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Impact of systematic false-negative test results on the performance of faecal occult blood screening

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Abstract

The impact of systematic false-negative test results on mortality reduction and on programme sensitivity of annual faecal occult blood testing in ages 50–84 years is explored using a microsimulation model. We made calculations for test sensitivities of 80, 50 and 30%. In order to reproduce a cancer detection rate of 2.2 per 1000 at the first screening, the corresponding mean preclinical sojourn times had to be 1.42, 2.30 and 3.84 years, respectively. The fraction systematic results among the false-negative results is varied between 0 and 100%. With 80% test sensitivity, the reduction in mortality due to screening decreases from 25% without systematic results to 23% when all false-negative results are systematic and the programme sensitivity decreases from 63 to 58%. With 30% test sensitivity, mortality reduction decreases from 21 to 11% and programme sensitivity decreases from 52 to 27%. The impact of systematic false-negative test results is important if annual FOBT screening is considered.

Keywords: Colorectal neoplasms; Mass screening; Computer simulation; Mortality; Sensitivity and specificity

1. Introduction

The effect of faecal occult blood test (FOBT) screening on colorectal cancer mortality partly depends on the sensitivity of the test. A major factor in the effect of FOBT screening is the early detection of preclinical cancer, although polyp removal after a positive faecal occult blood test may occasionally prevent cancer incidence and death. A proportion of the prevalent cancers at a faecal occult blood test will be missed because they do not bleed. Lesions not detected at one application of the test may be detected at a subsequent screening. However, the total fraction of preclinical cancers detected by a faecal occult blood screening programme is limited by the short duration of the early preclinical stages of cancer and by the fraction of the preclinical cancers that never bleed and thus will never be detected by faecal occult blood tests.

The favourable effect of faecal occult blood screening on colorectal cancer mortality has been shown in several randomised controlled trials [1–4]. However, trials are expensive and only a limited number of screening strategies can be evaluated in a trial. Therefore, models have been developed to estimate the effects and cost-effectiveness of other faecal occult blood screening strategies [5–9]. These models can be used to study alternative screening strategies that have not been evaluated in randomised trials, such as annual unrehydrated FOBT screening, or screening with new immunochemical tests [10]. All these models assume that every cancer in the population has an equal chance to bleed at a particular moment. This assumption has been questioned [11,12], because some preclinical cancers may never bleed, thus giving rise to systematic false-negative test results. It was stated that this phenomenon could have an important impact on results, and that it should be subjected to sensitivity analysis in order to make recommendations and should be subject to validation in future studies [11]. We will explore the impact of systematic false-negative test results using the MISCAN microsimulation model for evaluation of screening [13] which has been used to estimate the costs and savings of sigmoidoscopy screening [14].

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2. Patients and methods

Systematic test results are defined here as persistently false-negative results of FOBT in individuals with preclinical colorectal cancer due to the failure of the cancer to bleed. The impact of systematic negative results on mortality reduction and programme sensitivity of annual FOBT screening is studied with the MISCAN microsimulation model. This model includes an option that test results depend on previous test outcomes [13].

The sensitivity of most faecal occult blood tests for adenomas is low [15,16] because they rarely bleed. Thus, adenomas are mainly detected by chance at endoscopy following a coincidentally positive FOBT [17,18] and the issue of never-bleeding adenomas is not important. Therefore, we will neglect the possibility of detecting adenomas and we only need to make assumptions about the test sensitivity for cancer, about the sojourn time of preclinical cancer and about the potential occurrence of systematic negative test results.

