

The Psychological Impact of a Colorectal Cancer Diagnosis Following a Negative Fecal Occult Blood Test Result

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Abstract

Background: Screening using fecal occult blood testing (FOBT) reduces colorectal cancer mortality, but the test has low sensitivity. A "missed" cancer may cause psychologic harms in the screened population that partially counteract the benefits of early detection.

Methods: Three hundred and eleven people diagnosed with colorectal cancer (i) after a negative FOBT result (interval cancer), (ii) a positive result (screen-detected cancer), or (iii) in regions where screening was not offered, completed questions on quality of life (FACT-C), depression (CES-D), perceived diagnostic delay, and trust in the results of FOBT screening. Fifteen withheld consent to data matching with medical records, leaving a sample size of 296.

Results: Controlling for demographic and clinical variables, patients with an interval cancer reported poorer quality of life

(difference in means = 6.16, $P = 0.03$) and more diagnostic delay (OR, 0.37; $P = 0.02$) than patients with screen-detected disease, with no differences in depression. No differences were observed between the interval cancer group and the group not offered screening on these measures. Patients with an interval cancer reported the lowest levels of trust in FOBT.

Conclusions: An interval cancer has adverse effects on trust in FOBT, but does not result in worse psychologic outcomes compared with people diagnosed in areas with no screening program. People with an interval cancer report poorer quality of life than people with screen-detected disease.

Impact: Improvements in test sensitivity could improve quality of life among people who complete an FOB test over and above any benefits already conferred by earlier detection. *Cancer Epidemiol Biomarkers Prev*; 24(7); 1032–8. ©2015 AACR.

Introduction

Colorectal cancer is currently the fourth leading cause of cancer-related death worldwide (1), but mortality rates are declining in developed countries, and approximately half of this reduction has been attributed to the introduction of screening (2). Screening for colorectal cancer using fecal occult blood testing (FOBT) has been shown to reduce mortality by 16% among people invited to participate, and by 25% among those who complete at least one FOB test (3). Screening programs using FOBT are offered in a number of countries (4), and this means that increasing numbers of people will have their colorectal cancer diagnosed following participation in screening. In order for screening to do "more good

than harm," adverse effects, including effects on psychologic outcomes, need to be kept to a minimum.

To date, research into the psychologic impact of colorectal cancer screening has been broadly reassuring. No evidence of sustained anxiety has been found in people who receive a false-positive FOBT result (5). Research on people who received a positive result at screening (combining false-positive and true-positive results, and comparing them with people who had a negative result), has also reported no long-term effects on anxiety or worry about cancer (6), and no clinically significant effects on screen-specific anxiety, or quality of life, have been observed among people getting a positive result in fecal immunologic testing (7). Similarly, research into the detection of precancerous lesions (adenomatous polyps) has found little evidence of any impact on worry about cancer, or general anxiety (8), and patients diagnosed with colorectal cancer at flexible sigmoidoscopy screening reported relief that an earlier diagnosis had prevented a worse outcome than might have occurred in the absence of screening (9). However, the psychologic impact of false-negative screening results, where the screening result is normal (negative), but the person is later found to have cancer, could potentially have a more severe psychologic effect, especially if the patient fears that their cancer was "missed" at an earlier, more treatable, stage. Systematic reviews show that little research has examined the impact of false-negative results in cancer screening (10).

An interval colorectal cancer is defined as a "colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended

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exam" (11). In the FOBt pilots that were run in the United Kingdom before the introduction of national screening programs, interval cancer rates were between 30% and 50% (12, 13). Although some interval cancers will be tumors that developed since the screening test, the majority will have been missed by the test. False negatives are an inevitable part of screening, because most screening tests are less than 100% sensitive (14), but there is evidence people incorrectly assume that sensitivity levels are near-perfect (15), and attribute screening "failures" either to individual health professionals or laboratories (16). In addition, a large proportion of screening participants are unaware they may have a colorectal cancer despite a negative FOBt result (17). Anger and mistrust in the medical profession have been reported as common responses to medical errors in primary care (18), and in the field of antenatal screening, a false-negative result has been associated with poorer acceptance of a child with Downs' syndrome than if screening was declined (19). These findings suggest that if people believe there has been a medical "error" or delay in diagnosing their cancer, their adjustment may be compromised as a result. The aims of the present study were to test the hypotheses that patients with an interval colorectal cancer would have poorer quality of life, higher depression, greater perceived diagnostic delay, and lower trust in the results of FOBt screening, than either people with screen-detected colorectal cancer, or people diagnosed with colorectal cancer in areas of the country where screening was not offered.

