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Title:
Screening participation for people at increased risk of colorectal cancer due to family history: A systematic review and meta-analysis

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Abstract:

We conducted a systematic review and a meta-analysis of observational studies to identify and summarise the level of colorectal cancer (CRC) screening participation for people at increased risk due to family history of the disease. Medline, Cinhal, Embase and PsychInfo databases were comprehensively searched between January 1995 and May 2012 to identify relevant articles. To be included, studies had to report on screening for people who had at least one first-degree relative with CRC and no previous personal diagnosis of the disease. Pooled screening participation levels were calculated for each screening modality. Seventeen studies, accounting for a total of 13,269 subjects with a family history of CRC met the inclusion criteria. Seven studies, including a total of 6,901 subjects had a pooled faecal occult blood testing (FOBT) screening participation (at least once) of 25% (95% CI 12% to 38%). Five studies including a total of 5091 subjects had a pooled sigmoidoscopy-based screening participation (at least once) of 16% (95% CI 7% to 27%). Seven studies including a total of 9,965 subjects had pooled participation colonoscopy-based screening (at least once) of 40% (95% CI 26% to 54%). There was a significant level of screening heterogeneity between studies. This review identified a substantial underuse of CRC screening for people at increased risk of developing the disease. It highlights the potential opportunity that exists for increasing screening participation among this segment of the population and the need to adjust the current CRC screening policies towards that objective.

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers in the world. The disease causes over half a million deaths each year and accounts for approximately ten percent of total worldwide cancer diagnoses [1]. One of the most consistently shown risk factors for CRC is having a family history of the disease.[2-4] Between 25 to 62 percent of the familial risk of CRC can be explained by mutations in known high-risk genes [5]. Around 2% to 5% of all CRC cases are caused by familial syndromes caused by inherited genetic mutations, for example in the mismatch repair genes (Lynch syndrome) and in the *APC* gene (familial adenomatous polyposis) [6-8]. Carriers of mutations in these genes have substantially increased risks of cancer. The remainder of the familial aggregation remains unexplained, possibly due to undiscovered genetic factors and/or non-genetic factors that are shared by relatives. Until the familial risk is well understood for the majority of the population, personal risk assessment and identification of people susceptible to develop these uncharacterised familial CRCs continues to be based on family history of the disease.

Several population- and clinic-based studies have quantified the association of CRC risk and family history of CRC [2-4, 9-11]. For example, having a first-degree relative (FDR) with a previous diagnosis of CRC is associated with an increased personal risk between two and four fold depending on the age of diagnosis of the CRC and the age of the at-risk individual. Given the strength and consistency of such findings, in terms of disease prevention, family history of the disease provides a valuable risk assessment tool that has been used in many countries to recommend screening

modality and frequency.

Screening with faecal occults blood test (FOBT)—followed by diagnostic colonoscopy for positive tests—has been shown by randomised controlled trials (RCTs) to be effective in reducing CRC incidence and mortality in people at average- or "population-risk" [12-14]. Biennial FOBT screening from age 50 is now widely recommended by several published guidelines [15-18] and many countries have introduced mass screening programmes addressed to the general population. Although there are no randomised controlled trials of screening for those above average risk based on family history, specific screening recommendations exist, and despite some variation by country, most recommend more intensive and usually colonoscopy-based screening for people above average risk. To date, however, no country has funded screening programmes targeting persons at increase risk of CRC due to family history. Screening initiatives are designed for those at "population risk" and therefore may be inappropriate for individuals above that risk. Very little is known about the screening participation of those at familial risk of CRC. In the only review currently published on this topic, Rees and colleagues presented a first inventory of studies conducted up to 2007 reporting the level of screening participation in this population along with the level of genetic risk assessment services attendance. The review concluded that uptake of endoscopic screening when offered to individuals categorised as being at increased risk was generally high. The authors however, did not provide a precise estimate of CRC screening participation specific to people with a family history of CRC but no inherited genetic mutations. Also, the review did not exclude studies with screening participants having previously been diagnosed with CRC, thus combining surveillance with screening which might have resulted in an overestimation of

screening uptake [19].

To address these gaps, we conducted a systematic review and a meta-analysis of observational studies to identify and summarize the level of CRC screening participation for people at increased risk of CRC due to family history. Our primary objective was to update and extend on the study by Rees et al. by presenting a more specific and comprehensive assessment of the level of CRC screening participation among those at increased risk of the disease.

