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COLORECTAL CANCER SCREENING "LITERATURE REVIEW"

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Abstract:

According to the World Health Organization (WHO), screening consists of presumptively identifying, using tests applied in a systematic and standardized manner, subjects suffering from a previously past disease or abnormality. unnoticed. Screening tests must make it possible to divide people who are apparently healthy but who are probably suffering from a given disease or abnormality from those who are probably free from it, Four controlled population studies were carried out in Europe to test the feasibility and effectiveness of mass screening for colorectal cancer: Nottingham (Great Britain), Funen (Denmark), Burgundy (France) and Gothenburg (Sweden). . The first three studies included subjects aged 45 or 50 to 74 years old. The Hemoccult test was offered every 2 years to half of the target population, the other half served as a control. The Swedish study, involving subjects aged 60 to 64, is of limited interest because the screening test was only carried out twice with simple follow-up afterwards.

INTRODUCTION

According to the World Health Organization (WHO), screening consists of presumptively identifying, using tests applied in a systematic and standardized manner, subjects suffering from a previously past disease or abnormality. unnoticed. Screening tests must make it possible to distinguish between people who are apparently healthy but who are probably suffering from a given disease or abnormality and those who are probably free from it. The subpopulation with a higher probability of being affected, once identified, will be the subject of diagnostic investigations, then intervention. By the word "intervention" we mean a treatment, a preventive measure, or information deemed important for the sick person.

The evaluation of a public health action is the detailed analysis of all the questions which must a priori direct the implementation of this action and its evaluation. A screening program is by definition aimed at asymptomatic or apparently healthy individuals. It is therefore always appropriate to verify through an evaluation (i.e. before implementation in the population) that the advantages of the program outweigh its disadvantages. These must be known:

- decision-makers in order to nourish the reflection which accompanies the establishment of a program ;
- citizens in order to clarify their participation in a program. This evaluation may be followed by an "ongoing" or intermediate evaluation and then a final evaluation.

Screening consists of presumptively identifying, using tests applied in a systematic and standardized manner, subjects suffering from a disease or abnormality previously unnoticed **(WHO, 1960).**

1 History of screening

As early as the 1960s, the implementation of screening or early diagnosis strategies was already beginning to be studied. At the time, these were mainly health campaigns organized around infectious issues (tuberculosis, parasitoses, etc.) but also, in industrialized countries, around chronic pathologies (high blood pressure, diabetes, cancer, etc.).

In 1968, the WHO asked two researchers, Winston and Jungner , to work on screening, in order to lay down its fundamental principles, well-illuminated in Table **1.**

Table 1: Principles of early diagnosis by Winston and Jungner - 1968

1- The disease for which cases are being sought must constitute a serious threat to public health
2- A treatment of demonstrated effectiveness must be able to be administered to subjects in whom the disease has been detected
3- Appropriate means of diagnosis and treatment must be available
4- The disease must be detectable during a latency phase or at the start of the clinical phase
5- There must be an effective screening test or examination
6- The test used must be acceptable to the population
7- It is necessary to know the natural history of the disease, in particular its evolution from the latency phase to the symptomatic phase
8- The choice of subjects who will receive treatment must be made according to pre-established criteria
9- The cost of finding cases (including the costs of diagnosis and treatment of subjects recognized as ill) must not be disproportionate to the overall cost of medical care
10- We must ensure continuity of action in the search for cases and not consider it as an operation carried out "once and for all"

2 The different screening strategies for colorectal cancer

Screening strategies are very different depending on the country. Many factors must be taken into consideration when implementing these projects: demographic data, priorities in terms of policy and health policy, access to care, ethical and religious values, etc.

In the United States **[1]** , patients have, in theory, access to the examination of their choice (colonoscopy, immunological test, sigmoidoscopy , CT colonography). All possibilities are accessible and nationally recognized. But most often, it is health insurance that imposes the type of examination and many people simply do not have access to this preventive care. The recommended age range for screening is 50 to 75 years and the decision to perform it is individual.

Concerning Europe **[2,3]** : in 2003, recommendations on colorectal cancer screening were included in the European Code Against Cancer, then in 2007 taken up by the European Commission. However, the establishment of screening programs takes a long time and is sometimes stopped by economic problems, particularly in Eastern Europe. There is no consensus on the program to be developed. For example, Germany offers FOBTg or total colonoscopy to all subjects aged 40 to 74. In the United Kingdom, they offer FOBTg or short colonoscopy alone or combined with FOBTg in 60-74 year olds **[4].**

Many studies are underway, on a European or global scale, comparing different screening strategies as well as their cost-effectiveness ratio. They will certainly provide us with answers in order to introduce our screening strategies in terms of effectiveness and cost.

3 Objectives of the colorectal cancer screening program

On the one hand, it involves detecting cancer at an early stage. It is therefore necessary to demonstrate that treatment at an early stage improves the quality of care in terms of survival and/or allows more conservative therapy. We then hope to reduce morbidity, specific mortality but also the incidence of advanced forms. On the other hand, it is a question of reducing the incidence of cancer itself. This aspect is illustrated by the management of precancerous lesions, preventing the development of cancer.

4 Mass screening tests for colorectal cancer

We will call **a screening test** a test which, used a priori, makes it possible to select people carrying a defined condition from the general population. Evaluating a screening test means judging to what extent a screening test separates sick people from non-sick people and what factors cause this property to vary. The value of a screening method is always relative to a **reference method** .

Table **2** below schematically shows the main differences between screening tests and diagnostic tests.

