

# Detection of colorectal cancer in symptomatic outpatients without visible rectal bleeding: Validity of the fecal occult blood test

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**Background:** In 2002, a new diagnostic strategy in symptomatic outpatients without known established colorectal cancer risk factors aged 40 years or older was implemented in Denmark. Fecal occult blood test (Hemoccult Sensa<sup>®</sup>) was a part of that strategy in patients without visible rectal bleeding.

**Aims:** The aim was to assess the validity of the Hemoccult Sensa<sup>®</sup> test in detecting colorectal cancer in the above-mentioned outpatients.

**Patients:** Symptomatic outpatients without known established colorectal cancer risk factors and without visible rectal bleeding.

**Methods:** Hemoccult Sensa<sup>®</sup> was performed before endoscopic examination. Colorectal cancer was identified at histopathological examination. Patients completed a questionnaire about their symptoms before their first hospital appointment.

**Results:** Eight of 256 patients were found to have colorectal cancer. Median patient age was 63 years. The positive predictive value, negative predictive value, sensitivity, and specificity of Hemoccult Sensa<sup>®</sup> for colorectal cancer were 10.5% (95% confidence interval [CI]: 6.8–14.3), 99.0% (95% CI: 97.8–100.0), 75.0% (95% CI: 69.7–80.3), and 79.4% (95% CI: 74.5–84.4).

**Conclusions:** Hemoccult Sensa<sup>®</sup> as the initial examination in symptomatic outpatients without known established colorectal cancer risk factors presenting without rectal bleeding has to be used with caution. We did not find Hemoccult Sensa<sup>®</sup> test to be an acceptable alternative to flexible sigmoidoscopy.

**Keywords:** colorectal neoplasms, occult blood, diagnostic tests, sensitivity, specificity

## Introduction

Colorectal cancer (CRC) is one of the most common cancers in Westernized countries<sup>1,2</sup> and the number of cases is expected to rise as the population ages.<sup>3</sup> The vast majority of CRCs are found in patients without established CRC risk factors<sup>4</sup> who are diagnosed upon onset of symptoms or through routine screening. In Denmark, screening for CRC is not offered to the general public. In 2002, a new diagnostic strategy in symptomatic outpatients without known established CRC risk factors aged 40 or older and referred by general practitioners was implemented in Denmark. A fecal occult blood test (FOBT, Hemoccult Sensa<sup>®</sup>; Beckman Coulter GmbH, Krefeld, Germany) was a part of the strategy in patients without visible rectal bleeding. Symptoms indicative of CRC – changes in bowel habits, abdominal pain, and unintentional loss of weight – are also prevalent both in the general population and in patients with benign disease,<sup>5–9</sup> differentiation between patients with CRC and those with benign disease is difficult. Using patient history alone as an indication

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of CRC may lead many patients with benign conditions to undergo endoscopic examinations. Hemoccult Sensa® could be used as the initial diagnostic procedure for symptomatic outpatients without visible rectal bleeding.<sup>10</sup>

Earlier studies of the usefulness of FOBT in detecting CRC among symptomatic patients reported sensitivities ranging from 69% to 100%, specificities ranging from 73% to 89%, and positive predictive values ranging from 7% to 76%.<sup>10-14</sup> These studies either evaluated the Hemoccult and Hemoccult II tests, which are less sensitive to fecal blood than Hemoccult Sensa®, and/or did not take into consideration reason for colonoscopy referral (eg, symptoms or routine surveillance), risk profile (patients with vs patients without established CRC risk factors), or presence of visible rectal bleeding. We aimed to assess the validity of Hemoccult Sensa® in symptomatic outpatients without known established CRC risk factors aged 40 years or older presenting without visible rectal bleeding, and who were referred by general practitioners, by estimating the sensitivity, specificity, and predictive values of Hemoccult Sensa® for CRC.

## Patients and methods

This observational study took place in the surgical outpatient clinics at two public Danish hospitals in Aarhus County, Denmark (Randers Central Hospital [RCH] and Aarhus University Hospital [AUH]). These clinics are the primary referral centers in the two hospitals' catchment areas for patients with symptoms consistent with CRC.

