Detection of Colorectal Neoplasia in a Cohort Before and After the Change of Fecal Occult Blood Test in a French Colorectal Cancer Screening Program

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- OBJECTIVE:** To estimate the change in the participation rate and the change in neoplasia incidence before and after the change of the Fecal Occult Blood Test (FOBT) in the cohort included in the Colorectal Cancer Screening Program (CRCSP).
- METHODS:** Cohort of 279,210 people, aged 50–74 years, invited at least once before 2009, to participate in a CRCSP campaign. The participation rate and the cumulative neoplasia incidence were described on 4 campaigns (≤ 2008 , 2009–2010, 2011–2012 and 2013–2014) with a Guaiac FOBT (gFOBT) and a first campaign (2015–2016) with a Fecal Immunochemical Test (FIT). The cumulative incidence was estimated by the actuarial method and its confidence interval by the Greenwood method.
- RESULTS:** The participation rate decreased from 32.7% (first gFOBT-campaign) to 24.4% (fourth gFOBT-campaign) then, made a significant bound in the FIT-campaign (28.4%; $p < 0.001$). 35.4% of the 965 high-risk-polyps screened in this cohort were detected in the FIT-campaign. CRC incidence gradually decreased from 0.4 to 0.1/1000 person-years from the first to the fourth gFOBT-campaign before reaching a bound to 0.4/1000 person-years in the FIT-campaign.
- CONCLUSION:** Although it was still below the minimum European target (45%), the participation rate has increased between the last gFOBT-campaign and FIT-campaign, justifying the impact of promotional campaigns and the acceptance of the new test by people and GPs. A decline in the neoplasia incidence was observed between the initial and the fourth gFOBT-campaign. The change from gFOBT to FIT between the fourth and fifth campaigns, was associated with a significant increase in detection of neoplasia.

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INTRODUCTION

In France, Colorectal Cancer (CRC) meets all the conditions for the current organized fecal occult blood test (FOBT) screening program to be sustainable [1–3]. It is common with more than 42,000 new cases a year. It is serious by its mortality, about 18,000 deaths per year in France. When diagnosed at early stage, CRC can be cured in 9 cases out of 10. CRC could be prevented by the detection and treatment of precancerous lesions [1–3].

CRC Screening Program (CRCSP) allowed control of CRC incidence by the diagnosis and resection of pre-cancerous lesions [4, 5]. In addition, the search for occult bleeding by a guaiac test performed every 2 years reduces the mortality by CRC, provided that the participation of the population is at least 50% [2, 3]. This decrease in mortality is increased about by 1/3 in regular screening participants [2, 3, 6, 7].

In USA, to perpetuate this positive impact of screening, more than 300 healthcare organizations have committed to having 80% of adults aged 50 years and older regularly screened for colorectal cancer by 2018 [8, 9]. Within the European Union, the minimum target was set at 45% [10]. In France, despite the success of the program implementation, the participation rate which was very attractive in the pilot campaigns [11–13], rarely exceeds 30% in most districts. The distrust of some general practitioners not supporting the guaiac Fecal Occult Blood test (gFOBT) with low sensitivity/specificity and standard cut-off (300–600 $\mu\text{g/g}$ stool material) [14, 15] and the reluctance of patients for a test requiring three successive sampling were often mentioned as obstacles to this participation [16].

Fecal Immunochemical Test (FIT) OC-Sensor® with improved sensitivity/specificity was introduced in the French CRCSP in 2015

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[17, 18]. The positivity threshold of this FIT, requiring only one stool sample, was set at 150 ng hemoglobin/ml (Institut National du Cancer, www.e-cancer.fr). The Negative and Positive Predictive Value (PPV) of FIT were described in cohorts after a first, second, or even third campaign, but these FIT features are not described in large populations who have participated in several gFOBT screening campaigns. The aim of this study was to describe the dynamics of invitation and results in a cohort, in order to estimate the gain in terms of participation rate and detected neoplasia incidence induced by the introduction of the FIT after 4 gFOBT-campaigns.