Table 2: Main differences between screening test and diagnostic test

Screening test	**Diagnostic test**
Applied to apparently healthy people: − Practiced on groups of individuals − It does not constitute a basis for processing − Less precise than the diagnostic test − Costs less than the diagnostic test	Must give diagnostic certainty (specific examinations): − it is applied to people with defined disorders − essentially individual − it constitutes a basis for treatment − it is more precise than the screening test − it may cost more than the screening test

4 A Evaluation of a screening test

Intrinsic value of a measuring instrument

The value of a procedure is established based on a **reference method** recognized as reliable. Defining the validity of a test therefore means measuring the ability of the test to separate sick and non-sick subjects in whom the diagnosis has previously been established with certainty by a reference test. The two main qualities of a test, which define the **internal validity** (“ accuracy ”) of the measuring instrument **,** are **: sensitivity** : ability of the test to identify subjects suffering from the disease **, specificity** : ability of the test to identify healthy subjects.

Positive predictive value:

− Proportion of true positives among all positive test results

Negative predictive value:

− Proportion of true negatives among all negative test results

4. B Mass screening tests for colorectal cancer

4. B 1 Tests for occult blood in the stool

Guaiac tests

It was in 1864 that Van Deen developed the “guaiac” method for detecting occult bleeding in various environments **[5].** In the early 1900s, Boas used this method to diagnose gastric bleeding by the presence of blood in the stools **[6].** Then after multiple improvements, it was Greegor in 1967 who created the test, which could be used at home, by impregnating sheets of paper with guaiac.

In the laboratory, technicians read the test by adding a solution of hydrogen peroxide (oxygenated water).

The Hémoccult² test “is the reference test for colorectal cancer screening: it is the only one whose effectiveness has been demonstrated in terms of mortality in randomized controlled trials **[6,7]”.**

A meta-analysis of these studies shows a reduction in mortality from colorectal cancer of 16% for people randomized to the “screening” group compared to the “control ” group, and a reduction of 25% among subjects who actually participated in the minus one screening round **[8].** The positive reaction (blue color) is due to the peroxidase activity of hemoglobin **[9].** The sensitivity of the test, which is the proportion of subjects with an abnormal result (positive Hémoccult test) among all actually sick subjects **[8],** is between 50 and 60% for cancers **[10].** The specificity, which is the proportion of subjects having a negative Hémoccult test , if the disease is absent, amounts to 98% **[8] Figure 1.**

Figure 1: Hemoccult test

The positive predictive value, which is the proportion of actually sick subjects among those whose test has an abnormal result (positive Hémoccult ® test **),** is 10% for cancers and 30% for adenomas **.** This test presents the criteria required for mass screening **[11]** : it is simple, inexpensive, safe, acceptable to the population, reliable, reproducible, and demonstrated effectiveness. However, it has limitations related to its characteristics and the fact that cancers and adenomas only bleed intermittently. Thus, it lacks sensitivity and is not specific for colorectal cancer or adenoma: all digestive lesions that bleed (hemorrhoids, gastritis, etc.) and occult hemorrhages triggered by certain medications can lead to a positive test result. Hemoccult . It is also not specific for human hemoglobin: food sources of hemoglobin or myoglobin (red meat) and fruits and vegetables rich in peroxidase can lead to positive test responses (false positives) **[10]. .** Finally, vitamin C is the cause of false negatives, and taking iron colors the stools black, which can make it difficult to read the test. Certain rules can reduce the proportion of false positives and false negatives: stopping vitamin C, iron, nonsteroida1 anti-inflammatories and in particular aspirin, red meats and certain plants for at least 2 days [**10].**

Immunological tests [12]

International recommendations are to prefer the term “immunochemical test” rather than “immunological test” for the detection of occult blood in stools **.** However, the term “immunological test” is already widely used by practitioners . Immunological tests rely on an immunochemical reaction that detects globin, a protein component of hemoglobin that varies depending on the species. The antibodies used , mono- or poly-clonal, being specific for human globin, they do not suffer from interference with animal blood of food origin. Immunological tests are quite specific for colorectal bleeding because globin of more proximal origin is degraded in the digestive tract **[13]** . There are two categories: qualitative and quantitative tests.

- **Qualitative tests**

Many qualitative tests are marketed. Their reading is not automated. They also give a binary result and the positivity threshold is fixed by the manufacturer. Their performances are very heterogeneous, which considerably limits their interest. Their positivity rate ranges from 4.5 to 46.4%, their sensitivity for advanced adenomas from 25.4 to 71.5%, and their specificity from 58.8 to 96.7%.

- **Quantitative tests**

Quantitative tests make it possible to quantify the dose of hemoglobin per gram of stool (mg/g) or per milliliter of buffer (ng / mL). In fact, these tests are semi-quantitative because true quantification is impossible: blood distribution is heterogeneous in the stool and it is technically impossible to collect reproducible volumes of stool samples. Four tests are currently marketed in Europe **[14].** Only two have been evaluated in comparison with guaiac tests: OC-Sensor1 (Eiken) and FOB Gold1 (Beckman Coulter). They offer a number of advantages. In particular, their reading is automated and they make it possible to choose the positivity threshold, and therefore the sensitivities and specificity of the test, depending on the context in which it will be used (prevalence of neoplastic lesions, capacity to satisfy the demand for colonoscopies, budget available).