As of January 1st, 2003, about 91% of the 433,000 residents in the two hospitals' catchment areas were of Danish origin. The entire population of Denmark receives tax-supported health care from the National Health Service, which allows free access to primary care (general practitioners) and to public hospitals. The study period was September 1st, 2002 to December 31st, 2003 in RCH and October 1st, 2002 to December 31st, 2003 in AUH.

The study was approved by the local Scientific Ethics Committee and Danish Data Protection Agency.

## Identification of study participants

At AUH, an author (NCB) reviewed all referrals to the surgical outpatient clinic. At RCH, a consultant reviewed the referrals. At the conclusion of enrolment, NCB examined case notes at RCH to ensure strict adherence to inclusion and exclusion criteria. Patients without known established CRC risk factors aged 40 years or older referred by the general practitioners, with symptoms consistent with CRC, were included in the study. Patients younger than 40 years and

those with known established CRC risk factors (history of CRC or colorectal adenoma, inflammatory bowel disease, endometrial cancer, at least one first-degree relative under the age of 50 years with CRC or colorectal adenoma, familial hereditary nonpolyposis CRC, or familial adenomatous polyposis) were excluded. Eligible patients received a mailed questionnaire covering symptoms as well as CRC history among first-degree relatives. Completed questionnaires were collected during initial appointments at AUH or RCH. The examining endoscopist (surgeon or nurse) recorded the type of procedure performed (eg, flexible sigmoidoscopy [FS], colonoscopy, or FOBT) along with its findings on an examination form.

Data from the questionnaire and the examination form were entered into a database. Patients who reported CRC in first-degree relatives younger than 50 years of age were excluded.

From the database, we retrieved patients with available Hemoccult Sensa® test results who answered "no" or "don't know" to the questionnaire item about rectal bleeding in the past 12 months. The date of the Hemoccult Sensa® test and its results were obtained from the departments of biochemistry at AUH and RCH. These two departments analyzed both the tests done by the general practitioners and the surgical outpatient clinics. Only patients with a Hemoccult Sensa® test performed within two months preceding referral, or with a Hemoccult Sensa® test performed as the initial investigation at the surgical outpatient clinics were included in the analyses.

## Fecal occult blood test

The Hemoccult Sensa® test was distributed to patients either by their general practitioners before referral, or by hospital staff during the first visit to the surgical outpatient clinic. To decrease false-positive and false-negative rates, patients were asked to abstain from red meat, cauliflower, tomato, paprika, horseradish, banana, melon, and soya beans (peroxidase-rich vegetables), and to avoid large amounts of other fresh fruit and raw vegetables three days before collection of the first specimen and throughout the collection period. Except when treatment interruption entailed health risks, patients were also instructed to abstain from acetylsalicylic acid, other nonsteroidal anti-inflammatory drugs, adrenocortical hormones, and supplements containing iron and vitamin C. Stool specimens collected from three separate bowel movements were smeared on the Hemoccult Sensa® card windows and processed within six days of the final specimen collection.

To standardize results and facilitate data collection, Hemoccult Sensa® test cards from the study patients were

processed only by the participating hospitals' Biochemistry Departments.<sup>15</sup>

## Identification of patients with cancer Endoscopic examinations

If the Hemocult Sensa<sup>®</sup> test was negative, a FS was recommended; additional examinations were performed if indicated by symptoms and findings at FS. Patients whose FS revealed polyps were referred for colonoscopy. When the Hemocult Sensa<sup>®</sup> test result was positive, a colonoscopy was recommended. If a colonoscopy was incomplete a double-contrast barium enema (DBCE) or a virtual colonoscopy (VC) was performed.

All FS's were performed either by experienced nurse-endoscopists, surgeon-endoscopists (junior doctors and experienced surgeons). Colonoscopies were performed by experienced surgeon-endoscopists or by junior doctors supervised by an experienced surgeon-endoscopist.

All biopsied or excised tumors were submitted for histopathological examination.