METHODOLOGY

Studied population

The study focused on the prospective follow-up of a cohort of 279,210 people aged between 50 and 74 years. The cohort included people residing in the district of Seine-Saint-Denis (District-93) having been invited at least once to perform a screening test before 1 January 2009 (Year of generalization of CRCSP). District-93 is a French Department located in the north-east of Paris agglomeration. It has 236 km² and nearly 1.6 million inhabitants of whom nearly 29% would be <20 years old. It may be characterized by a high level of unemployment (18.5% in 2013), a lower educational level than its neighbor departments, and a slightly lower GPD per capita than the French average GPD [19]. The district-93 does not benefit from an adequate supply of healthcare services, especially regarding liberal medicine (National council of the order of the doctor), probably because of some degree of deprivation. The dynamics of follow-up as well as the incidence of neoplasia (adenomas and cancer) were described on the initial campaign (2008) and on the four successive campaigns before (2009–2010, 2011–2012, 2013–2014) and after the change of the screening test i.e. switch from gFOBT to FIT (2015–2016).

Follow-up of the cohort

In District-93, the local cancer screening managing center (CDC-93) organizes CRCSP campaigns according to the modalities in accordance with the national specifications of the CRCSP [11, 20]. Prior to 2009, because of logistical difficulties due to a pilot program that did not allow the invitation and follow-up of all the targeted population, the CDC-93 split the first cohort included in the CRCSP so that each person had at least one invitation between 2003 and 2008. Before each campaign, the date of eligible persons were transmitted by their health insurance plans. People were invited on their 50th birthday (first invitation) and every two years after a screening test until the age of 74 years. For each campaign, anyone invited and Not Living at the Address Indicated (NLAI) was re-invited during a subsequent campaign if their eligibility was confirmed by their health insurance plans. Any person who refused to participate with documentary evidence (signed letter), was not re-invited. Until 2014, there were two phases (medical and mailing) of distribution of screening tests. During the medical phase, the people targeted by the campaign received on the anniversary date an initial letter (R0) inviting them to withdraw the screening test at their General Practitioner (GP). Those who

did not perform the test after this R0 were relaunched once by a recall letter (R1) three months after R0. Three months after R1, a systematic phase of the test kit mailing accompanied by a second recall letter (R2), was organized for those who did not performed the screening test. After 2014, only a R2 without test kit was sent.

Anyone who tested negative was re-invited two years after the result. Anyone who tested positive was re-invited five years after a negative colonoscopy and excluded from the CRCSP after a positive colonoscopy (adenoma, cancer). Definitive exclusion was decided if people or GPs reported in a mailing response, a diagnosis justifying an exclusion (CRC, Polyp, Crohn's Disease, Familial Adenomatous Polyposis) or family history of CRC (1st degree before 65 years or 2 1st degree parents at any age) or any medical condition justifying definitive exclusion. Similarly, those who died and those who moved out of the district, were permanently excluded from the district's CRCSP. Temporary exclusion was decided in all cases where the postal response evoked a colonoscopy (performed in the last five years) or a colonography (performed in the last two years) without neoplasia.

Data collection, campaigns dynamics, and studied factors

The data for the 5 screening campaigns were extracted from the CDC-93's database. This database is regularly enriched by socio-demographic data, diagnosis (colonoscopy, histopathology) and follow-up data provided by partners (Health Insurance Plans, Medical Information Services, Gastroenterologists, Surgeons, GPs...).

For the analysis of the dynamics over 5 campaigns, the follow-up end date was fixed at 31 December 2016. The end of follow-up criterion was the screening of neoplasia, including Low-Risk-Polyps, High-Risk-Polyps and CRC. The diagnoses associated with CRC and polyps are those related to the C18-C20 and D12 codes of the 10th version of the WHO International Classification of Diseases (ICD10) [21]. CRC histopathology were coded according to the TNM classification [22]. CRC included Carcinoma/tumor in situ (TIS) [22, 23]. High-Risk-Polyps included adenomas ≥ 10 mm, adenomas with high grade dysplasia, Villous or Tubulo-villous adenomas and Serrated adenomas.

Follow-up was censored at the date of the event (if known) or at the date of announcement to the CDC-93, for persons definitively excluded for medical reasons, for those who died and for those who moved out of the district. Similarly, persons who have reached the age of 74 years old before the end-date were censored on the date of the last participation (if participant) or on the date corresponding to the end of the campaign in which they reached that age (if not participant). For any other person, considered unscathed in this analysis, especially lost to follow-up, having participated or not in a campaign and having never sent a mailing response, the follow-up was censored on the end date.

