

Can a print-based intervention increase screening for first degree relatives of people with colorectal cancer? A randomised controlled trial

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Colorectal cancer (CRC) affects around 1.36 million people each year, accounting for almost 10% of all cancers diagnosed.¹ Early detection through biennial fecal occult blood test (FOBT) has been shown to reduce CRC-related mortality by 15-25%.²

First degree relatives (FDRs) of patients with CRC are at higher risk of developing CRC than the general population.³ The level of risk depends on the number of relatives affected,⁴ the age at which relatives were diagnosed,⁵ and whether any high-risk features such as high-risk genes (e.g. hereditary nonpolyposis colorectal cancer) were identified in the affected relatives.⁶ The Australian National Health and Medical Research Council (NHMRC) defines three levels of risk for first degree relatives of CRC patients: at or slightly above average risk (Level 1); moderate risk (Level 2) and potentially high risk (Level 3). For those categorised at Level 1 risk, population-based screening recommendations for biennial FOBT are applicable; more intensive forms of screening such as colonoscopy or genetic testing are recommended for those at moderate or high risk.⁷

In Australia, the National Bowel Cancer Screening Program (NBCSP) was initiated in 2006. This involves the mail-out of an FOBT kit to people turning 50, 55, 60 and 65 years

Abstract

Objective: To test the effectiveness of a targeted print-based intervention to improve screening adherence in first degree relatives of people with colorectal cancer (CRC).

Methods: People with CRC and their adult first degree relatives were identified through a population-based cancer registry and randomly allocated as a family unit to the intervention or control condition. The control group received general information about CRC screening. The intervention group received printed advice regarding screening that was targeted to their risk level. Screening adherence was assessed at baseline and at 12 months via self report.

Results: 752 (25%) index cases and 574 (34%) eligible first degree relatives consented to take part in the trial and completed baseline interviews. At 12 months, 58% of first degree relatives in the control group and 61% in the intervention group were adherent to screening guidelines (mixed effects logistic regression group by time interaction effect =2.7; 95%CI=1.2-5.9; P=0.013). Subgroup analysis indicated that the intervention was only effective for those with the lowest risk.

Conclusions: Provision of personalised risk information may have a modest effect on adherence to CRC screening recommendations among first degree relatives of people diagnosed with CRC.

Implications: Improved strategies for identifying and engaging first degree relatives are needed to maximise the population impact of the intervention.

Key words: colorectal cancer, bowel cancer, population screening, Fecal Occult Blood Test, targeted advice, familial risk.

of age. An expansion to the program is in progress to enable biennial screening for all Australians aged between 50 and 74 by 2020.⁸ The NBCSP targets the general population and is not designed to address the screening needs of those with elevated levels of risk. The program advises those with a family history

of CRC to consult their GP for screening advice, but does not offer specific screening recommendations for this group. This means that there is no systematic mechanism in place for providing targeted screening advice to FDRs for whom population screening recommendations may be inappropriate.

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Submitted: December 2015; Revision requested: April 2016; Accepted: June 2016

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The authors have stated they have no conflict of interest.

Studies indicate that many FDRs are not being screened in accordance with guideline recommendations. Ait Ouakrim et al. found Australian self-reported lifetime screening adherence of 47% for FDRs at slightly above average risk.^{9,10} An Australian population survey of people aged 55–85 years reported screening adherence of 21% for those at or slightly above average risk and 45% for those at increased risk.¹¹

There is some evidence to suggest that telephone or face-to-face counselling is effective in improving screening rates among first degree relatives of CRC patients.^{12–14} However, such approaches may not be feasible to implement due to the costs involved. A mail-based approach, involving targeted screening advice is likely to be less costly to implement, and if effective, more sustainable. One US study found that targeted printed advice was more effective than generic advice in improving screening rates for FDRs;¹⁵ while another indicated that targeted and generic advice were equally effective at improving screening.¹⁶ In contrast, an Australian study found that a structured education brochure on screening had no impact on screening behaviour.¹⁷

The current study was undertaken as part of a larger trial that aimed to a) improve adherence to surveillance recommendations among people with colorectal cancer (index cases) and b) improve adherence to NHMRC screening recommendations for colorectal cancer among FDRs of people with colorectal cancer. Only results relating to aim 'b' are presented here.

