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Par

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CONTENT

Abbreviations:

CIS: Carcinoma in Situ

CRC: Colorectal cancer

FIT: Fecal Immunochemical Test

FOBT: Fecal Occult Blood Test

IBD: Inflammatory Bowel Disease

IC: Interval Cancer

ABSTRACT

Introduction. Colorectal cancer (CRC) is screened in France since 2008 using the fecal occult blood test (FOBT) HEMOCCULT II®. The aim of this study was to assess the characteristics of interval cancers (IC), defined as CRC diagnosed within two years following a negative FOBT.

Methods. All the CRC diagnosed in a two-year period (between January 2012 and December 2013) in patients who live in Maine et Loire, France, and aged between 50 to 74, were identified from pathology reports. Individuals were, then, divided according to their participation or not, and the results of the FOBT: screened detected cancers, interval cancers and non-responders. Their characteristics were recorded thanks to Cap Santé 49, the Maine et Loire cancer registry of that region.

Results. 342 CRC were diagnosed during this screening period. Of those, 54 were diagnosed after a negative test, 66 after a positive test. 184 patients didn't participate in the screening program. IC tend to be more frequent in the proximal colon ($p = 0.076$) than screened detected cancers, this tendency is confirmed in IC in women ($p=0.057$). IC are significantly diagnosed at a more advanced stage ($p<0.001$). In multivariate analysis, IC are significantly more frequent in proximal colon (OR: 2.47; 95% CI: 1.06-5.78; $p=0.037$) compared to the screened detected group. In the non-responders group, the proportion of cancer in the proximal colon (OR: 2.25; 95% CI: 1.10-4.59; $p=0.026$) and in the rectum (OR: 2.71; 95% CI: 1.31-5.64; $p=0.007$) is significantly higher than in the screened detected group.

Conclusions. FOBT preferentially detects distal CRC. IC are more frequently diagnosed at a more severe stage and in the proximal colon. Further explorations need to be done to improve the characterization of IC, especially biological data.

INTRODUCTION

Colorectal cancer (CRC) is a major public health concern. More than 40 000 cases are diagnosed each year in France; it is the third cancer in term of incidence in France in 2012 and the second in term of mortality [1]. Despite advances in medical care, about half of these will die because of their tumor.

Three major studies have shown that colorectal cancer screening using fecal occult blood test (FOBT) can reduce CRC mortality (up to 14 to 18%) [2, 3, 4, 5]. As a result of which, FOBT is employed in most countries for the screening of CRC in unselected patients. In France, screening is nationally organized since 2008. Every average risk individuals, aged between 50 and 74 years old, is invited to perform a guaiac-based test (Hemoccult II®), through their family doctor. Individuals with positive test are then, invited to perform a colonoscopy. The aims of this screening are to prevent death by detecting and treating curable lesions and to prevent CRC by removing adenomas.

However, if screening by FOBTs can reduce CRC mortality, an interval cancer (IC) may be diagnosed after a negative test. They are defined by a cancer diagnosed less than two years after a negative FOBT (ie, a complete screening round). They may be due to a false negative FOBT or to an agressive tumor that developed between two screening rounds. The rate of IC is important to evaluate a CRC screening program and is a key performance indicator. Although IC are inevitable in a screening program, their number should be as small as possible since a high proportion of IC would decrease screening effectiveness. Some studies suggest that the rate of IC is relatively high [6, 7]. No study has been published to our knowledge comparing the biological profiles of tumors detected by FOBTs and IC.

The aims of this study were to describe in a single screening round, the population involved in the discovery of an interval cancer, the free time interval before the onset of IC, the localization and the stage of the tumor, and its histological and biological characteristics including NRAS/KRAS and BRAF mutations and sporadic microsatellite instability. Biological data are not yet available and will therefore be not described in this work.

PATIENTS AND METHODS

Screening procedure

In France, the CRC screening campaigns are nationally organized since 2008. It consists in a biennial non-rehydrated guaiac-based fecal occult blood test (HEMOCCULT II®). This test detects the pseudo-peroxydase activity of heme. It is simple, inexpensive and acceptable to all people. It gives a qualitative result: positive or negative. Every average-risk individual aged 50 to 74, is invited to participate. They are defined by individuals aged more than 50 with no personal history of CRC or adenoma, familial history of CRC, inflammatory bowel disease (IBD), terminal disease or bedridden patient. It consists in taking two samples from each of three consecutive stools and and then sending the completed test cards by postal way to the central analysis center. The FOBTs were processed without rehydration according to a standardized procedure. In case of a positive test, subjects were invited to consult their general practitioner who redirect them, then, to a gastroenterologist to perform a full colonoscopy. In case of a negative test result, the subjects were informed of the test limitations and then of the necessity of a consultation in case of digestive symptoms.

