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Compliance to Company based Colorectal Cancer Screening In Germany using Fecal Immunochemical Test (FIT) - Results of Almost Half A Million FIT Test

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Abstract

Background

Despite the existence of the statutory early cancer detection program in Germany and the removal of financial barriers, which is frequently reported in the literature to be the main obstacle in screening, uptake of colorectal cancer screening remains quite low. The campaign for colorectal cancer screening in German companies reported in this article started in 2010. It was initiated because of the low compliance with opportunistic public colorectal cancer screening efforts. Its goal is to improve participation by offering an organized screening program using a simple test (FIT).

Methods

An offer for company employees is publicized through posters, company newsletters and the intranet. The difference between the positivity rates of those who returned the kits within 20 days and later than 20 days was assessed using the Z-test. The average time between a positive result and colonoscopy was estimated using the Poincaré plot method. The positive predictive values were calculated for carcinomas, advanced adenomas or any lesions. The sensitivity and specificity of immoCare-C published by Vogel et al. and Hundt et al. were used to derive the confidence intervals for the positive likelihood ratio (for carcinoma and any kind of adenoma).

Results

A total of 312,147 kits were returned and analyzed (return rate 70.2%). 5.6% gave a positive result. The PPV for cancer aged between 55 and 74 was 4.6% for men and women (95% CI: 2.38%-6.76% and 1.28%-7.99%, respectively), but 22% for men (95% CI: 17.93%-26.65%) and 8% for women (95%CI: 3.63%-12.26%) for advanced adenomas. The PPV for any lesion was higher for those with familial risk (49.3%) and 42.6% for those without familial risk (95% CI: 40.2%-45.0%), but with overlapping confidence intervals.

Conclusions

The reported sample is not representative. Although, offering CRC screening in companies may be an effective way of increasing uptake in the target population. Differences in the test performance between men and women need further evaluation.

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Running title: Company-based colorectal cancer screening in Germany using FIT

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Background

Screening for colorectal cancer (CRC) is encouraged worldwide. Furthermore, it is eligible for early detection due to the long preclinical phase of the disease. According to the statutory early cancer detection program in Germany (Das gesetzliche Früherkennungsprogramm) (1), all insured individuals are entitled to undergo colorectal cancer screening with a yearly guaiac-based occult blood stool test (gFOBT) starting at age 50 and a colonoscopy starting at 55 years, which may be repeated after 10 years if the findings are unremarkable. Alternatively, they may opt for a biennial gFOBT, which is standard screening in many countries.

Despite the existence of the program since 2002 and the removal of financial barriers, which is frequently reported in the literature to be the main obstacle in screening (2), uptake of colorectal cancer screening in Germany remains quite low. For example, only 23% of women and 26% of men in Germany have had a colonoscopy within the last 10 years. In addition, only 14% of women and 22% of men are reported to have undergone fecal occult blood testing (FOBT) (3). Furthermore, the repeated longitudinal adherence to FOBT, which is crucial for its effectiveness (4), has been reported to be quite lower than one-time uptake (5-7). Reasons to decline colonoscopy as an invasive screening go from "overstating the benefits" to "downstream effects and potential harms". Overall, opponents argue that most people undergoing screening are neither identified as having cancer nor protected from its developing (8).

A screening test must be well accepted. However, uptake of screening could be improved by offering methods that are more acceptable. Adler et al. (2014) reported that of the 63% who refused colonoscopy, 97% accepted an alternative non-invasive screening method (FOBT) or a minimally invasive technique (blood test) (9). This refers to both men and women. Despite the fact that colonoscopy is the "golden standard" screening tool for colorectal cancer and its precursor lesions, its actual benefit is diminished due to low uptake (10).

In recent years, the FIT (fecal immunochemical test), which is also known as iFOBT (immune fecal occult blood test), has emerged as an alternative to the guaiac-based test. Despite the lack of evidence of its effect on CRC mortality, it has shown better sensitivity for detection of carcinomas and adenomas, and acceptable specificity (11-13) over gFOBT, whereby the latter was shown to reduce mortality in a large meta-analysis (14). FIT has also been demonstrated to be more acceptable to the target population than gFOBT. In randomized studies, the response to invitations offering FIT screening was found to be up to 16% higher than that for gFOBT. This was attributed to the more acceptable collection method, the smaller number of fecal samples, and the lack of dietary restrictions (15-19). In addition, due to its quantitative nature, FIT hemoglobin cut-off levels can be tailored to the risk population and colonoscopy resources available.