Methods

Eligibility and recruitment of index cases

People with CRC, identified by the population-based Victorian Cancer Registry between 2009 and 2011, who were aged 18 or older, within 10 months of diagnosis, and English speaking were invited to participate in the trial.¹⁸ Consenting patients completed a computer-assisted telephone interview (CATI) which asked about: 1) family history of CRC, high-risk related cancers (e.g. endometrium, ovary, stomach, small bowel, renal pelvis, brain, or biliary tract), or high risk genes and familial adenomatous polyposis (FAP); and 2) total number of living FDRs over the age of 18, and whether the research team could invite the FDRs to participate.

Recruitment of FDRs. Patients could invite multiple FDRs to participate in the study and could choose how their FDRs were contacted about the study: 1) the patient was provided with a letter about the study that they could pass onto their relatives; 2) the research team contacted the relative(s) directly by mail. Approval for this study was obtained from the Cancer Council Victoria and the University of Newcastle Human Research Ethics Committees. The trial is registered with the Australian and New Zealand Clinical Trials Registry, registration number: 12609000628246.

Eligibility of FDRs

FDRs were eligible to participate in the trial if they were aged 18 or older, English speaking and able to provide informed consent. Information collected from the CRC patients was used to determine the family risk status of their FDRs based on the National Health and Medical Research Council's risk categories (see Supplementary Table 1).⁷ As part of our duty of care, all FDRs categorised to risk category 3 (potentially high risk) were sent the targeted intervention material and excluded from the study. Only those FDRs assigned to risk categories 1 (at or slightly above average risk) and 2 (moderately increased risk) were included in this study.

Consenting FDRs participated in a brief telephone screening interview to assess eligibility. Those with a prior diagnosis of CRC, advanced adenoma or FAP, or an inflammatory bowel disease (IBD) such as Crohn's disease or ulcerative colitis were ineligible.

Randomisation

Participating CRC patients and their FDRs were randomised (ratio 1:1) as a family unit to receive either standard information (control) or a targeted print-based intervention. Randomisation was conducted centrally using a computer-generated procedure. Interviewers were blind to participants' allocation.

Intervention group

FDRs randomised to the intervention group were sent a targeted letter that provided advice on recommended CRC screening tests and intervals based on their level of family risk. A brochure detailing the three risk levels and their corresponding screening recommendations was included. The GP of the FDR was sent a targeted letter

indicating the likely risk category of the first degree relative and a brochure on screening recommendations developed for health professionals.

Control group

FDRs assigned to the control group received a generic pamphlet on bowel cancer screening with population screening recommendations but no information about recommendations specific to different levels of risk.

Measures

Data were collected via CATI at baseline and by mailed paper and pencil survey at 12 month follow-up between February 2010 and November 2012. Age, gender, marital status, location, education, employment, and health insurance status of participants were collected by CATI at baseline. At baseline and 12 months follow-up FDRs were asked to provide self-reported information on their CRC screening history. Participants were asked if they had ever had an FOBT/Colonoscopy/Sigmoidoscopy and, if so, how long ago they had the test, and the reason for the test.

Classification of adherence

Based on responses to the baseline and follow-up surveys, participants were classified as adherent, or non-adherent to guideline recommendations. Those in the adherent group reported having had the appropriate test for their age and risk category in the recommended time frame. Those in the non-adherent group were over-screened (commenced screening younger than is recommended or had a more intensive test than recommended) or under-screened (overdue for screening or had a less intensive test than recommended).