The test sensitivity for cancer is assumed to be constant throughout the preclinical cancer phase, as in other models [5–7]. Test sensitivity refers to the sensitivity at the first screening. Because widely divergent estimates have been reported, simulations are done for three levels of test sensitivity of a hypothetical faecal occult blood test for cancer: 30, 50 and 80%. The upperbound of 80% is chosen because test sensitivity estimates based on the first screening in two randomised controlled trials were of this size [1,19]. Estimates around the lowerbound of 30% have also been reported [17,20]. Test sensitivity of both the Hemoccult test and the HemoQuant test was estimated to be 26% in patients with prior colorectal cancer [17]. Test sensitivity has been estimated to be 37% for Hemoccult II assuming colorectal cancer cases within 2 years after a negative screening to be false-negatives [20].

The sojourn time of preclinical cancer is chosen such that the simulated cancer detection rate in the first screening round is 2.2 per 1000 screenings. This 2.2 per 1000 resembles the detection rates found in the trials in Göteborg [19] and Nottingham [3], while other studies found slightly lower or higher rates [4,21–23]. This leads to a mean preclinical cancer duration of 1.42 years in the model variant with 80% test sensitivity, 2.30 years in the model variant with 50% test sensitivity and 3.84 years in the model variant with 30% test sensitivity. The duration of preclinical cancer follows an exponential probability distribution.

The impact on expected mortality reduction and programme sensitivity is evaluated for five levels of the proportion of cancers for which negative results are systematic: 0, 25, 50, 75 and 100%. If 0% of the negative results are systematic, then each preclinical cancer bleeds at random and the probability that a cancer bleeds at a test moment is equal to the test sensitivity. If 100% of the negative results are systematic, then a proportion of the preclinical cancers, equal to the test sensitivity, always bleed and will be detected by faecal occult blood tests, while the remaining cancers never bleed and thus will never be detected by the screening test. For instance, in the variant with 80% test sensitivity for cancer and 25% of the negative results being systematic, it is assumed that $0.25\times(1-0.8)=0.05$ of all preclinical cancers will always be missed because they never bleed. The other cancers have at each screening a probability of $0.8/(1-0.05)=0.84$ of being detected.

It is assumed that the age-specific incidence of colorectal cancer without screening equals the US Surveillance, Epidemiology and End Results (SEER) incidence in 1978, when almost no screening was performed [24]. The long-term disease-specific survival after clinical detection of cancer is assumed to be 50% on average, similar to the survival in 1974–1979 in the SEER registry [24]. We do not distinguish disease stages and, for predicting the mortality reduction, we assume that of those who would die of the disease without screening, 50% will be cured by early detection. This figure is based on the Minnesota study, where the 13-year survival is approximately 60% in the control group and approximately 80% in the screen-detected cases in the annually screened group [1], indicating that approximately 50% of the cases that would die from colorectal cancer without screening will survive when they are screen-detected. This figure could be biased by the lead-time in the screen-detected cases. However, the 10-year and 13-years survival in the screen-detected cases do not differ, suggesting that nearly all mortality from colorectal cancer will occur within 10 years after diagnosis.

Results are based on a simulation of 1 000 000 persons with an age distribution as for the 1993 US population. In this population, annual faecal occult blood screening is performed at ages 50 years to 84 years in the period 1993–2022. Compliance with screening and diagnostic follow-up is assumed to be 100%. The mortality reduction in the total US population and the programme sensitivity during the screening programme are calculated for all variants. The mortality reduction in the total population is calculated as the proportion among all deaths from colorectal cancer during the screening period 1993–2022 that is prevented by the early detection of cancer. The numerator of the programme sensitivity consists of all screen-detected cancers. The denominator of the programme sensitivity consists of all preclinical cancers in the screened age group that are prevalent at some moment during the screening period.