Methods

Selection criteria

We considered all observational cohort and cross-sectional studies reporting CRC screening participation of persons at increased risk of CRC because of their family history of the disease. To be included, studies had to report quantitative screening participation of individuals with at least one first-degree relative (FDR) with CRC and no previous personal diagnosis of the disease. Article inclusion was restricted to studies published in English or French and to studies reporting any of the three main CRC screening modalities, i.e., faecal occult blood test (FOBT), sigmoidoscopy and/or colonoscopy. Studies only reporting the screening participation of persons at average risk of CRC due to family history or at increased risk due to a known genetic mutation or a diagnosis of inflammatory bowel disease were also excluded. Similarly, studies reporting results from trials or health promotion interventions designed to improve CRC screening uptake were excluded from this review as we

estimated that their findings reflected the effectiveness of particular interventions rather that the level of screening participation in the population.

Search strategy

A literature search was undertaken to identify all studies meeting the selection criteria. The search strategy comprising selected MeSH and free text terms in relation to colorectal cancer screening and familial risk was developed with the assistance of a medical librarian. Medline, Cinhal, Embase and PsychInfo databases were comprehensively searched between January 1995 and May 2012 to identify relevant articles. We chose 1995 as the earliest date so as to focus our review on articles published since the first RCTs demonstrating the effectiveness of CRC screening. A first pass for eligibility was done based on titles and abstracts. References from all relevant articles were then checked for any additional publications. Full articles of potentially relevant studies were retrieved and assessed for final inclusion.

Data analysis

Methodological details from each study were recorded. Abstracted information included first author's name, date and country of the study, study design and participants' characteristics; the CRC screening modality assessed; the definition of familial risk of CRC and the proportion of participants who underwent screening, and if reported, whether they had done so for specified time periods prior to the survey (screening participation). Several studies reported estimated screening participation separately for more than one screening modality. For the purpose of the meta-analysis we treated modality-specific data as multiple studies within the same article, i.e.,

screening participation for each modality were included as separate terms in the meta-analysis. Pooled screening participation was calculated for each screening modality, following the method described by Mills et al. [20] and Stasi et al. [21]. To determine pooled screening participation, we first stabilized the variance of the raw proportions of participants who screened according to the Freeman-Tukey arcsine square root transformation [22]. Individual transformed proportions were then back-transformed and a random effects model was used to pool the data for summary estimates of screening participation. Forest plots were generated to show individual study screening participation and 95% confidence intervals (CI) in relation to the summary estimate. The I^2 statistic was used to assess heterogeneity among studies [23]. All statistical analyses were conducted using Stata 11.

Results

Our search identified a total of 4,986 articles. After examining titles and abstracts, we selected 181 articles for a more detailed consideration. Figure 1 summarises the article selection process. A total of 17 [24-40]. studies met the selection criteria. Sixteen studies were cross-sectional surveys of screening participation by family history of CRC based on self-reports. Of these, eight studies [24-26, 31, 33, 34, 38, 39] used existing population-based studies or cancer registries to identify and recruit CRC cases. These cases were then asked permission to contact their relatives for inclusion in the study. Three studies [27, 28, 30] were community-based including unaffected subjects who reported having a FDR with CRC. Four studies [27, 29, 36, 40] were hospital-based. CRC patients were identified in hospitals and asked permission to contact their unaffected FDRs. One study [37] used an advertising

campaign to recruit participants for a survey on screening practices. Included studies were published in four different countries (8 in the United States, 2 in Canada, 4 in Australia and 2 in France) between 1988 and 2012. The number of subjects included in all studies combined was 13,269 and ranging from 40 to 4308 participants per study (Table 1).

Familial risk

In all studies, family history of CRC was defined as having at least one FDR who had been diagnosed with CRC. In addition five of the 17 studies [24, 26, 28, 30, 36] used FDRs' age at diagnosis of CRC to define risk category.

Screening participation

Table 2 shows CRC screening participation within time periods prior to the survey (when available) reported in the included articles. Eight studies [25, 27, 29, 32-34, 38, 39] defined participation as ever having undergone a CRC screening test. Ten studies [24, 26, 28, 30, 31, 36, 37, 40] reported screening participation including the frequencies recommended by local guidelines. Only five studies [24, 26, 34, 38, 39] clearly distinguished between screening and diagnostic test by excluding subjects reporting diagnostic tests from their analysis. Finally, five studies [24, 26, 28, 30, 36] reported guideline-defined screening participation based on specific family histories of CRC (Table 3).

Meta-analysis

A total of 13,269 subjects with a family history of CRC, i.e., at least 1 FDR affected or with a previous diagnosis, were recruited across the 17 included studies. Figures 2-5 display forest plots showing the screening participation (ever) for each screening modality.

