per cent false detection rate based on the Benjamini–Hochberg criterion (BH+). All statistical analyses were performed using SPSS® version 24 (IBM, Armonk, New York, USA) or R version 3.4.0 (packages Epi 2.16, quantreg 5.3 and survival 2.41.3; https://www.r-project.org/).

Results

Between 2004 and 2011, 321 311 people were randomized into the screening or control arm. Owing to a delay between population sampling from the Central Population Registry and randomization, patients who had died before the randomization date (43 in the screening arm and 41 in the control arm) were excluded from the analyses. Thus, there were 160 719 and 160 508 individuals in the screening and control arms respectively (*Fig. 1*). The screening participation rate (individuals who returned the FOBT) was 69·2 per cent (men, 61·9 per cent; women, 76·3 per cent), and the proportion of positive FOBT results was 2·7 per cent in women and 4·7 per cent in men. The compliance rate for further colonoscopy was 84·6 per cent (proportion of people with a positive FOBT who actually underwent colonoscopy).

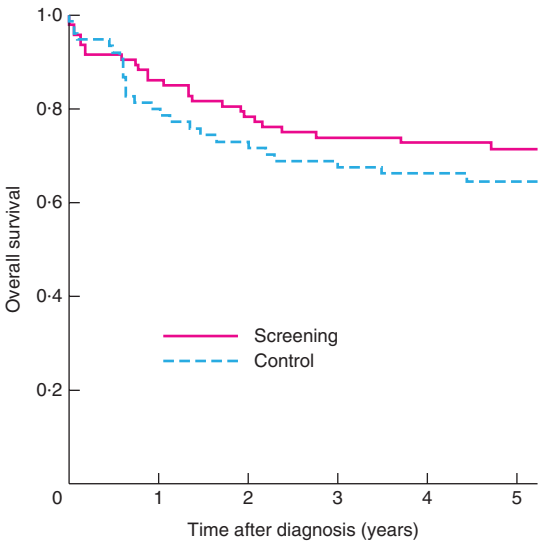
A total of 743 and 617 CRCs were detected in the screening and control arms respectively between 2004 and the end of 2011. Women were less often diagnosed with CRC than men: prevalence 0·37 *versus* 0·55 per cent respectively in the screening arm and 0·32 *versus* 0·45 per cent in the control arm (RR 0·82, 95 per cent c.i. 0·74 to 0·91; BH+). Women had more mucinous subtype adenocarcinomas than men: 60 (11·0 per cent) *versus* 51 (6·5 per cent) (RR 1·70, 1·19 to 2·43; BH+). Tumours were more often located on the right side in women than in men (RR 1·51, 1·26 to 1·80; BH+). The proportion of right- and left-sided tumours did not differ between the study arms (RR 1·05, 0·88 to 1·25) (*Fig. 2* and *Table 1*).

Symptoms

Almost none of the patients in the control arm were asymptomatic. There were 247 asymptomatic patients (33·6 per cent) in the screening arm and only 20 (3·3 per cent) in the control arm (RR 0·10, 95 per cent c.i. 0·06 to 0·15) (*Table 1*). Women were less often asymptomatic than men (RR 0·76, 0·61 to 0·93; BH+) but, of individual symptoms, only the prevalence of abdominal pain was significantly different between the sexes (RR 1·36, 1·12 to 1·67; BH+). The most common symptom in both study arms was intestinal bleeding (32·4 per cent) followed by a change in bowel habit (29·6 per cent), abdominal pain (21·9 per cent) and anaemia (16·6 per cent).