Statistical analysis

Sociodemographic characteristics of FDRs are presented for the control and intervention groups. A mixed effects logistic regression model that included group (control vs intervention), time (baseline vs follow-up), a group by time interaction, risk category (1 and 2), age (under 50 and over 50) and sex, while accounting for correlation among individuals in the same family and within individuals over time was fitted to the data. The group by time interaction term assessed, using the Wald test, whether adherence at follow-up differed between groups adjusting

for any baseline differences. The intervention effect is presented as the ratio of the odds of adherence at follow-up for intervention versus control group, relative to the odds of adherence at baseline for intervention versus control group, adjusted for other covariates included in the model, with 95% confidence intervals. A post hoc sub-group analysis was conducted separately for risk categories 1 and 2 to determine whether the intervention was effective for each risk category. The primary analysis was conducted as a complete case analysis, where those without follow-up data were excluded. As a sensitivity analysis we also undertook multiple imputation,¹⁹ imputing 20 datasets using a monotone imputation model that included adherence at baseline and follow-up, age category, sex, risk category, rurality, education, employment, whether Australian born, marital status, insurance status, relationship to index case, and whether or not other family members were included in the study; with separate imputation models for intervention and control groups. Estimates were then obtained using Rubin's rules.²⁰ All analyses were conducted in Stata 11.²¹

The study anticipated about 1,600 first degree relatives would be available at 12 month follow-up, which would provide 80% power, with a 5% significance level, and assuming a design effect of two for correlation of the outcome among family members, to detect a difference in guideline adherence of 10%.

Results

Sample characteristics

A total of 752 (25%) index cases were recruited to the study and completed the baseline interview on average 250 days (SD=104) after diagnosis. The index cases identified 3,594 family members who were potentially eligible to participate and provided contact details for 2,376 (66%). Of these, 905 (38%) agreed to participate in the study with 40 (4.4%) excluded following a screening interview due to ineligibility (CRC n=12; FAP n=11; IBD n=13; CRC and FAP n=2; CRC and IBD n=1; FAP and IBD n=1) and a further 46 (5.1%) not responding. A total of 819 (34%) FDRs completed the baseline interview and 245 (30%) were found to be at potentially high risk of CRC and thus excluded from the trial. The study included 574 FDRs: 252 (44%) in the intervention group and 322 (56%) in the control group. A flowchart of the recruitment process is in Figure 1.

Baseline characteristics were similar for the intervention and control groups, as shown in Table 1.

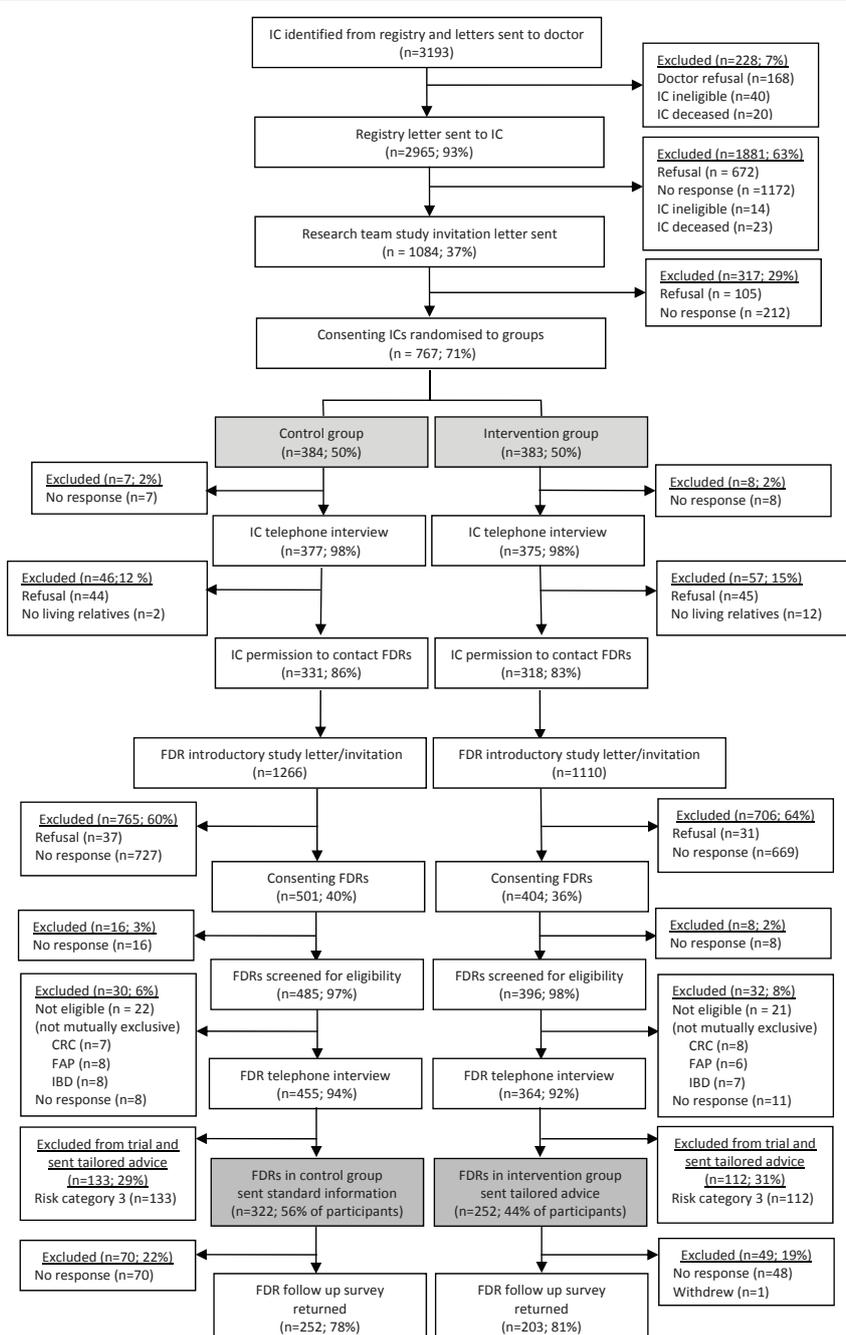
Follow-up surveys were sent to all 574 participants at 12 months post-baseline with a similar proportion of intervention (n=203, 81%) and control (n=252, 78%) participants providing follow-up data (Table 1).