In a sensitivity analysis, two major model assumptions are varied: the duration distribution of preclinical cancer and the detection rate at first screening. In a model variant, the preclinical cancer duration is not exponentially distributed, but distributed according to a

Weibull distribution with shape parameter 2, similar to shapes used in the modelling of cervical cancer [25], which results in less variance in preclinical cancer duration than an exponential distribution. In some FOBT studies, a detection rate around 1.8 instead of 2.2 per 1000 was observed in the first screening round [4,22]. Therefore, in another model variant, detection rate in the first screening round is assumed to be 1.8 per 1000. In both model variants, simulations are performed for test sensitivity levels of 30 and 80%. In the model variants with a Weibull distributed preclinical duration, the mean duration is the same as the mean preclinical duration in the model described above. For the model variants with a detection rate at first screening of 1.8 per 1000, the mean preclinical cancer duration is shortened to approximately $1.8/2.2 = 82\%$ of the duration in the baseline model and is 3.2 years when the test sensitivity is 30% and 1.17 years when the test sensitivity is 80%.

3. Results

Figs. 1 and 2 show the mortality reduction and programme sensitivity of annual faecal occult blood screening for different levels of the fraction systematic test results among false-negatives in model variants with 30, 50 and 80% sensitivity. One would expect that the mortality reduction is half the programme sensitivity, as each screen-detected cancer has a probability of 50% to be cured. However, the mortality reduction is less, because it is calculated over all colorectal cancer deaths between the ages of 0 and 100 years, while the programme sensitivity is calculated in the screened age group of 50–84 years. Furthermore, some of the prevented colorectal cancer deaths will occur after the end of the screening programme.

As can be seen from Figs. 1 and 2, the impact of systematic false-negative results is limited if the test sensitivity of a faecal occult blood test is high (80%). The programme sensitivity decreases from 63 to 58% while the mortality reduction decreases from 25 to 23%. This modest impact can be explained by the short mean duration of preclinical cancer, resulting in a low number of screenings at which a cancer can be missed. Moreover, even if all negative results are systematic, only 20% of all cancers do not bleed. In the case of a low test sensitivity (30%), the impact of systematic false-negative test results is larger and it can reduce the screening performance by approximately 50% both with respect to mortality (from 21 to 11%) and program sensitivity (from 52 to 27%). In the variant with 50% test sensitivity, systematic results can reduce mortality by 29% from 24 to 17%.

The variant with 80% test sensitivity gives a higher mortality reduction compared with a 30% test sensitivity, although the detection rate at the first screening round is equal. This is caused by the large number of interval cancers in the variant with 30% test sensitivity, in spite of a longer duration. In the variant with 80% test sensitivity and no systematic results, the programme sensitivity is only 63%. One would expect the programme sensitivity to be higher than the test sensitivity, because some of the lesions will be present at more than one screening examination. Nevertheless, this effect is contrabalanced by lesions that will develop and be clinically diagnosed in the interval between two screenings. In the case of 80% test sensitivity, the mean duration of preclinical cancer has to be very short in order to satisfy the detection rate at the first screening round, and 28% of the cancers will arise and be clinically diagnosed in the interval between two screenings. Therefore, the programme sensitivity is lower than the test sensitivity. In the variant with 30% test sensitivity and no systematic results, the programme sensitivity is

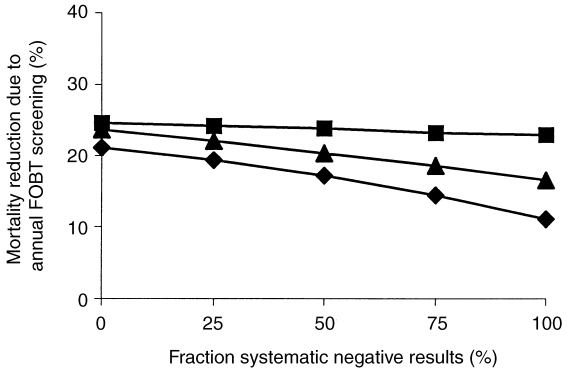

Fig. 1. Predicted impact of the fraction systematic negative test results on the mortality reduction of annual faecal occult blood (FOBT) screening during the period 1993–2022 in the population aged 50–84 years. ■, 80% test sensitivity and a mean preclinical sojourn time of 1.42 years; ▲, 50% test sensitivity and a mean preclinical sojourn time of 2.30 years; ◆, 30% test sensitivity and a mean preclinical sojourn time of 3.84 years.