TNM stage

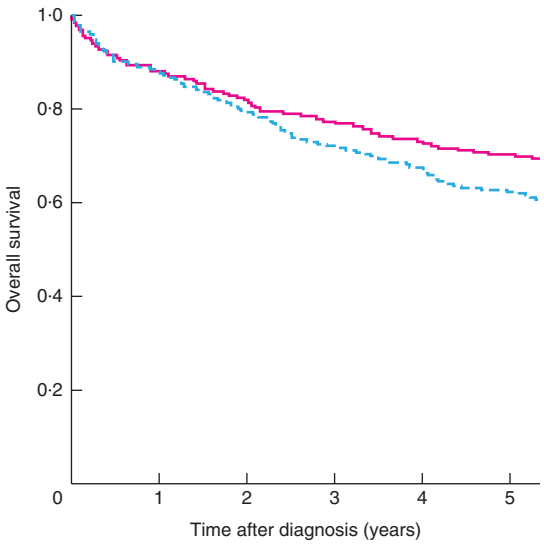
Cancers from the screening arm had a lower T category (RR 1·25, 95 per cent c.i. 1·16 to 1·35), N category (RR 1·14, 1·00 to 1·29) and M category (RR 1·33, 1·08 to 1·62) than those from the control arm (*Table 2*). In subgroup analyses, left-sided tumours in the screening arm had a lower T category (RR 1·30, 1·18 to 1·43), N category (RR 1·16, 1·00 to 1·35) and M category (RR 1·53, 1·19 to 1·97) than those in the control arm, whereas right-sided tumours had only a lower T category (RR 1·14, 1·02 to 1·28), but not N or M category in the screening arm. In women, the only differences between study arms were in the T and M categories of left-sided tumours. However, men with



No. at risk

Screening	95	78	71	65	63	46
Control	76	58	53	50	46	29

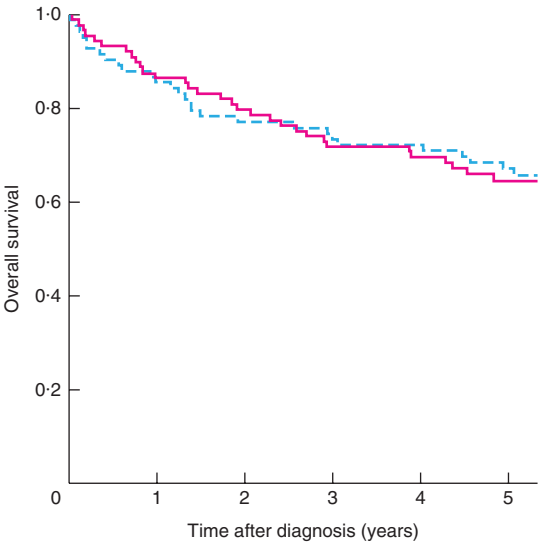
a Men, right-sided tumours



No. at risk

Screening	345	302	279	264	249	191
Control	285	248	225	204	188	129

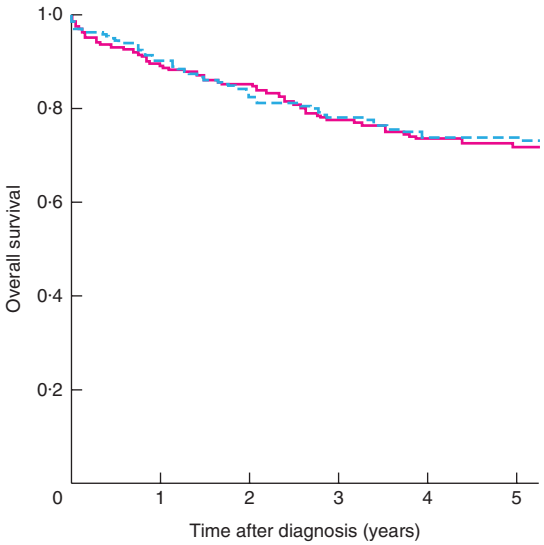
b Men, left-sided tumours



No. at risk

Screening	92	80	73	67	65	45
Control	86	74	67	63	62	47

c Women, right-sided tumours



No. at risk

Screening	208	188	179	163	155	112
Control	167	152	140	132	125	94

d Women, left-sided tumours

Fig. 4 Overall survival after diagnosis of colorectal cancer in the screening and control groups: **a** men with right-sided tumours, **b** men with left-sided tumours, **c** women with right-sided tumours and **d** women with left-sided tumours analysis (follow-up data missing for 1 patient)

left-sided tumours had higher T, N and M categories in the control arm, whereas men with right-sided tumours had only a higher T category in control arm.