## Follow up to identify missed cancers

Cases of CRC diagnosed after discharge from the surgical outpatient clinics and before January 1st, 2005 were considered to have been missed during the diagnostic examinations. To detect such missed cancers, we searched computerized records from the hospital discharge registries of Aarhus County and two adjoining counties, Viborg and North Jutland Counties January 1st, 2005. These registries were previously found to have high validity.<sup>16</sup> These population-based administrative public registries contain data on all nonpsychiatric hospital admissions since 1977, as well as data on outpatient and emergency visits since 1994. The registries include the unique personal identification numbers issued to all citizens of Denmark, as well as primary and secondary diagnoses coded by medical doctors at discharge according to the International Classification of Diseases (ICD). We used the following ICD, 10th revision (ICD-10) codes to identify patients with CRC at follow-up: DC18.0, DC18.2–18.9, DC19.9, and DC20.9.

Patients were classified as having CRC if endoscopy detected a malignancy (confirmed by histopathological examination) or if CRC were detected during the follow-up period (confirmed by histopathological examination).

## Statistical analysis

We estimated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of

Hemocult Sensa<sup>®</sup> for CRC. Sensitivity was defined as the proportion of people with CRC who had a positive result on Hemocult Sensa<sup>®</sup>; specificity was defined as the proportion of people without CRC who had a negative Hemocult Sensa<sup>®</sup>; PPV was defined as the probability of CRC in a patient with a positive Hemocult Sensa<sup>®</sup>; and NPV was defined as the probability of not having CRC given a negative Hemocult Sensa<sup>®</sup> test.<sup>17</sup> The statistical analysis was performed with STATA 8.0 software (Stata Corporation, College Station, TX, USA).

## Results

Two thousand four hundred eight outpatients without known established CRC risk factors aged 40 years or older with symptoms consistent with CRC were examined in the two surgical outpatient clinics during the study period. Twenty-six were excluded due to a questionnaire reporting of CRC in a first-degree relative aged younger than 50 years. Two hundred fifty-six patients who met the inclusion criteria for the present study (no self-reported rectal bleeding in the past 12 months, Hemocult Sensa<sup>®</sup> test as the initial investigation) were retrieved from the database. The median age of study patients was 63 years (range 40–94 years) with 62.5% of the patients aged 60 years or older. One hundred and eight (42.2%) were men. The symptoms and signs reported by the patients are listed in Table 1 and the primary discharge diagnoses are listed in Table 2.

In 11 patients, the colonoscopy was incomplete, and the patients subsequently received either a DCBE or a VC. One patient had FS and DBCE/VC, and 120 had only FS. Fifty-seven of the 256 patients had a positive Hemocult Sensa<sup>®</sup> test, and of these 56 underwent colonoscopy; the 57th patient had a cancer diagnosed at a FS. Of the

**Table 1** Symptoms and signs reported by referred outpatients undergoing a Hemocult Sensa<sup>®</sup> test as their initial examination

Symptom/sign	%
Fatigue	42.9
Weight loss	21.0
Anemia	12.0
Mucus discharge	23.7
Change in frequency of bowel movements	61.3
Change in consistency of stool	72.4
Insufficient rectal emptying	50.4
Abdominal pain	62.5
Colorectal cancer in first-degree relatives older than 50 years of age	8.0

**Table 2** Primary diagnoses at discharge of the 256 study patients by Hemoccult Sensa<sup>®</sup> result

Primary diagnosis	Positive (number)	Negative (number)
Colorectal cancer	6	2
Adenoma $\geq$ 10 mm	6	6
Adenoma <10 mm	4	26
Nonneoplastic polyps	6	24
Normal colon and rectum	22	98
Diverticular disease	7	33
Diverticulitis sequelae	1	2
Colitis		
Crohn's disease	0	1
Ulcerative colitis	0	0
Others	3	5
Angiodysplasia	2	1
Lymphoma	0	1
Total	57	199

199 patients with a negative Hemoccult Sensa<sup>®</sup> test, 119 had only FS, 79 had a colonoscopy, and one patient had FS and DBCE/VC. In total, 135 of the 256 eligible patients (52.7%) underwent colonoscopy.

