Current issues in colorectal cancer screening in France

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“ Colorectal cancer is a major public health issue. Colorectal cancer screening should be adapted to the level of risk. In subjects with high or very high risk, screening is carried out by colonoscopy. Where there is average risk, the basis of screening is an immunological fecal test performed every two years. This test, which is now available in 2015, can detect 7–8 out of 10 cancers, instead of just 3–4 for the Hemoccult ® test previously used. Increasing the participation of the target population is the major challenge in this action. The role of general practitioners and their corresponding gastroenterologists is central to this increase in participation. Colonoscopy could also be considered for people at average risk if there is a particular demand and if the risk–benefit ratio is clearly stated. Other tools may also be useful in specific circumstances: the fecal DNA test, rectosigmoidoscopy, and colon capsule endoscopy.”

A public health issue

Approximately 42,000 new cases of colorectal cancer are diagnosed each year in France. The lifetime risk for an individual of developing a colorectal cancer is in the order of 3–4%, with a very low risk before the age of 50 years that then steadily increases. Despite significant therapeutic advances and the possibility of earlier detection at a stage when the prognosis is more favorable, colorectal cancer remains the second leading cause of cancer mortality.

Increased risk

Individuals who have already had an adenoma or colorectal cancer, and those with at least one first-degree relative with a colorectal polyp or cancer have an increased relative risk, of between 2 and 4, depending on the age of onset and the type of index lesion [1].

The risk of colorectal cancer is also increased in Crohn's disease and ulcerative colitis (relative risk of approximately 2). This risk is observed when the inflammation has been poorly controlled, when it has been present for more than 10 years, when more than half of the colon is affected, and when sclerosing cholangitis or a family history of colon cancer are present [2].

The risk of colorectal cancer is very high in certain rare genetic conditions, such as familial adenomatous polyposis – linked to mutations in the APC gene (almost 100% risk of developing a cancer) or linked to MYH gene defects (relative risk greater than 30) – as well as Lynch syndrome (greater than 60% risk of developing a cancer).

The cancers diagnosed in these groups at high and very high risk represent approximately 20% of all colorectal cancers. The systematic identification of these circumstances and the implementation of regular surveillance by colonoscopy should allow for the management of most of this risk. The establishment of organized networks has facilitated progress, which should be further pursued [3].

It is recommended that all people over 40 years of age who have symptoms suggestive of colorectal cancer, both clinical – such as recent changes in bowel frequency (positive predictive value 14%) or rectal bleeding (positive predictive value 8%) –, or biological – such as iron-deficiency anemia without a gynecological explanation (positive predictive value 10%) –, consider undergoing a colonoscopy [4].

How to screen the "average-risk" population?

A "slow" natural history facilitating the screening

Most colorectal cancers are described as sporadic, that is they develop in subjects with none of the risk factors that are currently clearly identified. These sporadic cancers develop slowly over several years from benign precancerous lesions, or from adenomatous or serrated polyps. At the asymptomatic stage, advanced polyps and cancers can be the basis of intermittent occult bleeding. This bleeding can be identified in the stool by chemical (guaiac test, such as Hemoccult ®) or immunological (antibody against human hemoglobin) methods. The current screening program is based on this principle.

Hemoccult® : France at the forefront of organized screening

Performance of the Hemoccult ® test every two years can lead to a reduction of around 30% in colorectal cancer mortality in subjects participating in the screening program. This screening test has the advantage of being relatively simple and acceptable, safe, inexpensive, and with a proven efficacy. When the Hemoccult test is positive, which is the case in 2–3% of the subjects tested, a colonoscopy should be performed, which will generally reveal a cancer in just under 1 in 10 cases. After pilot programs were implemented in the early 2000s, colorectal cancer screening was generalized throughout the whole territory from 2008. France is thus one of the first countries to have proposed this test to all persons covered by social insurance aged between 50–74 years, as part of an organized program. One of the principal limitations of this program is insufficient participation, which has declined over time to around 32% of the target population according to the most recent estimates by the French National Institute for Health Surveillance ("Institut national de veille sanitaire"). This can be compared with the participation observed in the United Kingdom, which is of the order of 60%. The efficiency of a screening program depends not only on the performance of the test but also on the participation rate. The active involvement of general practitioners, which is an essential element of effectiveness in colorectal cancer screening, varies widely between different French "departments" (administrative regions) and

would seem to be diminishing over time.

Immunological tests; technical and conceptual progress

The French National Authority for Health ("*Haute autorité de santé*", HAS) recommended a switch to the use of immunological blood tests from 2008 onwards, as this method of detection of blood in the stool is more effective. However, a tender procedure was only implemented by the Public Health Insurance Fund ("*Caisse nationale d'assurance maladie*"), on government instruction, in 2014. The deployment of the new test is scheduled at the beginning of 2015. Whilst these immunological tests are still fecal tests, they require only a single stool sample, collected with a swab, as opposed to the Hemoccult ® test that requires six samples: two samples from three consecutive stools, collected using a spatula that is less easy to use. This test should, thus, be better accepted and better achieved by target individuals; an increase in participation somewhere between 0% and 15% is anticipated. Unlike that of the Hemoccult ® test, reading of the immunoassays is automated, which reduces the risk of human error. The cost will be broadly similar: although the unit cost is a little higher, the cost-effectiveness is similar.
At the chosen positivity threshold, the immunoassays can detect 7–8 cancers in 10, instead 3–4 cancers in 10 for the Hemoccult ® test (Table 1). They also detect three to four times as many advanced adenomas [5]. This ability to detect cancers at an early stage as well as advanced adenomas should allow not only the prevention of cancer deaths (cancers detected at an early stage), but also, ultimately, a reduction in the number of cancers (adenomas detected being removed during colonoscopy). General practitioners are at the heart of this screening program, as a test is performed more than 8 times out of 10 when it is actually prescribed by them. They must, therefore, be heavily involved in this change. Gastroenterologists, who are key partners in this action, as shown by the investment of their learned societies, need to motivate their general practitioner colleagues to increase participation.

