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## **Evaluation of A risk score based on dietary and lifestyle factors to target A population at risk in colorectal cancer screening**

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**Running title:** Lifestyle can impact colorectal cancer screening

## **ABSTRACT**

**BACKGROUND:** The aim of our study was to assess three risk scores to predict lesions, advanced neoplasia (high-risk adenomas and colorectal cancer (CRC)) and CRC in individuals who participate to colorectal cancer screening.

**METHODS:** The data of dietary and lifestyle risk factors were carried out during 2 mass screening campaigns in France (2013-2016) and the FOBT result was collected until December 2018. The colonoscopy result in positive FOBT was recovered. Three risk scores (Betés score, Kaminski score and adapted-HLI) were calculated to detect individuals at risk of lesions.

**RESULTS:** The Betés score had an AUROC of 0.63 (95% CI, [0.61-0.66]) for lesions, 0.65 (95% CI, [0.61-0.68]) for advanced neoplasia and 0.65 (95% CI, [0.58-0.72]) for predicting screen-detected CRC.

The adapted HLI score had an AUROC of 0.61 (95% CI, [0.58-0.65]) for lesions, 0.61 (95% CI, [0.56-0.65]) for advanced neoplasia and 0.55 (95% CI, [0.45-0.65]) for predicting screen-detected CRC.

The Kaminski score had an AUROC of 0.65 (95% CI, [0.63-0.68]) for lesions, 0.65 (95% CI, [0.61-0.68]) for advanced neoplasia and 0.69 (95% CI, [0.62-0.76]) for predicting screen-detected CRC.

**CONCLUSION:** A simple questionnaire based on CRC risk factors could help general practitioners to identify participants with higher risk of significant colorectal lesions and incite them to perform the fecal occult blood test.

**Key Words:** lifestyle risk factors, colorectal cancer screening

Our study shows that using of a quick and simple questionnaire based on well-established CRC risk factors, it may be possible to identify in average-risk population those subjects who must be convinced to participate in organized colorectal cancer screening in France where the participation rate to screening is low.

## **ABBREVIATIONS LIST**

CRC: colorectal cancer

HLL: Healthy lifestyle index

AUROC: area under the Receiver Operating Characteristic

CI: confidence interval

FOBT: fecal occult blood test

WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research

IDYLIC: Impact of DietarY and Lifestyle risk factors on Colorectal cancer screening

FFQ: food frequency questionnaire

IPAQ: International Physical Activity Questionnaire

IQR: interquartile range

INCa: Institut National du cancer

## INTRODUCTION

In France, colorectal cancer (CRC) ranks 3<sup>rd</sup> in men and 2<sup>nd</sup> in women for incidence, and 2<sup>nd</sup> mortality cause for both sexes [1]. The European 5-year relative survival rate was 57% for the colon and 56% for the rectum in the EURO CARE-5 study [2]. Because of its incidence, social consequences and cost related to its medical care, it represents a public health challenge. It has been clearly demonstrated that CRC screening campaigns can detect precancerous polyps that can be removed during a colonoscopy and therefore drastically reduces mortality due to this cancer [3–5]. In France, since end of 2008, adults aged 50 to 74 years old, considered as at average risk of CRC are invited to perform a fecal occult blood test (FOBT) every two years, followed by colonoscopy when this FOBT is positive. The nationwide participation rate was only 32.1% for the 2015-2016 campaign, exceeding 45% in only 3 of the 101 French geographic area [6]. This remains lower than the acceptable minimum rate of at least 45% and far from the desired target of at least 65% [7]. It is therefore necessary to develop strategies to sensitize the target population and enhance participation.

A large body of literature shows that, apart from hereditary factors and age, CRC risk is mainly induced by lifestyle [8–10]. According to the last report of World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) expert panel, there is convincing evidence that physical activity and foods containing dietary fiber are related to a lower CRC risk [11]. Garlic [12] and dairy products (including milk) [13] intakes also probably reduce CRC risk whereas tobacco smoking, alcohol drinks, high intakes of red or processed meat, have all been associated with an increased risk [11,14–18], just as diabetes [19], overweight and obesity [10,20] which are strongly linked to Western dietary pattern and insufficient physical activity, as reported by meta-analysis of Huxley and al [8].

Several studies have assessed risk score to predict CRC or precursors as advanced adenoma (adenomas  $\geq$  10mm, high-grade dysplasia or in situ carcinoma, villous component) or advanced neoplasia (CRC and high-risk adenomas) [21–24]. Betés et al [23] have developed a risk score in a population at average risk of CRC aged 40 years and over associated with advanced adenoma and based on age, gender and body mass index

(BMI). In a similar way, Aleksandrova et al. [21] have recently developed a healthy lifestyle index (HLI) composed of dietary and lifestyle factors (body mass index, physical activity, smoking status, limited alcohol consumption, healthy diet) having convincing or probable link to CRC according to WCRF/AICR. In this study, HLI was shown to be strongly associated with the incidence of CRC in a large European cohort of adults aged between 25 and 70 years [21]. Finally, Kaminski et al [22] developed a risk score to predict advanced neoplasia in population 40 to 66 years old based on age, gender, familial history of CRC, BMI and smoking status. None of these factors are however currently taken into account in defining national CRC screening strategies [25].

The objective of the present study entitled Impact of Dietary and Lifestyle risk factors on Colorectal cancer screening (IDYLIC) was to identify participants in national CRC screening campaign with higher risk of screened-detected lesions, advanced neoplasia (high-risk adenomas and CRC) and CRC thanks to a questionnaire-based risk score. We assess the discriminative value of three 'a priori' risk scores; the adapted-HLI, Kaminski's score and Betés' score and compare their performance to predict high-risk adenomas, advanced neoplasia and CRC.