In a randomized control trial (RCT) comparing FIT to colonoscopy as a primary screening tool, one-time FIT was non-inferior to colonoscopy in the detection of colorectal cancer, but had lower sensitivity for adenomas. This was viewed by the author to be a possible disadvantage in terms of CRC prevention as a goal of screening but also as a potential advantage in terms of reducing overdiagnosis and the accompanying unnecessary colonoscopy costs and complications. The difference in mortality will be assessed at the end of the ongoing 10-year trial. Overall, the colonoscopy complication rates were significantly lower in the FIT group than in the colonoscopy group, which is an important ethical consideration in terms of the "first do no harm" principle (10). The point has also been raised that large scale implementation of the FIT as a screening method may improve health care equity (20). Various studies have found that participation in fecal immunochemical testing is higher than in colonoscopy procedures, which could improve the overall diagnostic yield beyond the mere sensitivity and specificity of the test (9, 10, 21).

The campaign for colorectal cancer screening in German companies started in 2010. It was initiated because of the low compliance with opportunistic public colorectal cancer screening efforts. It started with 20 mid- and large-sized companies and now includes 350 member companies. Some companies expanded the offer to include retirees and employees' partners. Its goal is to improve participation by offering an organized screening program using a simple test (FIT). This program reaches out to eligible screenees, and especially men, because they make up a larger part of the workforce and are less likely to take part in the screening offer.

The objectives of this study are:

- To report the time frame of when the test requests were received
- To evaluate the return rate and return timing of the completed test
- To describe the positivity rates of the stool test and compare them between the early and late responders
- To describe the colonoscopy findings rate by age and sex
- To compare the predictive values of a positive test to detect carcinoma and advanced adenoma, as well as any lesions and subgroups
- To estimate the diagnostic performance of the immoCARE-C test for detection of adenomas, advanced adenomas and carcinomas expressed as positive likelihood ratio.

Methods

An offer for company employees to have an FIT (immoCare-C, CARE diagnostica Laborreagenzien GmbH) has been publicized through posters, company newsletters and the intranet. The target populations were employees of all ages of the participating companies in Germany. Some companies only make the offer to specific age groups (45–50), while others have no age restriction. Coupons are given to the employees so they can order the test kit from the diagnostic laboratory by mail or internet to be delivered to their home address. The tests are performed at home and then mailed to the laboratory. Test kits are sent out daily and analyzed by the lab on the same day they are received. A voluntary questionnaire to assess familial risk and a consent form to obtain possible follow-up colonoscopy data via a separate form (appendix) is also included with the test. The results are then mailed confidentially to the participants. In the case of a positive result, they are advised to see their primary care physician for further evaluation. The colonoscopy findings are categorized according to the most advanced histological finding such as polyps (including hyperplastic and inflammatory), non-advanced adenomas (1–3 tubular adenomas), advanced adenomas (4 or more, at least 1 lesion >= 1 cm or at least 1 lesion with villous component or high-grade dysplasia), and carcinomas (of the colon or rectum). A weekly statistical update of the stool tests is also sent to the companies.

All employees who have been participating are informed about an anonymous statistical analysis of the ongoing project by the laboratory and gave consent by sending their test kit to the laboratory.

For the draft of the manuscript, the authors from outside the laboratory only took note of descriptive numbers and rates for further statistical analysis. No data sets, either anonymized or encoded, were referred. Therefore, it was not necessary to obtain approval by the Ethical Committee of the University of Duisburg-Essen.

Laboratory Analysis

All test kits were analyzed at the Care diagnostica laboratory on the day they were received using immoCARE-C tests with a cut-off value of 50 ng Hb/ml buffer.