Table 1. Comparison of the key characteristics of the Hemoccult ® test and immunological tests.

	Hemoccult ®	Immunological test
Estimated sensitivity to detect a cancer (%)	30 to 40	70 to 80
Estimated sensitivity to detect an advanced adenoma (%)	10	35
Number of colonoscopies to detect a cancer (after a positive test)	15	10 to 15

Other screening methods

Many other biological and morphological methods are available or being evaluated.

The detection of anomalies in fecal DNA (investigation of deleterious mutations and/or methylation anomalies associated with colon carcinogenesis) coupled with an immunological fecal blood test has been proven to be superior in terms of sensitivity compared with the immunological fecal blood test alone [6]. The specific contribution of seeking such DNA abnormalities remains moderate, however, in comparison with the completion of a fecal immunological test alone (18% gain in sensitivity for detecting cancer). The contribution of this approach will show its cost-effectiveness when the proposed cost is known.

Several blood tests have been developed, mostly based on the detection of abnormalities in circulating DNA, in particular abnormal methylation, with promising results. However, the results are still insufficient (positive predictive value in the order of 30%) for these tests to be considered for use at the level of large populations, despite their advantages in terms of acceptability [7]. Moreover, none of the available blood tests have a good detection for advanced adenomas. Alternative blood tests based on RNA or proteome analysis are still at the stage of preliminary studies [8].

Colonoscopy proposed as a first-line screen from the age of 50 or 55 years is considered as an option for colorectal cancer screening in countries such as Germany, Poland, and the United States. The acceptability of this method is low when it is systematically proposed to the general population, with a rate of between 20% and 25% [9]. Participation seems to be higher, around 50%, when the examination is proposed by a general practitioner [10]. The number of colonoscopies that need to be performed in order to detect a cancer or advanced adenoma depends on age and sex, varying from 46 colonoscopies for a 45-year-old woman to 10 colonoscopies for a 60-year-old man, figures that are close to those observed after a positive fecal test [9, 11]. The decrease in specific mortality expected after undergoing a screening colonoscopy remains to be quantified precisely, available estimates varying between 50–90%, depending on the study [12]. Ongoing interventional studies, NordiCC, COLONPREV, CONFIRM, and SAVE, should allow a clarification of these figures. Colonoscopy first-line screening strategies appear to be less cost-effective than screening based on fecal tests (fecal immunochemical test, FIT) [13]. The contribution of new endoscopic techniques – such as the increased lateral viewing allowed by the Fuse (Full Spectrum ™ Endoscopy; vision at 330 °) or "Third Eye", technologies, or by use of a centering balloon and vital or electronic chromoendoscopy – and also the contributions of policies facilitating the better quality of the colonoscopies performed, need to be clarified in the context of screening.

The protective role of a screen by rectosigmoidoscopy, once or repeated every 10 years, has been demonstrated by several randomized studies, with a decrease of around 20% in specific mortality [12]. The main problem of this technique, as for colonoscopy, is its poor acceptability (30% uptake).

The coloscanner with air insufflation has been proposed by some authors for use in colorectal cancer screening [14]. Its sensitivity to detect patients having at least one adenoma greater than 6 mm has been estimated as 76%, but this varies depending on the center and technique [15]. Assessments by the French National Authority for Health, and by the US authorities for the Medicare and Medicaid programs have not selected this technique for colorectal cancer screening [16]. Its role in screening in high-risk cases is thus confined to subjects unable or unwilling to undergo a colonoscopy.

The sensitivity of colon capsule endoscopy to detect adenomas larger

than 6 mm is about 85%, which is higher than that of the coloscanner. The capsule is currently proposed as a second-line option, after a positive fecal test and when colonoscopy is not possible or refused. The value of colon capsule endoscopy as a first-line screen for colorectal cancer remains to be assessed in the general population. Preliminary studies are in progress. The anticipated participation rate might be higher than that observed for conventional colonoscopy, which would render this approach cost-effective. [17]. "New" capsules are at a preliminary study stage, including one that uses a very low level of X-rays to allow 3D visualization of the colon without the need for bowel preparation (Check-Cap).

A false "average risk"

Age and male gender are risk factors for colorectal cancer, as well as insufficient physical activity, obesity, diabetes, high cholesterol, chronic alcohol consumption, smoking, a diet high in red and cured meats and/or low in fruits and vegetables, calcium, and possibly folate and phenols, and the absence of chronic exposure to aspirin. These factors appear to be particularly harmful in combination or when there is a predisposing genetic background, characterized by certain polymorphisms affecting sensitive metabolic or immune pathways. In these situations, the risk level approaches that of "known" high-risk populations and colonoscopy screening could be envisaged. Scores have been proposed to better define risk levels, some of which are available online [18-20]. These scores are still insufficiently discriminating for use in the clinic and have not been validated for the French population. An original approach to the prediction of colorectal cancer risk using a mathematical algorithm based on the evolution of data from repeated complete blood counts is currently being evaluated.

Conflicts of interest

Robert Benamouzig, head of Avicenne University hospital and the director of a clinical research center, is principal investigator for several studies promoted by "Assistance Publique-Hôpitaux de Paris" and INRA. He is a member of the Scientific Board of Given Imaging, Covidien.

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