Screening adherence in control and Intervention groups from baseline to follow-up

Table 2 shows that at follow-up, 145 (58%) individuals in the control group and 124

(61%) in the intervention group were adherent to screening guidelines. Sixty-four (25%) and 55 (27%) were over-screened and 43 (17%) and 24 (12%) were under-screened in the control and intervention groups respectively. Most over-screening was due to having a more intensive test (e.g. colonoscopy) than recommended by the guidelines (33/55 (60%) of those over-screened in the intervention group and 35/64 (55%) in the control group); with the remainder due to screening at an earlier age than the guidelines recommend (22/55 (40%) in the intervention group and 29/64 (45%) in the control group).

Figure 1: Recruitment process flowchart.



There was a significant difference between adherence in the intervention and control groups at follow-up adjusting for differences at baseline (Table 3; Adjusted Intervention Effect=2.7; 95%CI=1.2-5.9; $p=0.013$).

Compared with younger people, those aged over 50 years had lower odds of adherence [OR = 0.07 (0.03-0.14), $p<0.0001$]. Participants in risk category 2 (OR = 2.8 (1.3-6.0), $p=0.010$) had higher odds of adherence compared to those in risk category 1. The results for the multiple imputation analysis were very similar (data not shown).

The post-hoc subgroup analysis found that screening adherence was higher for the intervention relative to the control group at follow-up (adjusted for baseline values) for risk category 1 participants (Adjusted Intervention Effect=3.9; 95%CI=1.6-9.6; $p=0.002$). There was no effect of the intervention for risk category 2 (Adjusted Intervention Effect=0.36; 95%CI=0.05-2.5; $p=0.299$).

Discussion

This is the first Australian trial to test the effectiveness of a population-based approach for improving screening among first degree relatives of people affected by colorectal cancer. It is also one of the few trials internationally that examine the impact of a registry-based approach to improve cancer screening. Because of the number of test options available, the measurement of CRC screening outcomes is challenging²² with most studies focusing on increasing the use of a single test type rather than adherence to guideline recommendations for people of different risk levels.