Participation was defined by performing a fecal occult blood test according to CRCSP specifications [11, 20]. However, at the end of each campaign, we have estimated people "up-to-date" with screening, anyone who has been screened or who has completed an exam that justifies a temporary or permanent exclusion from the CRCSP. The studied factors were gender, age (50–54, 55–59,

60–64, 65–69, and 70–74 years), the Health insurance plans (Caisse Primaire d'Assurance Maladie: CPAM, Mutuelle Générale de l'Éducation Nationale: MGEN, Régime Social des Indépendants: RSI, Mutuelle de la Fonction Publique: MFP, Régie Autonome des Transports Parisiens: RATP, Société Nationale des Chemins de Fer: SNCF, Other Plans), the change of health insurance plans or town of residence between two campaigns, the SMTK during a campaign and its frequency (0, 1–2, and 3–4).

Statistical analysis

The participation rate during a given campaign was the proportion of people who underwent a screening test among those invited to do so. For each campaign, NLAI-persons, those who refused, the excluded (temporary and definitive) were excluded from the denominator. This rate was described and compared between groups by a Pearson χ^2 test. In the same group, the difference in proportion between two campaigns was tested by Mac Nemar's Chi-2. The test's PPV was estimated by the proportion of cases with neoplasia in people who had a colonoscopy after a positive test. The cumulative incidence of Low-Risk-Polyps, High-Risk-Polyps and CRC were estimated using the actuarial method (life table) and their confidence intervals using the Greenwood method. Subjects contribute to the calculation of person-times since their inclusion in the cohort, until the date of occurrence of the event or until the follow-up end date or censorship date. The incidences were described by campaign and then compared between groups (gender, age, Health insurance plans, SMTK) by the log-rank test. All analyzes were carried out with STATA-13 software (College Station, Texas, USA) and $p < 0.05$ was considered for statistical significance.

RESULTS

Campaigns monitoring and participation

The cohort size decreased from 279,210 (48.9% women) in the first campaign (C-1) to 146,263 people in the fifth campaign (C-5), due to definitive medical exclusions (12856 cases from C-1 to C-5), moved out (3930 notifications from C-1 to C-5), deaths (1066 notifications from C-1 to C-5), last solicitations because of age (46373 cases from C-1 to C-4) and lost to follow-up (57,204 cases from C-1 to C-4) (Fig. 1). Whatever the sociodemographic characteristic (age, sex...), these people lost to follow-up were not statistically different (data not shown) from the others in the cohort.

With an average of 4 invitations (3.7 ± 1.5) per person, 40.7% of the cohort participated in at least one campaign but only 2.9% participated in all campaigns. The participation rate was 32.7% in C-1 and 28.4% in C-5, the decline observed was significant ($p < 0.001$). Similarly, its increase between C-4 and C-5 was significant ($p < 0.001$). 11.5% (4322 people) of the participants in FIT-campaign had not been screened in the previous 4 campaigns. Compared to the others, people aged 65–69 had a higher participation rate (36.8%) in C-1 ($p < 0.000$). Regardless of the campaign (C-2 to C-5), people who moved to another town before a campaign had a lower participation rate ($p < 0.000$) (Table 1).

Overall, 25,770 people were NLAI at least once during the studied period, among them, 1735 (6.7%) remained NLAI in all the campaigns. 3.2% (8878/279,210) of invitations in C-1 resulted in a NLAI. 6357 of these NLAI in C-1 received a new invitation in a subsequent campaign. The proportion of refusal decreased significantly from 11.9‰ in C-1 to 9.4 ‰ in C-4 and then to 4.2‰ in C-5. Re-inviting NLAI/Refusal accounted for 4.6% (9575 cases) of invitations in C-2. However, 2187 NLAI in C-1 who were under 74 years of age at the study end date, were never re-invited. After their refusal in C-1, 3226 out of 3327 people were re-invited at least once in the CRCSP (Fig. 1). Only 4.8% of these 3226 cases performed at least one screening test during a campaign subsequent to this refusal in C-1. This participation rate in a subsequent campaign after refusal was 3.1% after C-2, 2.2% after C-3 and 15% after C-4.