## **METHODS**

### Study population

This cross-sectional study was conducted during 4 years (2013-2016) and covered the last two CRC screening campaigns in the Maine-et-Loire area (France) managed locally by Cap Santé 49 which is the Maine and Loire screening center. In France, individuals at average risk of colorectal cancer aged 50 to 74 are invited by Cap Santé 49 to contact their general practitioners to realize a faecal occult blood test (FOBT) if they are asymptomatic. The guaiac-FOBT (Hemoccult<sup>®</sup>) was used from 2009 to June 2015 then replaced by faecal immunochemical test (OC Sensor<sup>®</sup>). The study questionnaire and an accompanying letter of information were distributed to screening attendees on FOBT test delivery. They were asked to return the questionnaire at the same time as the screening test using the prepaid envelope provided. The study protocol was approved by research and ethics committees (CCTIRS – N°12.144, CNIL – N°912248). If the test was positive individuals must do a colonoscopy. Thanks to Cap Santé 49, we collected data about the results of the test (positive or negative), diagnosis of adenomas, high-risk adenomas or CRC. A high-risk adenoma was defined by adenoma with size  $\geq 10$  mm, tubulovillous or villous adenoma, or high grade dysplasia including in situ carcinomas.

### *Construction of the questionnaire*

The study questionnaire was divided into several parts: socio-demographic characteristics, anthropometric data, medical history and medication, smoking status, alcohol consumption, usual diet and physical activity.

The dietary questionnaire was derived from a reproducible and validated semi-quantitative food frequency questionnaire (FFQ) adapted to dietary patterns of the French population [26]. We have selected from the original FFQ only those sections concerning food groups with a "convincing", "probable" or "suggestive" link with the risk of CRC according to the current scientific knowledge: red meat, processed meat, milk and other dairy products, foods containing dietary fiber, garlic, fruits and vegetables [8–10]. For some categories of foods, the questionnaire additionally included sets of color photographs showing different portion sizes,

which have been previously validated [27]. For the other food items, subjects were asked to report their consumption frequency on the basis of how many times they ate the standard portion size proposed.

The physical activity questionnaire was an adapted version (tabular form) of the International Physical Activity Questionnaire (IPAQ) [28]. Data processing and classification by physical activity category were strictly performed as recommended by the IPAQ group [29].

#### *Construction of risk scores*

The first scoring system was derived from Betés et al [23]. This score was based on gender (0 point for women and 2 for men), age (1 point from 51 to 60, 2 points from 61 to 70 and 3 points from 71 years old) and BMI (0 point < 25 kg/m<sup>2</sup>, 1 point for 26 to 35 kg/m<sup>2</sup> and 2 points for > 35 kg/m<sup>2</sup>). The second 'a priori' risk score was derived from the HLI recently proposed by Aleksandrova et al. [21], the adapted HLI. The data collected through our study questionnaire did not allow us to calculate the original version of the HLI. Our HLI-based risk score combined 5 lifestyle-related factors: overweight or obesity, smoking status, excessive alcohol consumption, low level of physical activity, and a low quality diet index based on 7 dietary factors presumably related to CRC (red meat, processed meat, milk and dairy products, fruits, vegetables, garlic, foods rich in dietary fiber). The global risk score was calculated by summing the binary score (0/1) for each lifestyle factors and thus ranges from 0 to 5. The third scoring system was derived from Kaminski et al [22]. The score comprised age (1 point from 50 to 54, 2 points from 55 to 59 and 3 points from 60 years old), gender (0 point for women and 2 for men), BMI (0 point < 29 kg/m<sup>2</sup>, 1 point for ≥30 kg/m<sup>2</sup>), smoking status (0 point for no smoker and 1 for current smoker) and we attributed 0 point for familial history of CRC.

#### *Study outcomes*

The primary endpoint was advanced neoplasia and CRC diagnosed by colonoscopy after a positive screening test. Only the three worst histological samples were collected for the present study and participants were classified according to the most high-risk histological lesion at screening colonoscopy: participants without adenoma or CRC, participants with CRC, participants with adenoma and participants with high-risk adenoma.

Participants with negative screening result were classified as having no CRC or adenoma. The detection rates were defined as the number of screened CRC, adenoma or high-risk adenomas per 1000 study participants. In order to reduce this bias, the results of the FIT were taken into account in the following screening campaigns. Scores were calculated taking into account these data.

### *Statistical analysis*

Participant characteristics were expressed as median (interquartile range) or frequency (%). Comparisons between groups (screen-detected CRC, screened-detected colorectal adenoma and high-risk adenoma, controls with no neoplasia at screening) were conducted using the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for categorical variables. The Cochran-Armitage trend test was used to assess whether or not there was an increase in the detection rate of CRC, colorectal adenoma and high-risk adenoma with increasing value of the developed lifestyle risk scores. The discriminatory power of each score was assessed using the area under the Receiver Operating Characteristic (AUROC) curve. The correctly classified patients, sensitivity, and specificity rates were also determined using the threshold defined by the maximum value of the Youden index with the best sensitivity. Differences in diagnostic accuracies were assessed using the paired McNemar test. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary NC, USA).