Non-vital outcomes

Patients with CRC in the control arm experienced significantly more non-radical surgery (26·8 *versus* 19·2 per cent; RR 1·39, 95 per cent c.i. 1·14 to 1·70; BH+), emergency surgery (14·1 *versus* 9·3 per cent; RR 1·51, 1·11 to 2·06; BH+) and administration of postoperative chemotherapy (62·8 *versus* 52·1 per cent; RR 1·20, 1·09 to 1·32; BH+) than those in the screening arm (*Fig. 3*). Controls also had more stomas, but this was not significant according to the Benjamini–Hochberg criterion (32·8 *versus* 27·3 per cent; RR 1·21, 1·02 to 1·43). After adjustment for T category (T0–2 *versus* T3–4), no significant differences were found in the rates of non-radical surgery (RR 1·13, 0·91 to 1·41), emergency surgery (RR 1·17, 0·85 to 1·61), postoperative chemotherapy (RR 0·99, 0·92 to 1·08) or stomas (RR 1·17, 0·98 to 1·39). In separate analyses of men and women, a statistically significant improvement in these non-vital outcomes was observed only in men.

Further subgroup analyses of left- and right-sided tumours indicated that the findings were restricted mainly to left-sided cancers. An exception was observed in men with right-sided tumours, who had emergency surgery significantly more often in the control arm compared with the screening arm (33 *versus* 15 per cent; RR 2·15, 1·20 to 4·07; BH+). Significantly more men with left-sided tumours in the control group than the screening group underwent non-radical surgery (26·2 *versus* 15·7 per cent; RR 1·67, 1·22 to 2·30; BH+) and postoperative chemotherapy (61·6 *versus* 48·2 per cent; RR 1·28, 1·10 to 1·48; BH+), and the stoma rate was increased but not significantly according to the Benjamini–Hochberg criterion (45·4 *versus* 36·1 per cent; RR 1·26, 1·04 to 1·53).

Survival

Survival was worse in controls than in the screening arm in men with CRC (hazard ratio (HR) 1·31, 95 per cent c.i. 1·05 to 1·64), but not in women (HR 1·07, 0·80 to 1·45). Among men, the 5-year overall survival (OS) rates were 68·8 *versus* 61·5 per cent in the screening *versus* control arms respectively, compared with 70·7 *versus* 71·5 per cent in women. Among men with left-sided tumours, survival was better in the screening arm than the control arm (HR 1·37, 1·06 to 1·77), but not in men with right-sided tumours (HR 1·19, 0·75 to 1·89) (*Fig. 4a,b*). Five-year OS rates in men with left-sided tumours were 70·0 per cent in the screening arm *versus* 62·1 per cent in the control arm; respective rates in men with right-sided tumours were 65 *versus* 59 per cent. In women, survival was similar in the screening and control arms regardless of whether the tumour was located on the right side (5-year OS rate 66 *versus* 67 per cent respectively; HR 1·19, 0·73 to 1·92) or left side (72·8 *versus* 74·9 per cent; HR 0·96, 0·65 to 1·41) (*Fig. 4c,d*). Interestingly, the 5-year OS rate in women both in the screening and control arms was similar to that of men in the screening arm (70·7, 71·5 and 68·8 per cent respectively).

Discussion

These data on biennial FOBT screening are based on the largest population-based randomized health services study, covering over 40 per cent of 60–69-year-old people living in Finland. The analysis revealed several important findings. There were substantial sex differences in laterality, histology and symptoms. Improvements in non-vital outcomes were observed in the screening group, but primarily in men with left-sided CRC. Additional analyses showed that men with left-sided tumours gained benefits from the screening in terms of lower TNM stage and better survival.