Figure 2: Immunological test

Practical aspects (Table 3)

In theory, certain foods (fruits and vegetables rich in animal blood peroxidase) can be sources of false positives with guaiac tests. In fact, a restrictive diet has never significantly improved their specificity, but risks leading to a drop in participation **[105].** A restrictive diet is therefore not recommended in the context of a CCR DO. There is also no significant drug interference. Likewise for immunological tests, no dietary or drug restrictions are necessary **[105].** Two studies suggest that taking aspirin increases the sensitivity of immunological tests for the detection of advanced neoplasia. However, this practice is not recommended at this time due to potential adverse effects.

Quantitative immunological tests come in the form of a plastic tube containing a buffer liquid closed by a cap on which is fixed a stick whose end is used to collect a stool sample of a few milligrams (2 to 10 mg), either by pricking or scraping the surface **Figure 3.** The same constraints apply to immunological tests and guaiac tests for sampling: the stool must be separated from the urine and the water in the bowl. One of the advantages of guaiac tests is their stability which allows an expiry period of 36 months and a period of 14 days between sampling and reading. The expiration time of quantitative immunological tests is half that, 18 months. Their stability is lower because globin is a protein.

Table 3: Compared characteristics of the Hemoccult1 and OC-Sensor1 tests

	Hemoccult1	OC-Sensor1
Diet	No	No
Drug interference	No	No
Number of samples	6	1
Expiration period (months)	36 months	18 months
Reading time (days)	< 14	<7
Detection threshold (mg Hb /g)	300	<10

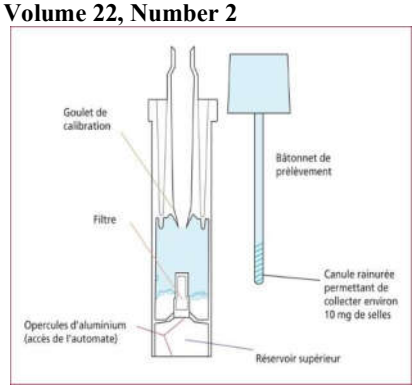

Figure 3: composition of the immunological test tube

More fragile than heme, likely to be degraded by proteases in the digestive lumen **[12]** . The buffer liquid contained in the tube is intended to minimize proteolysis of the globin between sampling and reading. Despite this, the fecal hemoglobin level decreases as the reading time increases, especially as the temperature is elevated **[15].** With the first buffers, the stability of immunological tests was relatively good at 4-8C (refrigerator) but could pose a problem in the event of high heat (above 25 to 30 8C). This is why it was recommended to reduce the time between sampling and reading to less than 7 days (vs. 14 days for guaiac tests). Seasonal variations were observed with the first immunological tests, with a drop in test sensitivity when summer temperatures were high. Their sensitivity, even reduced, would however remain higher than that of the guaiac test **[14].** Since these studies, immunoassay buffers, notably OC-Sensor1 and FOB Gold1, have been improved leading to better stability at elevated temperatures **[15].** There are no data on residual seasonal variations with these new buffers. In practice, it is therefore essential that 1) the sampling date is collected and taken into account in the quality assurance program of a CCR DO using quantitative immunological tests, and that 2) the time between sampling and reading is as short as possible (less than 7 days, or ideally less than 3 days).

Figure 4: quantitative immunological test machine

• **The time between sampling and reading should be as short as possible, ideally less than 3 days**

The use of automated systems makes it possible to significantly accelerate the reading rate of quantitative immunological tests. For example, the Eiken automaton allows a throughput of 280 analyzed tests per hour **Figure 4** .

• **Analytical performance**

Guaiac is always extracted from the resin of the Guaiacum officinale tree. Several guaiac tests are marketed, the performance of which varies greatly. Their detection threshold is nevertheless still relatively high, between 300 and 1,000 mg Hb /g of stools.

(Table 8) . It can be lowered by rehydrating the stool sample before reading, which increases sensitivity at the expense of specificity with an increase in the false positive rate. The sensitivity of immunological tests is greater than 200 mg Hb /g of stool **[105].** Performance (detection threshold, linearity, reproducibility, stability, etc.) varies depending on the tests. The OC-Sensor1 test is the best evaluated and its performance is superior to that of other tests **[15,16].** Its detection threshold is less than 10 mg Hb /g of stool and its linearity range extends from 10 to 200 mg Hb /g of stool (**Table 4).** To date, direct comparison of the results of different commercially available tests is difficult. Indeed, the weight of the stool sample taken and the volume of buffer in which it is stored vary depending on the manufacturer so that the results expressed as hemoglobin levels per milliliter of buffer are difficult to compare. Correspondence tables have been established to facilitate comparisons. Recommendations have been published for standardizing collection systems and how to report studies using these results in micrograms of hemoglobin per gram of stool rather than nano grams per milliliter of buffer.

