Research Article

Cancer Epidemiology, Biomarkers & Prevention

Comparison of Uptake of Colorectal Cancer Screening Based on Fecal Immunochemical Testing (FIT) in Males and Females: A Systematic Review and Meta-analysis

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Abstract

Background: Colorectal cancer is the third most common cancer in males and the second in females worldwide. Incidence and mortality are higher in men than women. Colorectal cancer screening is effective in reducing mortality. Internationally, fecal immunochemical testing (FIT) is increasingly being recommended as the primary screening test. This systematic review and meta-analysis aimed to determine whether uptake of FIT screening differs between men than women.

Methods: We searched PubMed and Embase for peer-reviewed articles published in English during 2000–2013 for randomized controlled trials (RCT) or observational studies of screening using FIT that quantified numbers invited and participating by gender. Meta-analysis was performed using a random effects model.

Results: Six hundred and eighty-five citations were identified, 19 meeting the inclusion criteria. Random effects meta-analysis found male uptake was significantly lower than female uptake [odds ratio (OR), 0.84; 95% confidence interval (CI), 0.75–0.95; $P < 0.01$]. This generally persisted throughout subgroup analysis of study design (RCTs vs. observational studies and study quality), screening organization (methods of invitation, number of samples, age range of screening, recommendations, and reminders), and setting.

Conclusions: Meta analysis of FIT screening studies indicates significantly lower uptake among men.

Impact: Further investigation is required into factors influencing acceptability and participation of FIT screening in both sexes.
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Introduction

Colorectal cancer is the third most common cancer diagnosed in males and the second most common in females (1). Worldwide more cases and deaths occur in males than females, with the age-standardized incidence rate 44% higher (20.6 vs. 14.3 per 100,000) and age-standardized mortality 45% higher in males (10.0 vs. 6.9 per 100,000; ref. 1). Most colorectal cancers are considered to arise from precancerous polyps; if left *in situ* polyps can progress to cancer over a 10- to 15-year period (2). However, colorectal cancer can be prevented, or treated effectively if detected early, through screening (3). Evidence indicates efficacy of screening in reducing cancer mortality and, in some instances, incidence (4–8).

A number of countries have implemented population-based colorectal cancer screening programs (9–11). Screening can be delivered through procedures conducted in a clinic or doctor's office, such as colonoscopy or flexible sigmoidoscopy (FS), or through noninvasive methods that are suitable to be undertaken in an individual's home, such as fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT). Currently, most programs that use fecal-based tests use FOBT (11, 12). However, FIT is a more specific and sensitive test (8) and recent guidelines recommend it as the initial screening modality (3, 13). In order for a screening program to be effective in reducing mortality it needs to be well organized and requires high uptake (3). It is well established that uptake is higher for noninvasive, than more invasive, colorectal cancer screening tests (14). In addition, recent evidence suggests uptake is higher with FITs than FOBTs (15). Furthermore, some studies suggest gender differentials in uptake; uptake is higher among men for more invasive procedures and higher among women for noninvasive tests (16–18). What remains to be established is whether there is gender difference in uptake of screening based on FIT.

The aim of this study was to conduct a systematic review and meta-analysis to determine whether uptake of FIT-based screening differs by gender. A secondary aim of the study was to assess factors that may influence any gender-based differences.

Materials and Methods

Search strategy and selection criteria

Citations published in peer-reviewed English journals during January 2000 to December 2013 that reported uptake of FIT-based screening in males and females, were identified from Pubmed and Embase using a structured search strategy. MeSH terms included "neoplasms," "malignancy," "early detection of cancer," "compliance," "adherence," "colon" and "rectum." Text word search

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terms included variations of "colorectal," "bowel," "colon," "rectal," "gastric," "cancer," "neoplasm," "malignant," "participation," "compliance," "uptake," "attendance," "FIT," "fecal," "fecal," "immunochemical," "test," "kits," "FOBT," "iFOBT," "occult," "blood," and "test." One author (N. Clarke) carried out the initial screening from the search strategy to remove ineligible citations such as duplicates, conference proceedings, letters, commentary, and editorials. Two authors (N. Clarke and A. Osborne) then independently determined eligibility based on the inclusion and exclusion criteria by reading the full text of the remaining articles. To be included in the review, FIT was required to be used as a primary screening (i.e., initial) test; studies in which FIT was used for triage of people with a positive primary screening test (e.g., FIT following gFOBT) were excluded. Studies which offered individual participants a choice of different screening tests, such as FIT or colonoscopy (i.e., in which the participant decided which test to undergo) were excluded. Studies or trials with a single group/test or multiple arms/tests and in which the screening test was assigned by the investigator were eligible for inclusion. In those with multiple arms, FIT had to be the primary test in at least one arm and only the arm(s) using FIT were included in the analysis. Studies were included if they reported: randomized controlled trials (RCT—experimental studies in which individuals are randomly allocated to receive or not receive an intervention and then followed to determine the effect of the intervention) in which one arm involved screening by FIT; observational studies (study designs that are not randomized control trials) in which FIT was the primary screening test; or screening programs in which FIT was the primary screening test. Studies were included if they reported numbers of people invited and screened by FIT by gender. Differences of opinion on study eligibility were resolved through discussion among the authors. A standardized form was developed to abstract data from eligible studies, including invitation and uptake figures by gender, study design, screening age range, invitation and recruitment methods, use of recommendations and reminders, and number of samples required.