Eight cancers were diagnosed in the 256 patients (3.1%; 95% confidence interval [CI]: 1.4%–6.1%). The tumor stages (according to Dukes), sites, and Hemoccult Sensa<sup>®</sup> test results are listed in Table 3. Of the six patients with cancer and positive Hemoccult Sensa<sup>®</sup> test, one had only FS and five underwent colonoscopy. One patient with cancer and negative Hemoccult Sensa<sup>®</sup> test underwent colonoscopy when found to have iron deficiency anemia. The other patient with CRC

**Table 3** Tumor site and stage and Hemoccult Sensa<sup>®</sup> test results for the eight patients with colorectal cancer

Tumor site	Tumor stage	Hemoccult Sensa <sup>®</sup>
Rectum	Dukes' stage B	Positive
Rectum	Dukes' stage B	Positive
Sigmoid colon	Dukes' stage B	Positive
Sigmoid colon	Adenocarcinoma in an adenoma (T1) <sup>a</sup>	Positive
Ascending colon	Dukes' stage D	Negative
Coecum	Dukes' stage B	Positive
Coecum	Dukes' stage B	Positive
Coecum and right flexure	Dukes' stage unknown. The patient had peritoneal dissemination	Negative

**Note:** <sup>a</sup>TNM classification.

and a negative Hemoccult Sensa<sup>®</sup> test was diagnosed at a DCBE following an inadequate FS.

No missed cancers were found at follow-up using the hospital discharge registries. Mean follow-up time was 18.1 months (range 0.1–28.0 months).

Six of the 57 patients with a positive Hemoccult Sensa<sup>®</sup> test were diagnosed with CRC (Table 2). Of the 199 patients with a negative Hemoccult Sensa<sup>®</sup> test, two were diagnosed with CRC. One patient with cancer also had a large adenoma (10 mm or larger). Of the 248 patients without cancer, 51 had a positive Hemoccult Sensa<sup>®</sup> test; ten of these were diagnosed with an adenoma, including six patients with adenomas 10 mm or larger. Of the 80 patients with a negative Hemoccult Sensa<sup>®</sup> test and complete visualization of their colons, 30 had an adenoma of any size (six of these were 10 mm or larger).

The PPV and NPV of Hemoccult Sensa<sup>®</sup> for CRC were 10.5% (95% CI: 6.8–14.3) and 99.0% (95% CI: 97.8–100.0). Sensitivity and specificity of Hemoccult Sensa<sup>®</sup> for CRC were 75.0% (95% CI: 69.7–80.3) and 79.4% (95% CI: 74.5–84.4).

In addition to the 256 study patients without visible rectal bleeding who were included in the present Hemoccult Sensa<sup>®</sup> validation study, 735 additional patients without visible rectal bleeding were examined who had no Hemoccult Sensa<sup>®</sup>, whose test was done after an endoscopic examination, or whose test took place more than two months before referral for endoscopic examination. Of these 735 patients, 28 (3.8%; 95% CI: 2.5–5.5) were diagnosed with CRC during the study period and follow-up period.

## Discussion

To the best of our knowledge, this study is the first to assess the diagnostic validity of Hemoccult Sensa<sup>®</sup> for CRC in symptomatic outpatients without known established CRC risk factors presenting without visible rectal bleeding. We found Hemoccult Sensa<sup>®</sup> to perform only relatively acceptable in distinguishing between patients with and without CRC, and for the time being we do not find it to be an acceptable alternative to FS as the initial examination.

One of the most important strengths of our study, is that its participants were representative of the patient population targeted for use of Hemoccult Sensa<sup>®</sup> in Denmark. By excluding patients with known established CRC risk factors, the risk profile among study subjects was homogeneous. This is particularly important since the predictive value of a test depends on the prevalence of the disease in the population, and the prevalence of CRC is expected to be less in a population without established

CRC risk factors than in a population with established CRC risk factors.<sup>17</sup>

Also, the study focused on patients who did not report rectal bleeding. The probability of CRC in patients with visible rectal bleeding is higher than in patients without visible rectal bleeding, and visible rectal bleeding increases the likelihood of a positive FOBT.<sup>18</sup> Analysis of a pooled sample of patients both with and without visible rectal bleeding may not have provided useful information about the test's value in each subgroup.

