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Effectiveness of Colorectal Cancer Screening in Detecting Earlier-Stage Disease—A Nationwide Cohort Study in Denmark

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BACKGROUND & AIMS: Most studies of the effectiveness of screening for colorectal cancer (CRC) using the fecal occult blood test tested the guaiac fecal occult blood test. However, the fecal immunochemical test (FIT) is now commonly used in screening. We aimed to evaluate the effectiveness of FIT-based screening for CRC on the number of incident CRC diagnoses and stage at diagnosis for individuals in Denmark who were invited for screening vs not yet invited. **METHODS:** We collected data for this register-based retrospective cohort study during the first 16 months of the prevalence round of a FIT-based CRC screening program (March 1, 2014 through June 30, 2015). A total of 402,826 residents of Denmark (50–72 years old) were randomly invited to undergo CRC screening within the study period, and 956,514 were invited thereafter. We obtained information on CRC diagnosis, date, and stage at diagnosis from the Danish Colorectal Cancer Group database. Cancer incidence per 100,000 invited/not yet invited individuals was calculated, along with the relative risk (RR) of CRC among invited compared with not yet invited individuals. **RESULTS:** CRC incidence during the study period was 339.4/100,000 invited individuals and 169.6/100,000 not yet invited individuals. CRC incidence increased with age among invited and not yet invited individuals. For invited women compared with not yet invited women, the RR of being diagnosed with stage I CRC was 3.39 (95% CI, 2.61–4.39), with stage II CRC was 2.16 (95% CI, 1.71–2.72), with stage III CRC was 1.37 (95% CI, 1.08–1.75), and with stage IV CRC was 0.92 (95% CI, 0.68–1.23). For invited men compared with not yet invited men, the RR of being diagnosed with stage I CRC was 3.71 (95% CI, 2.97–4.64); with stage II CRC was 2.26 (95% CI, 1.84–2.77), with stage III CRC was 1.88 (95% CI, 1.53–2.30), and with stage IV CRC was 1.20 (95% CI, 0.95–1.52). **CONCLUSIONS:** In analyzing data from a register-based cohort study in Denmark, we found that inviting individuals to undergo FIT-based CRC screening led to detection of almost 2-fold more cases of CRC than not inviting participants. The significant increase of CRC incidence among those invited for screening indicates a need for awareness of treatment capacity in countries introducing FIT-based CRC screening.

Keywords: Colon Cancer Mass Screening; Early Detection; Fecal; Neoplasms.

Colorectal cancer (CRC) represents a substantial portion of the overall burden of cancer in Europe. It is the third most common cancer among men and the second most common cancer among women, and IT represents 20% of all cancer-related deaths.[1] Survival is strongly associated with stage of disease at time of diagnosis. Five-year stage-specific survival rates range from greater than 90% for patients diagnosed with localized CRC to less than 15% for patients diagnosed with distant organ metastasis.[2,3] Because CRC symptoms are often diffuse with low positive predictive values, early-stage diagnosis is rare in symptomatic patients.[4]

CRC screening has been widely accepted as a public health policy in the European Union since its recommendation by the European Council in 2003. Of the 28 member states, 12 had population-based CRC screening programs in 2007.[5] In 2015, 20 states had either ongoing or complete rollout of programs, and another 3 member states were planning to start population-based programs.[6]

European Guidelines for quality assurance in CRC screening and diagnosis recommend the noninvasive fecal occult blood test (FOBT) as the primary screening method.[7] Biennial screening for CRC using guaiac FOBT has shown a 15% relative risk (RR) reduction in CRC mortality in general and a 25% RR reduction among those who participate at least once.[8] More recently, the fecal immunochemical test (FIT) has come into use, because studies have found it to be superior to guaiac FOBT with respect to detection rate, positive predictive value, and participation rate.[9–14] However, the effectiveness of FIT-based CRC screening on cancer incidence and stage of disease at time of diagnosis is not well documented.