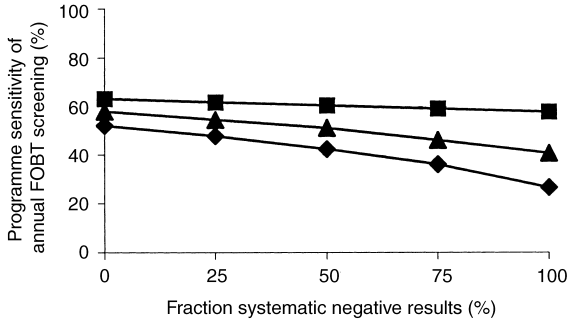

Fig. 2. Predicted impact of the fraction systematic negative test results on the program sensitivity of annual faecal occult blood (FOBT) screening during the period 1993–2022 in the population aged 50–84 years. ■, 80% test sensitivity and a mean preclinical sojourn time of 1.42 years; ▲, 50% test sensitivity and a mean preclinical sojourn time of 2.30 years; ◆, 30% test sensitivity and a mean preclinical sojourn time of 3.84 years.

52%. Here, the programme sensitivity is higher than the test sensitivity because of a longer mean duration of preclinical cancer.

The effect of systematic negative results in the model variants of the sensitivity analysis is similar to the effect in the baseline model. In the model with a Weibull distributed duration with shape 2 and 30% test sensitivity, systematic results can reduce mortality reduction by 52% from 27 to 13%. In these models, the number of fast-growing cancers is smaller than in the baseline model. Therefore, the probability that a missed preclinical cancer is detected at a next screening is higher than in the baseline model which causes the high mortality reduction compared with the baseline model. In the models with a detection rate of 1.8/1000 and 30% test sensitivity, systematic results can reduce mortality reduction by 45% from 20 to 11%. Here, the mean preclinical duration is shorter than in the baseline model and therefore the probability that a missed preclinical cancer is still preclinical at a next screening is smaller. Therefore, the impact of systematic negative test results is slightly smaller when the detection rate is smaller than in the baseline model.

When the mortality reduction of biennial FOBT screening is known from observations, what is the extra gain in mortality reduction if the number of screens is doubled by shortening the screening interval from 2 years to 1 year? Fig. 3 shows that the extra mortality reduction would be approximately 8% if no systematic negative results occur, but less when all negative results are systematic. For example, if the test sensitivity is approximately 62%, as estimated by Gyrd-Hansen and colleagues [26], annual screening instead of biennial screening reduces colorectal cancer mortality by 8% and by 4–5% when all false-negative results are systematic.

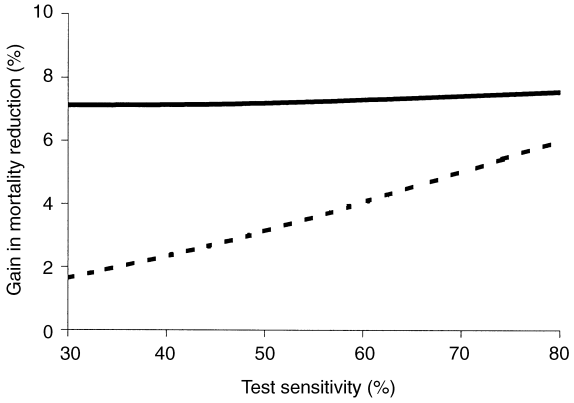

Fig. 3. Predicted absolute gain in reduction of colorectal cancer mortality by changing the interval of faecal occult blood screening from 2 years to 1 year. ——, 0% systematic negative results; ·····, 100% systematic negative results.