Seven studies [24-26, 28, 32, 37, 40], including a total 6,861 subjects, had a pooled FOBT screening participation (at least once) of 25% (95% CI 12% to 38%). Five studies [24, 32, 36, 37, 40] including a total of 5,091 subjects had a pooled CRC sigmoidoscopy screening participation (at least once) of 16% (95% CI 5% to 27%). Seven studies [24, 25, 28, 30-32, 36, 40] including a total of 9,965 subjects had a pooled colonoscopy screening participation (at least once) of 40% (95% CI 26% to 54%). Five studies reported guideline-defined screening participation. Pooled analysis of their results found that five-yearly colonoscopy screening was 31% (95% CI 12% to 51%) for a subset of 2,154 subjects categorised as having a strong family history of CRC (Table 3). Overall, there was strong evidence for heterogeneity between studies with an I^2>88% in all the meta-analysis conducted.

Discussion

The aim of this systematic review was to provide estimates of CRC screening participation for people with at least one affected FDR. This group comprises about 10% of the population, which has, on average, a two-fold increased risk of the disease. We identified 17 studies investigating the CRC screening practices in this segment of the population. Meta-analyses of the included studies' results showed that

the level of screening participation was low, with test-specific estimates of ever screening of 40%, 16% and 25% for colonoscopy, sigmoidoscopy and FOBT respectively. These results are markedly lower than the findings presented in the 2008 review conducted by Rees and co-authors, which reported uptake of endoscopic screening in this population to be *"often higher than 60%"* [19]. In contrast to our study, their study was not based on a meta-analysis and did not attempt to quantify summary test-specific screening participation estimates. Also, half of the studies included in the review included individuals attending genetic risk assessment services, and therefore under intensive surveillance programmes appropriate for mutation carriers with levels of adherence to colonoscopy ranging between 52% and 88%. Such tests may therefore be considered surveillance tests, rather than screening tests.. The estimate reported by Rees et al. is therefore likely to be a large overstatement of the true level of screening participation for those with a family history of CRC but no genetic mutation identified.

Clinical practice guidelines recommend that individuals at increased risk of CRC due to family history should have more intensive screening compared to those with no family history [15-18]. Our review shows that the overall, level of screening participation for such individuals is low. Of particular concern is the level of colonoscopic screening participation (40%), given that most guidelines recommend colonoscopy to be the primary screening modality for people above average risk of CRC. Guideline-defined screening participation was even lower (31%), which shows that similar to the average-risk population, screening recommendations for those most at risk of developing the disease are not being implemented.

Level of screening participation is a primary aspect on which the effectiveness of any particular screening strategy should be evaluated [41]. A high participation is a prerequisite condition without which screening is likely to have only a marginal impact on disease prevention and a limited beneficial effect at the population level. Low participation has been consistently observed for CRC screening [42-44], representing a major barrier to the effectiveness of many of the existing CRC screening programmes in terms of CRC incidence and mortality reduction. When effective modalities exist, screening is particularly relevant for populations at higher risk of developing a specific disease. Accordingly, failure to undergo screening in these increased-risk populations has a disproportionate negative effect in terms of disease prevention [45]. Given that all current CRC screening programmes are unfocused with respect to family history, our results highlight the important shortfall that exists in terms of prevention among those at increased risk of CRC. Including and assigning a higher priority to this segment of the population, could improve CRC screening strategies and have an important impact on CRC prevention as a whole by facilitating a more efficient allocation of limited screening resources.

Given the incapacity of most of the existing screening policies and programmes to implement appropriate screening practices in the population, system and policy level interventions are needed to improve the level of CRC screening participation among those most at risk. In this context, there are increasing calls to develop risk prediction models that will permit stratification of people for screening according to their personal risk of CRC [46]. This would enable more screening efforts and resources to improve screening participation for those most likely to develop CRC. Such risk prediction models have already been applied to a certain extent in breast cancer

screening and several prediction tools have been developed. For example, scientists from the United States National Cancer Institute have recently developed a breast cancer risk tool that predicts a woman's likelihood of developing the disease in the next 5 years and up to 90 years of age, after she enters personal information about 8 risk factors [47-49]. Several prediction models exist for CRC that use family history [50-52] however there are no models to date that use all known risk factors of CRC including family history, genetic factors and environmental/lifestyle factors [53]. As our understanding of the genetic features associated with CRC and their potential use to prevent the disease expand, rigorous CRC risk prediction and stratification tools will become available allowing personalised assessment of risk and appropriate screening recommendations [54, 55]. An initial step in this process would be to integrate the existing knowledge on the relationship between family history and CRC to the current CRC screening initiatives. This could substantially improve the overall preventive impact and cost-effectiveness of CRC screening, as a large group of people at increased risk of the disease, currently largely under-screened, could be systematically identified and offered appropriate screening.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis of studies investigating the screening practices of individuals with family history of CRC. One of the main strengths of this study is that it provides a broad overview of the level of participation of a segment of the population at significantly increased risk of CRC, and which has been under-studied in terms of screening practices evaluation. It also

summarises a large body of literature and presents precise and test-specific estimates of screening uptake that can be used to inform future CRC screening strategies.

