Colorectal cancers detected through screening are associated with lower stages and improved survival

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ABSTRACT

INTRODUCTION: Population screening for colorectal cancer (CRC) using faecal occult blood test (FOBT) will be introduced in Denmark in 2014. Prior to the implementation of the screening programme, a feasibility study was performed in 2005-2006. In this paper, occurrences of colorectal cancer in the feasibility study cohort were reviewed with respect to the effect of screening participation on stages and survival.

MATERIAL AND METHODS: All cases of CRC in a feasibility study cohort diagnosed from the beginning of the study until two years after the study ended were identified. Differences in the distribution of colon cancer stages and rectal cancer groups between the various screening categories were analysed through χ^2-tests. Survival analysis with respect to screening groups was done by Kaplan-Meier and Cox-Mantel hazard ratios, and survival was corrected for lead time.

RESULTS: Colon cancers detected through screening were diagnosed at significantly lower stages than among screening non-responders. There were relatively fewer locally advanced rectal cancers among patients diagnosed through positive FOBT than among non-responders. Survival among screening cancer patients was superior to that of all other screening groups. No effect of lead time was detected. Neither stage nor survival among patients who had a negative FOBT was inferior to the unscreened Danish population.

CONCLUSION: The positive effect on survival among screening cancer patients is neither outbalanced by more advanced cancers among FOBT-negative patients than among non-responders nor by risks reported for colonoscopy.

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The objective of population screening for colorectal cancer (CRC) is to reduce CRC mortality through early detection of cancers and removal of adenomatous polyps [1, 2]. In the setup used for the CRC screening programme planned to begin in Denmark in 2014, citizens aged 50-74 years are invited biennially to submit a sample of faeces, which will be analysed for the presence of occult blood (FOBT). A positive FOBT triggers an invitation for a full colonoscopy. The decision to implement this screening programme was partly based on the findings of a feasibility study performed in two Danish counties in 2005-2006 [3]. The purpose of the feasibility study was to gain practical and organisational experience and to test strategies for information, communication and invitation of the target population. This paper reviews the occurrence of colorectal cancer in the feasibility study cohort from the beginning of the study until two years after the study ended. The review is performed to assess the effect of screening participation on stages and survival.

MATERIAL AND METHODS

Study population

A cohort for a CRC screening feasibility study was formed in 2005. The study included 182,152 citizens living in Vejle or Copenhagen counties and born between 1/8-1931 and 1/8-1955. Testing consisted of a FOBT followed by a colonoscopy if the FOBT was positive. Data on screening participation in the two counties and results were retrieved from the screening centre at Vejle Hospital and from the Research Centre for Prevention and Health. The latter has previously analysed data from both counties [3].

Cases of CRC in the cohort diagnosed between 1/8-2005 and 31/12-2008 were identified using the registry of the Danish Colorectal Cancer Group (DCCG) [4]. Histological diagnosis was not available in the dataset for the Copenhagen part of the cohort. CRC cases in the Copenhagen cohort who were not registered by the DCCG among the cases with a positive FOBT with colonoscopic suspicion or uncertainty of cancer were manually retrieved from the national registry of patoanatomical diagnoses.

Data sources and variables

Each patient's screening status was determined by combining data from the two screening centres as well as the registered date of cancer diagnosis. A screening cancer is a cancer in a patient who had a positive FOBT and then received a cancer diagnosis on follow-up colonoscopy. A FOBT-negative cancer is a cancer in a patient who had a negative FOBT, but who was diagnosed with cancer within the above-mentioned period. A non-responder is a patient who had been invited, but declined participation. A late cancer is a cancer in a FOBT-positive patient that was not diagnosed at the colonoscopy trig-

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TABLE 1

Distribution of colon cancer stages within different groups in the cohort. Also shown is the distribution among patients in the same age group registered in the DCCG database. Percentages in late cancer and no colonoscopy groups are not given because of low number of patients.