Quality assessment

Eligible studies were assessed for methodologic quality using two instruments: the Cochrane risk of bias tool (19) for RCTs and the Newcastle–Ottawa Scale for observational studies (20). The Cochrane risk of bias tool assesses bias on six domains covering selection, performance, detection, attrition, reporting, and any other bias. For our review, we assessed only selection bias (random sequence generation), reporting, and other bias (comparability of confounding factors and appropriate use of statistical tests). Assessments of performance and detection bias were not carried out as many screening trials are unblinded; it is therefore likely that participants are aware of the arm to which they are assigned (21). Attrition bias or incomplete outcome data (including nonresponse, noncompliance or withdrawal) was not assessed because noncompliance was the outcome of interest. Cohort (study of groups of individuals, some of whom are exposed to an intervention and followed over time to determine the effect of the intervention on the outcome of interest) and cross-sectional studies (observation of a defined population at a single point in time or during a specific time interval where outcome and exposure are determined simultaneously) were assessed using the Newcastle–Ottawa Scale by awarding stars as an overall rating of three methodologic factors: selection [sample representativeness (1 star) and sample size (1 star)], comparability [authors controlled for or reported confounding factors for uptake by sex and age (1 star), and for other factors such as education, marital, income, or employment status (1 star)] and outcome [clear description of statistical analysis (1 star) and measurement of association or difference with confidence intervals (CI) and *P* values and use of appropriate statistical test (1 star)]. After risk of bias assessment, RCTs were also assessed for quality using the same criteria as observational studies. Studies were assessed overall based on the number of stars they had been awarded of a possible six, with 5 to 6 stars being considered high quality, 3 to 4 stars moderate quality, and 2 or less stars low quality.

Statistical methods

Within each study, participants were invited to complete one test. Studies that compared screening tests (multiple arms in RCTs) did not offer more than one choice of screening to each participant. Uptake was defined as the number of persons targeted (i.e., persons invited to participate in screening) who returned a completed FIT kit.

Studies were combined in a meta-analysis, conducted in Review Manager 5 (The Cochrane Collaboration). Because of the high level of heterogeneity, a random effects model was used. Subgroup analysis was also carried out to determine whether the effect estimates varied by study characteristics. Subgroups were defined on the basis of study quality (high, moderate, or low), study design (RCT or observational), age range of those invited to screening (40–75, 50, or older with no upper age limit), number of FIT samples required for test completion (1 or 2 or more samples), letter of invitation (with advance notification or without advance notification), test delivery method (test mailed to recipient or test collected by recipient), use of recommendations or endorsement of test (yes or no), and use of reminders (reminder provided or no reminder provided). Studies that did not report on these methods or that used different methods were excluded from relevant analysis. Only one study reported multiple screening rounds. This study (22) was very large (comprising 92% of the invited population and 87% of the screened population when all studies were combined) and reported six screening rounds (22). In the primary analysis, this study was included with data from 2004 (round 1). Six sensitivity analyses were conducted to determine their impact on the effect estimate: (i) excluding this study entirely; (ii) using round 2 data (2005), (iii) using round 3 data (2006), (iv) using round 4 data (2007), (v) using round 5 data (2008), and (vi) using round 6 data (2009).

Results

Study selection and characteristics

In total, 685 potentially eligible citations were identified. Following review, 19 studies were eligible for inclusion in the review and meta-analysis (22–40). A flow chart of the search strategy results is provided in Fig. 1. Study characteristics are summarized in Table 1. Six were RCTs, 12 were cross-sectional studies, and one was a cohort study. Nine studies originated from Europe, three from Asia, three from North America, three from Australia, and one from South America. Fifteen studies were population-based (i.e., studies in which screening is systematically offered by invitation to a defined population).

