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Effect of faecal occult blood testing on colorectal cancer mortality in the surveillance of subjects at moderate risk of colorectal neoplasia: a case-control study

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Abstract Colonoscopy is the established method of surveillance of subjects at high risk of developing colorectal neoplasia. Its role in the surveillance of a population at moderate risk is less clear, however, as the procedure is expensive, time consuming and occasionally hazardous. The aim of this study was to estimate by case-control methods the effect of faecal occult blood (FOB) screening on colorectal cancer (CRC) mortality in a population at moderate risk of developing CRC. Screening by FOB testing prior to diagnosis in patients over the age of 45 years who died of CRC diagnosed in 1989–1998 was compared with screening in controls matched with the case for age and sex. Information about episodes of FOB testing and potential confounders was obtained from the data collection system of the screening programme. Cases were less likely than controls to have ever been screened, with an odds ratio of 0.64 (95% confidence interval 0.34–1.15) for exposure to at least one FOB testing. There was no significant difference between the sub-groups according to gender, age at diagnosis or location of the cancer. The inverse association between screening for faecal occult blood and fatal colorectal cancer suggests that screening in a population at moderate risk of CRC can reduce mortality from CRC in this group.

Keywords Colorectal cancer · Screening · Faecal occult bloods

Introduction

Colorectal cancer (CRC) is a leading cause of illness and death in the Western world, with an estimated 169,400 new cases in the 12 countries of the European Community in 1990 [1], and resulting in approximately 20,000 deaths annually in the United Kingdom. In the absence of effective measures of primary prevention of CRC, and with the knowledge that surgical treatment at the early stages of malignancy is effective in improving survival rates [2], the past two decades have witnessed increased interest in CRC screening using faecal occult blood testing (FOBT). Four randomised controlled trials of general population screening [3, 4, 5, 6], together with data from several case-control studies from Europe, the United States and Japan [7, 8, 9, 10, 11, 12] have shown a reduction in CRC mortality in the screening group of the order of 15–20%. By itself however, such evidence of effectiveness in reducing mortality is insufficient to justify the implementation of a national mass population screening programme: logistical, ethical, psychological and economic issues are only some of the considerations that must be addressed in order that the chance that the patient will benefit from the screening procedure substantially outweighs the risk of harm from it. Indeed several authors have argued against the use of FOBT in screening the general population [13, 14].

Targeted screening may be a more efficient and cost-effective method of detecting early neoplasms than population screening. Colonoscopy is the established method of surveillance of subjects at high risk of developing colorectal neoplasia [15]. These are subjects with a well-

defined genetic predisposition, or a strong family history of CRC [16, 17]. There remains a broader 'middle' group of subjects, not so well-defined as the high-risk group, with characteristics placing them at slightly higher risk of developing CRC than the general population. A general practice based programme was initiated in Guildford (U.K.) to offer such individuals screening of faecal occult blood. This paper reports the results of a case-control study of the efficacy of FOBT screening among such a population.

Materials and methods

Study population

The design of the study has been reported previously [18]. Since 1987 individuals at higher than average risk of developing large bowel cancer have been identified from general practices in the Guildford area and offered opportunistic screening in the form of FOBT. Subjects with a positive result were invited to undergo a colonoscopy or double-contrast barium enema where complete endoscopic exploration of the colon was not possible.

For the purpose of this study we defined cases as individuals at risk those who were over 45 years of age with one or more of the following symptoms: rectal bleeding, change in bowel habit, abdominal pain, tenesmus, anal or rectal discomfort and anaemia, or a family history of one or more first-degree relatives with cancer of the bowel (at age 50 years or younger), breast, endometrium, liver, ovary or stomach. Patients with other potential sources of occult rectal bleeding such as haemorrhoids or ulcerative colitis were not excluded as it was felt that these diagnoses might conceal bleeding from a carcinoma.

The FOBT was performed using the haemoccult test, according to the manufacturers' instructions. A kit for testing FOB was given to patients, who were then asked to telephone the surgery for results. Completed kits were returned to the surgery and collected weekly, developed at the hospital, and the results posted back to the surgeries.

Screening history

The screening histories of the cases and controls were retrieved retrospectively from hospital or general practitioners' files; details of each participant's instances of faecal occult blood testing with respect to date, indication and outcome were recorded.

By definition, after the initial diagnosis of disease, an individual is no longer eligible for screening. The relevant screening history of the cases therefore consisted of all screening tests performed from the time screening started until the time of diagnosis, but no tests performed between diagnosis and death. The relevant screening history of a matched control was therefore also limited to the time interval during which screening tests on the case would have been included, i.e. until the time of diagnosis. For fatal cases of CRC detected by the screening FOBT, the FOBT that led to diagnosis was included with other screening FOBTs in all analyses.

Identification of cases and controls

Case subjects were defined as those who: (a) were diagnosed with adenocarcinoma of the colon or rectum between 1989 and 1998, who subsequently died before December 1998 as a result of this cancer; (b) were diagnosed as having CRC between the ages of 45 and 85 years after the screening programme was started; (c) had been living in the same area since the screening programme was started; (d) had not had previous histories of CRC before the screening programme was started in 1987. Cases were identified through the data collection system of the screening programme. The histological diagnosis of adenocarcinoma, its anatomical location, and the cause of the patient's death were verified by reviewing the computerised data base of the cases diagnosed as CRC. Death was attributed to CRC if advanced, or metastatic CRC was present at the time of death, or if the person died in the post-operative phase.