• **Clinical performance**

It is necessary to distinguish the sensitivity of the test itself, as measured when a single test is performed, from the sensitivity of a screening program based on the repetition, usually biennial, of the test. In terms of public health, it is the sensitivity of the program that matters more than that of the test. The poor sensitivity of the Hemoccult1 test is the argument usually put forward by promoters of immunological tests because the latter offer increased sensitivity for detecting cancers and especially advanced adenomas. The sensitivity of the Hemoccult1 test for the diagnosis of cancer is variously appreciated, with rates of 13 to 50% having been reported. A meta-analysis estimates this sensitivity at 35% **[18].** The sensitivity of biennial screening programs is estimated between 43 and 59%, better in men than in women, and for cancers of the distal colon than for those of the proximal colon. The performance of immunological tests varies depending on the test, the number of samples and the positivity threshold chosen, but their sensitivity is always higher than that of guaiac tests, and, under usual conditions of use, their specificity is always lower. In the context of a CCR OD program, these are the specificities and positive predictive value that must be prioritized so as not to impose the risks and constraints of an unnecessary colonoscopy on asymptomatic people free from any neoplastic lesion. The challenge is to choose the positivity threshold offering the best compromise. The lower this threshold, the more the sensitivity of the test increases, at the cost of an increase in the positivity rate (more colonoscopies) and a drop in specificity (more normal colonoscopies). For a sensitivity of 66 to 75% for CRC, the positivity rate is 5 to 6%, double that of the Hemoccult1 test, and the specificity of 95 to 96%, lower than that of Hemoccult (98 to 99 %) **.** At the same positivity rate, the predictive value of a positive quantitative immunological test (a single sample) is similar to that of the Hemoccult1 test for cancer and higher **[16, 17].** or equal **[16]** for advanced adenomas. The sensitivity of the immunological test for the diagnosis of advanced neoplasia is, like that of the guaiac test, significantly lower in women than in men **.** It seems higher for distal lesions than for proximal ones, but this difference is not observed by everyone. **[18, 19, 20]**

8. B. 2 Other tests for Colorectal Cancer Screening

Molecular tests:

It is important to research and develop alternative screening methods to the Hémoccult ® test, because of its low sensitivity. Various DNA alterations occur at each stage of colon carcinogenesis, from normal mucosa to invasive cancer, aberrant crypt and adenomatous polyp **[21].**

Every day, 10^{10} colonic cells are exfoliated. The amount of DNA isolated from stools is 4 to 5 times higher in patients with invasive cancer than in patients without colon tumors **[22].** Extraction of tumor DNA from stools, and its amplification, are possible; this has led to the realization of fecal tests detecting tumor DNA, potentially very sensitive and specific. A prospective study including 5,486 subjects showed four times greater sensitivity of the fecal test for detection of altered DNA compared to the Hémoccult test for the detection of invasive cancers, and twice as great for the detection of adenomas with severe dysplasia. This did not result in a loss of specificity **[23].** However, limitations exist regarding the generalizability of these tests. As there is a great heterogeneity of tumors, with genetic abnormalities different depending on the tumor stage (alteration in the genes APC, K-Ras, p53, Bat 56), the site of implantation of the tumor (right colon versus left colon) and

probably depending on the individual, there is no single molecular marker; a test capable of detecting a wide range of anomalies is therefore necessary. Recovering tumor DNA also requires optimal conditions, which are not always easy to achieve, so as not to reduce the sensitivity of the tests. These fecal tests are also still too expensive to be generalized. Molecular blood tests could be an alternative to fecal tests in the future. The advantage of blood sampling compared to stool collection is better acceptability by the population. Several techniques are thus studied: the detection of tumor antigens, anti-tumor autoantibodies and altered messenger RNA.

The search for serum DNA abnormalities, particularly mitochondrial DNA, is the most promising avenue.

Flexible rectosigmoidoscopy
Rectosigmoidoscopy is an endoscopic method allowing the examination of the lower third of the colon. Subjects with polyps in the distal colon have an increased risk of having polyps or cancer in the transverse colon and/or the right colon **[24,25].** In the event of a positive test, a full colonoscopy is necessary. Positivity is generally defined by the discovery of cancer or advanced adenoma(s) (with variations depending on the study). In 2000, European Union experts recommended carrying out randomized controlled trials to evaluate this screening method. Several trials are underway: in Italy, the USA, Norway and Great Britain. The methodology differs depending on the study. European studies suggest performing a single rectosigmoidoscopy between ages 55 and 64, in subjects at average risk. Small polyps are removed. If cancer or advanced adenomas are discovered, a total colonoscopy is then offered. In the American trial, a rectosigmoidoscopy is performed (between ages 55 and 74), with a follow-up 3 to 5 years later. There is no biopsy; in the event of an anomaly, the patient is referred to his treating physician for continued monitoring. These trials show relatively low participation from the population. There was no significant decline in colorectal cancer mortality in the Norwegian trial after 7 years of follow-up. The British trial **[26]** showed, after 11 years of follow-up, a 23% reduction in the incidence of colorectal cancers and a 31% reduction in mortality from colorectal cancer in the "screening" group compared to the group. " witness ". However, the people participating in the study are not necessarily representative of the general population: they said they were initially interested in screening after sending a questionnaire. The results of the American **[27]** and Italian **[28] trials** are expected in the coming years. Another Norwegian trial **[29]** was carried out: started in 1983, it offered flexible sigmoidoscopy to men and women aged 50 to 59, with total colonoscopy if a polyp was discovered. Participation was high (67%), but with a small number of people (400 people). In 1996, control colonoscopies were performed in the "screening" group and the "control" group. A drop in the incidence of colorectal cancers of 80% was observed in the "control" group, but with an increase in overall mortality. Flexible rectosigmoidoscopy has certain advantages: better sensitivity than tests for blood in the stool, and the possibility of removing the lesions visualized during the examination. It is quick (approximately 8 minutes), does not require general anesthesia, and can be performed on an outpatient basis after a simple enema by trained, non-medical personnel. It is less invasive than total colonoscopy. Studies comparing various screening methods show a detection rate (discovery of colorectal cancers or advanced adenomas per 100 people screened), as well as a diagnostic yield (discovery of colorectal cancers or advanced adenomas per 100 people invited), superior for flexible sigmoidoscopy compared to stool blood tests **[30,31].**