Across the 19 studies, a total of 2,650,358 [round 1; Park and colleagues (22)] individuals were invited to participate in FIT

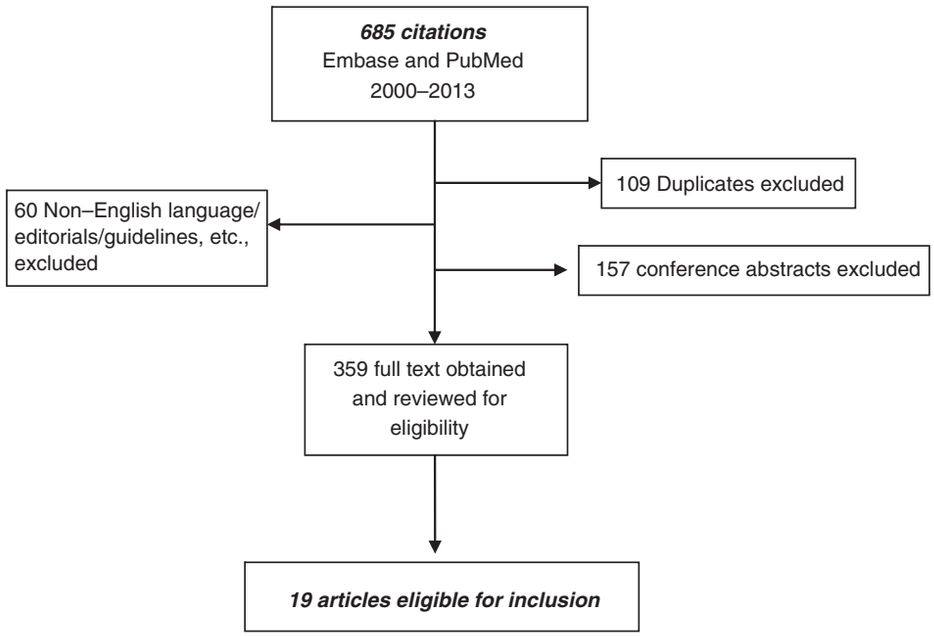

Figure 1.
Study flow diagram: result of search strategy.

screening and 407,451 were screened (uptake = 15.4%). Excluding the largest study (22), 384,979 were invited and 169,586 screened (uptake = 44.1%).

Meta-analysis

Uptake in males and females combined ranged from 11% (round 1; ref. 22) to 90% (Table 2; ref. 26). Meta-analysis of all included studies indicate significantly lower male uptake [odds ratio (OR), 0.84; 95% CI, 0.75–0.95; $P < 0.01$; Fig. 2).

Park and colleagues (22) account for 85% (round 1; round 2: 92%) of the entire screening population in the meta-analysis. In round 1 of this study, uptake was significantly higher in males than females (OR, 1.16; 95% CI, 1.15–1.17; $P < 0.01$; Table 2), while in the subsequent five rounds uptake was significantly lower in males than females (Table 2).

When the meta-analysis was repeated replacing the round 1 results of Park and colleagues (22) with those from each of the subsequent five rounds, this had little impact on the overall risk estimate which ranged between 0.83 and 0.84 (round 2: overall meta-analysis OR, 0.84; 95% CI, 0.77–0.90; $P < 0.01$; round 3: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$; round 5: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$; and round 6: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$). When Park and colleagues (22) was excluded entirely from the meta-analysis, male uptake remained significantly lower (OR, 0.83: 95% CI, 0.74–0.92; $P < 0.01$).

Quality assessment

Of the 19 studies, seven were deemed to be of low quality, and 12 were considered moderate quality, while none were deemed to be of high quality. Results are summarized in Table 3. Moderate quality studies had significantly lower uptake in males (OR, 0.81; 95% CI, 0.76–0.85; $P < 0.01$) while low-quality studies had nonsignificantly lower uptake in males (OR, 0.89; 95% CI, 0.63–1.26; $P = 0.51$); however, there was no significant difference in these subgroups ($P = 0.58$; Table 4). In addition, we repeated the meta-analysis restricted to moderate quality studies only; the lower uptake in males persisted and the effect size was very similar to that seen when all studies were included (moderate quality studies only: OR, 0.83; 95% CI, 0.71–0.96; $P = 0.01$).

Study design

Uptake was significantly lower in males than females in both RCTs (OR, 0.83; 95% CI, 0.71–0.97; $P = 0.02$) and observational studies (OR, 0.83; 95% CI, 0.76–0.91; $P < 0.01$; Table 4). There was nonsignificantly lower male uptake in studies which were not part of an organized screening program (OR, 0.74; 95% CI, 0.51–1.07; $P = 0.11$) as was the case for studies which were not population-based (OR, 0.88; 95% CI, 0.73–1.07; $P = 0.20$).

Setting

Uptake was significantly lower among males in studies based in Europe and Australia, nonsignificantly lower in studies based on North America and South America, and not different in studies based in Asia (Table 4) but, overall, subgroup differences for setting were nonsignificant ($P = 0.16$).

