Digestive and Liver Disease 44 (2012) 694–699

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Colorectal cancer screening: Why immunochemical faecal occult blood test performs as well with either one or two samples☆

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ARTICLE INFO

Article history:
Received 22 August 2011
Accepted 4 March 2012
Available online 22 April 2012

Keywords:
Colorectal neoplasm
Mass screening
Occult blood

ABSTRACT

Background: Immunochemical faecal occult blood tests perform as well with either one or two samples, and better than guaiac tests with 6 samples.
Aims: Clarifying relationship between tests' performance, bleeding pattern and observation level.
Methods: The data of 32,225 average-risk subjects who performed both Hemoccult II (guaiac) and Magstream (immunochemical) tests were re-analysed by varying the cutoff and number of samples of Magstream.
Results: The identical performances obtained using one or two samples of Magstream (lower cutoff for one sample) at the population level were explained by opposite patterns of bleeding according to the presence of advanced neoplasias. They translated into discrepancy at the individual level: for example a 60% increase in sensitivity and 20% in specificity observed with one (39 ng Hb/ml cutoff) or two samples (63 ng Hb/ml cutoff) Magstream compared with Hemoccult II meant that 28.5% of the subjects testing positive with one sample (18.0% in subjects with advanced neoplasias) would have been considered negative by using two samples of Magstream at a higher cutoff (and reciprocal).
Conclusion: The identical performance of immunochemical tests using one or two samples (different cutoff), explained by opposite pattern of bleeding according to advanced neoplasias is true only at the population level, the appropriate level for mass screening.

1. Introduction

Several studies have demonstrated that immunochemical (I-) faecal occult blood tests (FOBT) perform better than guaiac (G-) FOBT in screening for colorectal cancer [1–4]. These better performances are obtained while using fewer samples (one or two samples for the I-FOBT, instead of six samples obtained on three stools for the G-FOBT). In addition, for both the Magstream and the OC Sensor I-FOBTs, it has been demonstrated, that performing a single sample instead of two could provide similar performances, provided a different cutoff is chosen [5–7].

Recently several articles showed evidence of the poor stability of I-FOBTs to high storage temperature [8,9]. This led to some criticism of the I-FOBT, although variability with G-FOBT has also been described [10]. Scepticism appeared concerning the ability of one FOBT to perform as well as another one while using fewer samples [11]. Such scepticism could also be observed among general practitioners in charge of distributing the test to the population, and ultimately among the general population.

Furthermore, in countries where no FOBT colorectal cancer screening programme is ongoing, it seems that adherence to screening is greater with I-FOBT than with G-FOBT [2,3,12]. Nevertheless, in countries already using the G-FOBT (such as France) and given the age of the population concerned by colorectal cancer screening (50–74 years in most countries), we cannot exclude that some reluctance to changing the test is observed in the population simply due to force of habit. In addition, the high frequency of un-analyzable I-FOBT samples owing to the introduction of too much stools in the collecting tube illustrates patients' belief that the more faeces you collect, the more you increase the probability

☆ *Financial support*: The study was funded by INSERM National Health and Medical Research Institut, and the French Ministry of Health. The Magstream 1000 automat was provided on loan by the manufacturers.
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1590-8658/$36.00
doi:10.1016/j.dld.2012.03.005

of detecting any neoplasia. In this regard, decreasing the number of samples might engender concerns in patients.

Our objective therefore was to use real data to explain physiologically and epidemiologically why, and in which conditions, immunochemical FOBT can perform as well with either one or two samples, and in both cases better than a guaiac FOBT.

2. Patients and methods

We used data from a study comparing a G-FOBT (Hemoccult II test, SKD, France) and an I-FOBT (Magstream test, Fujirebio, Japan) among 32,225 average-risk subjects from the general population in Calvados (France). Details of the study design are reported elsewhere [1]. Briefly, 50–74 year-old subjects without any symptom related to colorectal cancer (CRC) and without any close family history of it were invited to perform both a G-FOBT Hemoccult II (two samples per stool on each of three consecutive stools), and an I-FOBT Magstream (one sample per stool on two consecutive stools). Use of the same stools was not mandatory. On the manufacturers' recommendation, each Magstream sample was considered as positive if the concentration of haemoglobin in the buffer was greater than 20 ng/ml. G-FOBT and I-FOBT were considered positive if at least one of the samples was positive. For the Magstream test, this strategy is hereafter termed MG2. The patient was only informed of the existence of a positive test, without specification of the name(s) of the positive test(s). Furthermore, for the Magstream test, although the result of the test is quantitative, the value obtained was transmitted neither to the patient nor to the physician. In the event of a positive test (G-FOBT and/or I-FOBT), the patient was invited to undergo a colonoscopy.

Advanced neoplasias were defined as high-risk adenomas (size > 9 mm, or with high-grade dysplasia) or invasive colorectal cancers (malignant cells beyond the *muscularis mucosae*).