Statistical Analysis

Return rates were monitored for the duration of the campaign. Participants were stratified based on the time between the test request and return (the date the completed test was received in the lab) in 10-day intervals and the test positivity rates were calculated per strata. The difference between the positivity rates of those who returned the kits within 20 days and later than 20 days was assessed using the Z-test. The average time between a positive result and colonoscopy was estimated using the Poincaré plot method. The positive predictive values (PPV) of the test for carcinomas, advanced adenomas or any lesions (carcinoma, adenoma or polyp) were calculated for men and women aged between 55–74 and for those with and without familial risk. The positive likelihood ratios of the test for those 55–74 years of age were calculated using the findings of 182,956 primary screening colonoscopies of the same age group in Germany as an estimate of the prevalence of CRC, advanced adenomas and adenomas (22). The sensitivity and specificity of immoCare-C published by Vogel et al. and Hundt et al. were used to derive the confidence intervals for the positive likelihood ratio (LR+) for carcinoma and any kind of adenoma (23, 24).

Results

We received a response from 444,888 individuals during the time of this study.

Figure 1 summarizes the number of requests, return rate, FIT positivity rates, colonoscopy forms received and their positivity rates.

From January 1, 2010 to December 31, 2013, the laboratory received 444,888 FIT test requests, of which 371,910 gave their age and sex (mean age: 58, SD= 4 years, 40% females). More men than women requested kits in all age groups except those under 30, which was probably a reflection of the level of representation of this age group in the workforce. A total of 312,147 kits were returned and analyzed corresponding to 70.2% of the kits requested (return rate). The return rates increased linearly with age, ranging between 49.4% in the below 30 age group and 90.8% in those above the age of 70, and were similar for men and women in each age group. None of the test kits were missing or had invalid results.

50% of the completed kits were returned within the first 24 days and 90% were returned within 81 days of when they were ordered (Figure 2).

Of the total kits analyzed, 5.6% gave a positive result. The test positivity rates were higher for men, except in the below 40 age groups (Figure 3) (p-value for total difference <0.0001).

The number of FIT requests, return rates, and the number and percentage of those who tested positive is shown in Table 1 by age and sex.

Those who returned the kits within 20 days were more likely to have a positive result than those who took longer to return them, with average positivity rates of 6% and 5.4%, respectively (p-value < 0.001).

The colonoscopy forms were received within 7 weeks on average after a positive stool test. The number of forms received and colonoscopy positivity rates (true positive stool test, including macroscopic finding of polyps, inflammatory lesions or suspicion of carcinomas) are shown in Table 1 and Figure 4. Further histological findings are shown in Table 2.

Of the colonoscopy forms received, 2.1% were carcinomas on histological evaluation, while 19.7% were adenomas, advanced adenomas (7.1%) or polyps (14.6%). 45.3% of the colonoscopies were unremarkable and the histological evaluation was either missing or categorized as "other" for the remaining 11.2%. Women had lower positivity rates in all age groups except those under 30, but this difference was only statistically significant for the 50 to 70 age group.

The PPV for cancer in the tested population of people aged between 55 and 74 was 4.6% for men and women (95% CI: 2.38%-6.76% and 1.28%-7.99%, respectively), but 22% for men (95% CI: 17.93%-26.65%) and 8% for women (95%CI: 3.63%-12.26%) for advanced adenomas. For any lesion, the PPV was 52% for men (95% CI: 46.48%-56.95%) and 25% for women (95% CI: 18.24%-32.09%). The PPV for any lesion was higher for those with familial risk (49.3%) and 42.6% for those without familial risk (95% CI: 40.2%-45.0%), but with overlapping confidence intervals.

The positive likelihood ratio estimates for those between the ages of 55-74 who had colonoscopy forms available (n= 498) are shown in Table 3 for carcinomas and adenomas.

Discussion

CRC is one of the leading causes of cancer-related deaths in men and women in Germany as well as in the United States. However, routine testing can actually prevent many cases of CRC or find it at an early stage, when treatment is most likely to be successful.