Study Population

The study population consisted of individuals who are eligible to the 2012-2013 screening campaign and who lived in Maine et Loire.

Data collection

Diagnosis of CRC was made most of the time by colonoscopy, or by surgery or hepatic puncture. Pathologists had to provide a copy of the report concerning CRC and adenomas. Pathological reports of colorectal cancer were reviewed from the Pathology Department of Angers University Hospital and from the *Centre de pathologie de l'Ouest*. All histological sampling in Maine et Loire were reviewed by these two centers. These data were then, compared to the registry of CAP SANTE 49, the regional analysis center that organizes CRC screening in *Maine et Loire*.

With the interrogation of CAP SANTE registry, we collected data on each patient concerning age, gender, their participation or not in screening and the screening test results. The staging tumor was done using the AJCC classification [8]. Lesions treated by endoscopic polypectomy and found to contain invasive cancer were classified as carcinoma in situ (CIS) and classed T0. Tumor differentiation and the presence of a colloid component were also assessed. Tumor sites were divided in three categories: rectum, distal colon (sigmoid and left colon) and proximal colon (transverse colon and right colon). We classified all cases of CRC as follows: screened detected cancers (CRC diagnosed after a positive FOBT), interval cancers (CRC diagnosed after a negative test and before further screening) and non-responders (CRC diagnosed in patients who hadn't been screened).

Study outcomes

The primary end point was to assess characteristics of interval cancers and to compare the screened detected and interval cancer groups. Secondary end point was to analyze biological data concerning NRAS/KRAS and BRAF mutations and MSI status. These results are not available for this work.

Statistical Analysis

Statistical analysis were performed using SAS software version 9.3 (SAS Institute INC., USA). Characteristic of patients were expressed as mean +/- standard deviation or frequency (%). Comparison between groups were performed using the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variables. We used a multivariate binary logistic regression model to assess differences in tumor localization between groups after adjustment for gender and age. Results were expressed as Odds Ratio (OR) with 95 % confidence intervals (CI). A *P* value <0.05 was considered statistically significant.

RESULTS

Within the given period (January 2012 to December 2013), 342 CRC were diagnosed in our study population. A total of 70241 FOBTs were performed and 1298 were positive. Of those 342 CRC, 120 patients performed FOBT and, from those, 66 tumors were detected after a positive FOBT (screened detected patients) and 54 were diagnosed within two years a negative FOBT (interval cancers patients). 184 individuals didn't attempt screening program (non-responders patients). 38 patients were excluded (age below 50, high risk individuals who shouldn't have been proposed to a screening or bedridden patients) (Fig. 1).

Participation rates is this screening campaign is 39.5%. The screening campaign sensitivity in our population study was 55%.

Characteristics of each subgroup are shown in tables 1 and 4. Age at diagnosis is not different in the three populations. Median age is 64.2 +/- 5.8 in the screened detected patients, 63.8 +/- 5.6 in the IC patients (p=0.597) and 63.5 +/- 6.4 in the non-responders patients (p=0.703). Gender distribution in these three groups is similar.

Rectal bleeding was the most frequent clinical symptom revealing interval cancer (Table 8).

When looking at the localization, the proportion of the proximal CRC in the IC group tend to be higher than in the screened detected group (p=0.076) (Table 1). When we looked at the localization by gender, proximal CRC were significantly more frequent in women in the IC group (p=0.057) than in the screened detected group (Table 2), this difference is not found in the male population (Table 3) and when we compared screened detected individuals and non responders (Table 5 and 6).

Considering stage at diagnosis, there were significantly more stage IV CRC in the IC group (p<0.001) than in the screened detected group (Table 1) and more stage IV CRC in the non-responders group than in the screened detected population (p=0.003) (Table 4).

There were no significant differences in term of histology between the three groups. Well, moderately and poorly differentiated adenocarcinoma were equally distributed in these groups (Table 1 to 4). Mucinous component was found in the three groups with no significance.

The delay between the completion of FOBT and the diagnosis Is shown in table 1. This delay is shorter in the screened detected group than in the IC group. 3.9 +/- 5.1 months in the first one and 13.7 +/- 6.5 in the second one (p<0.001) (Table 1). Moreover, more than 80% of the individuals in the screened detected group were diagnosed within six months after the test whereas 40% of the individuals in the IC group were diagnosed within 12 months after a negative test. There was no difference by adjusting the localization on delay (Table 9).