Letter of invitation

The recruitment methods used in the 16 studies that described this were heterogeneous. Invitations were made from a central screening location ($n = 10$), general practitioner (GP) clinics ($n = 4$), or through an index subject invited for cervical cancer screening ($n = 1$; Table 1). Nine studies used a letter of invitation mailed to subjects while three studies used an advance notification letter of invitation, mailing letters to inform subjects they would be invited, and subsequently mailing a letter of invitation to participate. One study used an advanced notification letter inviting subjects to complete a bowel cancer survey, subsequently mailing a test to responders. Subgroup differences for invitation methods were nonsignificant ($P = 0.41$). Male uptake was significantly

Table 1. Characteristics of the 19 studies on FIT uptake in males and females included in the meta-analysis

Study & year	Population based	Age range, y	Letter of invitation	Test delivery method	Recruitment location	Recommendation/ endorsement	Reminder	Number of samples and interval	Test	Country
Cohort studies										
Senore et al., 2012 (33)	Yes	58 and 60	Letter—no advance notification	Test collected	GP	GP	No reminder	1	OC Sensor	Italy
Cross-sectional studies										
Fenochi et al., 2006 (26)	No	50+	Not reported	Test collected	GP	GP	2-mo reminder	1	OC Hemodia	Uruguay
Gregory et al., 2011 (32)	Yes	50–74	Advance notification letter to screening survey	Test mailed	Central	No recommendion	6-wk reminder	Not reported	InSure	Australia
Kluhsman et al., 2012 (38)	No	50+	Face to face rec ruitment	Test collected	GP	GP	2 wks	Not reported	INSure	United States
Crotta et al., 2004 (25)	Yes	50–74	Letter—no advance notification	Test collected	Central	Mayor	2-mo reminder	1	OC Sensor, Japan	Italy
Chen et al., 2007 (27)	Yes	50+	Not reported	Test collected	Out-reach	Public health nurse	Not reported	1	Not reported	Taiwan
Parente et al., 2009 (29)	Yes	50–69	Letter—no advance notification	Test collected	Central	No recommendion	No reminders	1	HM-Jack	Italy
Levy et al., 2010 (30)	No	50–64	Advance notification letter	Test mailed	Central	No recommendion	Not reported	Not reported	Clearview ULTRA FOB	United States
Park et al., 2011 (22)	Yes	50+	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Republic of Korea
Cai et al., 2011 (31)	Yes	40–74	Not reported	Not reported	Not reported	Not reported	Not reported	2 at interval of 1 week	Not reported	China
Ferrari et al., 2012 (36)	Yes	50–69	Not reported	Not reported	Not reported	GP	Reminder - interval not reported	Not reported	Tes t tube	Italy
McDonald et al., 2012 (37)	Yes	50–74	Letter—no advance notification	Test mailed	Central	No recommendion	Not reported	1	Eiken	Scotland
Kelley et al., 2013 (40)	Yes	50–75	Letter—no advance notification	Test mailed	Not reported	Not reported	Not reported	2 at interval of 1 day	OC Sensor	Ireland
Randomized control trials										
Cole et al., 2002 (23)	No	50+	Letter—no advance notification	Test mailed	Central & GP	No recommendation/ practice/GP	6-wk reminder	3 interval not reported	Flexsure OBT	Australia
Cole et al., 2003 (24)	Yes	50–69	Letter—no advance notification	Test mailed	Central	No recommendion	6-wk reminder	3 (FlexSure OBT) interval not reported 2 (Insure) Interval not reported	FlexSure OBT/ InSure	Australia
Gupta et al., 2013 (39)	Yes	54–64	Letter—no advance notification	Test mail ed	Central	No recommendion	3-wk reminder	1	O C -Auto FIT C HEK	United States
Hol et al., 2012 (34)	Yes	50–74	Advance notification letter	Test mailed	Central	No recommendion	6-wk reminder	1	OC Sensor	the Netherlands
Quintero et al., 2012 (35)	Yes	50–69	Advance notification letter	Test collected	Central	GP/specialist	3- and 6-mo reminders	1	OC Sensor	Spain
van Rossum et al., 2008 (28)	Yes	50–75	Letter—no advance notification	Test mailed	Central	No recommendion	2-wk reminder	1	OC Sensor	the Netherlands

Table 2. Uptake figures by male and female for the 19 studies in meta-analysis with ORs, 95% CI, and *P* value