"The best test is the one that gets done"(25): People often prefer FIT compared with colonoscopy and it can be easily handled at home. Efforts to reduce CRC should increase the number of individuals who present for screening, such as engaging (male) workers in CRC screening in the workplace. It is simple, safe, and less expensive. This way makes it easier for people to get FIT kits in places other than a doctor's office.

At least 246 advanced lesions were found, corresponding to 9% of the colonoscopy reports. Assuming equal prevalence in all those with a positive stool test and 100% complete diagnostic evaluation following the results, 1,572 advanced lesions would be expected to have been found in those who had a stool test. Polyps were found in a further 14.6% of those who had undergone a follow-up colonoscopy.

Although women in the below 30 age group had higher stool test positivity rates and higher true positive results compared to older women, these results were not statistically significant and are based on few observations. The slight increase in stool test positivity in women under 40 could also be due to failure to follow the instructions to avoid sampling around the time of menstruation. For the most part, however, these do not fall within the recommended routine screening age. The follow-up colonoscopy positivity rates were generally significantly higher for men and so were the PPVs for advanced adenomas and any lesions. It is not clear whether this can be fully explained by the higher prevalence in men or the additional difference in test

Table 1: Test requests, return rates, number and positive results for those with complete age and sex information.

Sex	Age	Number requested	% return	Number positive	% positive	Number colposcopy forms received[a]	% colposcopy forms received[a]	Number positive colonoscopy[b]	% positive colonoscopy	p- value for difference in positive colonoscopy rates between men and women
male	-30	7730	49.8%	155	4.0%	12	7.7%	3	25.0%	0.408
female	-30	10284	49.4%	235	4.6%	15	6.4%	7	46.7%	
male	30-40	24313	60.4%	619	4.2%	66	10.7%	20	30.3%	0.770
female	30-40	22138	57.5%	564	4.4%	43	7.6%	12	27.9%	
male	40-50	84164	70.9%	3085	5.2%	355	11.5%	176	49.6%	0.120
female	40-50	56691	69.2%	1828	4.7%	216	11.8%	89	41.2%	
male	50-60	95225	75.9%	4781	6.6%	617	12.9%	407	66.0%	0.000*
female	50-60	51483	75.4%	2135	5.5%	245	11.5%	115	46.9%	
male	60-70	10589	82.6%	743	8.5%	104	14.0%	83	79.8%	0.004*
female	60-70	5970	84.1%	339	6.7%	59	17.4%	33	55.9%	
male	70-	1818	87.8%	182	11.4%	32	17.6%	16	50.0%	0.768
female	70-	1505	90.8%	126	9.2%	28	22.2%	13	46.4%	
Total male		**223839**	**71.9%**	**9565**	**5.9%**	**1186**	**12.4%**	**705**	**59.4%**	**0.000***
Total female		**148071**	**69.1%**	**5227**	**5.1%**	**606**	**11.6%**	**267**	**44.4%**	
Total		**371910**	**70.8%**	**14792**	**5.6%**	**1792**	**12.1%**	**974**	**54.4%**	

[a] Those who gave consent-.

[b] macroscopic finding of polyps, inflammatory lesions or suspicion of carcinoma

Table 2. Histological findings of positive colonoscopy

	Carcinoma	Advanced adenoma	Adenoma	polyps	unremarkable
Men	27	161	206	174	474
Women	11	47	61	87	337
total	**38**	**208**	**267**	**261**	**811**

Table 3. Likelihood ratio of a positive test for Adenoma (tubular), Advanced adenoma, Carcinoma and any adenoma, with 95% CI (using sensitivity and specificities given by Hundt et al. and Vogel et al.)