In multivariate analysis (Table 6), when compared to the screened detected group, IC were predominantly diagnosed in the proximal colon (OR: 2.47; 95% CI: 1.06-5.78; p=0.037) after adjustment for gender and age. When compared to the screened detected CRC group, CRC in the non responders group were significantly more frequently diagnose in the rectum (OR: 2.71; 95% CI: 1.31-5.64; p=0.007) and in the proximal colon (OR: 2.25; 95% CI: 1.10-4.59; p=0.026).

DISCUSSION

Interval cancers represent the major limitation of screening for colorectal cancer with the fecal guaiac-based occult blood test. The overall program sensitivity in this screening campaign was 55% which is consistent with the previous studies [5, 10,11,12]. Parcipation rate (39.5%) was below the required threshold for 50% but in France few regions have a participation rate that reaches 50%. Efforts in information and education have to continue to increase this participation rate.

The interval cancer rate was 45% in our study (54 IC diagnosed after a negative test among the 120 patients who participated in the screening campaign). Similar rates were found in the previous studies: 59.2 % in the Burgundy Study [2], 51.3 % in the Nottingham Study [3], 52,7 % in the Danish study [4] and more recently, 52 % in the Scottish Study [7] and 43.3 % in the Spanish study [6]. In these studies, the number of screening rounds ranged to 3 to 6 [2, 3, 4]. It is important to take in consideration this data because it has been suggested that the percentage of IC depends on the number of rounds [2, 6, 7, 9]. In fact, it is probable that the absolute number of IC varies little between rounds [7]. An explanation is that the low sensitivity of the guaiac-based test used in the main studies could have no effect on screening-resistant cancers. Otherwise, the results of the previous rounds were not taken into account at each round for all studies.

Both the positivity rate and cancer detection rate of FOBT are described to be higher in men that in women [13, 14]. It has already been shown that both the incidence and prevalence of CCR is higher among men that among women [15, 16] . The Scottish study found that IC were detected more frequently in women [7]. Some studies have suggested that sensitivity differs with gender [7, 17, 18]. The explanation of this difference is still unclear. Two hypothesis have been proposed by Steele et al [7]: a lower haemoglobin in women but this difference is very small and is not found after 10 years of menopause[19] or a slower colonic transit in women, which may dilutes the haemoglobin concentration in feces [20]. In our study, this difference is not found, probably due to the lack of statistic power.

In multivariate analysis, the proportion of proximal CRC is significantly higher in the IC individuals. This preferential localization is already described in the Scottish data [7] as well as IC described after a negative colonoscopy [21 22]. Thus, FOBT seems less sensitive for the right side of the colon than in the left side. Some reports showed that the proportion of interval cancers was higher among cancer of the rectal ampulla [7, 9]. We didn't find it in our study. An explanation could be that the guaiac-test relies on the presence of fecal haematin, which is released after degradation of haemoglobin. With the short passage through the rectum, haemoglobin does not have time to be hemolyzed [9].

Interval cancer can appear after a negative colonoscopy but their proportion is low between 2 and 6% [22]. It usually secondary to deficiency in colonoscopy quality rather than accelerated tumor biology because the majority of interval cancer occurs in this case within 3 years after the colonoscopy [23, 24]. More interestingly, it has been shown that after negative colonoscopy, IC occurred more often among women, in the right colon. Moreover, IC occurred more often after a negative colonoscopy proceeding after a positive FOBT, particularly among men [25].

The more advanced stage at diagnosis in IC and non-responders patients is consistent with the literature with a higher rate of stage III-IV tumors [7, 9].

Our study showed that more than one third of the IC (40,7%) were diagnosed less than 12 months after a negative FOBT. The invitation for this screening test, even if the result is negative, is like an alarm sign that alert the individuals who have symptoms to consult their family doctor or a gastroenterologist. Patients have to be informed that in case of symptoms, even if the FOBT is negative, they have to consult to program further exploration.

In published series, subjects with interval cancers had worse survival comparing to subjects screen-detected but higher survival comparing to those of the non-screened population [7]. This finding may reflect earlier diagnosis of CRC rather than later death (lead-time bias). Data on mortality in our study are unknown because monitoring was not long enough.