Our results indicated that the targeted intervention was effective at improving adherence at follow-up, but this was a small overall effect, with minimal between groups difference at follow-up. Further, post hoc subgroup analysis indicated that the intervention effect was only

statistically significant for those in category 1. This may be due to the lower baseline screening adherence rates observed for those in risk category 1 compared to those in risk category 2. This finding may also reflect that targeted recommendation provided to risk category 1 participants was in accordance with population-based screening recommendations. Thus, the information provided may have acted as a prompt or booster to other forms of screening information to which risk category 1 participants had been exposed to (e.g. via mass media, screening invitations received through the NBCSP). In addition the number of individuals in risk category 2 was small, thus there was low statistical power for this sub-group analysis.

There are few studies with which to directly compare these results. A Cochrane review on the impact of personalised risk communication on uptake of screening tests included a sub-analysis of studies on CRC screening. This showed that providing individuals with a CRC risk score or risk category resulted in greater uptake of tests than not providing this information.²³ However, the outcome assessed, screening uptake is not synonymous with screening adherence as assessed in the current study. Our outcome takes into account the potential for screening intervention to result in inappropriate increases in screening, and as such, may provide a better indication of the usefulness of the intervention. Glanz et al.¹³ used similar recruitment and had similar numbers of FDRs in their risk categories and found that face-to-face and telephone counselling was effective in improving CRC screening adherence.

Overall, our results and those of Glanz et al.¹³ are discouraging of a strategy that sources FDRs through index cases listed in a population-based registry. A mere quarter of eligible index cases agreed to their relatives being approached and, of these relatives, one-third agreed to be involved. This recruitment method is intensive with many steps involved to approach the FDRs. Our study showed that in Australia, at least, the scope of this strategy to make gains in adherence to screening guidelines is modest. Over half the participants were adherent to guidelines at baseline and nearly four fifths had been screened for CRC (includes over-screened). These rates exceed current population estimates⁹⁻¹¹ and are in part due to the inclusion of FDRs under age 50 who

Table 1: Demographic characteristics of first degree relatives (n=574) of CRC Index Cases.

	Control 322 (56%)		Intervention 252 (44%)	
	n (%)		n (%)	
Age	Mean=51yrs (SD=13.7)		Mean=51yrs (SD=13.9)	
under40	70 (22%)		53 (21%)	
40-50	84 (26%)		74 (29%)	
50-60	85 (26%)		62 (25%)	
60-70	49 (15%)		40 (16%)	
over 70	34 (11%)		23 (9%)	
Male	140 (43%)		103 (41%)	
Urban dwelling	196 (61%)		149 (59%)	
Australian born	292 (91%)		238 (94%)	
Married/De facto	259 (80%)		188 (75%)	
Education				
University degree	141 (44%)		116 (46%)	
Vocational training	70 (22%)		55 (22%)	
Secondary completed	42 (13%)		33 (13%)	
Secondary not completed	69 (21%)		48 (19%)	
Employment status				
Employed	235 (72%)		170 (67%)	
Do not do paid work	23 (7%)		27 (11%)	
Retired	52 (16%)		39 (15%)	
Missing	12 (4%)		16 (6%)	
Private health insurance	238 (74%)		178 (71%)	
Family Risk category				
At or slightly above average	257 (80%)		186 (74%)	
Moderately increased	65 (20%)		66 (26%)	
Relationship to Index case				
Parent	6 (2%)		5 (2%)	
Sibling	108 (34%)		78 (31%)	
Child	208 (65%)		169 (67%)	
Family member in sample	250 (78%)		180 (71%)	
Adherent at baseline	204 (64%)		145 (58%)	
Returned follow-up survey	252 (78%)		204 (81%)	

Table 2: Screening adherence at baseline and follow-up for FDRs.

	Baseline (N=574)		Follow-up (N=455)	
	control (N=322)	Intervention (N=252)	control (N=252)	Intervention (N=203)
Adherent	203(63%)	145(58%)	145(58%)	124(61%)
Non-adherent -Over screened	50(16%)	46(18%)	64(25%)	55(27%)
Non-adherent -Under screened	69(21%)	61(24%)	43(17%)	24(12%)

are adherent by not having screening. Our results also suggest that FDRs may already have received and acted on advice or been sensitised to act by the occurrence of cancer in their relative. In line with this, the pattern of increase between baseline and follow-up surveys in overscreening and of decrease in under-screening was very similar in the control and intervention groups.