Because the gold-standard (colonoscopy) was performed only in the event of a positive test, the sensitivity and specificity of the Magstream test could not be determined. However, a performance relative to the G-FOBT was achievable using the ratio of sensitivities (RSN) and the ratio of false positives (RFP), the latter being inversely correlated with specificity [13]. The ratio of sensitivities RSN_{AvsB} is computed as the ratio of the number true positives with test A on the number of true positives with test B. Then $RSN_{AvsB} > 1$ implies that the sensitivity of test A is greater than that of test B. The ratio of false positives RFP_{AvsB} is computed as the number of false positives with test A divided by the number of false positives with test B. Then $RFP_{AvsB} > 1$ implies that test A is less specific than test B. Considering a subject as true or false positive depends on the type of lesion targeted. For example, a patient with a high-risk adenoma and a positive test would be considered as a false positive if the targeted lesion is invasive cancer only, and as a true positive if the targeted lesion is advanced neoplasia (invasive cancer or high-risk adenoma). The targeted lesion is therefore specified with each ratio provided.

The data were re-assessed by considering that only one Magstream sample had been analysed (MG1), and varying the cut-off for both MG1 and MG2 analyses. Throughout the paper the number in parenthesis refers to the cutoff expressed in concentration of haemoglobin in the buffer. This concentration was derived from crude results of Magstream 1000 automat analyzer through an equation provided by the manufacturer. For example, $MG2_{(20)}$ means that the two-sample test was considered as positive if at least one of the samples contained a concentration of haemoglobin in the buffer greater than 20 ng/ml. The ratios RSN and RFP were calculated for MG1 and MG2 in reference to G-FOBT (RSN_{IvsG} and RFP_{IvsG}) for all the available cutoffs. A relative ROC curve was then drawn representing RFP in *x*-axis (instead of 1-specificity) and RSN in *y*-axis (instead of sensitivity). Interpretation of relative ROC curves is conducted exactly as classical ROC curves.

In addition, performances of MG1 and MG2 were compared using RSN and RFP in reference to MG2 ($RSN_{MG1vsMG2}$ and $RFP_{MG1vsMG2}$) for three specific situations: when the number of false positives (no advanced neoplasias) equals the one with Hemoccult II, when the positivity rate equals the one of Hemoccult II, and when the positivity rate associated with two samples equals the one associated with one sample at the manufacturer cutoff ($MG1_{(20)}$).

Statistical analysis was performed with SAS software version 9.2.

Table 1
Demographic characteristics of subjects.

	Subjects included	
N	32,225	
Male gender	13,394	41.6%
Age (years)		
50–54	5984	18.6%
55–59	7781	24.2%
60–64	5930	18.4%
65–69	6495	20.2%
70–74	6035	18.7%

3. Results

Subjects' characteristics are summarized in Table 1.

Fig. 1 provides the relative performances of MG1 and MG2 for a given positivity cutoff in reference to G-FOBT. The upper part of the figure represents RSN_{IvsG} for the detection of invasive cancers and high-risk adenomas, while the lower part represents RFP_{IvsG} for advanced neoplasias. As expected, at a given cutoff, the sensitivity for the detection of invasive cancers, high-risk adenomas or both was better using MG2 (greater RSN_{IvsG}) than MG1, but at the cost of a decrease in specificity (RFP_{IvsG} is greater). For both MG1 and MG2, the sensitivity increased and the specificity decreased as the cutoff expressed in haemoglobin concentration in the buffer decreased.

Fig. 2 shows that, as far as a gain in both sensitivity and specificity compared with Hemoccult II was expected (upper-left corner: $RSN_{IvsG} > 1$ and $RFP_{IvsG} < 1$), relative ROC curves associated with MG1 and MG2 were superimposed. This is observed both for the detection of invasive cancers alone (2A) or together with high-risk

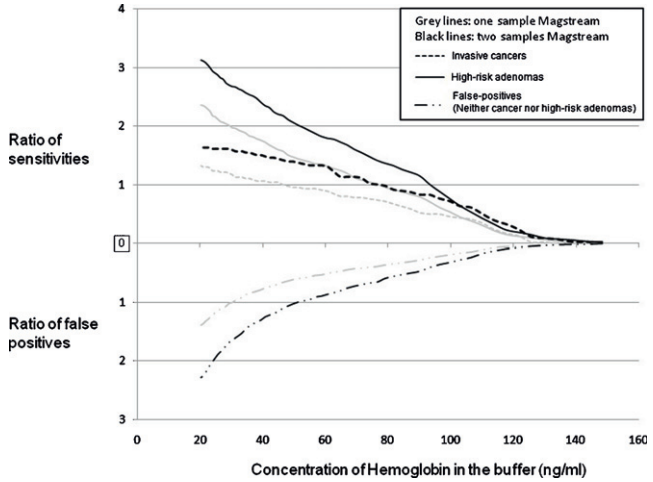

Fig. 1. Ratio of sensitivities (RSN) and ratio of false positives (RFP) for the detection of advanced neoplasias according to Magstream immunochemical faecal occult blood test result, in reference to Hemoccult II guaiac test. (RSN > 1 means that Magstream is more sensitive than Hemoccult II; RFP > 1 means that Magstream is less specific than Hemoccult II.)