4. Discussion

Ransohoff and coworkers [11] stated that "it is clear that how many cancers bleed and how often they bleed at detectable levels are critical features affecting the success of fecal occult blood tests and newer tests". This study shows that systematic false-negative FOBT results may have considerable impact on the expected mortality reduction and programme sensitivity of annual FOBT screening, in particular when the test sensitivity is low.

In this paper, a simplified model has been used to estimate the effect of systematic false-negative test results on mortality and programme sensitivity. For example, 100% participation in screening and diagnostic follow-up is assumed, while in reality performance is sub-optimal because some people come only occasionally to screening or do not comply with the diagnostic follow-up. Another simplification is that the impact of polyp removal and systematic negative results of polyps is neglected. This has been discussed in the Patients and methods section. Furthermore, it is assumed that the sensitivity is constant during the entire preclinical period. The potential impact of systematic negative test results is smaller in a situation where the test sensitivity shows a considerable increase during the preclinical period than in a situation with a constant test sensitivity and the same mean test sensitivity and preclinical duration. In the first situation, the probability is higher that a missed cancer will be detected at repeat screening because the probability that a screening test is positive increases during the preclinical period.

To estimate the fraction systematic negative results from observed data, one could examine the interval cancer rate in the years after first and repeat screening in combination with the background incidence. If the fraction of systematic negative results is 100%, only new cancers will be detected at repeat screening and the cancers missed at previous screenings will surface in the first years after the repeat screenings, resulting in relatively high interval cancer rates after repeat screening. For example, in the model variant with 30% test sensitivity, the incidence rate after the fourth screening varies between 50 and 75% of the background incidence rate, depending on the percentage systematic test results. Two FOBT trials published data on cancer incidence after each repeat screening [26,27]. However, the impact of systematic negative results would have been small in these studies, even if all negative results were systematic, because biennial screening was performed and thus most preclinical cancers at repeat screenings were new. Furthermore, in both studies the number of interval cancers after repeat screening is too small to reliably estimate the proportion of systematic negative results.

If the fraction systematic results is estimated from observations, the estimated fraction systematic results

depend on the assumed distribution of preclinical cancer duration. Preclinical cancers that will never be detected by faecal occult blood tests because of systematic negative results can equivalently be modelled as cancers with a preclinical duration of 0. Consequently, when it is assumed that many fast-growing preclinical cancers occur, the estimated fraction of systematic negative results is smaller than estimated assuming no fast-growing preclinical cancers. In our study, the duration of preclinical cancer is assumed to be exponentially distributed, similar to other colorectal cancer screening models [22,26].

A crude estimate for the percentage of systematic negative FOBT results can be derived from the results of FOBT in samples on 3 consecutive days. One study of immunochemical FOBT calculated the test sensitivity of the one-, two- and three-sample FOBT in 184 colorectal cancer patients [28]. FOBT revealed 125 positive results on the first day. If every cancer has the same chance to bleed at a certain moment, 6 patients (3%) would be expected to have three negative test samples. However, as many as 17 patients did not have any positive test samples, and the data are best reproduced when it is assumed that 24% of the negative results are systematic, i.e. 8% of all cancers never bleed. On the one hand, more than half of the patients in that study had symptoms, such as blood loss, and therefore the percentage of systematic negative results in preclinical cancer patients is likely to be higher. On the other hand, the test interval was only 1 day and some of the cancers that systematically did not bleed may bleed if the test is repeated after a few months. This suggests that the percentage of systematic negative results might be lower.

The possibility of systematic negative test results should be considered when recommendations for FOBT screening are derived. Gyrd-Hansen and colleagues [26] estimated the test sensitivity at 62%, and the mean sojourn time at 2.1 years. They suggest that the overall effectiveness of a Hemoccult II screening can be improved significantly by screening more frequently than every 2 years. However, our study shows that the mortality reduction of annual screening might be much lower than expected because of systematic negative results. The impact of systematic negative results is small when the test sensitivity is high. The impact of systematic false-negative tests is important if annual FOBT screening is considered.

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