Since 2015, a new test has replaced the HEMOCCULT II® : it is a quantitative fecal immunochemical test (FIT) named OC-Sensor®. This new test measures concentration of human hemoglobin in fecal samples and then, have a higher sensitivity than guaiac-based test and therefore could reduce the percentage of IC[26]. With the new FIT, participation rate should increase as the compliance seems to be higher [27]. In a 2001 Italian study, Zappa et al., have shown the risk of developing an interval cancer after a negative FOBT is almost three time higher compared to FIT [28]. These results have to be confirmed in France by another study using FIT. Haug et al. in 2011, showed that FIT is also more sensitive for detecting subjects with left colon cancer [29].

Our principal limitation is the rater small effective of our population and the fact that we included only one round of screening. Power of this study could have been stronger if more rounds were included.

Further explorations are underway to better understand the differences between the screened patients and the IC patients. Microsatellite instability as well as the KRAS/NRAS and BRAF status are being analyzed in our study. Indeed, it is possible that IC have different tumor biology than screened detected cancers. A previous study concerning interval cancer diagnosed after a colonoscopy suggest that those cancers are 4 times likely to be associated with microsatellite instability than non-interval cancer [30]. Other studies concerning interval cancers diagnosed after a colonoscopy have shown that KRAS mutation is inversely associated with interval cancers and with MSI [31]; and that BRAF mutation is not

associated with these interval cancers [32]. Richter et al showed that MSI pathway defects are present in a significant proportion of interval colon cancers. However, the KRAS, NRAS and BRAF status are not associated in interval cancer in this study [33].

CONCLUSION

Interval cancers represent a large number of CRC, which is one of the limitation of the screening program using FOBT. This rate should decrease with the new immunochemical test. Our study confirm that IC are more frequent in the proximal colon. The explanation of this distribution is not quite explain, which need further exploration like genetics of these cancers: microsatellite instability as well as the KRAS/NRAS and BRAF status are being analyzed.