A total of 30,036 temporary medical exclusions were motivated by colonoscopy performed before the invitation to the campaign. Proportion of colonoscopy accounted was 80.8% in C-1 (13,414 of the 16,601 temporary medical exclusions), 69.5% in C-2, 72.4% in C-3, 79.2% in C4 and 75.7% in C-5. The proportion of the cohort who would be considered to be up-to-date with screening was 36.9% after C1, 31.3% after C2, 32.1% after C-3, 25.8% after C-4, and 28.7% after C-5. 1.6% (2703/16601) of temporary exclusions in C-1 were not re-invited at the end of a theoretical delay (2.1 ± 1.7 years) of temporary exclusion (Fig. 1).

Incidence and characteristics of lesions

8561 persons had an event justifying a definitive exclusion, prior to the initial invitation date in the CRCSP. From the 270,649 people at risk, 1875 case of Low-Risk-Polyps, 965 case of High-Risk-Polyps and 441 case of CRC were screened. The PPV averaged 0.56 for the 4 gFOBT-campaigns and increased by 10 points after the introduction of FIT (Table 2). This FIT-campaign detected 25.5% of the 1875 Low-Risk-Polyps detected in the cohort, 35.4% of the 965 High-Risk-Polyps and 23.6% of the 441 CRCs (Table 3). Between C4 and C-5, the proportion of tubulo-villous adenomas and TIS increased by 8.2 and 51% respectively (Table 4).

Overall, the cumulative incidence of neoplasia was estimated at 1.8/1000 p-a [1.8–1.9] for an average duration of follow-up of 8.4 ± 2.0 years (minimum: 0 years and maximum: 13.9 years). In the restricted cohort to the 40.7% of people who performed at least 1 screening test, this overall incidence was 4.1/1000 p-a [3.9–4.2] (Table 5). Mean age (years) at neoplasia diagnosis was 64.1 ± 6.2 (low-risk-polyps: 63.6 ± 6.3 ; high-risk-polyps: 64.4 ± 6.0 ; CRC: 65.3 ± 6.1) and 72.9% of the CRC were detected before the age of 65 years (Table 5).

DISCUSSION

This study presented long-term follow-up of the cohort included in the CRCSP program in the district of Seine-Saint-Denis. This study distinguishes itself by the socio-demographic originality of the study population, initially naïve for CRC screening, and the long period of follow-up with transition between gFOBT and FIT. These results should be discussed at a time when controversy over the benefits of screening seems to be gaining ground. Indeed,

Fig. 1 Dynamics of invitation and follow-up of the cohort during the five campaigns

Table 1 Campaigns participation rate (PR), according to the cohort follow-up characteristics