Ethical approval and patient consent

Ethical approval was obtained from Riverside Research Ethics Committee (reference number: 09/H0706/41). Additional approval for identifying potential participants via database linkage was granted by the NHS National Services Scotland Privacy Advisory Committee, and the NHS National Services Scotland Community Health Index Advisory Group. Patient consent was implied by the completion and return of the questionnaire.

Materials and Methods

This was a cross-sectional study, comparing three groups of patients diagnosed with colorectal cancer. The first two groups were participants in the Scottish Demonstration Pilot of FOBt Screening for Colorectal Cancer, which ran between 2000 and 2007, and were either diagnosed with colorectal cancer after a negative test result (the interval cancer group) or after a positive test result (the screen-detected group). The third group was diagnosed with colorectal cancer during the same period, but had not been invited for screening because they lived outside the area covered by the pilot program. A questionnaire assessing psychologic outcomes was mailed to General Practices to send on to the identified patients in June 2012, with a reminder survey sent on to nonresponders in September 2012.

Our sample size was calculated to detect a medium effect size ($d = 0.5$) with $\alpha = 0.05$ and power = 0.95 between three groups (20). The effect size of 0.5 is considered the minimal important difference in quality of life measures (21), defined as the smallest difference that patients view as important (beneficial or harmful), and would result in a doctor considering a change in the patient's management (22). The number of responses required was 249. On the basis of previous mailed surveys with cancer patients (23) we anticipated a response rate of 60%; hence a minimum of 415 participants needed to be invited to reach this

number. Study attrition due to patients not meeting inclusion criteria, or general practitioners (GP) not wishing to take part in the research, was unknown, but was estimated at 35% (20% for patient exclusion (24) and 15% for GP nonparticipation), leaving a total sample size of 639 as the initial target.

Participants and recruitment

Potential participants were identified by linking the Scottish Cancer Registry and Scottish Colorectal Cancer Screening Pilot databases by their Community Health Index (CHI) number. Patients not offered screening were resident outside the pilot areas (i.e., not in NHS Fife, NHS Grampian, or NHS Tayside), and were identified as having a diagnosis of colorectal cancer using the Scottish Cancer Registry (ICD 10 C18-C20). Selection of patients in the group not offered screening was limited to people aged 50 to 69 at diagnosis, who were diagnosed within the time periods of the three rounds of the Pilot. Patients with an interval cancer were identified by matching the individuals invited to participate in the Scottish Colorectal Cancer Screening Pilot with the Scottish Cancer Registry, and establishing that their cancer had been diagnosed within 2 years of a negative screening result. Patients with screen-detected colorectal cancer were identified from the Scottish Colorectal Cancer Screening Pilot database. For each group, individuals were randomly selected, stratified by sex, from the relevant database pool. The CHI database was used to identify patients and GP details. The CHI is a unique identifier for individuals registered at general practices in Scotland, and contains information on date of birth and gender.

Practitioner Services Division at NHS National Services Scotland (NSS) coordinated patient contact via patient GPs. Patients identified as deceased, or as having moved from the area were excluded. Practitioner Services Division was given template letters for GPs and patients; they added GP and patient details, and forwarded the letters to the GPs to pass on to eligible patients. This process was approved by the Riverside Research Ethics Committee, NHS NSS Privacy Advisory Committee, and the NHS NSS Community Health Index Advisory Committee. GPs were asked to confirm the diagnosis of colorectal cancer, and exclude patients who were deceased or terminally ill, unable to speak or read English, or lacked the capacity to take some or all decisions for themselves because of mental disorder or inability to communicate.

Measures

The primary outcome was quality of life specific to colorectal cancer, which was measured using the FACT-C (25); participants were asked to indicate how they had been feeling during the past 7 days. Secondary outcomes were depression, perceived diagnostic delay, and trust in FOBt. Depression was measured with the 10 item version of the Center for Epidemiological Studies Depression scale (CES-D; ref. 26) asking people about their mood over the last 3 months. Perceived diagnostic delay was assessed with the item: "Do you think your cancer could have been diagnosed sooner than it was" with response options: "yes," "no," and "not sure." Trust in the results of FOBt screening was assessed with the item: "If you were to have an FOB test, would you trust the results of the test" with response options: "not at all," "somewhat," "moderately," and "very much" (from (27) with the addition of the response option "moderately").

Age, gender, Scottish Index of Multiple Deprivation (SIMD; ref. 28), years since diagnosis (length of time between diagnosis

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and completion of the questionnaire), Dukes' stage, and treatment received (radiotherapy and chemotherapy) were covariates. These were supplied by NHS NSS with patient consent. Comorbidities were self-reported and combined into a single variable "comorbidity" (Yes/No). Ethnicity and employment status were collected in the questionnaire for the purpose of describing the sample.