Our review has several limitations. First, as for any systematic review selective reporting and publication bias may have influenced the results of our meta-analysis and our conclusions. Given the limited number of studies identified for each screening modality, we were unable to formally assess the likelihood of publication bias in the different meta-analysis. As general rule, it has been recommended that tests for funnel plot asymmetry should not be used when there are fewer than ten studies in the meta-analysis otherwise test power is usually too low to distinguish chance from real asymmetry. When there is substantial heterogeneity—which is the case in this study—the minimum number of studies may be substantially more than ten [56].

It is also possible that during the article selection process some relevant studies were missed or inappropriately excluded. To minimise this, we used a highly sensitive literature search strategy to identify and consider all relevant studies. Second, we applied a very broad conceptual definition of CRC screening uptake and we limited participation to the minimal criteria of having at least one CRC screening test which was the definition used by all the studies included in this systematic review. Given the limitations of the individual studies used for this analysis we defined screening participation as having at least one screening test without stating the period (even though this varied by study, e.g., one test in a life time or one test within the past 1, 2, 5 or 10 years). Similarly, we were unable to consider consecutive use of a specific test or adherence to screening over-time, both key determinants for effectiveness. Third, only two of the included studies attempted to confirm participants' screening status

through medical records [34, 35] despite the reliability of self-reported information being a commonly recognised potential source of bias in studies of cancer screening behaviour [41]. In support of use of unverified reports of screening, previous research has shown that self-reported information is likely to provide sufficiently accurate estimates of the true frequencies of screening procedures, particularly for colonoscopy [57]. Fourth, most studies did not distinguish between screening and diagnostic procedures which would be expected to result in an upwardly biased estimate of the screening participation.

Heterogeneity between studies

Finally, there was important heterogeneity in the estimates of screening participation across studies. This was mainly due to the small number of studies available for each screening modality (7 for FOBT, 7 for colonoscopy and 5 for sigmoidoscopy), and to the variability of the definition of family history used to determine CRC risk categories. Our meta-analyses pooled screening participation of individuals with different thresholds of family history and therefore potentially very different levels of CRC risk with consequent differences in screening uptake. We also pooled results from studies drawn from over 15 years, a period over which CRC screening practices may have changed significantly. Another potential source of heterogeneity could be the differences in CRC screening activities between the 4 countries where the studies were conducted. Overall, the high level of heterogeneity observed in the different meta-analyses reflects the main limitation of our review, which is the methodological shortcomings of the included studies. It also shows the lack of agreement that exists among investigators regarding the approach and conceptual definitions to be used,

and more generally, the challenges in the study of CRC screening behaviour they face [41]. It is important to note however that it does not change the primary finding that CRC screening participation is low in the segment of the population most at risk due to family history of the disease.

In summary, our results show underuse of screening for people with family history of CRC. Particular attention should be paid to the fact that our estimates are likely to overstate screening participation given the important methodological limitations of the included studies. This highlights the large potential opportunity that exists for increasing screening participation among this segment of the population if more efforts were dedicated to target this group of population, and the need to adjust the current CRC screening policies towards that objective.

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Conflict of interest:

The authors declare that they have no conflict of interest

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Table 1. Characteristics of CRC screening participation studies

Study	Survey name/location	Design	Data collection period	Population	N	Age	Definitions of CRC family history	Screening test distinguished from diagnosis test Yes/No
Richardson et al. 1995[37]	Nationwide United States	Cross-sectional survey based on mailed questionnaire	1988	Co-twins of CRC cases	83	≥ 50 years	At least 1 FDR with CRC	No
Eisinger et al.1996[29]	Health examination campaign conducted by a French public health insurance centre France	Cross-sectional survey based on interview	1993	Random sample of members of a health insurance company	278	20-80 years	At least 1 FDR with CRC or > 1 FDR with CRC	No
Harris et al.1997[32]	New South Wales Australia	Cross-sectional survey based on self-administered questionnaires	1997	Unaffected FDR of CRC cases identified via the NSW Cancer Registry	225	39-90 years	At least 1 FDR with CRC	No
Clavel-Chapelon 1999[25]	E3N France	Prospective cohort	1999	Women members of a professional health insurance company	4308	40-65 years	At least 1 FDR with CRC	No
Codori 2001[27]	Baltimore United States	Cross-sectional survey based on self-administered questionnaires	2001	Unaffected FDR of CRC cases identified via the Johns Hopkins Hospital cancer clinics and CRC	1160	Not reported	At least 1 FDR with CRC	No