## RESULTS

The flow chart for the study population is presented in Figure 1. Of the 12,041 participants to the study questionnaire, 335 (2.8%) were excluded because they did not belong to the average-risk population targeted by the French organized CRC screening program. Among the remaining 11,706 participants, 716 (6.1%) had a positive screening test and 696 (97.2%) underwent colonoscopy. 20 participants were excluded (12 with positive test who have not realized colonoscopy and 8 with inconclusive colonoscopy) (11686 participants were included in our study). At initial collection (combined risk factor collection), 368 positive tests with 348 conclusive colonoscopies performed. In the successive campaigns carried out until December 2018 with FIT: 348 new positive FIT with 348 colonoscopies (Figure 1). CRC was diagnosed in 50 participants, i.e. a detection rate of 4.3‰ (among the 11,706 study participants), 151 had screen-detected colorectal adenoma without cancer (detection rate = 12.9‰) and 203 had high-risk adenoma (detection rate = 17.3‰).

### *Lifestyle risk factors associated with lesions*

The median age (IQR) of the study participants was 60.0 (54.0-65.0) years, and 47.2% were men. Table 1 presented lifestyle risk factors associated with screen detected adenoma, high-risk adenomas and CRC in comparison with no screen detected lesion in univariate analysis.

In forward multivariate analysis, screen detected lesions (adenomas, high-risk adenomas and CRC) were associated with male sex (OR=2.03 [1.60-2.58],  $p<0.0001$ ), BMI  $\geq 25$  kg/m<sup>2</sup> (OR=1.37 [1.10-1.71],  $p=0.005$ ), smoking (OR=2.16 [1.67-2.80],  $p<0.0001$ ), excessive alcohol consumption (OR=1.43 [1.13-1.81],  $p=0.003$ ), age (OR=1.02 year [1.00-1.04],  $p=0.026$ ) and garlic consumption (OR=0.94 [0.88-1.00],  $p=0.05$ ).

In forward multivariate analysis, screen detected advanced neoplasias (high-risk adenomas and CRC) were associated with male sex (OR=1.89 [1.39-2.56],  $p<0.0001$ ), BMI  $\geq 25$  kg/m<sup>2</sup> (OR=1.65 [1.24-2.21],  $p=0.001$ ), smoking (OR=1.52 [1.06-2.17],  $p=0.022$ ), excessive alcohol consumption (OR=1.59 [1.19-2.14],  $p=0.002$ ), age (OR=1.02 year [1.00-1.04],  $p=0.097$ ), garlic consumption (OR=0.92 [0.85-1.01],  $p=0.066$ ) and consumption of milk (OR=0.88 [0.76-1.02],  $p=0.098$ ).

### *Performance of risk scores*

The Betés score was available for 10161 participants and had an AUROC of 0.63 (95% CI, [0.61-0.66]) for lesions, 0.65 (95% CI, [0.61-0.68]) for advanced neoplasia and 0.65 (95% CI, [0.58-0.72]) for predicting screen-detected CRC. Higher risk score values were associated with higher rates of lesions ( $p<0.0001$ ), advanced neoplasia ( $p<0.0001$ ) and screen-detected CRC ( $p=0.005$ ) (Tableau 2A). Using a cut-off of 4, sensitivity and specificity were respectively 63.0% and 59.4% for lesions prediction; 65.9% and 59.1% for advanced neoplasia and 68.0% and 58.7% for CRC.

The adapted HLI score was available for 8647 participants and had an AUROC of 0.61 (95% CI, [0.58-0.65]) for lesions, 0.61 (95% CI, [0.56-0.65]) for advanced neoplasia and 0.55 (95% CI, [0.45-0.65]) for predicting screen-detected CRC. Higher risk score values were associated with higher rates of lesions ( $p<0.0001$ ) and advanced neoplasia ( $p<0.0001$ ) but not with higher rates of screen-detected CRC ( $p=0.278$ ) (Tableau 2B). Using a cut-off of 2, sensitivity and specificity were respectively 68.5% and 49.9% for lesions prediction, 67.9% and 49.7% for advanced neoplasia and 63.9% and 43.9% for CRC.

The Kaminski score was available for 10848 participants and had an AUROC of 0.65 (95% CI, [0.63-0.68]) for lesions, 0.65 (95% CI, [0.61-0.68]) for advanced neoplasia and 0.69 (95% CI, [0.62-0.76]) for predicting screen-detected CRC. Higher risk score values were associated with higher rates of lesions ( $p<0.0001$ ), advanced neoplasia ( $p<0.0001$ ) and higher rates of screen-detected CRC ( $p<0.0001$ ) (Tableau 2C). Using a cut-off of 4, sensitivity and specificity were respectively 66.8% and 56.2% for lesions prediction, 66.5% and 55.9% for advanced neoplasia and 75.0% and 55.6% for CRC.

### *Comparison of performance of the three scores*

Overall, the rate of well-classified subjects for advanced neoplasia was 59% with Betes score with cut-off of 4, 50.0% with HLI with cut-off of 2 and 56.3% with Kaminski score with cut-off of 4 and was significantly higher for Betés score than the two others ( $p<0.0001$ ). 7413 participants had available data for the three

scores: the AUROC for screen detected lesions was 0.67 [0.59-0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score (Figure 2A). For screen detected advanced neoplasia, the AUROC was 0.67 [0.59-0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score (Figure 2B). For screen detected CRC, the AUROC was 0.67 [0.59-0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score (Figure 2C).