	Total		Males		Females			
	Invited	Screened	Invited	Screened	Invited	Screened		
Author/year	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	OR (95% CI)	*P*
Park et al., 2011 Round 1 (22)	2,265,379	237,865 (10.5%)	969,813	105,710 (10.9%)	1,295,566	123,148 (10.2%)	1.16 (1.15–1.17)	$P < 0.05$
Park et al., 2011 Round 3 (22)	4,406,700	691,754 (15.7%)	2,062,961	307,381 (14.9%)	2,343,739	384,373 (16.4%)	0.89 (0.89–0.90)	$P < 0.05$
Park et al., 2011 Round 6 (22)	4,625,557	1,211,896 (26.2%)	2,150,635	535,508 (24.9%)	2,474,922	675,654 (27.3%)	0.88 (0.88–0.89)	$P < 0.05$
Cole et al., 2002 (23)	2,400	857 (35.7%)	1,094	375 (34.2%)	1,306	482 (36.9%)	0.89 (0.75–1.05)	$P = 0.18$
Cole et al., 2003 (24)	1,212	425 (35.1%)	592	196 (33.1%)	620	229 (36.9%)	0.85 (0.67–1.07)	$P = 0.33$
Crotta et al., 2004 (25)	2,961	1,631 (55.1%)	1,403	710 (50.6%)	1,558	921 (59.1%)	0.71 (0.61–0.82)	$P < 0.05$
Fenocchi et al., 2006 (26)	11,734	10,573 (90.1%)	3,663	3,282 (89.6%)	8,071	7,291 (90.3%)	0.92 (0.81–1.05)	$P = 0.22$
Chen et al., 2007 (27)	56,968	22,672 (39.8%)	21,502	9,481 (44.1%)	35,466	13,191 (37.2%)	1.33 (1.29–1.38)	$P < 0.05$
van Rossum et al., 2008 (28)	10,322	6,157 (59.6%)	5,037	2,820 (55.9%)	5,285	3,337 (63.1%)	0.74 (0.69–0.80)	$P < 0.05$
Parente et al., 2009 (29)	78,083	38,693 (49.6%)	37,838	18,314 (48.4%)	37,950	20,379 (53.7%)	0.81 (0.79–0.83)	$P < 0.05$
Levy et al., 2010 (30)	297	235 (79.1%)	131	131 (80.9%)	166	129 (77.7%)	1.22 (0.69–2.15)	$P = 0.50$
Cai et al., 2011 (31)	31,963	24,409 (76.4%)	16,169	11,962 (74.0%)	15,794	12,447 (79.0%)	0.76 (0.73–0.81)	$P < 0.05$
Gregory et al., 2011 (32)	375	192 (51.2%)	181	86 (47.5%)	194	106 (54.6%)	0.75 (0.50–1.13)	$P = 0.17$
Senore et al., 2012 (33)	37,691	7,281 (19.3%)	17,223	2,719 (15.8%)	20,468	4,562 (22.3%)	0.65 (0.62–0.69)	$P < 0.05$
Hol et al., 2012 (34)	4,407	1,092 (24.8%)	2,221	472 (21.3%)	2,186	620 (28.4%)	0.68 (0.59–0.78)	$P < 0.05$
Quintero et al., 2012 (35)	26,599	9,089 (34.2%)	12,156	4,145 (34.1%)	14,443	4,944 (34.2%)	0.99 (0.94–1.05)	$P = 0.82$
Ferrari et al., 2012 (36)	42,245	1,744 (41.3%)	20,311	7,980 (39.3%)	21,934	9,461 (43.0%)	0.85 (0.82–0.89)	$P < 0.05$
McDonald et al., 2012 (37)	66,225	38,720 (58.5%)	32,318	18,058 (55.8%)	33,907	20,662 (60.9%)	0.81 (0.79–0.84)	$P < 0.05$
Kluhsman et al., 2012 (38)	200	145 (72.5%)	50	29 (58.0%)	150	116 (77.0%)	0.40 (0.21–0.80)	$P < 0.05$
Gupta et al., 2013 (39)	1,593	648 (40.7%)	600	232 (38.7%)	993	416 (41.9%)	0.87 (0.71–1.08)	$P = 0.20$
Kelley et al., 2013 (40)	9,704	5,023 (51.8%)	4,499	2,177 (48.4%)	5,205	2,846 (54.7%)	0.78 (0.72–0.84)	$P < 0.05$

lower in studies that did not use an advance notification letter of invitation (OR, 0.77; 95% CI, 0.73–0.82; $P < 0.01$) while there was nonsignificantly lower male uptake in studies using a letter with advance notification (OR, 0.89; 95% CI, 0.64–1.23; $P = 0.47$; Table 4).

Test delivery method

Several studies ($n = 7$) required the participant to collect the test from a GP, nurse, or pharmacist, while nine studies mailed the test. Subgroup differences for test delivery methods were nonsignificant ($P = 0.65$). Male uptake was significantly lower in studies which mailed the test to participants' homes (OR, 0.79; 95% CI, 0.75–0.83; $P < 0.01$) and nonsignificantly lower in studies which required participants to collect the test (OR, 0.83; 95% CI, 0.66–1.05; $P = 0.13$; Table 4).

Screening recommendations

Eight studies used recommendations or endorsement of screening, either by a GP, nurse, or local Mayor. Subgroup differences were nonsignificant for use or nonuse of recommendations ($P = 0.54$). Those studies that provided a screening recommendation had nonsignificantly lower uptake in males (OR, 0.85; 95% CI, 0.68–1.05; $P = 0.13$) while there was significantly lower male uptake in studies that did not use recommendations (OR, 0.79; 95% CI, 0.76–0.82; $P < 0.01$; Table 4).