The aim of this study was to evaluate the effectiveness of FIT-based prevalence CRC screening. We did so by comparing the number of incident CRC diagnoses and stage of disease at time of diagnosis in randomly selected individuals invited to participate in CRC screening compared with individuals not yet invited to screening.

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test; ICD, *International Classification of Diseases*; RR, relative risk.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The fecal immunochemical test (FIT) has proven superior to guaiac fecal occult blood test with respect to detection rate. However, the effect of FIT-based CRC screening on cancer incidence and stage of disease at time of diagnosis is not well documented.

NEW FINDINGS

Introducing FIT-based CRC screening doubles the incidence of CRC and more than triples the incidence of stage I CRC.

LIMITATIONS

Generalizability to other settings requires similar background CRC prevalence and participation rates are similar.

IMPACT

Cancer screening programs improve early detection and require careful planning, to not only deliver screening, but also to provide appropriate follow-up for positive tests and care for cancers found.

Methods

Setting

The Danish CRC screening program was introduced nationally in January 2014, with the first invitations sent in March 2014. The program includes all individuals aged 50–74 years and is free of charge. Invitations are mailed directly to the individuals along with the screening kit (OC Sensor System; Eiken Chemical Company, Tokyo, Japan), instructions on how to collect the fecal sample and a preaddressed, prepaid return envelope. No dietary restrictions before testing are needed, and only 1 sample is necessary. The sample is sealed and returned by ordinary mail to the laboratory.[15] If a sample is not returned within 45 days, 1 reminder is sent. Test results are sent to the individuals within 7 days after the sample is received at the laboratory. In the case of a positive result (>100 ng hemoglobin/mL buffer), the individual receives an appointment to have a colonoscopy within 14 days in a local colonoscopy department. If the individual does not attend the colonoscopy, 2 reminders are sent, followed by 1 telephone call.[16]

Participation rate within 3 months after invitation was 64% for the first 10 months of the screening program, and the positivity rate was 6.8%. A total of 88% attended diagnostic colonoscopy within 2 months after the positive test result.[17] Physicians cannot order FIT outside the screening program. However, family physicians have the possibility of referring symptomatic patients directly to a colonoscopy. Before introducing the national CRC screening program, no screening of asymptomatic individuals was conducted.

All individuals in the age group are invited to participate, but it is specified in the invitation letter that those who are already participating in a surveillance program after having received a CRC or adenoma diagnosis should not participate in the screening program. Those with ulcerative colitis or Crohn's disease should discuss with their physician whether participation would be relevant for them.

The national program is being phased in over a 4-year period (prevalence round). During this period, all individuals in the target population are invited once before the end of 2017. After this, the target population will receive biennial invitations. During the prevalence round, individuals aged 50–74 years on January 1, 2014 are invited randomly according to their month of birth. A computer-generated randomization list of the birth months was created May 3, 2013 using Stata 11.2 (Stata Corp., College Station, TX). The pace at which invitations were generated was increased during the prevalence round as the organization gained colonoscopy capacity. Thus, approximately one third of participants were invited within the first 2 calendar years, and approximately two thirds were invited during the last 2 years of the prevalence round. Individuals turning 50 years old during the prevalence round were invited just before their birthdays, as were individuals turning 75 years old, if they had not been invited earlier.

Design

The study was designed as a register-based retrospective cohort study of the effectiveness of the CRC screening program with a study period from March 1, 2014 to June 30, 2015.

Study Population

All men and women residing in Denmark and aged 50–72 years on January 1, 2014 (born January 1, 1941 – December 31, 1963) were eligible for inclusion in the study. Those older than 72 years were excluded from this study because they turned 75 years during the study period. If they had been included, this age group would have been overrepresented in the group of invited individuals compared with the not yet invited individuals. Those invited to participate in CRC screening from July 1 through December 31, 2015 were excluded to ensure a minimum of 6 months of follow-up from the invitation. Furthermore, we excluded those who had been diagnosed with CRC, ulcerative colitis, or Crohn's disease before their invitation to participate in screening (Figure 1).