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FIGURES

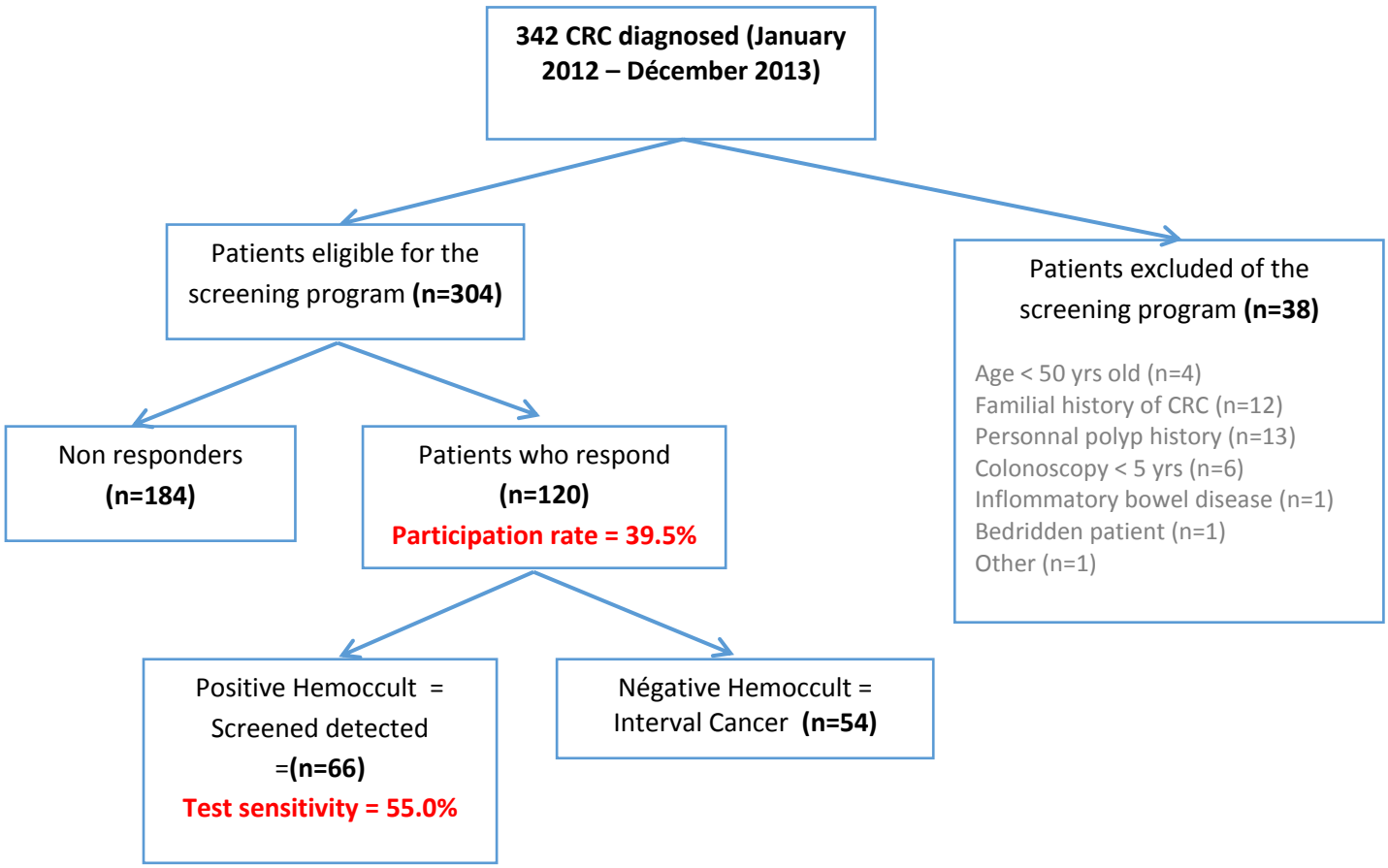

Figure 1. Flowchart of the screening process. Classification of patients according to the HEMOCCULT II® results.

TABLES

TABLE 1. Comparative Analysis between screened detected cancers and IC.

	Screened detected cancers(n=66)	**IC (n=54)**	***P-value*** [1]
Age at diagnostic (years old)	64.2 ± 5.8	63.8 ± 5.6	*0.597*
Age at diagnostic in classes			*0.752*
50-54	4 (6.1%)	2 (3.7%)	
55-59	12 (18.2%)	14 (25.9%)	
60-64	16 (24.2%)	15 (27.8%)	
65-69	20 (30.3%)	15 (27.8%)	
70-74	14 (21.2%)	8 (14.8%)	
Gender			*0.464*
Men	40 (60.6%)	29 (53.7%)	
Women	26 (39.4%)	25 (46.3%)	
Tumor localization			*0.076*
Distal	36 (55.4%)	22 (40.7%)	
Proximal	15 (23.1%)	23 (42.6%)	
Rectum	14 (21.5%)	9 (16.7%)	
Tumor classification			*<0.001*
0	14 (22.2%)	2 (3.8%)	
I	14 (22.2%)	5 (9.6%)	
II	10 (15.9%)	19 (36.5%)	
III	19 (30.2%)	11 (21.2%)	
IV	6 (9.5%)	15 (28.8%)	
Histology			*0.096*
Well-differenciated adenocarcinoma	23 (34.9%)	22 (40.7%)	
Moderately differenciated adenocarcinoma	34 (51.5%)	27 (50.0%)	
Poorly-differenciated adenocarcinoma	1 (1.5%)	3 (5.6%)	
Other adenocarcinoma	8 (12.1%)	1 (1.9%)	
Intra-epithelial neoplasia	0 (0.0%)	1 (1.9%)	
Mucinous component			
Present	4 (6.1%)	8 (14.1%)	*0.134*
Period between test and diagnostis (months)	3.9 ± 5.1	13.7 ± 6.5	*<0.001*
Period in classes			*<0.001*
]0-6]	57 (86.4%)	8 (14.8%)	
]6-12]	4 (6.1%)	14 (25.9%)	
]12-18]	1 (1.5%)	17 (31.5%)	
]18-24]	4 (6.1%)	15 (27.8%)	

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variables*

TABLE 2. Comparative analysis between screened detected cancers and IC in women.