LR+ (95% CI)	55-74 all	55-74 men	55-74 women
Adenoma	2.5	3.7	1.3
Advanced adenomas	4.4	4.6	2.0
carcinomas	9.5 (7.9 - 10.7)	7.8 (6.2 - 10.0)	9.9 (7.3 - 13.4)
Any adenoma	3.1 (2.6 - 3.5)	3.4 (7.3 - 13.4)	1.5 (1.0 - 2.2)

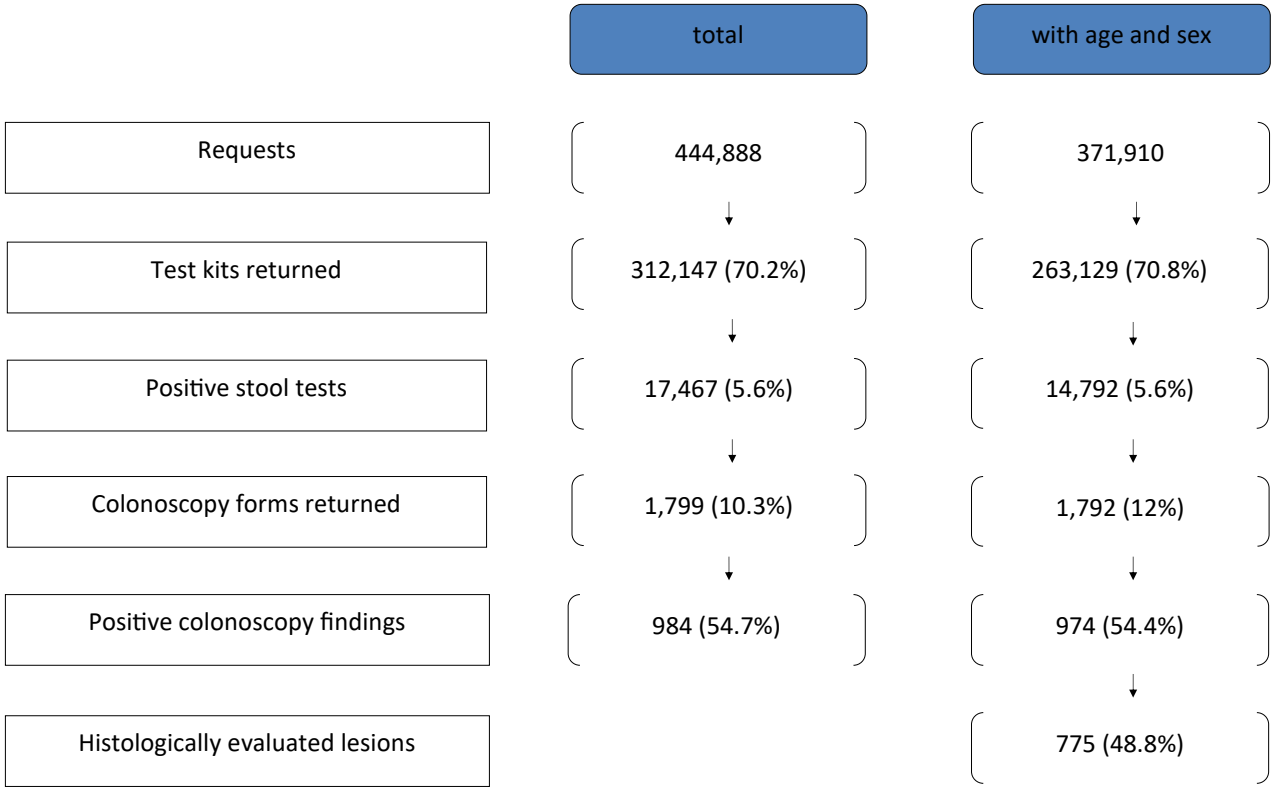

Figure 1. Overview of requests and test kits teturned

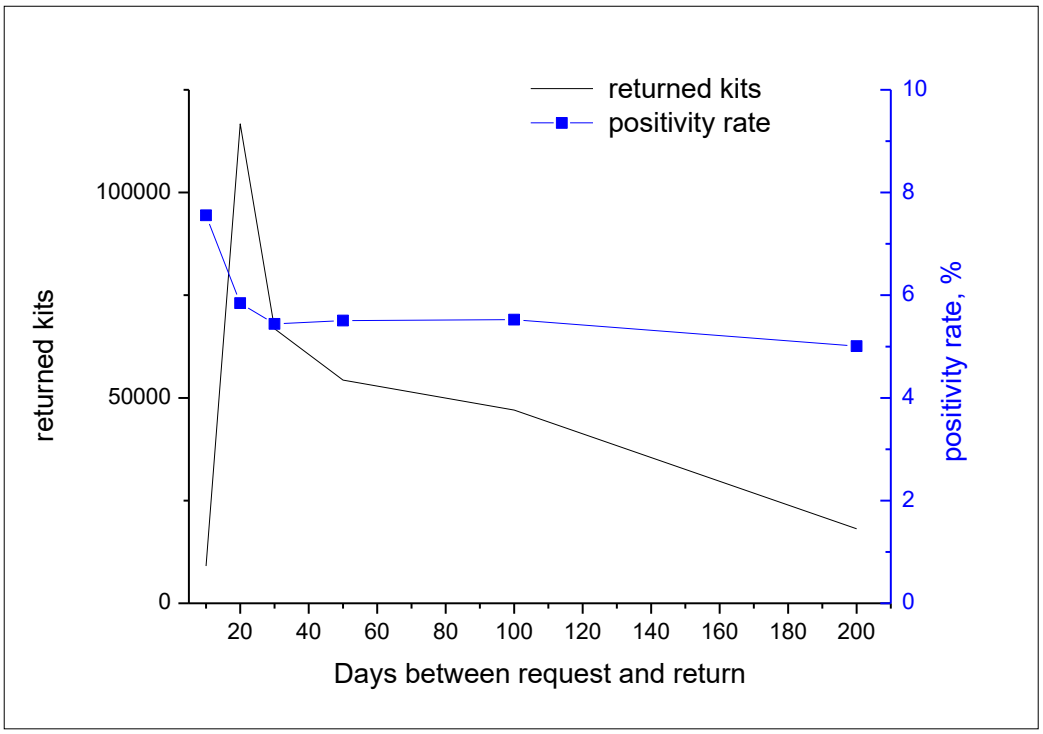

Figure 2. Period between test kit request and and positivity rate

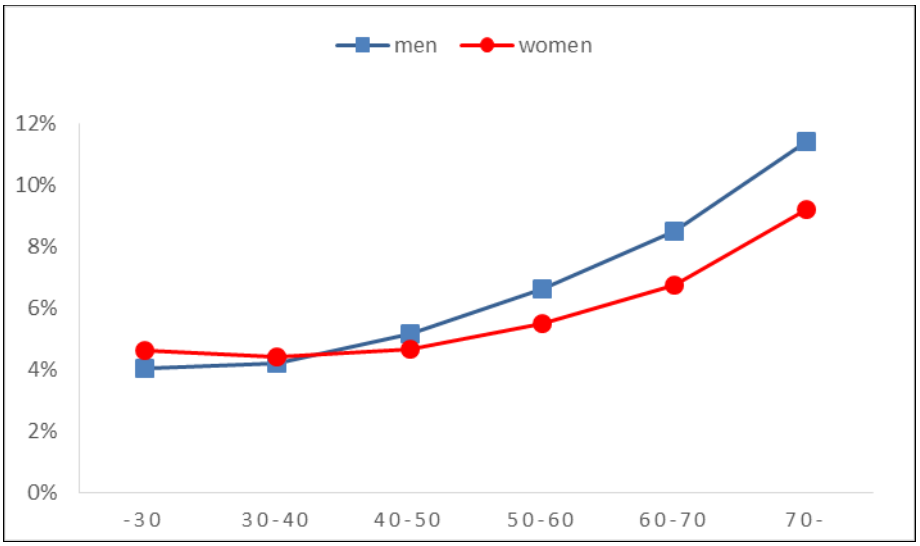

Figure 3. Stool test positivity rates for men and women by age

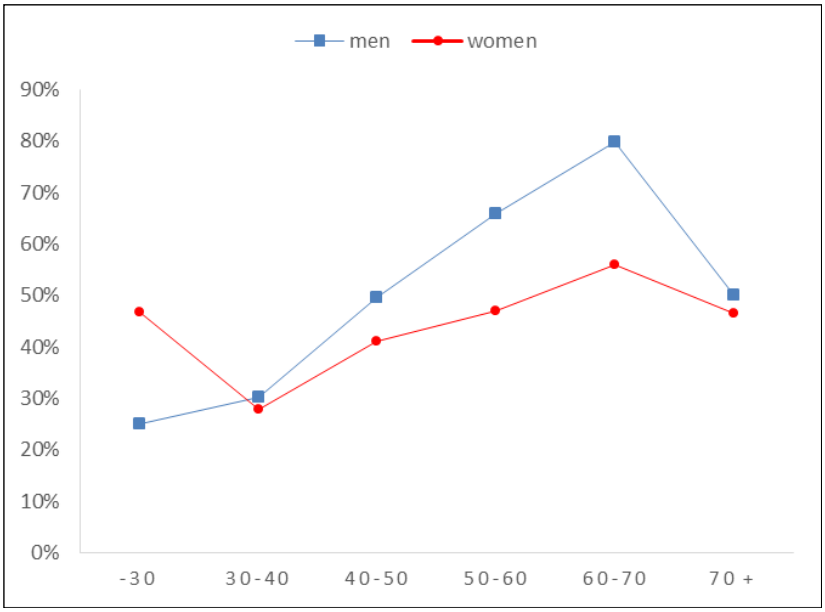

Figure 4. True positive rates (polyps, inflammatory lesions or suspicion of carcinoma) in returned colonoscopy forms for men and women.

performance between men and women. The likelihood ratio, which should theoretically be independent of prevalence, was also higher for men for detection of adenomas but lower for carcinomas, with the latter being statistically non-significant and based on few observations.

Hundt et al. reported a positive likelihood ratio (LR+) of 3.46 (95% CI: 2.22-5.40) for any adenoma, which was similar to our value of 3.1 (95% CI: 2.56-3.54). They found the PPV of the test to be higher for any adenoma at 60.5% (48.7%-71.6%) vs. 39% (95% CI: 34.85%-43.40%), which could be due to their exclusion of symptomatic participants (25).

Strengths of the study include the large sample size and long follow-up time. In addition, our study evaluated the performance of a FIT-based CRC screening program, which increasingly replaces FOBT but is deficient in a systematic evaluation.