To make sure that exclusion criteria were the same among invited and not yet invited individuals, the latter were given a pseudo invitation date. The pseudo invitation dates were distributed in the exact same way as the invitation dates of the invited individuals. This was done by first giving all not yet invited individuals a unique random number between 0 and 1. This group was thereafter ranked according to this random number. If x% of the invited group were invited on the first invitation date, the first x% of the not yet invited group were given this date as their pseudo invitation date.

Ethics Approval

According to Danish legislation and the Central Denmark Region Committees on Biomedical Research Ethics, the study did not require ethical approval because it was based on register data. The same institutions waived patient consent for use of register data. In accordance with Danish law, the study was approved by the Danish Data Protection Agency (J. no.: 2012-58-0006/1-16-02-396-16).

Data

The study population was identified using the Danish Central Registration System, which includes information on

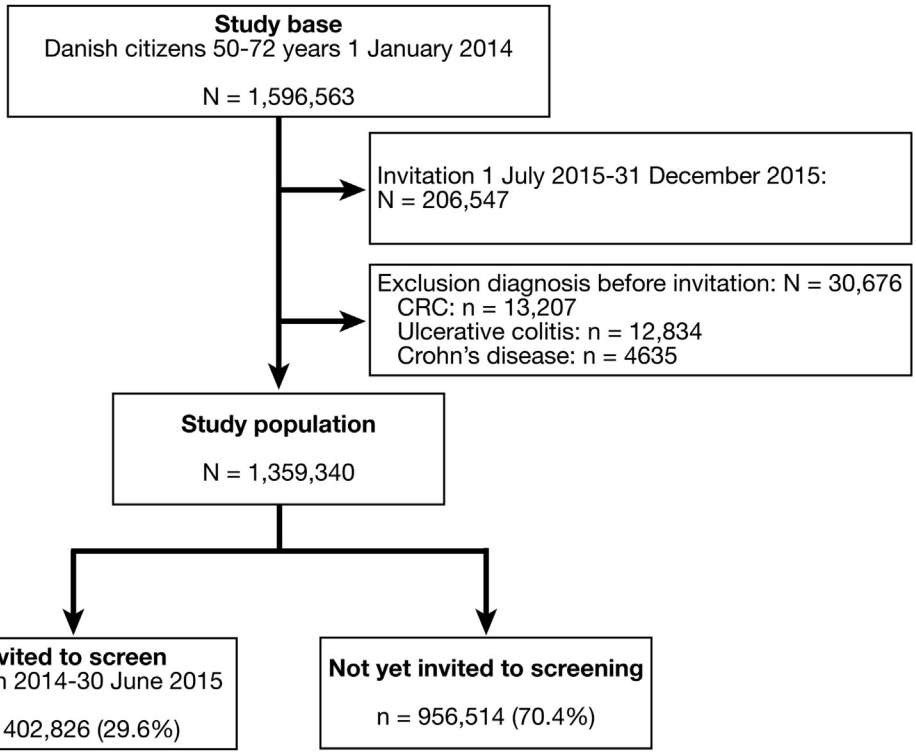

Figure 1. Flow chart of inclusion in the study.

date of birth, sex, and a unique identification number for all individuals residing in Denmark.[18]

Information on CRC diagnosis, date, and stage of disease at time of diagnosis during the study period was retrieved from the Danish Colorectal Cancer Group's (https://DCCG.dk) database. During the study period, stage at time of diagnosis was classified according to the 5th edition of the Union for International Cancer Control's TNM classification[19] using data from both the surgical and pathology proforma (based on the clinical and/or pathologic M category and the pathologic T and N categories).[20] Accordingly, stage at time of diagnosis was defined as stage I (tumor extends no deeper than the muscularis propria [T1 or T2]), stage II (tumor extends through the muscularis propria [T3] or involves the peritoneum and/or neighboring organs/structures T4)], stage III (tumor with metastases to regional lymph nodes), and stage IV (tumor with distant metastases).