Statistical analysis

Predictors of quality of life, depression, and trust in the results of FOBt screening were analyzed using linear regression, with diagnostic group dummy coded, and the interval cancer group entered as the reference category. Predictors of perceived diagnostic delay were analyzed using logistic regression with the response options "not sure" and "no" combined. Regression analyses were repeated controlling for age, gender, deprivation, time since diagnosis, receipt of radiotherapy or chemotherapy, and presence of comorbidities; Dukes' stage at diagnosis was not included, because it correlated highly with having chemotherapy, and had higher rates of missing data than the chemotherapy variable. The same pattern of results was observed if Dukes' stage was entered into the analysis instead of receipt of chemotherapy. All statistical analyses were two-sided and performed using SPSS version 20.

Response rate

GPs were sent the research invitation letters for 675 patients, of whom 142 were not contacted because the GP indicated that the patient met one or more of the exclusion criteria ($n = 70$), or the GP did not wish to participate in the research ($n = 72$); leaving 533 patients who were (apparently) mailed a questionnaire. Patients were invited to return the questionnaire blank if they did not wish to participate, but unless the questionnaire was returned, there was no way of confirming that it had definitely been forwarded to the patient. Assuming that all nonreturned questionnaires had been mailed out, the questionnaire response rate was 58.3% ($N = 311$), of whom 15 withheld consent for data-matching to NSS. This left 296 as the principal sample for analysis; a response rate of 55.5%. There

were 91 in the group not offered screening, 106 in the screen-detected group, and 99 in the interval cancer group.

Scores on the FACT-C and CES-D were only computed if patients had answered at least 50% of the items (or 50% of the items of subscales in the case of the FACT-C), otherwise they were recorded as missing. Missing data were 5% or higher for Dukes' stage, receipt of radiotherapy, and the FACT-C, but less than 5% for all the other variables (see Tables 1 and 2). The proportion of missing data on the FACT-C was unrelated to group status. Linear and logistic regressions were run both with complete cases, and with data imputed for missing values, using multiple imputation (29).

Results

Background variables

Descriptive and clinical characteristics of the whole sample, and the three groups separately, are shown in Tables 1 and 2. The average age was 69 years, ranging from 56 to 81; consistent with the age of invitation to the Scottish Colorectal Cancer Screening Pilot (50–69) and time since diagnosis. Time since diagnosis ranged from 3.5 to 12 years. The sample was less deprived than the general population of Scotland, with more than 20% in each of the higher quintiles. The current sample reported similar quality of life scores to those reported in other studies of people with colorectal cancer (25, 30).

Controlling for age, gender, deprivation, time since diagnosis, treatment (chemotherapy or radiotherapy), and comorbidities, patients with an interval cancer reported poorer quality of life and were more likely to perceive a delay in their diagnosis than patients with screen-detected disease, although there were no differences in depression between the two groups (see Table 3). However, patients with an interval cancer did not differ on quality of life, depression, or perceptions of diagnostic delay, compared with patients who had not been offered screening. Patients with an interval cancer reported lower trust in the results of FOBt than patients in areas where screening was not offered and patients with screen-detected disease (see Table 3). Group differences in quality of life, depression, perceived diagnostic delay, and

Table 1. Demographic characteristics of patients with different screening histories

	Overall (<i>N</i> = 296)	Interval (<i>n</i> = 99)	Screen- detected (<i>n</i> = 106)	Not offered screening (<i>n</i> = 91)	<i>P</i>
Age when completed study (y) ^a , mean (SD)	69.0 (5.8)	68.5 (5.9)	69.8 (5.7)	68.4 (5.7)	0.17
Men ^a	146 (49)	44 (44)	56 (53)	46 (51)	0.47
SIMD (fifths) ^b					0.29
1 (most deprived)	22 (8)	9 (9)	7 (7)	6 (7)	
2	50 (17)	14 (15)	17 (16)	19 (21)	
3	71 (24)	21 (22)	28 (26)	22 (24)	
4	79 (27)	35 (36)	24 (23)	20 (22)	
5 (least deprived)	71 (24)	17 (18)	30 (28)	24 (26)	
Employment status ^b					0.25
Working (full-time, part-time, self-employed)	54 (18)	25 (26)	16 (15)	13 (14)	
Retired	220 (75)	66 (67)	82 (78)	72 (80)	
Other (home maker, students, unemployed, too ill to work/disabled)	19 (7)	7 (7)	7 (7)	5 (6)	
Ethnic group ^b					—
White	291 (99)	98 (99)	103 (98)	90 (100)	
Non-white	3 (1)	1 (1)	2 (2)	0 (0)	

NOTE: Values are numbers (percentages) unless stated otherwise.