Video colonoscopy.
It is the reference examination for the diagnosis and treatment of colonic polyps, as well as for the diagnosis of colorectal cancer ("gold standard"), due to its sensitivity and specificity. It allows lesions to be detected and removed in a single examination. Endoscopic polypectomy results in a reduction in the incidence of colorectal cancer **[32].** Unlike rectosigmoidoscopy, this examination allows the detection of lesions in the proximal colon, if the preparation is of good quality, and in the absence of technical difficulties or obstructive colorectal lesions **[33].** However, there is no randomized controlled trial showing a decrease in colorectal cancer incidence and mortality by the use of colonoscopy as a screening method. A trial of this type is currently underway in several Northern European countries **.** Some studies **[34,35]** show a reduction in the risk of colorectal cancer limited to the left colon. Possible explanations include: the difficulty of carrying out an adequate preparation at the level of the proximal colon, the preponderance of flat lesions that are difficult to detect and resectable at the level of the proximal colon, technical difficulties in reaching the cecum, and a different carcinogenesis with more aggressive tumors. at the level of the right colon. In addition, its cost, the low participation of the population, the need for colonic preparation, often general anesthesia, and the possible complications (although rare), make the generalization of colonoscopy difficult to accept in the context of mass screening. After a total colonoscopy with or without polypectomy, the perforation rates are 0.41% and 0.17%, respectively. Sedation can also induce complications, as can colonic preparation. The oral preparation can in fact lead to renal failure (acute or chronic), with tubular deposits of calcium and phosphorus **[36].**

Virtual colonoscopy.
It brings together all the techniques for reconstructing images of the colon in two or three dimensions, mainly by colonoscanner (helical scanner). It has the advantage over video colonoscopy of being able to explore the entire thickness of the colon wall and the entire peritoneal cavity, and does not require sedation. Additionally, the risk of complications is low. The rate of perforations in particular, which is lower compared to video colonoscopy. Thus, the rate of serious complications was 0.08% during a British retrospective study involving 17,067 subjects (no deaths) **[37].** You need a high-performance scanner and program, as well as a trained radiologist. This method also requires colonic preparation, insufflation (with air or CO2), and irradiation. Finally, since removal of polyps is not possible by virtual colonoscopy, complementary video colonoscopy is used to treat the lesions. Sensitivity can be increased by a technique of marking stools with an iodized contrast product, called "tagging": the iodine mixes with the stools, making it possible, by difference in density, to distinguish residual stools from polyps or cancers. Computer software can also help the radiologist to detect polyps.

Virtual colonoscopy is not a first-line colonic exploration test, but a possible alternative in certain specific situations. [38] :

-after an incomplete video colonoscopy,
-in the event of colic symptoms suggestive of a tumor, if video colonoscopy is refused by the patient (after complete and fair information) or compromised by comorbidities,
-as part of organized screening for colorectal cancer in subjects at average risk, if the stool blood test is positive and the video colonoscopy is compromised by comorbidities,
-in patients at high risk of colorectal cancer, in the event of refusal of video colonoscopy (after complete and fair information to the patient), or in the event of comorbidities making it difficult to perform video colonoscopy.
But also that the discovery of a polyp of 6 mm or more following a virtual colonoscopy requires the patient to be referred for a biopsy or excision of this lesion; it cannot rule on the action to be taken in the event of discovery of a polyp of less than 6 mm
Finally, it should be noted that the problem of irradiation of the population could be solved in the future by the development of virtual colonoscopy by magnetic resonance.

Barium enema.
Less and less used, it corresponds to an exploration of the colon using a radiopaque contrast product introduced through the rectum. Air is introduced in addition to the barium to perform a double contrast examination. The barium enema allows you to fully visualize the colon; it can thus be carried out in the event of an incomplete colonoscopy. Complications are rare: a British study showed a perforation rate of one in 25,000 (with 10% death among these perforations) **[39].** The sensitivity and specificity of double contrast barium enema for the diagnosis of colon cancer are 84% and 97.5%, respectively. Regarding large polyps (>1 cm), the sensitivity and specificity are around 80% **[40].** However, the sensitivity of barium enema for the detection of small polyps (<5 mm) is low **[41].** This examination is also possible in situations where colonoscopy may prove dangerous (severe respiratory or heart failure), in the event of colon obstruction, or if colonoscopy is refused by the patient. If there is suspicion of colonic perforation, the barium should be replaced with a water-soluble contrast medium. This examination is increasingly being supplanted by the growing use of virtual colonoscopy, particularly in cases of incomplete video colonoscopy.

The colonic video capsule.
It is ingested by mouth and progresses through intestinal peristalsis. Elimination is natural, approximately 8 hours after ingestion.
A first generation of capsules (Pillcam colon) has been developed: two pilot studies have shown the feasibility and safety of the endoscopic video capsule **[42,43].** A study comparing this " Pillcam colon" capsule to traditional colonoscopy showed a sensitivity of 64% for the detection of polyps of at least 6 mm, with a specificity of 84%. This technique does not require insufflation, no anesthesia, no irradiation but quite extensive intestinal preparation. The quality of the preparation indeed influences the detection rate of colonic lesions. The video capsule has few side effects, especially in relation to intestinal preparation (nausea, abdominal discomfort). The blocking of the capsule is exceptional. Sensitivity has been improved with the development of a second generation of colon video capsules: " Pillcam colon 2".
Equipped with two cameras allowing almost 360° viewing, it transmits data to a recording box that the patient wears as a holter. The images are viewed and interpreted in a delayed manner, the interpretation time rarely exceeding 30 minutes.
The sensitivity of " Pillcam colon 2" for the detection of polyps is around 90%, with a specificity ranging from 76 to 89% depending on the size of the polyps **[44].** This technique therefore presents significant advantages, but it remains under evaluation, its place in the context of colorectal cancer screening not yet being specified.