	Screened detected cancer (n=26)	**Interval cancers (n=25)**	***P-value*[1]**
Age at diagnostic (years old)	63.9 ± 6.5	63.6 ± 5.6	*0.859*
Age at diagnostic in classes			*0.358*
50-54	2 (7.7%)	0 (0.0%)	
55-59	7 (26.9%)	8 (32.0%)	
60-64	4 (15.4%)	8 (32.0%)	
65-69	5 (19.2%)	5 (20.0%)	
70-74	8 (30.8%)	4 (16.0%)	
Tumor localization			*0.057*
Distal	13 (52.0%)	9 (36.0%)	
Proximal	6 (24.0%)	14 (56.0%)	
Rectum	6 (24.0%)	2 (8.0%)	
Tumor classification			*0.014*
0	6 (24.0%)	1 (4.2%)	
I	5 (20.0%)	4 (16.7%)	
II	4 (16.0%)	10 (41.7%)	
III	8 (32.0%)	2 (8.3%)	
IV	2 (8.0%)	7 (29.2%)	
Histology			*0.679*
Well-differenciated adenocarcinoma	11 (42.3%)	8 (32.0%)	
Moderately differenciated adenocarcinoma	13 (50.0%)	14 (56.0%)	
Poorly-differenciated adenocarcinoma	0 (0.0%)	1 (4.0%)	
Other adenocarcinoma	2 (7.7%)	1 (4.0%)	
Intra-epithelial neoplasia	0 (0.0%)	1 (4.0%)	
Mucinous component			
Present	1 (3.9%)	3 (12.0%)	*0.350*
Period between test and diagnostis (months)	4.2 ± 5.5	12.2 ± 5.4	*<0.001*
Period in classes			*<0.001*
]0-6]	22 (84.6%)	4 (16.0%)	
]6-12]	2 (7.7%)	8 (32.0%)	
]12-18]	0 (0.0%)	9 (36.0%)	
]18-24]	2 (7.7%)	4 (16.0%)	

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variable*

TABLE 3. Comparative analysis between screened detected cancers and IC men.

	Screened detected cancers (n=40)	**IC (n=29)**	***P-value*[1]**
Age at diagnostic (years old)	64.4 ± 5.4	63.9 ± 5.7	*0.703*
Age at diagnostic in classes			*0.893*
50-54	2 (5.0%)	2 (6.9%)	
55-59	5 (12.5%)	6 (20.7%)	
60-64	12 (30.0%)	7 (24.1%)	
65-69	15 (37.5%)	10 (34.5%)	
70-74	6 (15.0%)	4 (13.8%)	
Tumor localization			*0.555*
Distal	23 (57.5%)	13 (44.8%)	
Proximal	9 (22.5%)	9 (31.0%)	
Rectum	8 (20.0%)	7 (24.1%)	
Tumor classification			*0.011*
0	8 (21.1%)	1 (3.6%)	
I	9 (23.7%)	1 (3.6%)	
II	6 (15.8%)	9 (32.1%)	
III	11 (28.9%)	9 (32.1%)	
IV	4 (10.5%)	8 (28.6%)	
Histology			*0.060*
Well-differenciated adenocarcinoma	12 (30.0%)	14 (48.3%)	
Moderately differenciated adenocarcinoma	21 (52.5%)	13 (44.8%)	
Poorly-differenciated adenocarcinoma	1 (2.5%)	2 (6.9%)	
Other adenocarcinoma	6 (15.0%)	0 (0.0%)	
Intra-epithelial neoplasia	0 (0.0%)	0 (0.0%)	
Mucinous component			*0.267*
Present	3 (7.5%)	5 (17.4%)	
Period between test and diagnostis (months)	3.7 ± 5.0	14.9 ± 7.2	*<0.001*
Period in classes			*<0.001*
]0-6]	35 (87.5%)	4 (13.8%)	
]6-12]	2 (5.0%)	6 (20.7%)	
]12-18]	1 (2.5%)	8 (27.6%)	
]18-24]	2 (5.0%)	11 (37.9%)	

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variable*

TABLE 4. Comparative analysis between screened detected and non-screened detected cancers.

	Screened detected cancers (n=66)	**Non-screened detected (n=184)**	***P-value*[1]**
Age at diagnostic (years old)	64.2 ± 5.8	63.5 ± 6.4	*0.703*
Age at diagnostic in classes			*0.560*
50-54	4 (6.1%)	24 (13.1%)	
55-59	12 (18.2%)	31 (16.9%)	
60-64	16 (24.2%)	47 (25.7%)	
65-69	20 (30.3%)	51 (27.9%)	
70-74	14 (21.2%)	30 (16.4%)	
Gender			*0.768*
Men	40 (60.6%)	116 (63.0%)	
Women	26 (39.4%)	68 (37.0%)	
Tumor localization			*0.018*
Distal	36 (55.4%)	58 (34.7%)	
Proximal	15 (23.1%)	52 (31.1%)	
Rectum	14 (21.5%)	57 (34.1%)	
Tumor classification			*0.003*
0	14 (22.2%)	15 (9.0%)	
I	14 (22.2%)	18 (10.8%)	
II	10 (15.9%)	42 (25.3%)	
III	19 (30.2%)	53 (31.9%)	
IV	6 (9.5%)	38 (22.9%)	
Histology			*0.739*
Well-differenciated adenocarcinoma	23 (34.8%)	59 (32.1%)	
Moderately differenciated adenocarcinoma	34 (51.5%)	105 (57.1%)	
Poorly-differenciated adenocarcinoma	1 (1.5%)	4 (2.2%)	
Other adenocarcinoma	8 (12.1%)	14 (7.6%)	
Intra-epithelial neoplasia	0 (0.0%)	2 (1.1%)	
Mucinous component			
Present	4 (6.1%)	28 (15.2%)	*0.084*

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variable*

TABLE 5. Comparative analysis between screened detected and non-screened detected cancers in women.