Several potential study weaknesses must be noted. We attempted to control for differential recall by selecting patients on the basis of symptoms experienced and reported in the questionnaire before the first visit to the surgical outpatient clinics. We cannot exclude some selection bias, because a part of the 735 additional patients without visible rectal bleeding might have been referred directly to colonoscopy due to the severity or duration of the symptom. However, the prevalence of CRC among these additional patients was only slightly different from the prevalence in the study population.

We included patients regardless of whether they had undergone a FOBT on the recommendation of their general practitioner. It is possible that patients with a negative Hemocult Sensa<sup>®</sup> test performed in the general practice setting may have been less likely to receive a referral to a surgical outpatient clinic, while patients with severe symptoms were more likely to be referred. If all patients who had a Hemocult Sensa<sup>®</sup> test at the recommendation of their general practitioners were uniformly referred to the hospital clinics, the proportion of study participants with a negative Hemocult Sensa<sup>®</sup> may have been higher.

For a number of reasons, our calculation of the sensitivity of Hemocult Sensa<sup>®</sup> for CRC is likely to be overestimated. First, because of the selective approach used in the standard diagnostic regimen, colonoscopy was performed in only about half of study patients. If all patients had undergone colonoscopy, we may have diagnosed more cases of proximal CRC. Second, a cancer missed by Hemocult Sensa<sup>®</sup> might not have been detected within our study's follow-up period.<sup>19</sup> Finally, CRC and adenomas are more likely to bleed than normal colon mucosa; interruption of anticoagulant therapy during stool collection was considered too risky, and this may have increased the rate of positive tests in especially study patients with neoplasm.

To reduce the false-positive rate from ingested peroxidase, it is recommended that dietary and medication restrictions be imposed three days prior to starting the Hemocult Sensa<sup>®</sup> test.<sup>20</sup> As we were unable to monitor patient adherence to

these restrictions, low compliance may have contributed to the relatively low specificity and PPV for CRC.

Adenomas smaller than 10 mm were more prevalent in patients with a negative Hemocult Sensa<sup>®</sup> test than in patients with a positive test (13.1% vs 7.0%), suggesting that such adenomas may be found by chance, as indicated in another study.<sup>21</sup>

An earlier study found that FOBT has a low sensitivity for detecting rectal cancer.<sup>11</sup> We were not able to confirm or disprove this finding, owing to our study's limited sample size; however, all patients with rectal cancers had a positive Hemocult Sensa<sup>®</sup>. This concordance may arise because Hemocult Sensa<sup>®</sup> is a more sensitive test than Hemocult and Hemocult II.<sup>22,23</sup>

Our estimated values of sensitivity, specificity, and PPV are consistent with those reported previously for different patient populations.<sup>13,14,24</sup> A study which examined Hemocult Sensa<sup>®</sup> in a patient sample with the same CRC prevalence as in our study also found the same value for sensitivity. Unlike ours, that study included patients with one or fewer weekly episodes of visible bright red blood per rectum, thereby increasing the likelihood of a positive Hemocult Sensa<sup>®</sup>.<sup>14</sup>

Our PPV for CRC was similar to that reported for patients undergoing routine screening.<sup>24</sup> While this finding was unexpected, it may be explained by the fact that the vast majority of patients in the screening population were men, who are at increased risk of advanced polyps and cancers.<sup>25</sup> Our estimates of sensitivity, specificity, and PPV were very similar to that found in one study which evaluated the less sensitive test Hemocult II in referred symptomatic patients. Unlike ours, that study included patients with established CRC risk factors and patients with rectal bleeding.<sup>13</sup>

In conclusion, we found Hemocult Sensa<sup>®</sup> only to have relatively acceptable sensitivity and specificity for CRC in symptomatic outpatients without known established CRC risk factors presenting without visible rectal bleeding. Moreover, a considerable number of patients with a positive test had no significant colorectal pathology. Thus, we do not find that Hemocult Sensa<sup>®</sup> is an acceptable alternative to FS as the initial examination in symptomatic patients without known established CRC risk factors presenting without rectal bleeding, especially because FS is a safe examination, has a relatively high sensitivity for CRC and can be performed in outpatients without sedation and analgesia.

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