		registry						
Cockburn 2002[26]	New South Wales Australia	Cross-sectional survey based on computer-assisted telephone interviews	2000	Randomly selected households from the electronic NSW telephone directory	40	≥ 40 years	At least 1 FDR with CRC diagnosed < 55yrs	Yes
Manne 2002[35]	North-East United States	Cross-sectional survey based on computer-assisted telephone interviews	2002	Unaffected FDR of CRC cases recruited from oncology and surgical practices at four cancer centres	504	≥ 35 years	At least 1 FDR with CRC diagnosed < 56yrs	No
Trasher 2002[40]	Erie County, New York	Cross-sectional survey based on Community-based interviews	1999	Participants to a community-based FOBT screening programme	564	≥ 50 years	At least 1 FDR with CRC	No
Madlensky 2003[34]	Ontario Colon Cancer Family Registry Canada	Cross-sectional survey based on self-administered questionnaires	2003	Eligible participants to the OCCFR study	368	≥ 35 years	At least 1 FDR with CRC	Yes
Fletcher 2007[30]	Large HMO in the greater Boston United States	Cross-sectional survey based on mailed questionnaires	2004	Random sample of the group practice members	215	35-55 years	At least 1 FDR with CRC diagnosed ≤ 60 years or ≥ 1 FDR with CRC diagnosed at any age or 1 FDR with CRC diagnosed ≥ 60 years or 2 SDR with CRC	No

Table 1 *(continued)*

Shah I 2007[39]	NHIS United States	Cross-sectional survey based on interviews	2002	Men from randomly selected households in the United States	177	40-79 years	At least 1 FDR with CRC	Yes
Shah II 2007[38]	NHIS United States	Cross-sectional survey based on interviews	2002	Women from randomly selected households in the United States	338	40-79 years	At least 1 FDR with CRC	Yes
Griffitch 2008[31]	Maryland Cancer Survey United States	Cross-sectional survey based on computer-assisted telephone interviews	2002	Random sample of Maryland residents	381	≥ 50 years	At least 1 FDR with CRC	No
Murff 2008[36]	SCCS United States	Cross-sectional survey based on a mailed questionnaire	2002-2006	Siblings of CRC cases	2591	40-79 years	1 FDR with CRC diagnosed ≥50 years or At least 1 FDR with CRC diagnosed ≤ 50 years or ≥ 1 FDR with CRC diagnosed at any age	No
Mack 2009[33]	Calgary Health Region Canada	Cross-sectional survey based on self-administered questionnaires	2009	Unaffected FDR of CRC cases identified via the Alberta Cancer Registry	356	≥ 40 years	At least 1 FDR with CRC	No
Ait Ouakrim 2012[24]	ACCFR Australia	Cross-sectional survey based on self-administered questionnaire and telephone interviews	1997-2001	Unaffected FDR of CRC cases identified via the Victorian Cancer Registry	1628	≥18 years	At least 1 FDR with CRC diagnosed ≤ 55 years or ≥ 2 FDR with CRC diagnosed at any age or	Yes

							At least 3 FDR diagnosed with CRC at any age or ≥2 FDR or a combination of FDR and SDR on the same side of the family diagnosed ≤ 50 years	
Courtney 2012[28]	HCS Australia	Cross-sectional survey based on self-administered questionnaire	2009	Unaffected FDR of CRC cases identified via the New South Wales electoral role	53	56-88 years	At least 1 FDR with CRC diagnosed ≤ 55 years or ≥2 FDR with CRC diagnosed at any age or At least 3 FDR diagnosed with CRC at any age or ≥2 FDR or a combination of FDR and SDR on the same side of the family diagnosed ≤ 50 years	Not specified

SCCS: Southern Community Cohort Study, E3N: Etude Epidemiologique de Femmes de la Mutuelle Generale de l'Education Nationale part of the European Prospective Investigation on Cancer, FDR: First Degree Relative; HMO: Health Maintenance Organisation, NHIS: National Health Interview Survey, OCCFR: Ontario Familial Colon Cancer Registry, ACCFR: Australasian Colorectal Cancer Family Registry, HCS: Hunter Community Study

Table 2: Estimates of colorectal cancer screening participation by screening modality