It is possible the procedure followed had unmeasured benefits for high-risk FDRs who were excluded due to the urgent (ethical) need to send them targeted advice rather than risk allocating them to a control group with no intervention. Hence the benefits of the strategy implemented in this study are probably greater than we report here.

Most of the study participants who were non-adherent at follow-up were over-screened (having a test at a younger age than recommended or having a more intensive test than recommended). This indicates that different strategies may be needed to shift those who are due/overdue for a test compared to those who are over-screened due to age or test type. There is a paucity of research on reducing rates of over-screening. However, in the context of limited health care resources, this is an important focus for future research. For example, one recent study assessed colonoscopy waiting times in public hospitals in South Australia for patients who had returned a positive FOBT through the National Bowel Cancer Screening Program. Results indicated that only 23% of cases underwent colonoscopy within the 30-day benchmark.²⁴ It is likely that the proportion of patients with a positive FOBT who receive a colonoscopy within recommended time frames could be increased by reducing inappropriate screening colonoscopies.

Limitations

Selection bias may have operated at two levels: the modest consent rate of index cases (25%) completing the baseline interview and subsequently, the consent rate of first degree relatives referred to the study by them (38%). It is also possible that there were biases introduced due to the two different methods used for recruitment of FDRs. In particular, where index cases opted to pass on the study invitation to their FDR, we had no way of knowing whether this information was received. Thus, the factors influencing non-response may have differed by recruitment method. Due to recruitment taking longer than anticipated, we also had to terminate

Table 3: Mixed effects model with adherence to screening as the outcome under a complete case analysis framework (N=574 with 119 missing adherence at follow-up).

		Adherent at baseline N(%)	Adherent at follow-up N(%)	Odds ratio (95% CI)	P value*
Group	Control	203 (63%)	145 (58%)		
	Intervention	145 (58%)	124 (61%)	0.56 (0.28-1.2)	0.115
Time	Baseline	348 (61%)			
	Follow-up		269 (59%)	0.62 (0.37-1.0)	0.069
Age	Under 50	232 (83%)	140 (68%)		
	Over 50	116 (40%)	129 (52%)	0.07 (0.03-0.14)	<0.001
Risk category	category 1	260 (59%)	196 (55%)		
	category 2	88 (67%)	73 (75%)	2.8 (1.3-6.0)	0.010
Sex	Male	151 (62%)	111 (59%)		
	Female	197 (60%)	158 (59%)	0.75 (0.41-1.4)	0.345
Group x time interaction			2.7 (1.2-5.9)#	0.013	

* p-value for Wald tests

Interaction Effect: Odds ratio for adherence in intervention versus control at follow-up relative to odds ratio for adherence in intervention versus control at baseline.

recruitment prior to reaching our target sample size. The consent rate was similar to Glanz et al.¹³ using a similar registry-based recruitment method to contact FDRs. The loss to follow-up at 12 months was 21% and was similar for the intervention and control groups; however, the overall sample obtained was smaller than planned, which resulted in the detectable difference being larger than anticipated.

A further bias to the study may come from the reliance on self-reported screening history. Previous studies, however, have found high rates of specificity and sensitivity between self-reported screening history and documented screening tests for both FOBTs (82% sensitivity and 78% specificity) and endoscopy (79% sensitivity and 90% specificity).²⁵

Conclusions

Our results indicate that targeted print-based information on CRC screening may have a modest effect on improving adherence to CRC screening recommendations among FDRs of people with colorectal cancer. Low participation rates to the study, however, are likely to have affected both the generalisability and efficiency of the intervention. Further work is needed to improve participation of index cases and FDRs in order to maximise the population impact of the intervention.

Funding

This research was supported by a National Health and Medical Research Council grant (Grant ID 510776), a Strategic Research Partnership Grant from Cancer Council NSW

to the Newcastle Cancer Control Collaborative (New-3C), and infrastructure funding from the Hunter Medical Research Institute.

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