There are several possible explanations for the observed discrepancy according to sex. Colorectal tumours in women were more often located on the right side of the colon, as has been reported previously[18–20]. Longer passage of faecal blood may lower the sensitivity of the test and produce a false-negative result; this is supported by the fact that, although screening uptake was higher in women (76·3 *versus* 61·9 per cent), positive results were less frequent than in men (2·7 *versus* 4·7 per cent). The finding that FOBT screening seemed ineffective in women could be related to the fact that women had more right-sided tumours and that screening with FOBT can be ineffective in detecting early right-sided colonic cancers in either sex. In addition, more women in the screening arm were symptomatic (abdominal pain), indicating that they might be more sensitive to the symptoms of CRC. Men who may not experience symptoms or who ignore them might benefit more from screening. It is interesting to note that even the higher participation rates in women did not translate into beneficial outcomes, further supporting the notion that FOBT screening is ineffective in women. It was also found that screening benefits men with left-sided CRC across all TNM categories, but among women with left-sided tumours only the T and M categories were lower in the screening group *versus* controls. This could indicate a difference in the biology of tumour dissemination between men and women. The improvements in survival and non-vital outcomes in men with left-sided tumours are

most likely due to lower TNM stage in this subgroup. This is supported by the finding that the observed differences disappeared when outcomes were adjusted for T category. Fewer CRCs were detected in women in both study arms, which may be attributed to the fact that the incidence increases with age[21] and this increase has been reported to occur later in women[22]. Although the set age range for screening (60–69 years) appears to be sufficient for substantial improvements for men, women might benefit from screening at an older age.

The strength of this study is its findings regarding parameters that were not investigated in earlier FOBT screening trials[4–7]. In addition to survival benefits, it is important to know the influence of screening on other important measures, such as stomas, which are associated with reduced quality of life[23] and commonly cause complications (21–70 per cent)[24]. These were reduced in the screening arm in men, although the reduction was not statistically significant according to the Benjamini–Hochberg criterion. From the point of view of healthcare expenditure, it is also crucial to determine the proportion of emergency surgery and the need for postoperative chemotherapy, as both increase costs and potentially influence patients' quality of life. Non-radical and emergency surgery was rarer in the screening arm than in the control arm among men. Another retrospective study[25] comparing two cohorts from different eras found a similar reduction in emergency surgery in patients undergoing CRC screening. In addition to increased costs, emergency resections have a negative impact on survival compared with elective resections[26,27].

The largest randomized FOBT trials were half the size of the present randomized health services study on CRC screening (Nottingham trial, 152 850 individuals; Göteborg trial, 68 308; Funen trial, 61 933; Minnesota trial, 46 551)[4–7]. A meta-analysis[8] that included the latest data from these trials estimated the reduction in CRC-specific mortality to be 18 per cent, but no reduction in overall mortality was found in an intention-to-treat analysis. The Nottingham trial[15] reported CRC mortality ratios for men and women separately and, in contrast to the present authors' previous finding[12], there was no difference between men and women (RR for screening *versus* control arm 0·90 in women and 0·91 in men). However, the Minnesota trial[13] reported that the reduction in CRC mortality was larger for men than for women.

Tumour location appeared to be the most likely explanation for the sex disparity observed in the present study. Only men with left-sided tumours had improved survival and lower TNM categories in the screening arm compared with the control arm. The Nottingham trial[15] reported similar RRs for screened *versus* control populations for CRC mortality in the proximal (to the sigmoid colon) and distal colorectum (RR 0·93 and 0·89 respectively), but both sexes were analysed together. The Funen trial[28] revealed that FOBT screening tended to reduce mortality rates among patients with proximal compared with distal tumours, but the difference was not significant ($P = 0{\cdot}13$). Although most CRCs are left-sided, the present results suggest that FOBT is ineffective for screening right-sided tumours.

In addition to the guaiac FOBT used here and in other trials, the faecal immunochemical test (FIT) has also been used for CRC screening. FIT has a high specificity, but randomized screening trials of its effectiveness are lacking[29]. Therefore, it is not yet possible to compare fully the effectiveness of FOBT and FIT as a screening method. Flexible sigmoidoscopy has been shown to reduce CRC mortality by 21 per cent, on average, in randomized screening trials[9]. Colonoscopy is recommended if polyps are discovered during sigmoidoscopy in such trials. Thus, patients with positive sigmoidoscopy findings will require a second bowel preparation and two appointments, compared with one for patients with a positive FOBT. In theory, the screening method that should improve the outcomes of patients with right-sided CRC is colonoscopy; however, this procedure is invasive, more expensive, requires more healthcare resources and might attract fewer participants than FOBT. CT colonography might be more favourable in this regard, but has other specific disadvantages (such as radiation exposure), and its efficacy as a screening method has not yet been investigated[30]. Although randomized trials of colonoscopy for screening are ongoing, no results have been published to date. As the results of the Finnish randomized programme using FOBT as the primary test did not find a difference between arms in CRC-specific or overall mortality[12], CRC screening was stopped in Finland in 2014. Currently, implementation of more individualized screening programmes is under consideration.