To exclude individuals with CRC before invitation, information on CRC diagnoses was retrieved from the Danish National Cancer Register.[21] From 1943–1978, CRC diagnoses were classified according to the *International Classification of Diseases* (ICD) Revision 7 (codes 153 and 154) and the ICD-10 thereafter (codes DC18 and DC20). Data on ulcerative colitis (ICD10 code DK51) or Crohn's disease (ICD10 code DK50) were collected from the Danish National Patient Register, which includes information on diagnosis and date of diagnosis for hospital activities in both public and private hospitals.[22,23]

Information on the date of screening invitation was retrieved from the Danish CRC Screening Database, which monitors the quality of the screening program.[17,24] Those who were a priori randomized to be invited to CRC screening from March 1, 2014 to June 30, 2015 were classified as invited to screening, and those randomized to be invited from January 1, 2016 to December 31, 2017 were classified as not yet invited.

Analyses

The cancer incidence per 100,000 invited/not yet invited individuals in the study period was calculated along with the RR of CRC among invited compared with not yet invited individuals with 95% confidence intervals (CIs). Stage of disease at time of diagnosis was likewise calculated per 100,000 and RR with 95% CI. All results were stratified according to sex and presented for the age groups 50–59 years, 60–64 years, 65–69 years and 70–72 years (50–54 and 55–59 years were pooled because of low cancer incidence in the youngest ages). Age was calculated at date of invitation.

All analyses were conducted using Stata, version 14 (Stata Corp, College Station, TX).

Results

A total of 1,596,563 individuals were eligible for inclusion into the study. Of those, 206,547 were excluded because they were invited to CRC screening between July 1, 2015 and December 31, 2015 (follow-up period). Another 30,676 were excluded because they had been diagnosed with CRC, ulcerative colitis, or Crohn's disease before the date of invitation (pseudo date for the not yet invited). Thus, a total of 1,359,340 individuals were included in the study. Of these, 29.6% were invited, and 70.4% were not invited to participate in CRC screening (Figure 1).

Age distribution was similar in both groups, even though the not yet invited individuals were slightly older than the invited individuals. Stage of disease at time of diagnosis was

Table 1. Characteristics of the Study Population (N = 1,359,340) Specified for Those Invited to Screening and Those Not Yet Invited, n (%)

Characteristics	Invited to screening	Not yet invited to screening
Total	402,826 (29.6)	956,514 (70.4)
Age group in years		
50–59	171,924 (42.7)	403,835 (42.2)
60–64	85,663 (21.3)	204,468 (21.4)
65–69	91,231 (22.7)	215,152 (22.5)
70–72	54,008 (13.4)	133,059 (13.9)
Sex		
Women	203,515 (50.5)	481,223 (50.3)
Men	199,311 (49.5)	475,291 (49.7)
Cancer		
Yes	1,367 (0.34)	1,622 (0.17)
No	401,459 (99.66)	954,892 (99.83)
Stage		
I	335 (24.5)	223 (13.8)
II	314 (23.0)	337 (20.8)
III	266 (19.5)	385 (23.7)
IV	167 (12.2)	367 (22.6)
Unknown	285 (20.9)	310 (19.1)

unknown for 19.9% of the CRC cases; this involved, more specifically, 20.9% of the invited individuals compared with 19.1% of the not yet invited individuals (Table 1).

Cancer Incidence

The overall CRC incidence during the study period was 339.4/100,000 for invited and 169.6/100,000 for not yet invited individuals. For both invited and not yet invited individuals, CRC incidence rose with age, especially for invited men (Figure 2).

The overall RR of being diagnosed with CRC in the study period was 1.81 (95% CI, 1.62–2.03) for invited women compared with not yet invited women. For men, the corresponding overall RR was 2.15 (95% CI, 1.96–2.36) for invited men compared with not yet invited men. For men, the RR rose with age, ranging from 1.84 (95% CI, 1.48–2.30) among 50- to 59-year-olds to 2.66 (95% CI, 2.22–3.18) among 70- to 72-year-olds (Table 2).