Study	N	Time periods	CRC Screening			
			Uptake estimate	By sex	By age	By risk category
FOBT						
Richardson 1995[37]	83	Within 1 year	42.3%	Female		
		Within 1-3 years	29.5%	Female		
		Within 3-5 years	7.7%	Female		
		≥ 5 years	29.5%	Female		
		Never	11.5%	Female		
Harris 1997[32]	225	Ever	22%			
Clavel-Chapelon 1999[25]	4308	Ever	23.8			
Cockburn 2002[26]	40	Within 1 year	2.6%			
		Within 2 years	2.6%			
		Within 3 years	2.6%			
		Never	92.1			
Trasher 2002[40]	564	Within 1 to 2 years	6%			
		Never	70%			
Ait Ouakrim 2012[24]	1236	Ever	1.2%			>1 FDR or 1 FDR diagnosed < 55 years
	392	Ever	2.1%			≥3 FDR *
Courtney 2012[28]	34	Within 2 years	15%			>1 FDR or 1 FDR diagnosed < 55 years
		≥ 2 years	27%			
		Never	51%			
		Not sure	6%			
	19	Within 2 years	21%			≥3 FDR *
		≥ 2 years	16%			
		Never	58%			
		Not sure	5%			
Sigmoidoscopy						
Richardson 1995[37]	83	Within 1 year	16%	Female		
		Within 1-3 years	25.3%	Female		
		Within 3-5 years	8%	Female		
		≥ 5 years	20%	Female		
		Never	30.7%	Female		
Harris 1997[32]	225	Ever	17%			
Trasher 2002[40]	564	Within 5 years	9%			
		Never	91%			
Murff 2008[36]	2591	Within 5 years	61 (2.3%)		< 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			69 (2.7%)		≥ 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			64 (2.5%)		< 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
			166 (6.4%)		≥ 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
Ait Ouakrim 2012[24]	1236	Ever	1.1%			>1 FDR or 1 FDR diagnosed < 50 years
	392	Ever	2%			≥3 FDR *
Colonoscopy						
Clavel-Chapelon 1999[25]	4308	Ever	25.5%			
Trasher 2002[40]	564	Within 10 years	21%			
		Never	61%			
Fletcher 2007[30]	215	Within 5 years	6%		< 50 yrs	Strong FH of CRC
			8.3%		≥ 50 yrs	Strong FH of CRC
Griffith 2008[31]	381	Within 10 years	59.5%			
Murff 2008[36]	2591	Within 5 years	3.6%		< 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			6.2%		≥ 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			4.5%		< 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
			14.5%		≥ 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
		Within 10 years	4.4%		< 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			6.7%		≥ 50 yrs	>1 FDR or 1 FDR diagnosed < 50 yrs
			4.8%		< 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
			15.9%		≥ 50 yrs	1 FDR diagnosed at age ≥ 50 yrs
Ait Ouakrim 2012[24]	1236	Within 5 years	6%			>1 FDR or 1 FDR diagnosed < 50 yrs
		Ever	20%			
		Never	74%			
	392	Within 2 years	1%			≥3 FDR *
		Ever	36%			
		Never	63%			
Courtney 2012[28]	34	Within 2 years	14%			>1 FDR or 1 FDR diagnosed < 55 years
		≥ 2 years	26%			
		Never	32%			

		Not sure	0%			
	19	Within 2 years	52%			≥3 FDR *
		≥ 2 years	21%			
		Never	21%			
		Not sure	5%			
Endoscopy						
Eisinger 1996[29]	278	Ever	30.6%			1 FDR diagnosed
			1.8%			> 1 FDR diagnosed
Codori 2001[27]	1160	Ever	60%			
Cockburn 2002[26]	40	Within 1 year	10%			
		Within 2 years	12.5%			
		Within 3 years	5%			
		Within 4 years	2.5%			
		≥ 5 years	10%			
		Never	57.5%			
Any screening test						
Manne 2002[35]	504	Ever	57%			
Madlensky 2003[34]		Ever	64%			
Fletcher 2007[30]	215	Sigmoidoscopy every 5 years and FOBT every year, OR colonoscopy every 10 years	7.4%		< 50 yrs	Intermediate FH of CRC
			33%		≥ 50 yrs	Intermediate FH of CRC
Shah I 2007[39]	177	Ever	84%	Male	≥ 50 yrs	
			15.8%	Male	<50 yrs	
Shah II 2007[38]	338	Ever	57%	Female	≥ 50 yrs	
			8.9%	Female	< 50 yrs	
Mack 2009[33]	356	Ever	70%			

Table 3. Studies having used guideline-based definition of CRC screening participation and risk

Study	Guidelines used	Definition of CRC family history	Screening frequency	N*	Appropriate screening (%)
Murff 2008[36]	Winawer et al 2003[58]	1 FDR diagnosed at age <50 y or ≥ 2 FDR	At least one colonoscopy in the last 5 years	793	255 (32%)
Fletcher 2007[30]	HVMA	1 FDR diagnosed at age ≤60 y or ≥ 2 FDR	At least one colonoscopy in the last 5 years	53	31 (58%)
Cockburn 2002[26]	NHMRC 1999	1 FDR diagnosed at age ≤55 y or ≥ 2 FDR	At least one colonoscopy in the last 5 years	38	12 (31%)
Ait Ouakrim 2012[24]	NHMRC 2005[15]	1 FDR diagnosed at age ≤55 y or ≥ 2 FDR	At least one colonoscopy in the last 5 years	1236	70 (6%)
Courtney 2012[28]	NHMRC 2005[15]	1 FDR diagnosed at age ≤55 y or ≥ 2 FDR	At least one colonoscopy in the last 5 years	34	14 (41%)