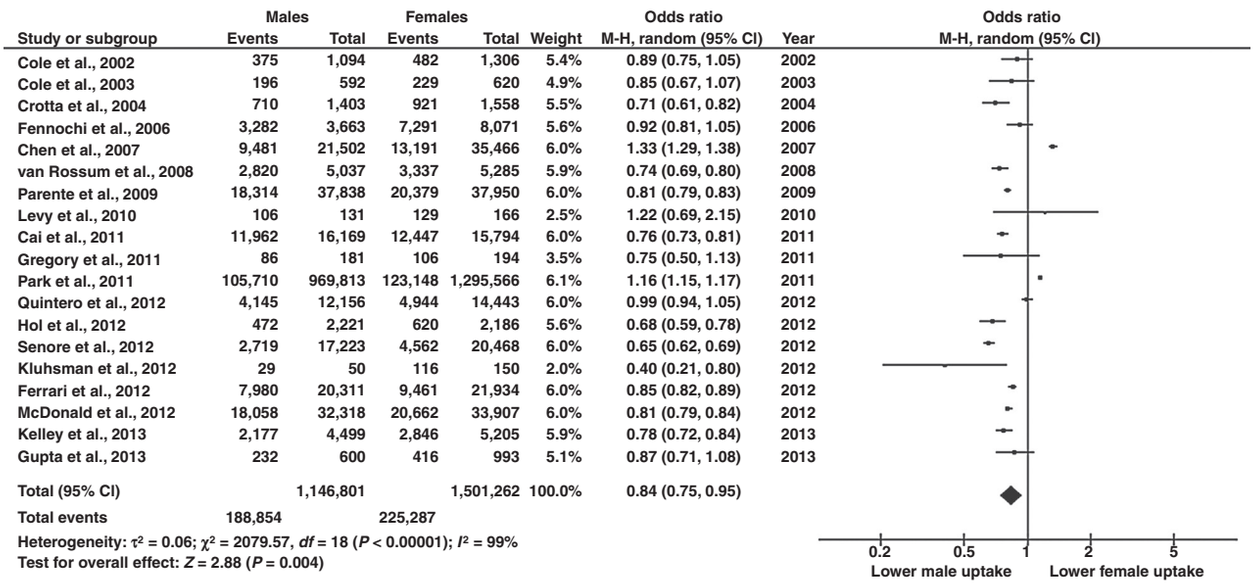

Figure 2.
Forest plot corresponding to the main random effects meta-analysis of 19 estimates quantifying the relationship between gender and uptake of FIT-based colorectal cancer screening.

Table 3. The Newcastle–Ottawa scale of included studies: reviewers judgment

	Sample representativeness (selection)	Sample size (selection)	Counfounding controlled (comparability)	Statistical tests (outcome)	Total stars and quality rating
Park et al., 2011 (22)	*	*		*	3/6 moderate
Cole et al., 2002 (23)	*	*		**	4/6 moderate
Cole et al., 2003 (24)	*	*		**	4/6 moderate
Crotta et al., 2004 (25)	*	*			2/6 low
Fenochi et al., 2006 (26)			*		1/6 low
Chen et al., 2007 (27)	*				1/6 low
van Rossum et al., 2008 (28)	*	*		**	4/6 moderate
Parente et al., 2009 (29)	*	*			2/6 low
Levy et al., 2010 (30)				*	1/6 low
Cai et al., 2011 (31)	*	*		**	4/6 moderate
Gregory et al., 2011 (32)	*			*	2/6 low
Senore et al., 2012 (33)	*	*		*	3/6 moderate
Hol et al., 2012 (34)	*	*		**	4/6 moderate
Quintero et al., 2012 (35)	*	*		**	4/6 moderate
Ferrari et al., 2012 (36)	*	*	**		4/6 moderate
McDonald et al., 2012 (37)	*	*		*	3/6 moderate
Kluhsman et al., 2012 (38)				*	1/6 low
Gupta et al., 2013 (39)		*		**	3/6 moderate
Kelley et al., 2013 (40)	*	*		**	4/6 moderate

Screening age range

Subgroup differences were nonsignificant for screening studies targeting different age ranges ($P = 0.28$). Uptake was significantly lower in males when screening was targeted at those of ages 40 to 75 years (OR, 0.79; 95% CI, 0.74–0.84; $P < 0.01$) while uptake targeted at those of ages 50 years and over with no upper age limit was similar in males and females (OR, 0.92; 95% CI, 0.70–1.19; $P = 0.51$; Table 4).