5 Mass screening for colorectal cancer by looking for occult bleeding in the stool.
In the current state of our knowledge, only a screening strategy concerning subjects of both sexes over 50 years old can change the problem posed by colorectal cancer in the short term. A screening strategy limited to high-risk subjects would have a modest effect. In almost 80% of cases, colorectal cancer occurs in people who do not belong to a known high-risk group. Insufficient knowledge of the causes of colorectal cancer currently does not make it possible to define a primary prevention policy.

a) Mass screening for colorectal cancer by looking for occult bleeding in the stool is a validated strategy
Case-control studies carried out in populations where screening has been implemented represent a means of retrospectively evaluating the theoretical effectiveness of screening. They consist of comparing the screening history of subjects who died from colorectal cancer to that of controls matched for sex, age and place of residence. Six case-control studies have been published (**Table 5).** The Hemoccult test was the screening test in 5 studies **[45, 46, 47, 48,49]** and an immunological test in the sixth **[50].** Although there are some discrepancies between studies, the results suggest that a reduction in colorectal cancer mortality of 30 to 40% can be achieved in subjects who participate in screening compared to nonparticipants (**Table 5)** . In case-control studies, the reduction in the risk of death depends only on the ratio of case/control participation, i.e. it is independent of the level of participation. This means that the results are valid assuming a participation rate of 100%. These studies make it possible to measure the effectiveness of screening under ideal conditions, never carried out in practice. The first randomized controlled study was carried out in Minnesota in 46,551 volunteers aged 50 to 80 years at the start of the study **[51].** They were randomized into 3 groups: Annual Hemoccult , Hemoccult every 2 years and control group. In this population, 90% of subjects took at least one screening test and 46% of the population participated

in all screening campaigns. The positivity rate of the test, read after rehydration, was on average 9.8%. Due to the high positivity rate, 38% of subjects screened annually had a colonoscopy during the study period. With a follow-up of 13 years, mortality from colorectal cancer was reduced by 33% in the Hemoccult group. annual compared to the control group ($P < 0.05$) and 6% in the Hemoccult group every 2 years (not significant). It has been suggested that one-third to one-half of the reduction in mortality at 13 years was attributable to colonoscopy **[52]** . The authors of the Minnesota study disputed these results **[53]** . They estimate that detection by colonoscopy of non-bleeding cancers explains only 1/4 to 1/6 of the 33% reduction in colorectal cancer mortality. Screening was stopped after 13 years, but the cohort continued to be followed. Recently, additional results have been published. After 18 years, the reduction in mortality was 33% in the group screened every year and 21% in the group screened every 2 years **[54]** . The reduction in incidence was 20% and 17%, respectively **[55].** This result is important. It suggests that the annual or biennial search for occult bleeding in the stools makes it possible to both reduce mortality from colorectal cancer through earlier detection of cancers but also to reduce the incidence through the detection of adenomas. The effect of the high rate of colonoscopy in decreasing the incidence has not been evaluated. The results of this study cannot be extrapolated to a general population: participation is much higher than in an unselected population and we almost completely ignore the group of non-participants in whom the stage of diagnosis is often late, overall more advanced than in the general population. Additionally, there are not enough endoscopists to deal with a 10% positivity rate in a population.

Tableau 5 : Résultats des études cas-témoins du dépistage du cancer colorectal

Tableau I. – Evaluation du dépistage du cancer colorectal, résultats des études cas-témoins.

Evaluation of colorectal cancer screening: results of case-control studies.

	Références	Test	Proportion de sujets ayant participé au dépistage (%)		Odds-ratio
			Cas	Témoins (IC 95 %)	
Californie	[10]	Hemoccult®	31,5	42,8	0,7 (0,5-0,9)
Sarre	[11]	Hemoccult®			
— Hommes			17,8	15,0	1,2 (07-0,9)
— Femmes			16,2	29,4	0,5 (0,3-0,8)
Seattle	[12]	Hemoccult®	8,3	15,6	0,5 (0,3-0,9)
Japon	[15]	Immunologique	5,9	12,1	0,4 (0,1-0,9)
Florence	[13]	Hemoccult®	22,3	28,5	0,6 (0,4-0,9)
Bourgogne	[14]	Hemoccult®	49,4	61,1	0,7 (0,5-0,9)

IC 95 % : intervalle de confiance à 95 %.

Four controlled population studies were carried out in Europe: Nottingham (Great Britain), Funen (Denmark), Burgundy (France) and Gothenburg (Sweden **) (Table_6)** . The first three studies included subjects aged 45 or 50 years to 74 years **[56,57,58]** . The Hemoccult test was offered every 2 years to half of the target population, the other half served as a control. The Swedish study, involving subjects aged 60 to 64 years, is of limited interest because the screening test was only carried out twice with simple follow-up afterwards **[59]** . The test was offered without dietary restrictions in the English and French studies, with exclusion of red meat, fresh fruit, iron, vitamin C, aspirin and anti- inflammatories in the 3 days preceding the test. In Sweden, the test was partially rehydrated in the first campaign, completely in the second. The French study was the only one to include treating physicians in the distribution of the test. In In the other three studies, we simply sent the test by post with possible reminders.