Stage of Disease at Time of Diagnosis

For all ages and both sexes, the RR of being diagnosed at any stage compared with not yet invited individuals decreased with increasing stage. Thus, the RR of an invited woman/man being diagnosed at stage I compared with a not yet invited woman/man was 3.39 (95% CI, 2.61–4.39)/3.71 (95% CI, 2.97–4.64); at stage II, it was 2.16 (95% CI, 1.71–2.72)/2.26 (95% CI, 1.84–2.77); at stage III, it was 1.37 (95% CI, 1.08–1.75)/1.88 (95% CI, 1.53–2.30); and at stage IV, it was 0.92 (95% CI, 0.68–1.23)/1.20 (95% CI, 0.95–1.52). The RR of being diagnosed at stage I varied with age for men and women. It reached a maximum at 5.32 (95% CI, 2.76–10.23) for women aged 60–64 years and at 4.50 (95% CI, 2.69–7.54) for the youngest men. There was no statistically significant difference in the RR of being diagnosed at stage IV between invited and not yet invited individuals. For the youngest women/men, the RR of being diagnosed with stage IV CRC was 0.66 (95% CI, 0.34–1.29) for the invited individuals compared with 0.83 (95% CI,

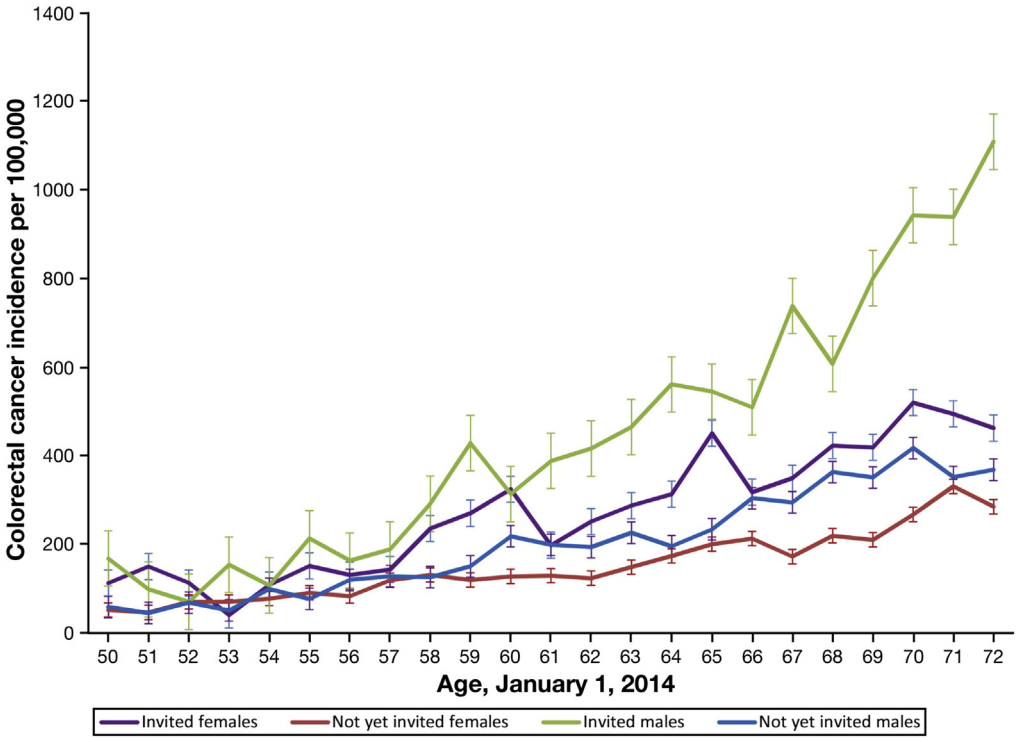

Figure 2. Incidence of colorectal cancer per 100,000 for invited and not yet invited women and men.