* Subset of the total number of participants in each study categorised as "above average risk of CRC", FDR: first degree relative, HVMA: Harvard Vanguard Medical Associates, NHMRC: National Health and Medical Research Counc

Figure 1. Flowchart of study selection process

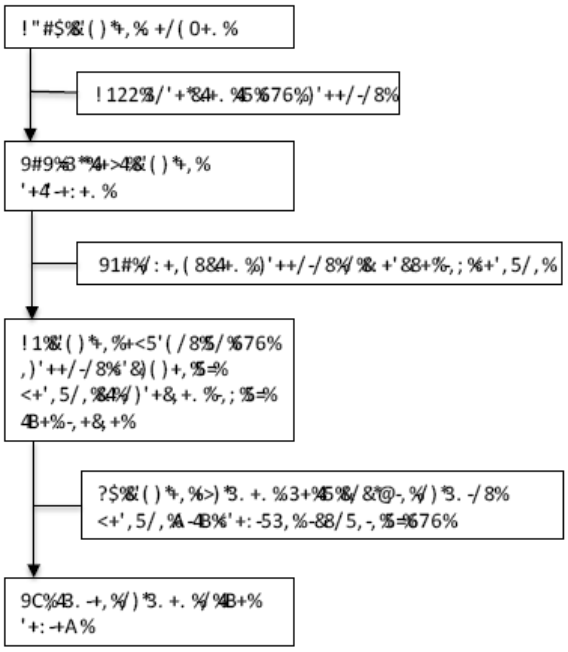


Figure 2. Level of FOBT screening participation for first-degree relatives of CRC cases.

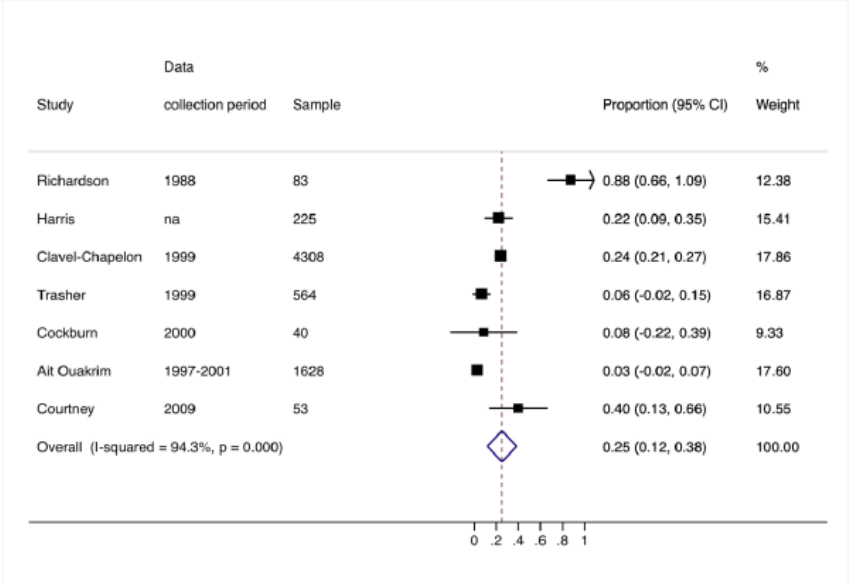


Figure 3. Level of sigmoidoscopy screening participation for first-degree relatives of CRC cases.