Tableau 6 : les études de population d'évaluation du test Hemoccult

Tableau II. – Les études de population d'évaluation du test Hemoccult®.

Population-based trials of Hemoccult® screening for colorectal cancer.

	Nottingham Angleterre [9]	Funen Danemark [8]	Bourgogne France [21]	Goteborg Suède [22]
Population incluse	152 850	61 933	91 553	63 308
Année de début	1981	1986	1988	1982
Groupe d'âge	50-74	45-74	45-74	60-64
Test de dépistage	Hemoccult® non réhydraté	Hemoccult® non réhydraté	Hemoccult® non réhydraté	Hemoccult® réhydraté
Répétition du test	Tous les 2 ans	Tous les 2 ans	Tous les 2 ans	2 campagnes seulement
Régime	oui	non	non	oui
Mode de distribution du test	Postal	Postal et relances	Médecins et postal	Postal et relances

The results of the studies are now available (**Table 7).** The participation rate in the first campaign was between 53 and 67%. The positivity rate of the test carried out without dietary restrictions was 2.1% in the first campaign, 1.3% in subsequent campaigns. It was lower if a diet was offered, higher if the test was rehydrated. The predictive value for cancer was just over 10% and the diagnostic stage was less advanced in the population included in the screening program than in the control population. In the Danish study, with a follow-up of 10 years, there was a reduction in mortality of 18% (OR = 0.82; 95% CI: 0.68-0.99). In the English study [9] , with a mean follow-up of 7.8 years the reduction in mortality was 15% (OR = 0.85; 95% CI: 0.74-0.98). The low follow-up for part of the English cohort reduces the power of this study. If all subjects had been followed for 10 years, the reduction in mortality would probably be greater, with the benefit of screening starting to appear after a follow-up of 5 or 6 years. The reduction in mortality, with a follow-up of 9 years, was 14% in Burgundy **[60]** . The 10-year results will be available soon. Overall, converging data suggests that performing a Hemoccult test every 2 years helps reduce mortality from colorectal cancer. They also indicate that for a mass screening policy to be effective, it must be carefully organized to reproduce the conditions of experimental studies .

Tableau 7 : Résultats des études d'évaluation dans une population bien définie du test Hemocult

Tableau III. – Résultats des études d'évaluation dans une population bien définie du test Hemoccult®.
Evaluation of colorectal cancer screening: results of population based-studies.

	Nottingham Angleterre [9]	Funen Danemark [8]	Bourgogne France [23]	Goteborg Suède [22]
Participation				
— Au moins 1 test	60 %	67 %	68 %	69 %
— 1re campagne	54 %	67 %	53 %	66 %
— Répétition test	Toutes campagnes (3 à 6) : 38 %	5 campagnes 46 %	5 campagnes 37 %	2 campagnes 60 %
Taux de positivité				
— 1re campagne	2,1 %	1,0 %	2,1 %	6,3 %
— Campagnes ultérieures	1,3 %	1,1 %	1,3 %	5,6 %*
VPP cancer	11,5 %	12,2 %	11,4 %	4,7 %
Proportion cancer stade I				
— Population dépistée	20 %	22 %	29 %	non donné
— Population témoin	11 %	11 %	21 %	non donné
Durée du suivi	7-8 ans	10 ans	9 ans	8,3 ans en moyenne
RR de décès par cancer colorectal	0,85 (0,68-0,99)	0,82 (0,74-0,99)	0,86 (0,71-1,12)	0,88 (0,71-1,03)

** test réhydraté. VPP : valeur prédictive positive.*
RR : risque relatif.

b) Conditions for the effectiveness of mass screening:

- Population participation in screening must be high

The performance of the screening test and its acceptability are the elements on which the effectiveness of the screening program will depend. With a test which in absolute terms (participation rate of 100%) makes it possible to reduce mortality linked to cancer by 40%, we only observe a reduction in mortality of 4% if participation is 10%. In such a situation, a few individuals benefit from the program, but clinicians and health authorities do not see the problem posed by the disease detected evolving significantly. At a time when health spending must be rationalized as best as possible, a program with a low participation rate is not acceptable to society. The participation rate in the first campaign was 66% in Denmark **[61]** and Sweden **[62]** , and 53% in England **[63]** and France **[64]** (**Table 7).** Subsequently, 80 to 90% of subjects who have completed the screening test once continue to participate in screening campaigns. In practice, the participation rate in each campaign must be at least 50% to observe a significant reduction in colorectal cancer mortality by offering a biennial test.

- The training of general practitioners and occupational physicians is an essential point:

The Saône-et-Loire study suggests that the two factors that most encourage individuals to participate in screening are the explanations given by the doctor and the information document sent to each person concerned at the start of the campaign. The media campaigns have done little to motivate, but they have helped doctors who believe their patients expected to be approached. The quality of the prior training of general practitioners and occupational physicians is the main determinant of population participation **[65]** . This must be done in small groups, so that doctors can have an active role, that is to say, ask questions or give their opinion. This is the way for them to understand the problem of screening and then be able to get actively involved. We have designed a film providing the main information on the epidemiology of colorectal cancer and the organization of its screening. It only lasts 15 minutes to allow for long discussions. It is not intended to say everything on the subject, but to provoke questions and discussion. It is led by a general practitioner and an expert who has mastered the subject. A special mobilization effort must be made for these meetings. Indeed, 85% of the tests given by treating physicians or occupational physicians during the first campaign are done, 91% on average during subsequent campaigns **[66],** this awareness and training methodology is effective since 90% of general practitioners in Saône-et-Loire actively distributed the test **[67]** . Such a strategy is cumbersome but it is now well established that it allows the start and sustainability of the screening program. The specifications for colorectal cancer screening provide that it will be necessary to prove that half of the general practitioners and the workplace have participated in this training for the screening program to be able to start.