Table 2. Incidence per 100,000 and Relative Risk (RR) With 95% Confidence Intervals (95% CI) of Colorectal Cancer and Stage at Time of Diagnosis for Invited vs Not Yet Invited Individuals by Sex and Age Group

	Cancer invited/ not yet invited RR (95% CI)	Stage I invited/ not yet invited RR (95% CI)	Stage II invited/ not yet invited RR (95% CI)	Stage III invited/ not yet invited RR (95% CI)	Stage IV invited/ not yet invited RR (95% CI)
Women					
Total	264.8/146.3	68.3/20.2	67.3/31.2	51.1/37.2	29.5/32.2
	1.81 (1.62–2.03)	3.39 (2.61–4.39)	2.16 (1.71–2.72)	1.37 (1.08–1.75)	0.92 (0.68–1.23)
50–59 y	134.2/84.3	38.5/9.0	29.2/17.0	29.2/22.4	12.8/19.4
	1.59 (1.26–2.02)	4.29 (2.42–7.62)	1.72 (1.03–2.88)	1.30 (0.80–2.12)	0.66 (0.34–1.29)
60–64 y	270.9/134.0	67.2/12.6	76.4/23.3	34.7/36.9	37.0/37.9
	2.02 (1.58–2.59)	5.32 (2.76–10.23)	3.28 (1.94–5.54)	0.94 (0.52–1.71)	0.98 (0.55–1.75)
65–69 y	387.1/198.2	101.2/33.0	101.2/37.6	71.1/50.5	40.9/40.4
	1.95 (1.60–2.37)	3.07 (1.99–4.73)	2.69 (1.77–4.09)	1.41 (0.92–2.17)	1.01 (0.59–1.74)
70–72 y	453.9/263.4	106.4/43.7	113.5/74.2	109.9/59.7	49.6/48.0
	1.72 (1.37–2.16)	2.44 (1.47–4.04)	1.53 (0.98–2.34)	1.84 (1.16–2.94)	1.03 (0.55–1.93)
Men					
Total	415.1/193.5	98.3/26.5	88.8/39.3	81.3/43.3	53.7/44.6
	2.15 (1.96–2.36)	3.71 (2.97–4.64)	2.26 (1.84–2.77)	1.88 (1.53–2.30)	1.20 (0.95–1.52)
50–59 y	162.4/88.1	48.7/10.8	26.7/14.8	33.6/21.6	15.1/18.2
	1.84 (1.48–2.30)	4.50 (2.69–7.54)	1.81 (1.05–3.11)	1.55 (0.97–2.48)	0.83 (0.44–1.56)
60–64 y	400.2/201.0	80.0/29.6	77.7/37.5	73.0/42.4	54.1/53.2
	1.99 (1.63–2.44)	2.71 (1.66–4.42)	2.08 (1.30–3.31)	1.72 (1.09–2.73)	1.02 (0.62–1.66)
65–69 y	615.3/288.3	131.7/33.0	142.8/68.8	125.0/68.8	83.0/63.1
	2.12 (1.8–2.50)	3.99 (2.63–6.07)	2.08 (1.49–2.90)	1.82 (1.28–2.57)	1.31 (0.88–1.95)
70–72 y	945.6/357.1	236.4/60.6	220.9/71.5	178.3/71.5	131.8/83.9
	2.66 (2.22–3.18)	3.90 (2.61–5.83)	3.09 (2.10–4.56)	2.49 (1.66–3.75)	1.57 (1.02–2.41)

0.44–1.56) for the not yet invited individuals. For men, we observed a tendency toward higher RR of being diagnosed with stage IV CRC with increasing age. Their RR peaked at 1.57 (95% CI, 1.02–2.41) at age 70–72 years (Table 2).

Discussion

Main Findings

In this nationwide cohort study based on data from highly valid registers, the effectiveness of the prevalence round of a FIT-based CRC screening program was evident in both the number of incident CRC diagnoses and the recorded stage of disease at time of diagnosis. The CRC incidence was almost doubled in invited compared with the not yet invited individuals and more than tripled for those diagnosed with stage I CRC. The RR of being diagnosed with stage I CRC for invited compared with the not yet invited individuals was highest for the youngest age groups.