For each case, two controls were randomly selected from the files of the general practitioners in such a way as to reflect the level of screening activity in the population from which the cases arose and, specifically, were matched with cases for age and sex. They were required to have been alive at the time when the matched case patient died; the date of diagnosis of the case was applied to the case-control matched set as the reference date, so as to ensure comparable intervals for the screening history of cases and controls; each control in the matched set thus had the same opportunity as the corresponding case of undergoing a screening test.

With this choice of case and control, one is estimating the relative risk of dying from the disease between groups with different screening histories. Efficacy of FOBT screening in reducing mortality from CRC is suggested if a screening history is more common among controls than cases. A previous history of adenomatous polyps or nonfatal cancer was not a grounds for exclusion.

Table 1 shows the main characteristics of cases and controls. The mean age at diagnosis was 68.5 years for cases and 68.6 years for controls. A total of 146 fatal cases of CRC (89 men, 57 women) met the case definition; 292 controls were eligible according to the criteria set above. The anatomical distribution of the fatal cancers included 94 (64.4%) originating in the rectum or sigmoid colon, 14 (9.6%) in the left colon, 10 (6.8%) in the transverse colon, and 28 (19.2%) in the right colon. Of these cancers, seven (4.8%) were of Dukes' A histological staging, 38 (26.0%) were Dukes' B, and 101 (69.2%) Dukes' C or D.

Table 1 Characteristics of cases (deaths from colorectal cancer) and controls

Characteristics	Patients (*n*=146)		Controls (*n*=292)	
	n	%	*n*	%
Age at diagnosis (years)				
45–55	22	15.1	43	14.7
55–64	23	15.8	46	15.8
65–74	61	41.8	122	41.8
75–85	40	27.4	81	27.7
Gender				
Male	89	61.0	178	61.0
Female	57	39.0	114	39.0
Anatomical location of cancer				
Colon	56	38.4	–	–
Rectum	74	50.6	–	–
Undefined	16	11.0	–	–

Statistical analysis

Conditional logistic regression analysis was used to estimate odds ratios and the corresponding 95% confidence intervals (95% CI)

for death from CRC. For any screening test that leads to early detection, it is less likely that a case patient would have subsequent tests, because the earlier tests would have had some chance of detecting the cancer, thus making further screening impossible. An adjustment for previous screening examinations controls for this bias. Separate odds ratios were also calculated for gender, age at diagnosis, and anatomical location of the cancer (colon and rectum).

Results

Of the 146 cases, 17 (11.6%) had been screened and 129 had not, whereas of the 292 controls, 50 (17.1%) had been screened and 242 had not. Thus a significantly smaller proportion of cases than of controls underwent screening by FOBT during the study period. This was statistically significant ($P<0.01$). The odds ratio of having been exposed to one or more FOBT during the whole study period relative to unscreened persons was 0.64 (95% CI 0.34–1.15). Thus, relative to unscreened persons, the risk for fatal CRC was reduced by 36% among those who had an FOBT.

The OR for developing fatal cancer did not differ significantly between the sub-groups according to gender (0.64 and 0.63 for men and women, respectively), age at diagnosis (0.68 and 0.60 for individuals aged under 60 years and those over 60, respectively) or anatomical location (0.62 and 0.69 for cancers of the rectum and colon, respectively).

Discussion

This study suggests a 36% reduction in CRC mortality for individuals screened by FOBT. The magnitude of the reduction in this study is considerably greater than that reported in randomised controlled trials of general population screening, where the combined evidence from a meta-analysis review suggests a point estimate reduction of 16% [19], although the reduction could be as great as 23% or as little as 7%. Our figures also show a slightly greater reduction in mortality than in case-control studies of general population screening [8, 9, 10, 11, 12], where reductions in the order of 20–30% have been reported. There are no published results of any other case-control studies of targeted screening using FOBT, but our results are very close to the projected 33% reduction in CRC mortality rate that has been calculated for asymptomatic individuals with a family history of the disease by employing annual FOB screening [20].

Our figures must be interpreted with caution, however. The confidence intervals were wide, and chance, confounder factors and other unmeasured factors may explain at least in part the observed association. The price when randomisation is abandoned is the probable introduction of factors that may differ between screened and unscreened persons, especially the issue of comparability of individuals regarding their underlying risk of the occurrence of the cancer in question. Also, the retrospective ascertainment of screening history is often inaccurate, sometimes differentially so between cases and controls. Notwithstanding this, several aspects seem to be consistent with true efficacy. Firstly, the sensitivity of FOBT in patients is probably no better than 50% for cancer [21, 22]; the efficacy of a screening test cannot be higher than its sensitivity, and our data are consistent with this. Also, the analysis in this study was conducted without regard to the time that screening occurred, and this might have obscured a possible benefit of the tests performed within the relatively short period during which screening for faecal occult blood is capable of achieving detection.