However, our study has limitations. Since we do not know how many people were reached by the campaign, we cannot calculate the response rate (neither for men/women accordingly) or compare it to other methods such as personal invitation letters.

We used the prevalence data from another study conducted in Germany to calculate the LR+, which did not report the age distribution of the participants. Therefore, there may be some discrepancy with our group's prevalence, even though our reported LR+ was similar to previously published ones. This sample is not representative of the corresponding age group in the general population because it does not include retirees or those working outside the scope of company employment, although many companies did extend their offer to former employees and employees' partners.

Talking with peers and family has been reported to be a key factor in influencing uptake of CRC screening (26,28), thus the influence of colleagues may have a positive effect on participation. However, this initiative from the participating companies offers a diagnostic tool to their employees to prevent colon cancer, which caused 15.8 and 23.3 lost workdays/1000 employees in 2012 for both women and men (27).

Conclusions

Offering CRC screening in companies may be an effective way of increasing uptake in the target population. Differences in the test performance between men and women need further evaluation.

List of Abbreviations

Colorectal cancer (CRC)
Guaiac-based occult blood stool test (gFOBT)
Fecal immunochemical test (FIT)fecal occult blood testing (FOBT)
Randomized control trial (RCT)
Positive predictive values (PPV)
Likelihood ratio (LR+)

Declarations

Ethics approval and consent to participate

All employees who have been participating are informed about anonymous statistical analysis of the ongoing project by the laboratory and gave consent by sending their test kit to the laboratory.

For the draft of the manuscript, the authors from outside the laboratory only took note of descriptive numbers and rates for further statistical analysis. No data sets, either anonymized or encoded, were referred. Therefore, it was not necessary to obtain approval by the Ethical Committee of the University of Duisburg-Essen.

Consent for publication

Availability of data and material

In spite of anonymity, the datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Authors' contributions

CP drafted the manuscript and performed the statistical analysis. EA performed the statistical analysis under the supervision of CP. DG participated in the data collection and the statistical analysis.

All authors have critically reviewed the content and have approved the final version submitted for publication.

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