^aNo missing data.

^bMissing data <5%; where there are missing data, the percentage is the valid percentage.

Table 2. Clinical characteristics of people with different screening histories

	Overall	Interval	Screen-detected	Not offered screening	P
Time since diagnosis (y), ^a mean (SD)	7.7 (2.2)	6.6 (2.2) ^{de}	8.6 (1.8) ^f	7.7 (1.9)	<0.001
Dukes' stage ^c					0.04
A	68 (26)	21 (23) ^d	32 (35) ^f	15 (18)	
B	104 (40)	37 (41)	33 (37)	34 (42)	
C	84 (32)	31 (34)	24 (27)	29 (36)	
D	6 (2)	2 (2)	1 (1)	3 (4)	
Surgery ^b					—
Yes	286 (98)	95 (99)	100 (94)	91 (100)	
No	7 (2)	1 (1)	6 (6)	0 (0)	
Radiotherapy ^c					0.22
Yes	37 (14)	16 (18) ^(e)	13 (13)	8 (9)	
No	238 (86)	71 (82)	89 (87)	78 (91)	
Chemotherapy ^b					0.08
Yes	119 (42)	43 (47) ^d	34 (33) ^(f)	42 (47)	
No	163 (58)	48 (53)	68 (67)	47 (53)	
Comorbidities ^a					0.20
Yes	208 (70)	69 (70) ^(e)	69 (65)	70 (77)	
No	88 (30)	30 (30)	35 (37)	21 (23)	

NOTE: Values are numbers (percentages) unless stated otherwise.

^aNo missing data.

^bMissing data <5%.

^cMissing data >5%. Where there are missing data, the percentage is the valid percentage.

^dSignificant difference between Interval cancer and Screen-detected cancer groups.

^eSignificant difference between Interval and Non-screened cancer groups; (e) approaches significance.

^fSignificant difference between Screen-detected and Non-screened cancer groups; (f) approaches significance.

trust in the results of FOBt, remained the same when analyses were re-run using multiple imputation for missing data.

Discussion

Patients who had an interval colorectal cancer showed no evidence of worse quality of life, depression, or perceived delay in having their cancer diagnosed, than patients who had not been invited for screening, but they did have worse quality of life and higher perceived delay, than patients who received a screen-detected diagnosis. These results are reassuring in terms of concern about additional psychologic harms associated with an interval cancer. The most plausible interpretation of the pattern of differences between the three groups is that a screen-detected colorectal cancer diagnosis has a longer-term protective effect on quality of life, even after controlling for many possible confounders. This is a positive finding for colorectal cancer screening. As might be expected, patients diagnosed with colorectal cancer after a negative screening result reported lower trust in the results of FOBt screening, and this is potentially a cause for concern. Medical mistrust has been associated with reduced willingness to undergo cancer screening, particularly among ethnic minority groups and people with lower socioeconomic status (31–33). These studies assessed trust in "medical people" among members of the public, the majority of whom would not have had cancer. Mistrust in the results of a specific test among people who had an interval cancer may have different effects on behavior. In the United Kingdom at least, people with an interval cancer would not be offered another FOB test, but would be put on a surveillance schedule involving regular colonoscopies, CT scans, and blood tests. However, it is possible that mistrust among this patient group could affect screening participation among their friends and family. Given the current interval cancer rate associated with FOBt screening, it could be argued that the levels of trust in FOBt screening

among people with an interval cancer are more realistic than those among people with screen-detected disease. Either way, efforts should be focused on improving the public's understanding of the limitations of screening tests.

This is the first study to examine the psychologic consequences of having an interval cancer, and benefits from validated measures of quality of life and depression, and data derived from NHS records on demographic and clinical characteristics except for comorbidities. Although there were more than 5% missing data, which raise concern about bias, rates of missing data were similar across groups, and the results remained the same when data were imputed for missing values. Although quality of life, depression, and trust in FOB tests were assessed at the time of the survey, perceived diagnostic delay was assessed retrospectively, and may have reduced over time.