This study has several limitations. Some of the screen-detected cancers may have been overdiagnosed, although it is likely that the proportion of overdiagnoses is low. In the Minnesota trial[31], only 6–9 per cent of screen-detected cases were estimated to be overdiagnoses. In the Nottingham trial[32], little evidence was found in support of an overdiagnosis bias. The present data suggest that roughly 30 per cent of cancers were screen-detected in the screening arm (difference between proportions of asymptomatic cases in the study arms, $33{\cdot}6 - 3{\cdot}3 = 30{\cdot}3$ per cent). Even if 10 per cent of screen-detected cases were overdiagnosed, this would still represent only 3 per cent of all cases in the screening arm. Therefore, any bias from overdiagnosis is likely to be small. Furthermore, estimates

for sex differences were adjusted for study arm, which further reduces such bias.

Survival analyses are also affected by lead time bias, the magnitude of which remains unclear. However, as survival did not improve significantly in women, even with bias owing to overdiagnosis and lead time, it is even clearer that FOBT screening is not beneficial in women. Furthermore, the present study was a retrospective cross-sectional analysis of patients diagnosed with CRC within the population based on a randomized health services study, where the diagnostic and treatment strategies in different hospitals were not standardized. On the other hand, the study design was pragmatic, and is thus more likely to represent real-life clinical care scenarios.

Even though over 320 000 people were randomized and more than 1300 patients with CRC were analysed, subgroup analyses might have suffered from lack of statistical power. Many of the effects in women were in the same direction as those in men, but remained statistically non-significant. Should there be any significant effect if larger groups were analysed, the clinical relevance would still be minor. This is also reflected in the survival curves, which are identical in the screening and control arms in women. Survival improvements occurring contemporaneously with adoption of the Finnish screening programme in the municipality were observed in patients with CRC not invited for screening[33]. Such an improvement in the control population would be likely to also translate to improvements in controls in non-vital outcomes and cancer stage. Therefore, the control *versus* screening comparisons reported here probably understate the effect of the screening programme on such outcomes.

This investigation of patients with CRC, based on a large population-based randomized health services study, found biennial guaiac FOBT screening to be associated with lower proportions of non-radical surgery, emergency surgery and postoperative chemotherapy, as well as improved TNM categories and OS, in men. Improvements were observed mainly in patients with left-sided tumours. FOBT screening did not appear to be associated with lower TNM categories or survival among 60–69-year-old women with CRC. Therefore, screening by different methods or at different intervals or ages should be considered among women. The sex discrepancy in outcomes may be due to factors related to the incidence, symptoms and location of colorectal tumours.

Acknowledgements

This study was supported financially by Vatsatautien Tutkimussäätiö, Helsinki University Hospital research funds, Mary and Georg Ehrnrooth's Foundation, and Cancer Foundation Finland.

Disclosure: The authors declare no conflict of interest.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359–E386.

2 Alexiusdottir KK, Möller PH, Snaebjornsson P, Jonasson L, Olafsdottir EJ, Björnsson ES *et al.* Association of symptoms of colon cancer patients with tumor location and TNM tumor stage. *Scand J Gastroenterol* 2012; **47**: 795–801.

3 Inadomi JM. Screening for colorectal neoplasia. *N Engl J Med* 2017; **376**: 149–156.

4 Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW *et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472–1477.

5 Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; **348**: 1467–1471.

6 Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008; **95**: 1029–1036.

7 Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365–1371.

8 Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P. Screening for colorectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer* 2016; **15**: 298–313.