6 The Mass Screening Program must be organized and evaluated

Many people imagine that once we have experimental proof of the effectiveness of cancer screening, it is enough to implement it to obtain a reduction in mortality. Numerous examples indicate that a screening program can have almost zero effectiveness with many deleterious effects **[68]** . A group of experts from the International Agency for Research on Cancer studied the results of 11 cervical cancer screening programs **[69].** The false negative rate ranged from 10 to 40%, with the highest percentages seen in the least organized programs. The evaluation of breast cancer screening programs by mammography has often led to disappointing results. The failure of the German colorectal cancer screening program in place since 1977 is demonstrative **[70]** . Individual screening, limited to voluntary subjects, is ethically reprehensible. It leaves out a large part of the population. Participation is not sufficient to achieve a significant reduction in mortality. The impossibility of controlling practical prescriptions leads to over-testing certain individuals with the consequence of the risk of increasing the number of unnecessary examinations, sometimes potentially dangerous, such as colonoscopy. It is

the responsibility of decision-makers to seek efficiency. They cannot simply serve a small proportion of the population by committing significant resources.

Tableau 8 : Participation au dépistage du CCR expériences française

Tableau IV. – Participation au dépistage du cancer colorectal par la recherche d'un saignement occulte dans les selles. Les expériences françaises.

Participation on faecal occult blood screening for colorectal cancer. French experiences.

Envoi d'une prise en charge permettant d'obtenir gratuitement le test de dépistage chez le pharmacien		
— Calvados	(86-87)	20 %
— Finistère	(88-89)	22 %
— Landes	(90-92)	22 %
— Aquitaine	(90-92)	25 %
	(96-97)	12 %
— Nord-Pas de Calais	(90-92)	21 %
— Picardie	(93-95)	22 %
Envoi d'une prise en charge pour consultation de dépistage aux femmes de 50 à 69 ans		
— Isère	(91-92)	25 %
Distribution par médecins puis envoi d'une prise en charge		
— Calvados	(91-93)	43 %
Distribution par les médecins et envoi postal du test		
— Saône-et-Loire	(88-98)	53 à 58 %
— Calvados	(91)	55 %
— Oise	(90-92)	49 %

All experience indicates that a screening program can only be designed and implemented:

- if it is organized with great rigor,
- if it is subject to ongoing evaluation,
- if there is a quality assurance system for screening but also for the diagnostic and therapeutic management of cancers detected,
- if he has the necessary means.

C) Quality criteria for a mass screening program

Any organized screening program must include a quality assurance program. We absolutely must know if the participation rate is sufficient, monitor the positivity rate of the screening test, evaluate the quality of care up to treatment, and know the harmful effects of screening. The main quality criteria of a screening program using the Hemoccult test are given in **table 9.**

Tableau 9 : Critère de qualité d'un programme de dépistage par test hemoccult

Tableau V. – Critères de qualité d'un programme de dépistage par le test Hemoccult®.
Quality assurance of screening with Hemoccult® test.

Taux de participation	
Globale à chaque campagne	> 50 %
Répétition des tests chez les participants	> 80 %
Taux de positivité	
Initial	2 à 3 %
Ultérieur	1 à 2 %
Taux de coloscopie parmi les positifs	> 90 %
Valeur prédictive positive	
Cancer	> 10 %
Adénome	30 à 40 %
Taux de cancers stade I parmi les cancers dépistés	> 40 %

7 . Ethics and Colorectal Cancer Screening

1 Individual choice : An individual's right to refuse or accept a screening test is a fundamental ethical principle **[71, 72, 73]** . To fully exercise this freedom of choice and make a quality decision, the individual must know all the options available to them, fully understand the scientific data on the potential benefits, adverse effects and possible complications linked to screening and When establishing the diagnosis, decide the role they wish to take in the decision-making process, obtain the necessary support and finally analyze the situation according to their own values and preferences.

2 The right to information and the right to privacy : The creation of accurate information which must be transmitted to the people invited in order to support quality decision-making on their part, requires access to information from of the analysis of data from participants, but also from non-participants. The right to information of those invited and the right to privacy of patients must therefore be reconciled in order to constitute a body of fair and valid information **[74].**

3 Social equity : in a more global vision of the health system, the implementation of a screening program could be done at the expense of other programs or medical interventions whose relative cost is lower, whose effect on mortality or benefits are higher or are more likely to alleviate suffering **[75, 76].** According to the principle of social equity, the effort dedicated to screening must therefore not take up a disproportionate share of the care services and resources required for people already suffering from symptoms, colorectal cancer or other pathologies requiring the same resources and services. Finally, a screening program requires the establishment of quality assurance and evaluation procedures as well as the establishment of performance measures in all spheres of activity involved. People who do not participate in the screening program (by refusal or because they are not part of the target population) would suffer harm if, for the same required clinical service, it was not offered according to the same procedures. . Respect for social equity in the implementation of a population screening intervention must therefore be able to count on active monitoring of all non-program aspects that could be affected by screening.

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