## DISCUSSION

This cross-sectional study on participants in the French CRC organized screening program from 2013 to 2016 demonstrates that a high proportion of individuals with screen-detected CRC could be identified prior to screening using a questionnaire-based risk score on dietary and other lifestyle-related factors. The three risk scores also showed some ability, although in a lower extent, for stratifying average-risk individuals according to their risk of significant lesions detection.

A number of scoring tools have been proposed for assessing the risk of CRC or high-risk colorectal neoplasia [24,30]. Most have been developed within a colonoscopy-based screening program, primarily in studies that did not exclude individuals with higher risk due to a family history of CRC and/or personal predisposing factors. Fewer risk scores have been proposed in average-risk populations [30–33]. In a recent study within the Bowel Cancer Screening in Norwegians aged 50-74, it has been shown that the probability of having a screen-detected high-risk colorectal neoplasia was inversely associated with a healthy lifestyle score based on body mass index, smoking status, alcohol intake, physical activity, consumption of fruits and vegetables, meat, processed meat, and fatty fish [33].

The published prediction models and risk scores were designed and evaluated as stratification tools either for CRC only, or for combined CRC and high-risk adenomas [30–33]. In agreement with our results, a recent case-control study in the United States demonstrated that the risk of colorectal polyps increased progressively with an increasing number of CRC lifestyle risk factors [34]. These findings support a deleterious effect of poor lifestyle habits throughout the continuum from precancerous adenomatous polyps to colorectal cancer. This was confirmed by the last report of WCRF that supports legumes intakes, dietary fibre, dietary vitamin E, calcium, vitamin D, vitamin C and physical activity decrease colorectal adenomas risk whereas alcohol, red or processed meat increase this risk [35]. Another study have evaluate the association of colorectal polyps and CRC with lifestyle factors in a population with fecal immunochemical test positive

and found an association with obesity and smoking with high-risk adenomas and smoking and alcohol with CRC [36].

In our study, the presence of an adenoma was associated with male sex, diabetes, smoking, higher consumption of processed meat and lower consumption of vegetable. The presence of a high-risk adenoma was associated with male sex ( $p < 0.0001$ ), BMI  $\geq 25$  kg/m<sup>2</sup> ( $p < 0.0001$ ), smoking ( $p < 0.0001$ ), alcohol ( $p = 0.003$ ), lower consumption of garlic ( $p < 0.0001$ ), fruit ( $p = 0.014$ ), and vegetables ( $p = 0.008$ ) and CRC was associated with male sex ( $p = 0.006$ ), age ( $p = 0.044$ ), BMI  $\geq 25$  kg/m<sup>2</sup> ( $p = 0.014$ ) and alcohol ( $p = 0.010$ ). A similarly study found an association between overweight and smoking with high-risk adenomas but no association with alcohol was reported [36]. As reported in this study, we do not find an association between diabetes and high-risk adenomas or CRC but we found this association with colorectal adenomas. In our study, alcohol and overweight seem to be participated to degeneration of adenoma in high-risk adenoma and CRC. The evidence of relation between fruit and vegetable intakes and CRC is only "suggestive" in the 2011 WCRF/AIRC expert report [9] and according to an updated critical review of the literature of the French National Institute of Cancer (INCa) [10]. Despite, the observed inverse significant associations are consistent with a recent meta-analysis conducted by Johnson et al. [37]. Dietary fiber intake was not associated with screen-detected CRC and adenoma in our study. However, we evaluated only consumption of high-rich fiber foods while WCRF/AICR and INCa highlighted an inverse relationship with total dietary fiber intakes [9,10]. Similarly, no relationship was found with total dairy products. This may be related to the pattern of dairy products consumption in the present study population. Indeed, the association between milk intake and CRC is judged as "probable" [9,10] whereas the relation with cheese intake is more controversial [10]. No relationship was found between physical activity and lesions contrary to a meta-analyses of colorectal cancer risk factors [10]. To date, almost all of the proposed risk scores are derived from multivariate outcome regression models in diverse populations, so they rely on heterogeneous combinations of factors. In contrast, the three scoring systems in this study are based on an *a priori* approach including well-established CRC risk factors according

to the most recent scientific knowledge [8–10]. We have assessed three different risk scores to predict high-risk adenomas, CRC and advanced neoplasia. Although the three risk scores demonstrated only moderate to good discriminative ability, their AUROCs were comparable with those of previous risk prediction models [30–33]. The Betés score had a higher rate of correctly classified subjects, but we were only able to evaluate an adapted version of the HLI scoring system. Further studies should evaluate the discriminative ability of HLI as initially designed.

One of the strengths of our study is that it was conducted on the population currently targeted by the age-based screening strategy in place in France, as in other European countries. Our food assessment tool is derived from the dietary questionnaire of a large French cohort study that has been validated against 24-hour dietary records [26]. Our physical activity questionnaire was a tabular form version of the IPAQ, a standardized tool for assessing habitual physical activity in populations from different countries and socio-cultural contexts [28]. It is important to note that all study participants completed the lifestyle questionnaire before receiving their screening results. The present study has some limitations though. For practical reasons, the study was conducted within a geographical area limited to the Maine-et-Loire department. An additional concern was the selection bias due to voluntary participation to the study from the whole population targeted by the organized screening program. In our study, the proportion of participants with a positive screening test, as the detection rates for CRC and adenoma, were similar to those reported for the French population overall. In addition, study subjects both with and without complete data for calculating lifestyle scores did not significantly differ in screening outcomes. Moreover selection of the population participating in screening is very different from the general population. It is well known that low socioeconomic status is associated with low participation, while the risk of CRC is higher due to higher risk diet and lifestyle. This could influence predictive scores.