9 Holme Ø, Schoen RE, Senore C, Segnan N, Hoff G, Løberg M *et al.* Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. *BMJ* 2017; **356**: i6673.

10 Holme Ø, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G. Flexible sigmoidoscopy *versus* faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev* 2013: (9)CD009259.

11 Malila N, Anttila A, Hakama M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. *J Med Screen* 2005; **12**: 28–32.

12 Pitkäniemi J, Seppä K, Hakama M, Malminiemi O, Palva T, Vuoristo MS *et al.* Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. *BMJ Open Gastroenterol* 2015; **2**: e000034.

13 Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS *et al.* Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013; **369**: 1106–1114.

14 McClements PL, Madurasinghe V, Thomson CS, Fraser CG, Carey FA, Steele RJ *et al.* Impact of the UK colorectal

cancer screening pilot studies on incidence, stage distribution and mortality trends. *Cancer Epidemiol* 2012; **36**: e232–e242.
15 Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012; **61**: 1036–1040.
16 Leinonen MK, Miettinen J, Heikkinen S, Pitkäniemi J, Malila N. Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours. *Eur J Cancer* 2017; **77**: 31–39.
17 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). *AJCC Cancer Staging Manual* (7th edn). Springer: New York, 2010.
18 McCashland TM, Brand R, Lyden E, de Garmo P; CORI Research Project. Gender differences in colorectal polyps and tumors. *Am J Gastroenterol* 2001; **96**: 882–886.
19 Forsberg AM, Kjellström L, Agréus L, Nixon Andreasson A, Nyhlin H, Talley NJ *et al.* Prevalence of colonic neoplasia and advanced lesions in the normal population: a prospective population-based colonoscopy study. *Scand J Gastroenterol* 2012; **47**: 184–190.
20 Gaitonde SG, Nissan A, Protić M, Stojadinovic A, Wainberg ZA, Chen DC *et al.* Sex-specific differences in colon cancer when quality measures are adhered to: results from international, prospective, multicenter clinical trials. *J Am Coll Surg* 2017; **225**: 85–92.
21 Brændegaard Winther S, Baatrup G, Pfeiffer P, Qvortrup C. Academy of Geriatric Cancer Research (AgeCare). Trends in colorectal cancer in the elderly in Denmark, 1980–2012. *Acta Oncol* 2016; **55**(Suppl 1): 29–39.
22 Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. *Br J Cancer* 2007; **96**: 828–831.
23 Vonk-Klaassen SM, de Vocht HM, den Ouden ME, Eddes EH, Schuurmans MJ. Ostomy-related problems and their impact on quality of life of colorectal cancer ostomates: a systematic review. *Qual Life Res* 2016; **25**: 125–133.
24 Shabbir J, Britton DC. Stoma complications: a literature overview. *Colorectal Dis* 2010; **12**: 958–964.
25 Askari A, Nachiappan S, Currie A, Bottle A, Abercrombie J, Athanasiou T *et al.* Who requires emergency surgery for colorectal cancer and can national screening programmes reduce this need? *Int J Surg* 2017; **42**: 60–68.
26 Bass G, Fleming C, Conneely J, Martin Z, Mealy K. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. *Dis Colon Rectum* 2009; **52**: 678–684.
27 McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. *Br J Surg* 2004; **91**: 605–609.
28 Kronborg O, Jørgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol* 2004; **39**: 846–851.
29 Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014; **160**: 171.
30 Lieberman D, Ladabaum U, Cruz-Correa M, Ginsburg C, Inadomi JM, Kim LS *et al.* Screening for colorectal cancer and evolving issues for physicians and patients: a review. *JAMA* 2016; **316**: 2135–2145.
31 Luo D, Cambon AC, Wu D. Evaluating the long-term effect of FOBT in colorectal cancer screening. *Cancer Epidemiol* 2012; **36**: e54–e60.
32 Robinson MH, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NC *et al.* The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. *Gut* 1999; **45**: 588–592.
33 Miettinen J, Malila N, Hakama M, Pitkäniemi J. Spillover improved survival in non-invited patients of the colorectal cancer screening programme. *J Med Screen* 2018; **25**: 134–140.