Strengths and Limitations

A major strength of the present study was the randomized invitation procedure in the prevalence round of the national CRC screening program. To our knowledge, this is the only study in which the effect of FIT-based CRC screening has been evaluated in a randomized design. Nevertheless, we observed differences between the invited and the not yet invited group. Invited individuals were slightly younger than the not yet invited individuals (50–59 years, 42.7% vs 42.2%; 70–72 years, 13.4% vs 13.9%). By chance, the birth months January and February were both randomized to the last part of the prevalence round. This explains the age difference between invited and not yet invited individuals. The randomized design should eliminate differences between invited and not yet invited individuals with respect to other potential confounders such as socioeconomic status and comorbidity. However, the data did not allow us to analyze for potential differences.

Designing the study as an effectiveness study eliminates the risk of healthy screened bias because we measure the effect of being invited, not the effect of participating, which may be influenced by the healthy screenee's individual characteristics.

The register-based approach can potentially reduce information and selection bias. Information on date of invitation was derived from the Danish CRC Screening Database, which is used in the daily administration of the screening program. Information about invitation date is very valid and is applied with the exact same distribution when providing not yet invited individuals with a pseudo date. Likewise, information on cancer diagnosis and stage of disease at time of diagnosis was retrieved from the Danish Colorectal Cancer Group's database, which has very valid information, with more than 95% completeness in including patients with colorectal cancer.[20] Still, there is a risk of information bias due to the high number of missing data on stage at time of diagnosis. If any of the TNM categories are missing, it is not possible to classify the Union for International Cancer Control stage. If a patient is registered with metastases (M1), stage is always classified as stage IV.

However, when no metastases are registered and the T or N category is missing, staging is not possible. According to the Danish Colorectal Cancer Group's database, 22% of patients diagnosed with CRC in 2016 had missing stage because of no information on metastases (1.5%), only local resection of the tumor (7.2%), no resection (8.0%), or neo-adjuvant treatment (5.3%). Among those participating in screening, 0.8% had missing stage because of no information on metastases, 13.5% had only local resection, 6.5% had no resection, and 3.3% had neo-adjuvant treatment. Thus, there may be a more favorable stage distribution among those invited to screening than among those not invited, causing the results of this study to be conservative estimates of the effectiveness of CRC screening.[25] Finally, a comprehensive national campaign was launched to increase awareness of CRC symptoms and the importance of consulting a general practitioner in case of symptoms. This campaign was launched alongside the introduction of the national CRC screening program. This may have spurred some individuals to consult their general practitioner earlier than they would have without the campaign; and even though both invited and the not yet invited individuals were prompted, the effect may have been more pronounced among the not yet invited individuals because they were not given the opportunity to participate in screening. Hence, our estimates of the RR are minimum estimates.

The results of this study could be generalized to other settings that introduce a FIT-based CRC program if background CRC prevalence and participation rates are similar. However, attention must be paid to the applied FIT brand because there may be differences in performance among brands.[26]

Interpretation and Other Studies

The aim of CRC screening is 2-fold: to reduce the incidence of CRC by detecting and removing adenomas and to reduce mortality by detecting CRC at an early stage. Progression from adenomas to CRC is a multistep process with a natural history of at least 10 years.[27,28] Hence, the effect of removing adenomas will not be prominent within the first many years of a CRC screening program. In line with this, introducing the FIT-based CRC screening program increases the incidence of CRC. The CRC incidence increases with age, more for men than for women.[29] This partly explains the greater increase in CRC incidence among elderly men than among women. The greater incidence among invited men than among not yet invited men could further be explained by the fact that men in general consult their physicians less frequently than women.[30]