	Screened detected cancers (n=26)	**Non screened detected cancers (n=68)**	***P-value*[1]**
Age at diagnostic (years old)	63.9 ± 6.5	64.3 ± 7.2	*0.703*
Age at diagnostic in classes			*0.501*
50-54	2 (7.7%)	10 (14.7%)	
55-59	7 (26.9%)	11 (16.2%)	
60-64	4 (15.4%)	9 (13.2%)	
65-69	5 (19.2%)	22 (32.4%)	
70-74	8 (30.8%)	16 (23.5%)	
Tumor localization			*0.559*
Distal	13 (52.0%)	26 (42.6%)	
Proximal	6 (24.0%)	22 (36.1%)	
Rectum	6 (24.0%)	13 (21.3%)	
Tumor classification			*0.085*
0	6 (24.0%)	5 (8.1%)	
I	5 (20.0%)	6 (9.7%)	
II	4 (16.0%)	14 (22.6%)	
III	8 (32.0%)	21 (33.9%)	
IV	2 (8.0%)	16 (25.8%)	
Histology			*0.862*
Well-differenciated adenocarcinoma	11 (42.3%)	25 (36.8%)	
Moderately differenciated adenocarcinoma	13 (50.0%)	37 (54.4%)	
Poorly-differenciated adenocarcinoma	0 (0.0%)	2 (2.9%)	
Other adenocarcinoma	2 (7.7%)	3 (4.4%)	
Intra-epithelial neoplasia	0 (0.0%)	1 (1.1%)	
Mucinous component			
Present	1 (3.9%)	13 (19.1%)	*0.102*

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variable*

TABLE 6. Comparative analysis between screened detected and non-screened detected cancers in men.

	Screened detected cancers(n=40)	**Non screened detected cancer (n=116)**	***P-value*[1]**
Age at diagnostic (years old)	64.4 ± 5.4	63.0 ± 5.9	*0.703*
Age at diagnostic in classes			*0.472*
50-54	2 (5.0%)	14 (12.2%)	
55-59	5 (12.5%)	20 (17.4%)	
60-64	12 (30.0%)	38 (33.0%)	
65-69	15 (37.5%)	29 (25.2%)	
70-74	6 (15.0%)	14 (12.2%)	
Tumor localization			*0.007*
Distal	23 (57.5%)	32 (30.2%)	
Proximal	9 (22.5%)	30 (28.3%)	
Rectum	8 (20.0%)	44 (41.5%)	
Tumor classification			*0.072*
0	8 (21.1%)	10 (9.6%)	
I	9 (23.7%)	12 (11.5%)	
II	6 (15.8%)	28 (26.9%)	
III	11 (28.9%)	32 (30.8%)	
IV	4 (10.5%)	22 (21.2%)	
Histology			*0.737*
Well-differenciated adenocarcinoma	12 (30.0%)	34 (29.3%)	
Moderately differenciated adenocarcinoma	21 (52.5%)	68 (58.6%)	
Poorly-differenciated adenocarcinoma	1 (2.5%)	2 (1.7%)	
Other adenocarcinoma	6 (15.0%)	11 (9.5%)	
Intra-epithelial neoplasia	0 (0.0%)	1 (0.9%)	
Mucinous component			
Present	3 (7.5%)	15 (12.9%)	*0.566*

[1] *P-value for the non-parametric Wilcoxon-Mann-Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variable*

TABLE 7. Multivariate analysis.