We acknowledge that it could have a misclassification because we consider that subjects with a negative screening test had no CRC or adenoma. To reduce this bias, the FOBT results were collected until December 2018. The colonoscopy results in positive FOBT were recovered.

In conclusion, the present study suggests that risk scores based on well-established lifestyle-related CRC risk factors may accurately stratify patients according to their risk of significant colorectal lesions. Recent studies show that most people are not aware of the relationship between lifestyle factors and colorectal cancer [38,39]. With this short questionnaire, health practitioners could have a simple tool to convince those who are reluctant to use the fecal occult blood test and thus increase the participation rate in mass screening for colorectal cancer.

**Declaration of conflict of interest:** All authors have nothing to disclose concerning this study.

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## REFERENCES

1. Projection de l'incidence et de la mortalité par cancer en France métropolitaine en 2015 / 2015 / Maladies chroniques et traumatismes / Rapports et synthèses / Publications et outils / Accueil [Internet]. [cited 2018 Feb 20]. Available from: <http://invs.santepubliquefrance.fr/fr./Publications-et-outils/Rapports-et-syntheses/Maladies-chroniques-et-traumatismes/2015/Projection-de-l-incidence-et-de-la-mortalite-par-cancer-en-France-metropolitaine-en-2015>
2. Holleczer B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. *Eur J Cancer Oxf Engl* 1990. 2015;51:2158–68.
3. Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology*. 2004;126:1674–80.
4. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol*. 2008;103:1541–9.
5. Zauber AG. The impact of screening on colorectal cancer mortality and incidence: has it really made a difference? *Dig Dis Sci*. 2015;60:681–91.
6. Participation rate in the organized colorectal cancer screening program 2015-2016 / Evaluation indicators / Evaluation of the colorectal cancer screening program [Internet]. [cited 2018 Feb 20]. Available from: <http://invs.santepubliquefrance.fr/fr./Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-colorectal/Indicateurs-d-evaluation/Taux-de-participation-au-programme-de-depistage-organise-du-cancer-colorectal-2015-2016>
7. Navarro M, Nicolas A, Ferrandez A, Lanás A. Colorectal cancer population screening programs worldwide in 2016: An update. *World J Gastroenterol*. 2017;23:3632–42.

8. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*. 2009;125:171–80.
9. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011 [Internet]. [cited 2018 Feb 21]. Available from: <https://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf>
10. Latino-Martel P, Cottet V, Druesne-Pecollo N, Pierre FHF, Touillaud M, Touvier M, et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. *Crit Rev Oncol Hematol*. 2016;99:308–23.
11. World cancer research Fund/american Institute for Cancer Resaerch. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. [Internet]. [cited 2020 May 14]. Available from: Available at [dietandcancerreport.org](http://dietandcancerreport.org)
12. Ngo SNT, Williams DB, Cobiac L, Head RJ. Does garlic reduce risk of colorectal cancer? A systematic review. *J Nutr*. 2007;137:2264–9.
13. Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. *Ann Oncol Off J Eur Soc Med Oncol*. 2012;23:37–45.
14. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008;300:2765–78.
15. Bernstein AM, Song M, Zhang X, Pan A, Wang M, Fuchs CS, et al. Processed and Unprocessed Red Meat and Risk of Colorectal Cancer: Analysis by Tumor Location and Modification by Time. *PLoS ONE* [Internet]. Public Library of Science; 2015 [cited 2020 Jun 6];10. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4549221/>
16. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer

risk factors. *Cancer Causes Control CCC*. 2013;24:1207–22.

17. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16:1599–600.

18. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol Off J Eur Soc Med Oncol*. 2011;22:1958–72.

19. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. *J Clin Oncol Off J Am Soc Clin Oncol*. 2012;30:53–9.

20. Okabayashi K, Ashrafian H, Hasegawa H, Yoo J-H, Patel VM, Harling L, et al. Body mass index category as a risk factor for colorectal adenomas: a systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107:1175–85; quiz 1186.

21. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med*. 2014;12:168.

22. Kaminski MF, Polkowski M, Kraszewska E, Rupinski M, Butruk E, Regula J. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. *Gut*. 2014;63:1112–9.

23. Betés M, Muñoz-Navas MA, Duque JM, Angós R, Macías E, Súbtil JC, et al. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. *Am J Gastroenterol*. 2003;98:2648–54.

24. Usher-Smith JA, Walter FM, Emery JD, Win AK, Griffin SJ. Risk Prediction Models for Colorectal Cancer: A Systematic Review. *Cancer Prev Res Phila Pa*. 2016;9:13–26.

25. Inadomi JM. Screening for Colorectal Neoplasia. *N Engl J Med*. 2017;376:1599–600.

26. Kesse-Guyot E, Castetbon K, Touvier M, Hercberg S, Galan P. Relative validity and reproducibility of a food frequency questionnaire designed for French adults. *Ann Nutr Metab*. 2010;57:153–62.

27. le Moullec N, Deheeger M, Preziosi P, Monteiro P, Valeix P, Rolland M, et al. Validation of the Photo-

Manual used for the food survey of the SU.VI.MAX study. *Cah Nutr Diet*. 1996;31:158–64.

28. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381–95.

29. Fan M, Lyu J, He P. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ).2005. *Zhonghua Liu Xing Bing Xue Za Zhi Zhonghua Liuxingbingxue Zazhi*. 2014;35:961–4.

30. Ma GK, Ladabaum U. Personalizing colorectal cancer screening: a systematic review of models to predict risk of colorectal neoplasia. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2014;12:1624-1634.e1.