	DCCG, n (%)	Uninvited, n (%)	Non-responders, n (%)	Screening cancer, n (%)	Negative FOBT, n (%)	Late cancer, n	No colonoscopy, n
Stage 1	525 (11)	8 (8)	21 (8)	49 (42)	16 (12)	4	1
Stage 2	1,458 (32)	34 (32)	82 (32)	28 (24)	47 (34)	1	0
Stage 3	1,271 (28)	24 (23)	73 (29)	32 (27)	30 (22)	3	1
Stage 4	1,180 (26)	37 (36)	74 (29)	9 (8)	42 (31)	1	0
Not staged	82(2)	1 (1)	4 (2)	0	2 (1)	0	0
Total	4,516	104	254	118	137	9	2

DCCG = Danish Colorectal Cancer Group; FOBT = faecal occult blood test.

TABLE 2

Distribution of rectal cancer groups within different groups in the cohort. Also shown is the distribution among all Danish patients in the same age group registered in the DCCG database. Percentages in late cancer and no colonoscopy groups are not given because of low number of patients.

	DCCG, n (%)	Unscreened, n (%)	Non-responders, n (%)	Screening cancers, n (%)	Negative FOBT, n (%)	Late cancer, n	No colonoscopy, n
Localised	1,478 (56)	29 (51)	62 (45)	28 (64)	48 (62)	0	0
Locally advanced	927 (35)	26 (45)	75 (55)	16 (36)	29 (38)	2	1
Unknown	236 (9)	2 (4)	0 (0)	0 (0)	0 (0)	0	0
Total	2,641	57	137	44	77	2	1

DCCG = Danish Colorectal Cancer Group; FOBT = faecal occult blood test.

gered by the test result. The term uninvited is used for those patients within the cohort who were not invited to participate and who were then diagnosed with cancer.

Information on colon cancer stages was determined from the pathology reports in combination with information on distant metastasis from the DCCG database. In stage 1, the cancer is confined within the colon wall. In stage 2, the cancer has infiltrated through the colon wall, but has not spread to lymph nodes. In stage 3, the cancer has spread to regional lymph nodes (regardless if it has infiltrated through the bowel wall or not). In stage 4, the cancer has metastasised to extraregional locations. Stages 1 and 2 combined were considered to be early-stage colon cancer; and stages 3, 4 and not staged combined were considered to be late-stage colon cancers. Rectal cancers were divided into localised and locally advanced based on the indication for neoadjuvant radiochemotherapy. In March 2013, the cohort was linked with the Danish Central Person Registry to determine the vital status of cohort participants. If the person was dead, we retrieved information on the date of death.

Statistics

Differences in the distribution of colon cancer stages and rectal cancer groups between the various screening categories were analysed through χ^2-tests. Survival analysis with respect to screening groups was done by Kaplan-Meier and Cox-Mantel hazard ratios. Entry time was the date of CRC diagnosis and the follow-up ended at the date of death or on 13 March 2013, whichever came first. Testing for lead time bias was done as suggested by Kafadar & Prorok [5], where entry date was the date of study start, i.e. 1 August 2005. The data were analyzed using the statistical computer software NCSS 2007 version 07.1.5.

Trial registration: not relevant.

RESULTS

A total of 942 cases of CRC within the cohort and diagnosed between August 2006 and December 2008 were identified. Of these, 624 were colon cancers and 318 were rectal cancers.