Characteristics	Campaigns participation rate				
	Total invited (PR in %)				
	≤2008	2009–2010	2011–2012	2013–2014	2015–2016
Overall participation rate	241,770 (32.7)	187,614 (28.8)	169,369 (30.5)	145,614 (24.4)	132,473 (28.4)
PR at 6 months of the initial invitation	241,770 (18.1)	187,614 (16.9)	169,369 (17.5)	145,614 (12.4)	132,473 (13.4)
PR after SMTK	159,826 (13.7)	139,929 (11.5)	121,976 (11.8)	47,910 (11.6)	...
<i>Gender</i>	***	***	***	***	***
Female	117,011 (36.0)	88,967 (31.8)	82,308 (34.1)	71,214 (27.2)	65,873 (31.5)
Male	124,759 (29.7)	98,647 (26.1)	87,061 (27.1)	74,400 (21.7)	66,600 (25.4)
<i>Age (year) at the invitation</i>	***	***	***	***	***
50–54	76,191 (30.3)	39,589 (23.9)	17,553 (28.1)	–	–
55–59	60,698 (33.7)	55,135 (27.6)	54,384 (27.9)	47,325 (22.1)	24,456 (26.0)
60–64	43,940 (34.7)	41,960 (31.7)	44,541 (32.4)	42,374 (25.0)	44,850 (28.5)
65–69	29,366 (36.8)	27,589 (31.7)	30,260 (32.0)	33,936 (25.3)	38,794 (29.5)
≥70	31,575 (30.2)	23,341 (31.5)	22,631 (32.7)	21,979 (26.8)	24,373 (28.9)
<i>Health insurance plans</i>	***	***	***	***	***
CPAM	20,6332 (32.0)	161,412 (28.4)	144,380 (29.8)	125,791 (23.8)	114,093 (27.7)
MGEN	7322 (44.4)	5307 (35.6)	5450 (40.2)	4740 (31.8)	4459 (37.3)
RSI	9420 (26.0)	7217 (22.5)	6834 (24.1)	5167 (18.4)	4596 (22.8)
MFP	2645 (39.4)	2071 (33.6)	1936 (36.5)	1716 (28.3)	1452 (33.8)
RATP/SNCF	3609 (38.8)	2716 (35.9)	2433 (36.4)	2045 (29.0)	1809 (33.8)
Other plans	12,442 (40.1)	8891 (34.9)	8336 (37.2)	6155 (33.2)	6064 (36.4)
<i>Change of health insurance plan</i>		NS	**	*	NS
No	241,770 (32.7)	184,924 (28.8)	166,567 (30.5)	143,089 (24.4)	131,292 (28.4)
Yes	–	2690 (28.3)	2802 (28.2)	2525 (22.7)	1181 (26.8)
<i>Change of residence town</i>		***	***	***	***
No	241,770 (32.7)	180,753 (29.2)	164,552 (30.7)	142,925 (24.5)	130,063 (28.5)
Yes	–	6861 (18.3)	4817 (24.3)	2689 (20.6)	2410 (22.9)

NS not significant, SMTK systematic mailing of the test kit, CPAM Caisse Primaire d'assurance Maladie, MGEN Mutuelle Générale de l'Education Nationale, RSI Régime Social des Indépendants, MFP Mutuelle de la Fonction Publique, RATP Régie Autonome des Transports Parisiens, SNCF Société Nationale des Chemins de Fer
0.01 < p < 0.05; **0.001 < p ≤ 0.01; ***p ≤ 0.001

Welch and Robertson, evoking a still limited adherence to screening, do not intend to explain the decline in CRC deaths by screening [5]. However, in the US, it was determined that Increasing CRC screening rates to 80% would reduce CRC incidence rates by 17% and mortality rates by 19% during short-term follow-up [9]. Here the impact of the CRCSP is evaluated not only in terms of the incidence of lesions detected but especially in terms of the impact of the change of screening test on this incidence.

The incidence of detected CRC in this study remains below those reported at the national level [11]. The fall in incidence from one campaign to another, observed before the change of the screening test, has already been mentioned in another European

study [24]. Similarly, compared with gFOBT, the performance of FIT in the detection of precancerous/cancerous lesions has been widely documented [25]. This study is distinguished by the fact that it allows to see in the same cohort this decline in incidences over time and the sudden increase attributable to the performance of the new screening test.

The high incidence of High-Risk-Polyps observed, converges with the high rate of detection of advanced adenomas (4.2/1000) that emerged from the first evaluation between 2008 and 2009 in the district [11]. The prevalence of tubulo-villous adenomas remained constant despite the change of the screening test. In contrast, the decline initiated by the proportion of TIS over the

Table 2 Evolution of the positive predictive value

Campaigns	Number of tests performed	Number (%) of positive tests*	Number(%) of colonoscopies completed after positive tests**	Positive predictive value (PPV)	
				Count of patients with screened neoplasia	PPV
≤2008	79,059	2379 (3.0)	1864 (78.4)	1030	0.55
2009–2010	54,033	1247 (2.3)	1049 (84.1)	604	0.58
2011–2012	51,658	975 (1.9)	817 (83.8)	452	0.55
2013–2014	35,530	545 (1.5)	463 (85.0)	270	0.58
2015–2016	37,622	2075 (5.5)	1364 (65.7)	925	0.68

*The denominator is the number of tests performed

**The denominator is the number of positive tests

Table 3 Cumulative Incidence of neoplasia by follow-up period (campaigns)