The generally higher reduction in mortality in case-control studies noted above may be due to the fact that in a case-control study, attenders are compared with non-attenders, while in randomised clinical trials the comparison is between an entire study group and an entire control group, so that compliance to testing and contamination of the control group can affect the final result.

Although randomised controlled trials and case-control studies of population screening have all shown a significant reduction in CRC mortality, the indications for implementation of a screening programme using FOBT remain far from clear. In North America, for example, considerable controversy remains as to what represents the most cost-effective approach to screening for CRC. The American Cancer Society recommends annual FOBT *and* flexible sigmoidoscopy every 3 to 5 years beginning at the age of 50 years in asymptomatic, average-risk individuals [23], whereas the American Gastroenterological Association Panel recommends flexible sigmoidoscopy every 5 years *and/or* yearly FOBT [24].

The implementation of a national screening programme of the general population using FOBT would add a considerable burden to health service resources in terms of follow-up examinations, such as colonoscopy. The additional workload can be estimated by extrapolating the data from the Nottingham study to the United Kingdom as a whole [25]. Using a biennial screening protocol, and assuming a compliance rate of 55%, it has been estimated that an additional 77,000 colonoscopies would be required each year. Notwithstanding the practical and logistical implications of such a burden, a further problem is the finite risk of colonic perforation and resultant mortality [20]. Calculations of the risks of colonoscopy in screening patients who have undergone previous polypectomy have shown that if the residual risk to a 50-year-old man is 1 in 40 and the effectiveness of colonoscopy at 3-year intervals is 100% in preventing CRC death, 283 colonoscopies would be required to prevent one cancer death, incurring 0.6 colonic perforations and 0.04 perforation-related deaths [26]. Hence screening

would be 25 times more likely to prevent a cancer death than to cause a death. This level of benefit may be acceptable, but if the residual risk of the screened population is only 1 in 80, and colonoscopy is 50% effective in preventing cancer death (a more likely estimate than 100%), the benefit becomes even less obvious, as screening would be only 6 times more likely to prevent a death than to cause one: although 1131 colonoscopies would be required to prevent one cancer death, there would be 2.3 colonic perforations, 0.17 procedure-related deaths and a cost of £190,000. Similarly, using a complex mathematical model and certain fundamental assumptions, it has been calculated that an annual FOB test would prevent 71 per 10,000 men screened dying from the cancer that they would have developed had they not been screened. This, however, translates into a mean increase life expectancy of only 30.6 days for the screened population as a whole.

Deeper scrutiny of the results of mass screening programmes raises further interesting points. Firstly, reductions in CRC mortality achieved by the immense UK and Danish trials were modest, in the order of 15–18%. Translated in absolute terms, these figures indicate that for 1000 persons invited for FOBT screening once every 2 years during 10 years, one death due to CRC would be avoided [27]. Secondly, in both the UK and Danish trials, interval cancers were more numerous than screen-detected CRCs, probably because among screened subjects, more attention was paid to early symptoms, prompting earlier diagnosis of malignant lesions. The modest reduction in CRC mortality may have therefore been in part due to better medical attention for those subjects who were randomised in the screening group. Finally, it cannot be assumed that the modest gains in CRC mortality can be replicated in other European countries given the important discrepancies in health care systems throughout Europe.

As a screening measure it would therefore seem that targeted screening may be a more efficient and cost-effective method of detecting early neoplasms than population screening and should have a more favourable risk-benefit ratio. How this is best achieved remains controversial. The gold standard for screening is endoscopic visualisation of the colon. Thus, a reduction of 85% mortality using colonoscopic screening, compared to 33% using FOBT has been calculated. This is due to the far higher sensitivity of colonoscopy, and the beneficial early detection and removal of benign and early malignant colorectal neoplasms. In a previous study by the same group of screening by FOBT for colorectal neoplasia in a targeted high-risk population, a sensitivity and specificity of 63% and 96%, respectively, and a positive predictive value for all neoplasia of 29% were found [18]. This is still considerably lower than equivalent colonoscopic figures, and it remains contentious whether a group of patients who have been identified as high risk, and who know that fact, should be offered a test whose sensitivity is demonstrably lower than that of colonoscopy, where a reduction in CRC mortality of 85% has been calculated [20]. Immunological tests for FOBT which are highly sensitive but lack the specificity required for population screening may become valuable if used more widely. A case-control study using an immunochemical haemagglutination test in Japan has reported a reduction in mortality from CRC of 60% [10] although the specificity of this test is not well established at a population level, and the test is expensive and more difficult to analyse.

When screening an intermediate risk group as in this study, the drawbacks associated with colonoscopy become more apparent. This procedure is expensive, time consuming and carries a finite risk of colonic perforation and resultant mortality [20, 26, 28, 29]. In addition, other harmful screening effects include disruption to lifestyle, the stress and discomfort of testing and further investigations, and the anxiety caused by false-positive tests [30].

Further studies which take these considerations as well as economic factors into account are needed to compare the overall efficacy of colonoscopic screening of a high-risk population with that of a FOBT screening programme.

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