Fenocchi and colleagues (26) and Ferrari Bravo and colleagues (36) reported uptake by age and gender. In the former, uptake was nonsignificantly lower in males in people of ages 50 to 69 years (OR, 0.93; 95% CI, 0.81–1.07; $P = 0.32$) and those of ages 70 years or older (OR, 0.71; 95% CI, 0.41–1.29; $P = 0.22$). In the latter, uptake in males was significantly lower in those of ages 50 to 59 years (OR, 0.76; 95% CI, 0.72–0.81; $P < 0.01$) and in those of ages 60 to 69 years (OR, 0.94; 95% CI, 0.88–0.99; $P = 0.02$), but did not differ in those of ages 70 71 years (OR, 1.05; 95% CI, 0.87–1.27; $P = 0.56$).

Number of FIT samples required

Fourteen studies reported the number of samples requested; 10 studies requested one sample and four requested two or three samples over varying time intervals. The subgroup differences for the number of samples required were nonsignificant ($P = 0.42$). The OR for male uptake was significantly lower in both subgroups (one sample: OR, 0.84; 95% CI, 0.71–0.98: $P = 0.03$; two/three samples: OR, 0.78; 95% CI, 0.74–0.82; $P < 0.01$; Table 4).

Screening reminders

Ten studies reported the use of reminders (varying from 2 weeks to 6 months; Table 1) and two studies reported using no reminders. Male uptake was significantly lower in both subgroups (Table 4) with no difference in these subgroups ($P = 0.51$).

Discussion

This systematic review and meta-analysis is the first to examine whether there are gender differences in uptake of FIT-based colorectal cancer screening. It provides valuable information for screening agencies relating to the implementation and delivery of program. Overall, uptake in males was 16% lower than in females, and this was statistically significant. Although there was notable heterogeneity between studies in terms of design and screening organization, as well as overall uptake, lower uptake in males persisted across subgroups by study design, setting, methods of invitation and delivery, use of recommendations, screening age range, number of samples, and use of reminders.

Of note was the similar uptake in males and females in studies based in Asia, which contrasted with studies from other settings. Studies from Asia had similar uptake in males and females, whereas studies from Europe reported lower uptake among men. Although subgroup differences were nonsignificant across countries, much of the data required for inclusion in subgroup analysis was not reported in the studies from Asia. Therefore, the possibility that cultural or social factors may be responsible for differential uptake in males and females cannot be entirely discounted. It will be interesting to observe uptake of FIT-based screening in future studies within countries in Asia in comparison with Europe and Australia.

There was also no significant difference in male and female uptake in studies of low quality. Most of these required the participant to collect the test, so the effect estimate may reflect this. Test collection from a GP clinic, pharmacist, or distribution center (nurse) requires the participant to make face-to-face contact with a health professional and may act as an encouragement or endorsement of the test in addition to providing access to information about the test and how to carry it out. Studies of low quality also had quite high overall uptake, and the effect estimate may reflect this rather than the low quality *per se*.

Although there was no formal difference in subgroups defined by whether or not there was a recommendation or endorsement of the test, it was noteworthy that uptake was only significantly lower in males than females in studies in which no recommendation was used. Other evidence suggests that lack of a doctor recommendation is an important barrier to colorectal cancer screening (41). Our findings suggest that contact with, or endorsement of the test through a health professional (GP, nurse, and pharmacist) may serve to encourage men to complete the screening test. This

Table 4. Summary of primary and subgroup random effects meta-analysis

Subgroup	Number of studies	OR 95% CI	I^2	*P*
Primary meta analysis	19	0.84 (0.75–0.95)	99%	<**0.01**
Study quality				
Moderate	14	0.81 (0.76–0.85)	95%	<**0.01**
Low	5	0.89 (0.63–1.26)	96%	0.51
Subgroup differences		—	0%	0.58
Study design				
RCTs	6	0.83 (0.71–0.97)	91%	**0.02**
Observational	13	0.83 (0.76–0.91)	98%	<**0.01**
Subgroup differences			0%	0.99
Study setting				
Europe	9	0.78 (0.73–0.84)	95%	<**0.05**
North America	3	0.79 (0.49–1.28)	68%	0.35
Asia	3	0.97 (0.73–1.28)	100%	0.81
South America	1	0.92 (0.81–1.05)	—	—
Australia	3	0.86 (0.76–0.98)	0%	**0.03**
Subgroup differences		—	38%	0.16
Letter of invitation				
Letter without advance notification	9	0.77 (0.73–0.82)	87%	<**0.01**
Letter with advance notification[a]	3	0.89 (0.64–1.23)	92%	0.47
Subgroup differences		—	0%	0.41
Test delivery				
Test mailed	9	0.79 (0.75–0.83)	45%	<**0.01**
Test collected	7	0.83 (0.66–1.05)	99%	0.13
Subgroup differences		—	0%	0.64
Recommendation				
Recommendation provided	8	0.85 (0.68–1.05)	99%	0.13
No recommendation provided	7	0.79 (0.76–0.82)	45%	<**0.01**
Subgroup differences		—	0%	0.54
Screening age range				
40–75	14	0.79 (0.74–0.84)	92%	<**0.01**
50+ (5)	5	0.92 (0.70–1.19)	99%	0.51
Subgroup differences		—	13%	0.28
Number of samples				
1 sample (10)	10	0.84 (0.71–0.98)	99%	**0.03**
2 or more samples (4)	4	0.78 (0.74–0.82)	13%	<**0.01**
Subgroup differences		—	0%	0.42
Screening reminders				
No reminder provided	2	0.85 (0.75–0.96)	73%	**0.01**
Reminder provided	10	0.81 (0.73–0.89)	87%	<**0.01**
Subgroup differences		—	0%	0.51