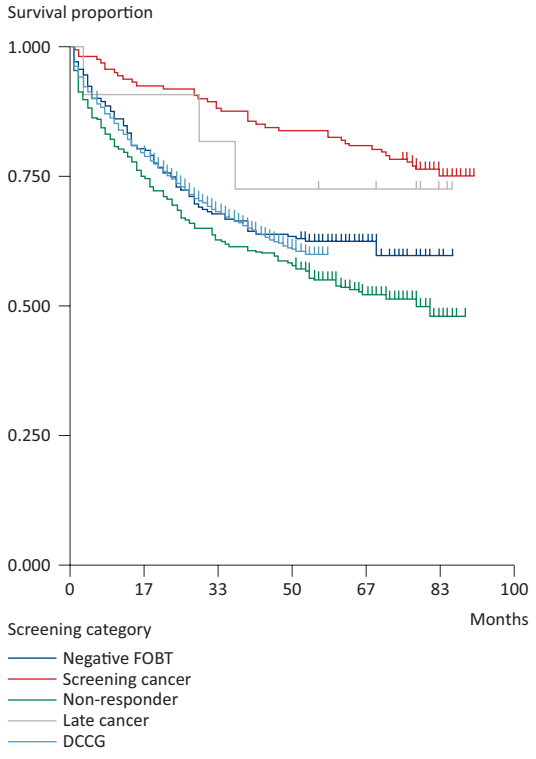
In total, 162 screening cancers (96 males and 66 females; mean age 64.9 years) were diagnosed. On follow-up, 39 were deceased. The number of FOBT-negative cancers was 214 (100 males and 114 females; mean age 66.7 years). On follow-up, 79 of them were diseased. The number of non-responder cancers was 391 (219 males and 172 females; mean age 67.1 years). On follow-up, 183 of them were deceased. The number of cancers diagnosed in people in the cohort who had not received an invitation was 161 (81 males and 80 females; mean age 65.1 years). On follow-up, 88 were deceased. There were 11 late cancers (six males and five females; mean age 62.6 years). Of these, adenomatous polyps were found in six patients and the cancers were detected on a follow-up colonoscopy. The diagnosis was made a median 9.4 months after the positive FOBT test (range 2-28 months). On follow-up, three of them were dead. Among those who had a positive FOBT but declined colonoscopy, three (two males and one female; mean age 68.7 years) were diagnosed with CRC. On follow-up, one was deceased. Among the uninvited, 161 were diagnosed with CRC (80 females and 81 males; mean age 65.1 years). A total of 88 were deceased at follow-up.

Colon cancer stages

The distribution of colon cancer stages is shown in **Table 1**. There was no significant difference in the stage distribution between the uninvited group and the Danish population aged 50-74 years ($\chi^2_{(4)} = 6.16$; $p = 0.19$). CRC in the screening cancer group was diagnosed at significantly lower stages than CRC among non-responders ($\chi^2_{(4)} = 67.99$; $p < 0.01$). The statistical significance was

FIGURE 1

Kaplan-Meier plot showing overall survival among patients in the cohort who had been invited to participate in the study and patients in the same age group registered in the DCCG database. There was no difference in survival between non-responders and uninvited cases. The three patients with positive faecal occult blood test who declined colonoscopy have been omitted from the curve.



DCCG = Danish Colorectal Cancer Group; FOBT = faecal occult blood test.

TABLE 3

Cox-Mantel death hazard ratios.

	Cox-Mantel hazard ratio		Cox-Mantel hazard ratio, corrected for lead time	
	ratio (95% CI)	p-value	ratio (95% CI)	p-value
Non-responder/unscreened	0.89 (0.68-1.15)	0.36	NA	NA
Non-responder/no colonoscopy	1.75 (0.39-7.78)	0.57	NA	NA
Non-responder/late cancer	2.16 (0.98-4.76)	0.18	NA	NA
Non-responder/screening cancer	2.70 (2.05-3.55)	< 0.01	2.49 (1.89-3.28)	< 0.01
Non-responder/negative FOBT	1.31 (1.02-1.69)	0.04	NA	NA
Non-responder/DCCG	1.15 (0.98-1.36)	0.06	NA	NA
Screening cancer/unscreened	0.32 (0.32-0.46)	< 0.01	0.29 (0.20-0.41)	< 0.01
Screening cancer/no colonoscopy	0.55 (0.04-7.76)	0.6	0.62 (0.05-7.54)	0.78
Screening cancer/late cancer	0.78 (0.17-2.74)	0.52	0.77 (0.20-2.86)	0.82
Screening cancer/negative FOBT	0.47 (0.33-0.67)	< 0.01	0.54 (0.38-0.76)	< 0.01
Screening cancer/DCCG	0.44 (0.36-0.55)	< 0.01	0.52 (0.42-0.66)	< 0.01
Negative FOBT/unscreened	0.67 (0.49-0.91)	0.01	NA	NA
Negative FOBT/no colonoscopy	1.37 (0.25-7.45)	0.75	NA	NA
Negative FOBT/late cancer	1.44 (0.54-3.82)	0.53	NA	NA
Negative FOBT/DCCG	0.94 (0.75-1.16)	0.55	NA	NA

CI = confidence limits; DCCG = Danish Colorectal Cancer Group; FOBT = faecal occult blood test; NA = not assessed.