The sample was less deprived than the general population of Scotland; but uptake of FOBt screening is itself related to (lower) deprivation (34), and hence the sample fits the profile of people who attend screening, so it may not limit the generalizability of the results. Other factors, however, might influence generalizability: Response rates were below 60% and responders were almost exclusively from white ethnic backgrounds, with nonmetastatic disease. No data were available on the GP practices who took part in the study. This is because of the way the study datasets were linked, with GP details being added at the end, and therefore not appearing in the study dataset. There was, therefore, no way of comparing GP responders with nonresponders to see whether GP response was biased and any implications this might have had for the results of the study. The context of the study was the pilot screening program run in Scotland, and public expectations about the program may have been lower than in screening programs that have been running for longer. This means that differences between the interval and not-offered-screening groups may be more apparent in the future. In addition, there may be cultural differences in expectations about the quality and accuracy of screening

Table 3. Quality of life specific to colorectal cancer, depression, perceived diagnostic delay, and trust in the results of any future FOBT among patients with different screening histories

Variables	Interval cancer	Comparison with screen-detected			Comparison with not offered screening		
		Screen-detected	Unadjusted difference (95% CIs)	Adjusted difference ^c (95% CIs)	Not offered screening	Difference (95% CIs)	Adjusted difference ^c (95% CIs)
Quality of life (FACT-C) ^b (0-136)	108.26 (18.37; n = 90)	116.57 (13.63; 8.31 (3.43-13.20))	<0.001	6.16 (0.65-11.66)	110.67 (18.53; 2.41 (-2.65 to 7.47))	1.70 (-3.67 to 7.07)	0.54
Depression ^a (0-30)	5.23 (4.54; n = 98)	3.97 (4.14; -1.26 (-0.03 to -2.49))	0.05	-0.68 (-2.05 to 0.69)	5.36 (4.72; 0.14 (-1.15 to 1.42))	0.84	0.58
Perceived diagnostic delay (n and % yes vs. no or not sure) ^a	30 (31)	15 (14)	0.01	OR: 0.37 (0.17-0.83)	34 (37)	0.35	0.58
Trust in the results if were to have an FOB test (1-4) ^b	2.74 (1.06; n = 99)	3.84 (0.46; 1.10 (0.90-1.31))	<0.001	1.11 (0.87-1.35)	OR: 1.33 (0.73-2.44)	0.86 (0.63-1.09)	<0.001

NOTE: Values are means (values for delay are frequencies and ORs).

^aMissing data <5%.^bMissing data >5%.^cAdjusted for age, gender, deprivation, time since diagnosis, receipt of radiotherapy or chemotherapy, and presence of comorbidities.

programs, and different responses may be observed in other countries and ethnic groups.

Having a cancer "missed" at FOBT screening can be attributed to the cancer not bleeding at the time of the test, rather than a poor quality test or human error. This may mean that adverse psychological outcomes would be lower than for interval cancers in other screening programs (e.g., breast) where attributions of blame to other people or the quality of the service could more easily be made. Finally, patients were, on average, six to eight years post-diagnosis, and any adverse psychological impact of an interval cancer might have attenuated over time, or be absent, as a result of survivor bias and the fact that any delay in diagnosis had not proved fatal.

We are not aware of any other studies examining the psychological outcomes associated with an interval cancer with which to compare these results. Two prospective studies on breast cancer patients found no differences between women with a screen-detected versus symptomatically-detected (i.e., non-screened) breast cancer in psychiatric morbidity (35) or affective disorder (36), but did not focus on whether the non-screen-detected cases were interval cancers. Psychological effects following screening are more likely to be detected using cancer-specific rather than generic measures (such as anxiety or depression; refs. 37, 38), so it is an advantage that the present study used a cancer-specific measure of quality of life as well as depression.

The reasons for better longer-term quality of life among people with screen-detected colorectal cancer are unknown, although previous research has indicated that patients diagnosed at screening perceive themselves to be "lucky" to have benefited from early detection. But there may be other explanations: Screening is more likely to detect cancers in the left side of the colon (39), and future research could assess differences in quality of life by tumor location, as well as differences in treatment outcomes or patient experiences, that might contribute to superior longer-term quality of life among people with screen-detected colorectal cancer. More research is needed into public understanding of the risks of a false-negative result at screening. This could indicate a need for patient education to promote better understanding of the limitations of colorectal cancer screening tests, and ensure that patients receiving a negative result do not experience false reassurance or ignore subsequent cancer symptoms. Given the likelihood of interval cancers, it is important to consider how trust in the screening program can be maintained into the future.

Disclosure of Potential Conflicts of Interest

N. Sevdalis is a Professor of Implementation Science and Patient Safety at the Collaboration for Leadership in Applied Health Research and Care South London, reports receiving a commercial research grant from Sanofi Pasteur, and is a consultant/advisory board member for London Safety and Training Solutions. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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