Cumulative incidences of neoplasia (CIN)								
Campaigns	Number of persons at risk at the period beginning	Person-year	Low risk polyps		High risk polyps		Colorectal cancer	
			Case	CIN/1000 P-Y [95% CI]	Case	CIN/1000 P-Y [95% CI]	Case	CIN/1000 P-Y [95% CI]
≤2008	270,649	3111087.9	681	2.2 [2.0; 2.4]	211	0.6 [0.6; 0.8]	138	0.4 [0.4; 0.5]
2009–2010	232,255	455934.6	325	0.7 [0.6; 0.8]	193	0.4 [0.4; 0.5]	86	0.2 [0.2; 0.2]
2011–2012	200,844	395860.1	243	0.6 [0.5; 0.7]	140	0.4 [0.3; 0.4]	69	0.2 [0.1; 0.2]
2013–2014	172,081	339752.4	147	0.4 [0.4; 0.5]	79	0.2 [0.2; 0.3]	44	0.1 [0.1; 0.2]
2015–2016	144,574	286226.3	479	1.7 [1.5; 1.8]	342	1.2 [1.1; 1.3]	104	0.4 [0.3; 0.4]
Total	270,649	1788961.3	1875	1.0 [1.0; 1.1]	965	0.5 [0.5; 0.6]	441	0.2 [0.2; 0.3]

P-Y person-year, CI confidence interval

last three gFOBT-campaigns, was interrupted by the change of the screening test. This is consistent with the literature on FIT performance in the early detection of precancerous lesions and noninvasive cancers [26]. The incidence of CRC increases significantly with age [1, 27]. Between 40 and 80 years of age, the incidence doubles almost every 10 years [28].

In terms of campaign participation, the need of additional means and strategies seems obvious. Indeed, in addition to being below the national average, the participation rate observed from the first to the last campaign in this cohort remains well below the minimum acceptable 45% European target [10]. It must be admitted that since the generalization of CRCSP, the national participation rate has never exceeded 35% [11]. For some, in addition to socio-demographic characteristics, the communication breakdown between doctor and patient is a contributing factor to the low participation rate and its gradual decline [29]. For others, the test itself may have been a limiting factor since gFOBT identified only 50% of CRCs and one third of adenomas [14]. In addition, the need to collect several stool samples induced patient-side reluctance [14, 16]. These findings are consistent with this study which

shows a decrease in the proportion of refusals and a rebound in the participation rate after the change of the test despite stopping the mailing of the test kit. This study could motivate general practitioners, previously reluctant, to offer the new screening test to their patients.

To support participation observed after the test change, promotional actions already in progress and aimed to make a real change in behavior towards health prevention programs should be perpetuated. Indeed, as other secondary prevention programs (for example vaccination), participation in CRCSP remains highly dependent on socio-cultural factors. In the USA, the literature is eloquent on the link between the racial and/or ethnic group and participation in a screening campaign [30, 31]. Racial/ethnic disparities in CRC screening are major challenges for prevention programs. For these authors, cancer control efforts are local and require locally relevant information to assess needs. This observation could be consistent with any impact analysis of socio-cultural determinants of participation in the CRCSP in the district-93 which is probably the most cosmopolitan French district and therefore the most comparable to some American areas in term of socio-cultural diversity.

Table 4 Histopathological features of detected neoplasia, by campaign

Features	Campaigns					Total
	≤2008	2009–2010	2011–2012	2013–2014	2015–2016	
High risk polyps (n)	211	193	140	79	342	965
Adenomas ≥10mm/ serrated adenomas (%)	0.0	1.0	2.9	5.1	5.0	2.8
Tubulo-villous (%)	81.5	92.2	85.0	88.6	88.3	87.1
Villous (%)	1.9	3.6	5.7	1.3	2.0	2.8
Adenomas + high grade dysplasia (%)	16.6	3.1	6.4	5.0	4.7	7.3
Histopathology of colorectal cancer (n)	138	86	69	44	104	441
Tumor in situ (%)	21.0	26.7	23.2	15.9	24.0	22.7
T _{1/2} N ₀ M ₀ (%)	18.1	17.4	23.2	27.3	13.5	18.6
T _{3/4} N ₀ M ₀ (%)	13.8	23.3	20.3	27.3	7.7	16.5
T _{1/2/3/4} N _{1/2} M ₀ (%)	22.4	16.3	15.9	9.1	13.5	16.8
T ₀₋₄ N _{1/2} M ₁ (%)	8.0	5.8	8.7	9.1	1.9	6.4
Unknown (%)	16.7	10.5	8.7	11.4	39.4	19.0