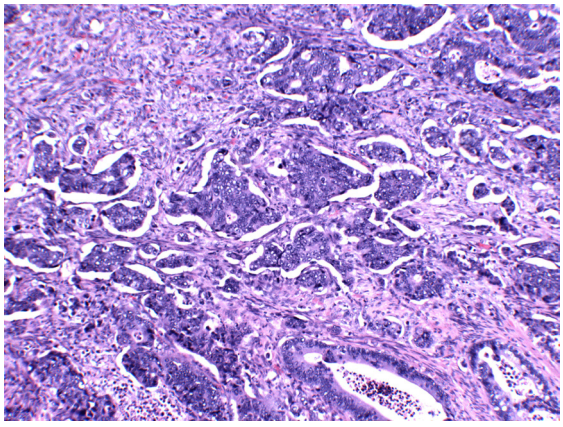
retained when dividing stages into early and late stage cancers ($\chi^2_{(1)} = 19.69$; $p < 0.01$) The observed earlier stages in the negative FOBT group compared with the non-responder group was not statistically significant ($\chi^2_{(1)} = 1.08$; $p = 0.30$). The observed difference in stage distribution between the late cancers and the non-responder cancers was statistically significant ($\chi^2_{(4)} = 14.39$; $p < 0.01$). But this significance was absent when comparing early-stage and late-stage cancers ($\chi^2_{(1)} = 0.81$; $p = 0.37$).There were no differences in the stage distribution of cancers among FOBT-negative and non-responders, respectively, diagnosed within 24 months after invitation or later (FOBT-negative: $\chi^2_{(4)} = 3.07$; $p = 0.55$, non-responders: $\chi^2_{(4)} = 1.03$; $p = 0.91$).

Rectal cancer groups

The distribution of rectal cancer groups is shown in **Table 2**. There was no statistical significance between the group proportions in the unscreened part of the cohort and the Danish population aged 50-74 years $\chi^2_{(2)} = 3.87$; $p = 0.14$. The observed difference between the screening cancers and the non-responders was statistically significant $\chi^2_{(1)} = 4.50$; $p = 0.03$). And so was the difference between non-responder cancers and FOBT-negative patients ($\chi^2_{(1)} = 5.75$; $p = 0.02$). The proportion of rectal cancers that were locally advanced was significantly higher in the non-responder group than in the Danish population in the same age range ($\chi^2_{(2)} = 35.26$; $p < 0.01$). There were no differences in the distribution of cancers among FOBT-negative and non-responders, respectively, diagnosed within 24 months after invitation or later (FOBT-negative: $\chi^2_{(1)} = 0.06$; $p = 0.80$, non-responders: $\chi^2_{(1)} = 2.26.03$; $p = 0.13$) (Data not shown). Among the localised rectal cancers, the same trends as for colon were seen – a non-significant tendency towards lower stages in the negative FOBT group compared with the non-responder group, and a significantly lower stage distribution among screening cancers compared with the non-responder cancers (data not shown).

Survival

A Kaplan-Meier plot showing overall survival among the various screening groups and the complete DCCG population in the same age group is shown in **Figure 1**. Calculations of Cox-Mantel death hazard ratios groups are shown in **Table 3**. The observed better survival in the late cancer group compared with the negative FOBT group and the non-responder group was not statistically significant. However, the association was imprecisely estimated due to a small number of patients in the late



Haematoxylin and eosin-stained section of a colorectal adenocarcinoma.

cancer group (n = 11). Survival of the FOBT-negative patients matches that of the DCCG population. When considering the five-year survival, there is a small overlap between the 95% confidence limits between the negative FOBT group (0.63 (0.56-0.69)) and the non-responder group (0.53 (0.49-0.59)). The five-year survival for the screening cancer group was 0.80 (0.73-0.88).