31. Cai Q-C, Yu E-D, Xiao Y, Bai W-Y, Chen X, He L-P, et al. Derivation and validation of a prediction rule for estimating advanced colorectal neoplasm risk in average-risk Chinese. *Am J Epidemiol*. 2012;175:584–93.

32. Schroy PC, Wong JB, O'Brien MJ, Chen CA, Griffith JL. A Risk Prediction Index for Advanced Colorectal Neoplasia at Screening Colonoscopy. *Am J Gastroenterol*. 2015;110:1062–71.

33. Knudsen MD, de Lange T, Botteri E, Nguyen D-H, Evensen H, Steen CB, et al. Favorable lifestyle before diagnosis associated with lower risk of screen-detected advanced colorectal neoplasia. *World J Gastroenterol*. 2016;22:6276–86.

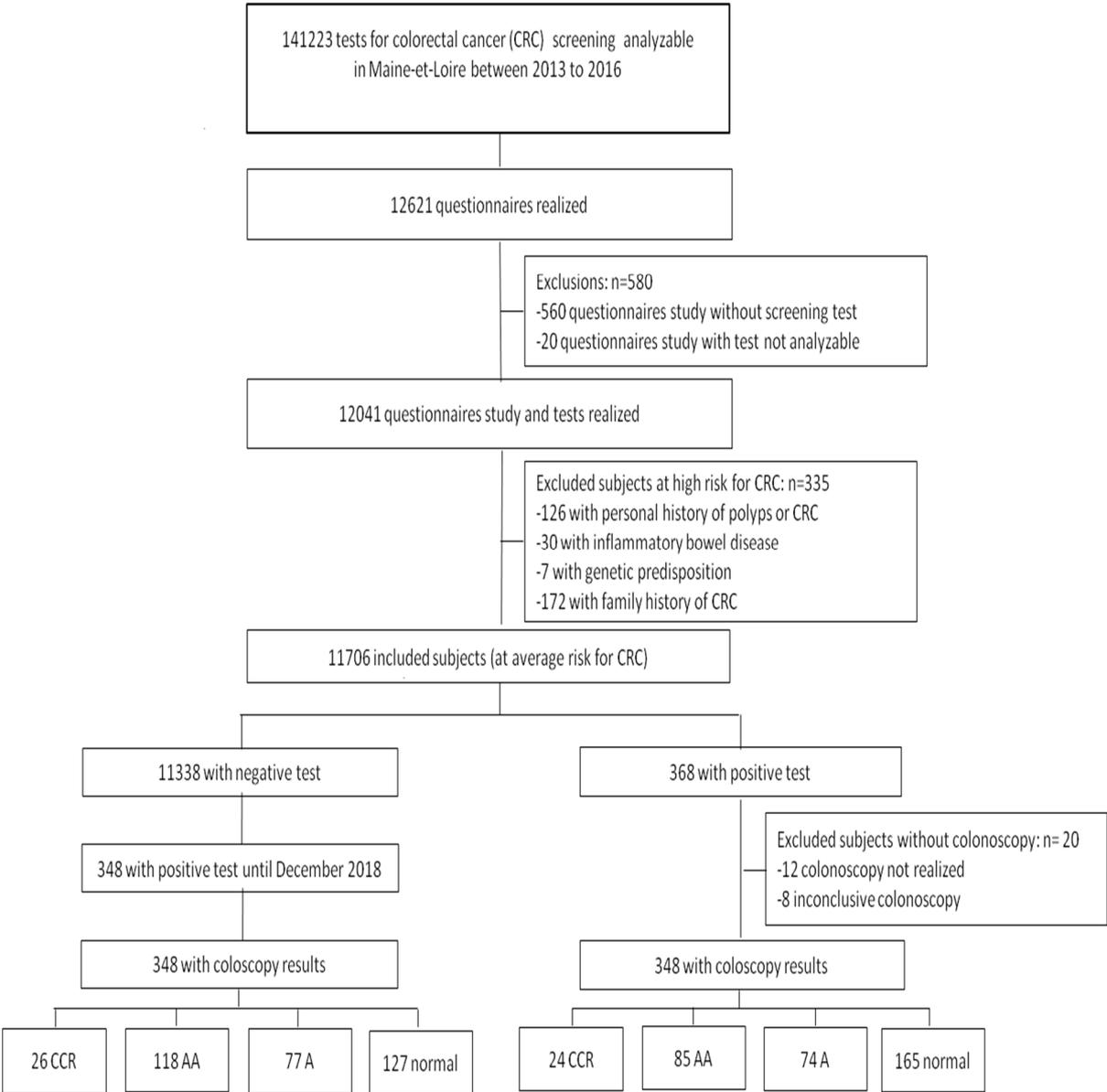
34. Fu Z, Shrubsole MJ, Smalley WE, Wu H, Chen Z, Shyr Y, et al. Lifestyle factors and their combined impact on the risk of colorectal polyps. *Am J Epidemiol*. 2012;176:766–76.

35. World Cancer Research Fund International Systematic Literature Review The Associations between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer [Internet]. [cited 2018 Jun 14]. Available from: <https://www.wcrf.org/sites/default/files/colorectal-cancer-slr.pdf>

36. Colussi D, Fabbri M, Zagari RM, Montale A, Bazzoli F, Ricciardiello L. Lifestyle factors and risk for colorectal polyps and cancer at index colonoscopy in a FIT-positive screening population. *United Eur Gastroenterol J*. 2018;6:935–42.

37. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control CCC*. 2013;24:1207–22.
38. Bittner Fagan H, Sifri R, Wender R, Schumacher E, Reed JF. Weight status and perception of colorectal cancer risk. *J Am Board Fam Med JABFM*. 2012;25:792–7.
39. Anderson AS, Caswell S, Macleod M, Craigie AM, Stead M, Steele RJC, et al. Awareness of Lifestyle and Colorectal Cancer Risk: Findings from the BeWEL Study. *BioMed Res Int*. 2015;2015:871613.

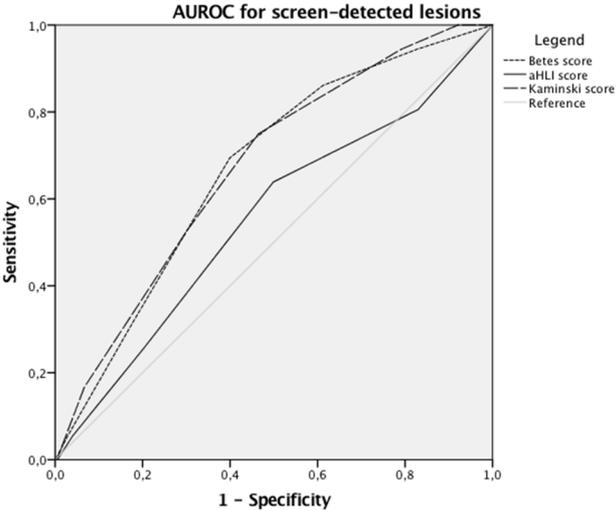
Figure 1: Flow chart



A: adenoma; AA: high-risk adenoma; CCR: colorectal cancer.

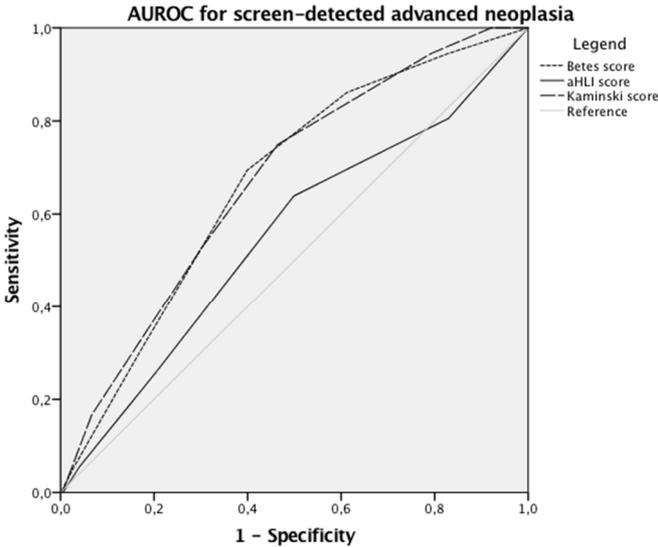
Figure 2: Diagnostic performances of the three risk scores to predict high-risk adenomas, CRC and advanced neoplasia (high-risk adenomas and CRC)

A. Performance for screen detected lesions



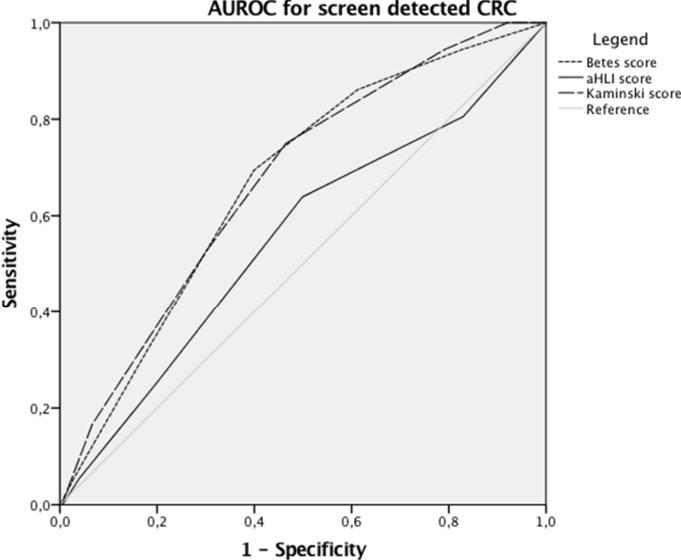
AUROC=0.67 [0.59-0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score.

B. Performance for screen detected advanced neoplasia



AUROC=0.67 [0.59 to 0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score.

C. Performance for screen detected CRC



AUROC=0.67 [0.59-0.75] for Betés score, 0.55 [0.45 to 0.65] for adapted HLI score and 0.67 [0.59 to 0.75] for Kaminski score.