NOTE: Values in bold indicate $P < 0.05$.

[a]Advance notification indicates pre-invitation letter, followed by invitation letter.

has been noted elsewhere, where male compliance with medical procedures is increased when encouraged by a medical professional (42).

Although subgroup differences were (once again) nonsignificant, studies that were not population-based did not have significantly lower uptake in males. Although the studies which were not population-based differed in many ways, in three of four the screening invitation was endorsed through a GP or GP practice while two required the participant to collect the test. Therefore it cannot be ruled out that the nonsignificantly lower uptake in males may be a result of test collection and GP recommendation.

Age is an important predictor of colorectal cancer risk. Here, male uptake was not significantly different from female uptake in studies targeting those of ages 50 years and over with no upper age limit. However, this may be a result of the fact that some studies involved test collection (3 of the 5 studies) and/or recommendations to complete the test by a GP (4 of the 5 studies), as opposed to older men being more likely to participate in screening. Further investigation is required to assess if there is differential uptake between younger and older males in FIT-based screening and, if so, what may be driving such differences.

Cole and colleagues (24) have reported that participation in their study was significantly improved (increase in relative risk of participation of 30%) through simplification of the sampling method (using two rather than three samples); this did not differ by gender, age, or socioeconomic status. In this meta-analysis, there were no subgroup differences in effect estimates according to whether studies required a single, or more, samples. Further investigation is required to assess if there is differential uptake in males and females when different FIT sampling strategies are used.

Although there is tentative evidence from this review that requiring participants to collect the test, using a GP recommendation and using an advance notification results in similar uptake in males and females, the general lack of significant subgroup differences suggest that study design or screening organization may not be the important drivers of poorer male uptake. However, these elements may help inform development of a taxonomy of compliance in particular groups, such as those based on sex or other background characteristics. Further research in identifying and expanding on such taxonomy is warranted. Given the dearth of evidence regarding reasons for nonparticipation in FIT

screening in males and females, and the fact that FOBT and FIT may be considered somewhat similar from the point of view of screening invitees, it is worth considering what is known about drivers of home-based FOBT screening (non)participation. An early review of colorectal cancer screening uptake using FOBT reported that the main factors for noncompliance with screening were: conflicts with work or family, inconvenience, being too busy, or being away, lack of interest and costs (43). In addition, the same review reported that noncompliance was associated with having no current health problems, being too embarrassed to complete the test, feeling the test was too unpleasant, being anxious and not wanting to know the test results (43). These findings are in line with Chapple and colleagues (44) in the UK FOBT screening program.

The evidence base for reasons underlying gender-based differences in colorectal cancer screening uptake is very limited, and even less is known about uptake in FIT based screening specifically. Recently Ritvo and colleagues (45) suggested that males may procrastinate about colorectal cancer screening, but that, underlying this, is a deeper fatalism about cancer disease and a disbelief in the preventative–protective elements of screening. It has also been reported that males use primary care services less frequently than women (46) perhaps making them less inclined to be screened when offered the opportunity. In addition, White and colleagues (46) suggest that, in Europe, the general absence of male targeted health care programs may hinder men's ability to identify as participants in health care. These observations indicate that studies are now required exploring cultural norms surrounding, psychologic and other barriers to, and facilitators of, FIT screening and how these may differ between the sexes. It would be useful to explore these barriers and facilitators through theory-based research into gender differences in preventive health behaviors.

Conclusion

Uptake of FIT-based colorectal cancer screening among males is significantly lower than among females. Although studies differed in design and screening organization methods, poorer male uptake persisted throughout subgroup analysis. Further investigation is required into why men are less likely to attend FIT screening and what factors may act as barriers or facilitators to screening uptake in men and women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: N. Clarke, L. Sharp, P.M. Kearney
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Clarke
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Clarke, L. Sharp, A. Osborne, P.M. Kearney
Writing, review, and/or revision of the manuscript: N. Clarke, L. Sharp, A. Osborne, P.M. Kearney
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Clarke
Study supervision: L. Sharp, P.M. Kearney

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