DISCUSSION

We were able to separate the individuals in the cohort who were diagnosed with cancer into categories that occur in screening programmes. We also identified cases diagnosed before the screening invitation was sent out, which constitutes a group of uninvited individuals. The stage distribution the uninvited group did not differ from that of the rest of the unscreened Danish Population, which suggests that the study cohort is representative of the Danish population.

It has been reported that 174 screening cancers were detected in the feasibility study [3]. We were able to identify 162. There may be many reasons for this discrepancy. The argument can be made that the five polyps that were diagnosed as adenomas on biopsies, but turned out to be cancers on removal should be classified as screening cancers rather than as late cancers. Our strategy for case identification would not find cancers not in the DCCG registry among the FOBT-positive patients from Copenhagen where cancer was not suspected on colonoscopy. Such cancers are typically small cancers in adenomatous polyps, and they are not likely to reduce the effect on survival and stage distribution of screening cancers found in this study.

CRCs detected through screening were diagnosed at significantly lower stages compared with the other groups. Overall survival was also superior. The data do not indicate that lead time bias is a plausible explanation. This is in accordance with findings of other studies on CRC screening [6, 7]. In the upcoming screening programme, FOBT will be an immunologically based test, whereas FOBT was a chemically based test in the feasibility study. This has the potential to increase the proportion of screening cancers as the test is more sensitive and only requires one faeces sample.

A concern raised is that individuals with a false negative FOBT will be diagnosed at a more advanced stage than unscreened CRC cases attributable to a sense of false security. The data in this study do not support this assertion. In this study, the survival of FOBT-negative CRC patients was similar to the survival seen in the DCCG population. The observation that FOBT-negative colon cancers were diagnosed at lower stages than cancers in unscreened and non-responder colon cancer cases did not reach statistical significance. Because of a low number of cases, a type 2 error is a distinct possibility.

Negative colonoscopies in FOBT-positive cancer patients are rare. For this reason, an impact on survival cannot be determined from our data.

In Denmark, rectal cancers are treated with long-course chemoradiation if they are located below 10 cm from the anal verge, and the distance from the mesorectal fascia is less than 5 mm (locally advanced). Chemoradiation influences stage at operation. For this reason, the proportion of rectal cancers that are locally advanced is more informative than stage at operation in the context of determining the effect of screening. The difference in distribution between the screening cancers and non-responder cancers was statistically significant ($p = 0.03$). Because of a low number of rectal screening cancers, a type 1 error cannot be completely ruled out. A concern raised by proponents of CRC screening is that the focus on the risk of colonoscopy by opponents may result in more advanced stage at diagnosis. No such effect can be detected in this study for colon cancers. Rectal cancers among non-responders were more advanced at diagnosis than among screening participants and the unscreened population. This phenomenon was more pronounced in rectal cancers diagnosed within 24 months of invitation than in rectal cancers diagnosed later. The difference was not large enough to be statistically significant. Survival of cancer diagnosed through screening is superior to survival to cancers detected otherwise. This is well-established [8] and was also seen in this study. An important finding of this study is a survival benefit in patients with a FOBT-negative CRC compared with CRC in non-responders. The benefit is small but measurable. It has been shown that socioeconomic factors influenced screening participation in this feasibility study [9]. This as well as poor health is a probable explanation for this small survival difference.

CONCLUSION

In this cohort, participation in screening for colorectal

cancers significantly reduced mortality compared with non-participation as well as being unscreened. Furthermore, treatment of CRC in screening participants is more gentle because the cancers are less advanced. In accordance with findings of other studies, the experience of the feasibility study indicates that the benefits of implementing FOBT screening for CRC by far outweigh the reported risks associated with having a colonoscopy [6]. A low complication rate of screening colonoscopy was also seen in this cohort [3]. A false negative FOBT does not result in inferior survival compared with no screening.

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