Table 1: Participant characteristics according to screening test outcome

	Controls n=11282	Adenoma n= 151	High-risk adenoma n= 203	Cancer n=50	Adenoma vs control p-value	High-risk adenoma Vs controls P-value	Cancer Vs control p-value
Male sex, n %	5228 46.3	105 69.5	142 70.0	37 74.0	0.0001	0.0001	0.0001
Age (yr), median [IQR]	60.00 [54.0-65.0]	60.00 [56.0-65.0]	61.00 [54.00-66.00]	63.00 [57.0-68.00]	0.667	0.522	0.010
Overweight and obesity No of subjects with available data BMI>25 kg/m <sup>2</sup> -no (%)	11007 5470 (49.7)	148 85 (57.4)	201 133 (66.2)	50 32 (64.0)	0.068	0.0001	0.044
Diabetes No of subjects with available data Diabetics- No (%)	11015 707 (6.4)	146 17 (11.6)	199 16 (8.0)	50 8 (16.0)	0.014	0.380	0.014
Smoking status No of subjects with available data Current smokers- No (%)	10684 1284 (12.0)	146 42 (28.8)	196 44 (22.4)	48 4 (8.3)	0.000	0.0001	0.514
Physical activity No of subjects with available data Absent/low No (%) Moderate No (%) High No (%)	9615 3515 (36.6) 3040 (31.6) 3060 (31.8)	124 57 (46.0) 32 (25.8) 35 (28.2)	171 65 (38.0) 45 (26.3) 61 (35.7)	42 13 (31.0) 17 (40.5) 12 (28.6)	0.093	0.305	0.455
Alcoholic beverage consumption No of subjects with available data >2 glasses/day (Men)/ >1 glass/day (women)	11134 2372 (21.3)	148 41 (27.7)	199 73 (36.7)	49 18 (36.7)	0.069	0.0001	0.011

Processed meat intake (g/day)					0.002	0.113	0.862
No of subjects with available data	11096	150	197	50			
Median [IQR]	7.00 [3.50-20.00]	15.20 [5.30-25.00]	10.00 [4.00-20.00]	10.00 [3.50-20.0]			
Red meat intake (g/day)					0.163	0.301	0.660
No of subjects with available data	11082	149	200	49			
Median [IQR]	42.00 [16.00-66.00]	52.00 [18.20-80.00]	52.00 [18.20-66.00]	52.00 [18.20-55.00]			
Garlic intake (number of time/week)					0.338	0.004	0.687
No of subjects with available data	11061	149	198	50			
Median [IQR]	1.00[0.00-2.00]	1.00 [0.00-2.00]	0.70[0.00-2.00]	1.00 [0.20-3.00]			
Milk and dairy products (serving/day)					0.254	0.005	0.181
No of subjects with available data	10999	146	194	49			
Median [IQR]	1.40 [1.00-2.00]	1.00 [1.00-2.00]	1.00 [1.00-2.00]	1.00 [1.00-2.00]			
Fruit intake (g/day)					0.057	0.0001	0.421
No of subjects with available data	11073	150	199	50			
Median [IQR]	90.00 [72.00-225.00]	90.00 [36.00-225.00]	90.00 [36.00-225.00]	90.00 [36.00-225.00]			
Vegetable intake (g/day)					0.035	0.009	0.959
No of subjects with available data	10999	148	199	49			
Median [IQR]	80.00 [40.00-125.00]	80.00 [40.00-100.00]	60.00 [40.00-100.00]	80.00 [40.00-125.00]			
Consumption of high fiber foods (bread, cereals, pasta and rice)					0.801	0.942	0.772
No of subjects with available data	11150	150	200	23			

available data							
Occasionally/Never-no (%)	4356 (39.1)	57 (38.0)	79 (39.5)	9 (39.1)			

BMI: body mass index

Table 2: Distribution of the number of subjects with high-risk adenoma, CRC and advanced neoplasia according to the risk score.

A. Betés score

Betés score	1	2	3	4	5	6	7	Total	p
No adenoma or CRC, n	1582 (16.1)	2093 (21.4)	2143 (21.9)	2252 (23.0)	1392 (14.2)	322 (3.3)	15 (0.2)	9799	
Lesions, n (%)	22 (6.1)	50 (13.8)	62 (17.1)	116 (32.0)	95 (26.2)	17 (4.7)	0	362	<0.0001
CRC, n (%)	4 (8.0)	4 (8.0)	8 (16.0)	18 (36.0)	12 (24.0)	4 (8.0)	0	50	0.005
Advanced neoplasia, n (%)	11 (4.8)	32 (14.0)	35 (15.3)	77 (33.6)	62 (27.1)	12 (5.2)	0	229	<0.0001

B. Adapted-HLI score

Adapted HLI	0	1	2	3	4	5	Total	p
No adenoma or CRC, n	1412 (16.9)	2760 (33.0)	2517 (30.1)	1327 (15.9)	292 (3.5)	47 (0.6)	8355	
Lesions, n (%)	31 (10.6)	61 (20.9)	100 (34.2)	167 (22.9)	27 (9.2)	6 (2.1)	59	<0.0001
CRC, n (%)	7 (19.4)	6 (16.7)	14 (38.9)	7 (19.4)	2 (5.6)	0	36	0.278
Advanced neoplasia, n	23 (12.5)	36 (19.6)	61 (33.2)	43 (23.4)	19 (10.3)	2 (1.1)	184	<0.0001

C. Kaminski score

Kaminski score	1	2	3	4	5	6	7	Total	p
No adenoma or CRC, n	1143 (10.9)	1293 (12.4)	3449 (33.0)	1688 (16.1)	2251 (21.5)	601 (5.7)	38 (0.4)	10463	
Lesions, n (%)	13 (3.4)	23 (6.0)	92 (23.9)	69 (17.9)	115 (29.9)	70 (18.2)	3 (0.8)	385	<0.0001
CRC, n (%)	0 (0.0)	3 (6.3)	9 (18.8)	11 (22.9)	16 (33.3)	9 (18.8)	0	48	<0.0001
Advanced neoplasia, n	10 (4.1)	14 (5.8)	57 (23.6)	44 (18.2)	76 (31.4)	39 (16.1)	2 (0.8)	242	<0.0001

CRC: colorectal cancer