	IC *vs* Non screened detected cancers			**Non responders *vs* screened detected cances**		
	OR	(CI 95%)	*P-value*	OR	(CI 95%)	*P-value*
Age at diagnostic (years)	0.98	(0.92-1.05)	*0.616*	0.97	(0.92-1.02)	*0.212*
Gender						
Men	1	-	-	1	-	-
Women	1.23	(0.58-2.61)	*0.597*	1.02	(0.55-1.87)	*0.961*
Tumor localization						
Distal	1	-	-	1	-	-
Proximal	**2.47**	**(1.06-5.78)**	***0.037***	**2.25**	**(1.10-4.59)**	***0.026***
Rectum	1.09	(0.40-2.96)	*0.866*	**2.71**	**(1.31-5.64)**	***0.007***

OR = Odds-Ratio ; CI=Confidence Interval

Table 8. Symptoms that lead to diagnosis of IC

Symptoms	**Numbers of patients**
Rectorraghia	14
Anemia	11
Hepatic metastasis	7
Anal Abscess	1
Occlusion or sub-occlusion	7
Abdominal mass	5
Transit disorders	3
Cerebral metastasis	2
Abdominal pain	2
Pulmonary embolism	1
Rectal syndrome	1

Table 9. Analysis of the location after adjustment for the diagnosis delay.

	Screened detected cancers (n=66)	IC (n=54)	*P-value* [1]
Delay ≤ 6 months : Tumor localization			*0.095*
Distal	30 (53.6%)	3 (37.5%)	
Proximal	14 (25.0%)	5 (62.5%)	
Rectum	12 (21.4%)	0 (0.0%)	
Delay > 6 months : Tumor localization			*0.259*
Distal	6 (66.7%)	19 (41.3%)	
Proximal	1 (11.1%)	18 (39.1%)	
Rectum	2 (22.2%)	9 (19.6%)	

[1] *P-value of the Fisher test*

Gazon Florine

CANCERS D'INTERVALLE LORS D'UNE CAMPAGNE DE DEPISTAGE DU CANCER COLO-RECTAL PAR LE TEST HEMOCCULT II® DANS LE DEPARTEMENT DU MAINE ET LOIRE

RÉSUMÉ

Introduction. Le cancer colorectal (CCR) est un des cancers bénéficiant en France, d'un dépistage organisé depuis 2008, par un test de recherche de sang dans les selles, le test HEMOCCULT II®. L'objectif de cette étude était d'étudier les caractéristiques des cancers d'intervalle (cancer diagnostiqué dans les 2 ans suivant un test de dépistage négatif).

Méthodes. La totalité des cancers colorectaux diagnostiqués sur une période de 2 ans dans le Maine et Loire (de Janvier 2012 à Décembre 2013) a été recueillie via les comptes rendus histologiques, chez la population étudiée (patients à risque modéré de cancer colorectal, âgés de 50 à 74 ans et résidant dans le Maine et Loire). Les patients ont été alors séparés en trois groupes selon leur participation au dépistage et le résultat de celui-ci : les patients dépistés, les cancers d'intervalle et les non participants. Les caractéristiques des différents groupes ont ensuite été recueillies.

Résultats. 342 CCR ont été diagnostiqués pendant la période étudiée. 54 ont été diagnostiqués après un test de dépistage négatif, et 66 après un test positif. 184 patients n'ont pas participé au dépistage organisé. Les cancers d'intervalle sont plus fréquents dans le côlon proximal (p=0.076) que les cancers des patients dépistés. Il y a siginificativement plus de cancers du côlon proximal chez les femmes dans le groupe cancers d'intervalle que dans le groupe des cancers dépistés (p=0.057). Les cancers d'intervalle sont diagnostiqués à un stade plus tardif que les cancers dépistés (p<0.001). En analyse multivariée, les cancers d'intervalle sont significativement plus fréquents dans le côlon proximal que dans le groupe des patients dépistés (OR: 2.47; 95% CI: 1.06-5.78; p=0.037). Dans le groupe des non participants, les cancers sont significativement plus souvent localisés dans le côlon proximal (OR: 2.25; 95% CI: 1.10-4.59; p=0.026) et le rectum (OR: 2.71; 95% CI: 1.31-5.64; p=0.007), que dans le groupe des cancers dépistés.

Conclusion. Les cancers d'intervalle sont diagnostiqués à un stade plus avancé et sont localisés préférentiellement dans le colon proximal. Le test HEMOCCULT II® détecte de façon préférentielle les cancers du colon distal. D'autres paramètres, notamment biologiques, sont en cours d'analyse et ne seront pas exposés dans ce travail.

MOTS-CLÉS

HEMOCCULT II® — Dépistage

Cancer colorectal — Cancer d'intervalle

Sensibilité

FORMAT

☐ **Mémoire**

☒ **Article**[1] **:** ☒ à soumettre ☐ soumis ☐ accepté pour publication ☐ publié

suivi par : Pr CAROLI-BOSC

[1] statut au moment de la soutenance