Studies of the effectiveness of FIT-based CRC screening programs are sparse. However, our findings of a more favorable stage distribution among those invited to participate in screening are in line with other studies of the effect of guaiac FOBT.[31–33] Furthermore, 1 relatively small study of the effect of the first round of a FIT-based screening program was found.[34] This study showed an even more favorable stage distribution among screening-detected CRC cases than our study (stage I, 54.7% screening-detected cases compared with 24.5% in our study and 10.0% symptomatically detected cases compared with 13.8% in our study; stage VI, 4.2% screening-detected cases compared with 12.2% in our study and 21.0% symptomatically detected cases compared with 22.6% in our study). As in our study, this study also based staging on surgical and pathologic information. Despite the fact that there might be small differences in coding practices among countries, and although this study had a slightly younger study population and we may have underestimated the number of stage I cases, especially among uninvited individuals, we believe that the lower rates in our study were most likely due to our study being an effectiveness study. We did not distinguish between CRCs diagnosed after a positive FIT but measured an overall effect in the group of invited individuals also containing symptomatically detected cases. Thus, our study provides a more realistic measure of the stage distribution in a prevalent screening population because it takes nonparticipation into consideration.

If screening works as intended and finds cancers earlier, the RR of being diagnosed in stage IV should be lower for invited than for not yet invited individuals. However, because this was the prevalence round of the screening program, cancers that have developed into stage IV before the initial screening cannot be detected at an earlier stage. Because of this and the fact that screening will detect some individuals with stage IV cancer who would have become symptomatic without screening and would have received a diagnosis after our study period ended, the RR of stage IV cancers is not significantly lowered. This affects the results of the present study because of the relatively short period of follow-up for those invited late in the study period. When a screening program is past the prevalence round, the incidence of stage IV cancer should decrease among invited compared with not yet invited individuals.

The tendency to have more frequent diagnoses of lower stages among the youngest individuals was expected because the cancer had fewer years to progress. Furthermore, this tendency may also indicate length time bias due to slower progression of CRC among the youngest individuals, providing a better opportunity to detect cancer in early stages.[35] However, progression rates are similar in both sexes,[35] so the progression rates do not explain the tendency toward differences between the RR of diagnosing stage IV CRC in men and women. Different symptom appraisal and health care–seeking behaviors in men and women may explain the tendency toward lower RR of stage IV cancer among invited women than among not yet invited women and the higher RR of stage IV among invited men than among not yet invited men. It is well known that symptoms of CRC are common even though they yield low positive predictive values.[4] Hence, women with abdominal symptoms consult their physicians more often than men with abdominal sympoms.[36] Furthermore, especially men with low anxiety levels take significantly longer to recognize the seriousness of their symptoms, which delays help seeking.[37] It may be hypothesized that men who hesitate to contact their physicians may participate in CRC screening, which would explain the elevated RR of being diagnosed

with stage IV CRC, peaking at 1.57 for men aged 70–72 years.

The results of this study indicate that the FIT-based CRC screening program detects CRC in earlier stages and thereby secures a better prognosis for the patients. However, there is a lack of evidence of how much overdiagnosis the introduction of a FIT-based CRC screening program entails. "Overdiagnosis" is defined as detection of cancers that would not have been clinically identified in someone's remaining lifetime.[38] Overdiagnosis is not easily assessed, because it is not possible to know at an individual level who would have died of other causes before the CRC became symptomatic.[38,39] However, it is important to follow the development in cancer incidence, stage distribution, and CRC mortality, because FIT performance may change in subsequent rounds of screening.[40] In particular, the risk of stage IV cancers should decrease significantly, because prognosis is worse for those diagnosed as being at stage IV, even though there are different degrees of severity of stage IV.

Conclusion

The findings from this study substantiate the introduction of FIT-based CRC screening to detect CRC in earlier stages and thereby secure better prognosis for the patients. The significant increase in detection of CRC in the prevalence round calls for awareness of treatment capacity in countries introducing FIT-based CRC screening in the future.

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Author contributions
Mette Bach Larsen, Sisse Njor, and Berit Andersen designed the study. Mette Bach Larsen, Sisse Njor, and Peter Ingeholm categorized the data. Mette Bach Larsen analyzed the data, created the tables and figures, and drafted the manuscript. All of the contributors critically reviewed and approved the manuscript.

Conflicts of interest
The authors disclose no conflicts.