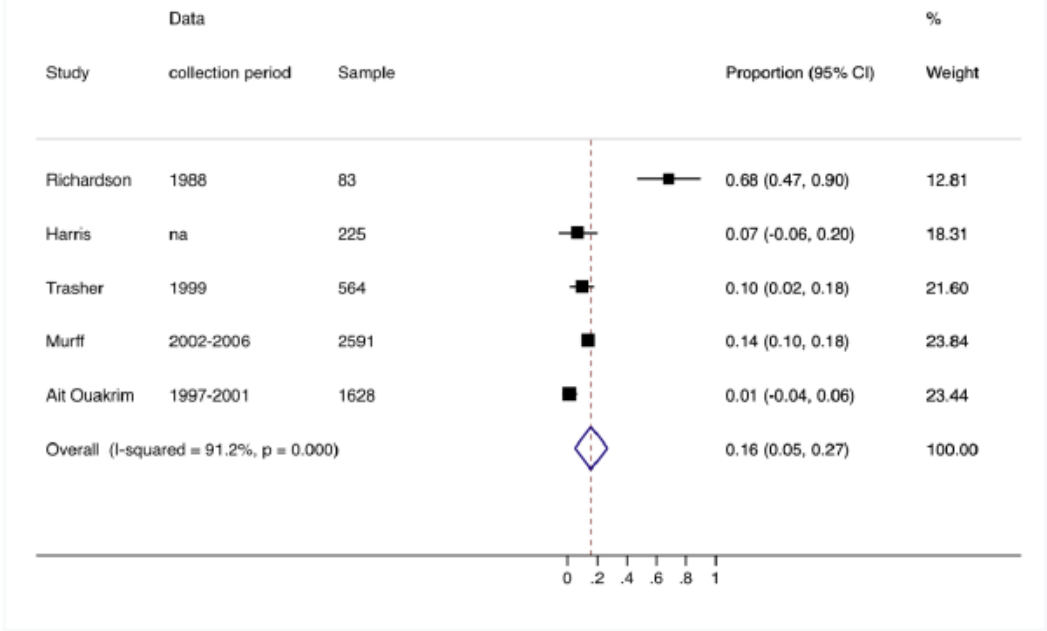


Figure 4. Level of colonoscopy screening participation for first-degree relatives of CRC cases.

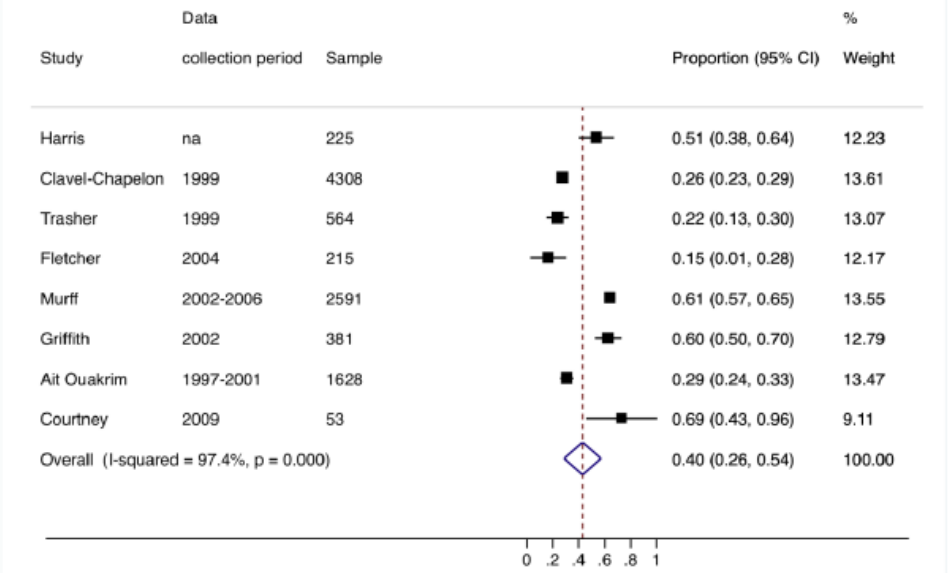
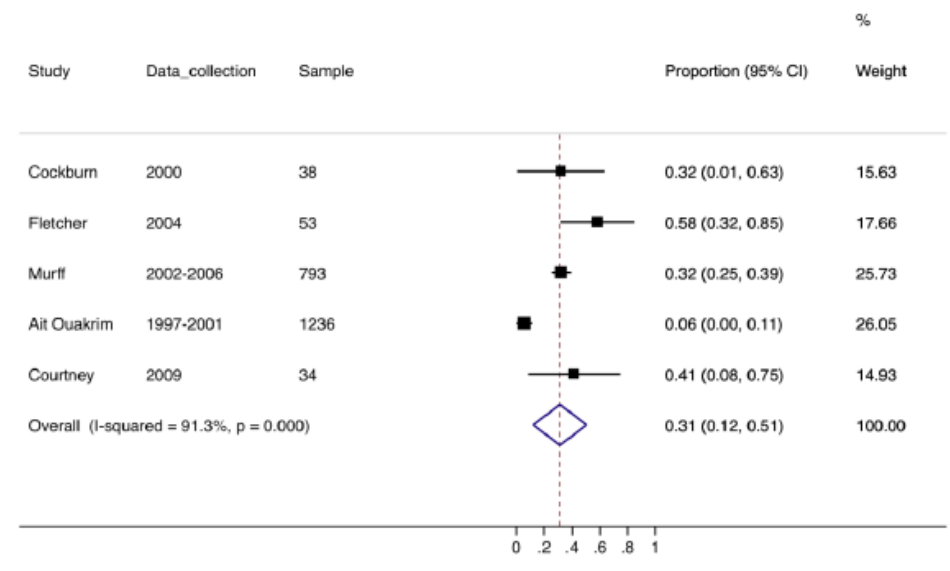


Figure 5. Level of guideline-defined screening participation for first-degree relatives of CRC cases*.



* Five-yearly colonoscopy