Table 5 Cumulative Incidence of neoplasia according to the cohort characteristics at baseline

Cumulative incidences of neoplasia (CIN)										
Characteristics	Low risk polyps				High risk polyps			Colorectal cancer		
	P-Y	Case	CIN /1000 P-Y [95% CI]	p	Case	CIN /1000 P-Y [95% CI]	p	Case	CIN /1000 P-Y [95% CI]	p
<i>Gender</i>				***			***			***
Female (n= 131,713)	868626.0	741	0.9 [0.8; 0.9]		334	0.4 [0.3; 0.4]		157	0.2 [0.2; 0.2]	
Male (n= 138,936)	920235.3	1134	1.2 [1.2; 1.3]		631	0.7 [0.6; 0.74]		284	0.3 [0.3; 0.3]	
<i>Age (year) at baseline</i>				***			***			*
50–54 (n= 83,619)	642940.3	511	0.7 [0.7; 0.9]		261	0.4 [0.4; 0.5]		87	0.1 [0.1; 0.2]	
55–59 (n= 67,395)	498058.6	509	1.0 [0.9; 1.1]		276	0.6 [0.5; 0.6]		99	0.2 [0.2; 0.2]	
60–64 (n= 49,589)	367918.1	466	1.3 [1.2; 1.4]		238	0.6 [0.6; 0.7]		121	0.3 [0.3; 0.4]	
65–69 (n= 33,818)	205785.5	246	1.2 [1.1; 1.4]		129	0.6 [0.5; 0.7]		89	0.4 [0.4; 0.5]	
≥70 (n= 36,228)	74158.8	143	1.9 [1.6; 2.3]		61	0.8 [0.6; 1.1]		45	0.6 [0.5; 0.8]	
<i>Health Insurance Plans at baseline</i>				NS			NS			
CPAM (n= 230,489)	1532163.7	1598	1.0 [1.0; 1.1]		812	0.5 [0.5; 0.8]		358	0.2 [0.2; 0.2]	
MGEN (n= 8291)	53610.6	51	1.0 [0.7; 1.3]		38	0.7 [0.5; 1.0]		14	0.3 [0.2; 0.4]	
RSI (n= 10,621)	66287.8	65	1.0 [0.8; 1.3]		29	0.4 [0.3; 0.6]		17	0.3 [0.2; 0.4]	
MFP (n= 3008)	20453.8	20	1.0 [0.6; 1.5]		11	0.5 [0.3; 1.0]		6	0.3 [0.1; 0.7]	
RATP/SNCF (n= 4178)	25889.1	34	1.3 [0.9; 1.8]		21	0.8 [0.5; 1.2]		11	0.4 [0.2; 0.8]	
Other plans (n= 14,062)	90456.4	107	1.2 [1.0; 1.4]		54	0.6 [0.5; 0.8]		35	0.4 [0.3; 0.5]	
<i>SMTK frequency</i>				***			***			***
Never SMTK (n= 33,428)	89779.6	165	1.8 [1.6; 2.1]		68	0.8 [0.6; 1.0]		40	0.4 [0.3; 0.6]	
1–2 SMTK (n= 93,543)	486413.3	1078	2.2 [2.1; 2.4]		507	1.0 [1.0; 1.1]		257	0.5 [0.5; 0.6]	
3–4 SMTK (n= 143,678)	1212668.4	632	0.5 [0.5; 0.6]		390	0.3 [0.3; 0.4]		144	0.1 [0.1; 0.1]	
Total (270,649)	1788961.3	1875	1.0 [1.0; 1.1]		965	0.5 [0.5; 0.6]		441	0.2 [0.2; 0.3]	
≥1 Participation (113,591)	831666.0	1875	2.3 [2.2; 2.4]		965	1.2 [1.1; 1.2]		441	0.5 [0.5; 0.6]	

CI confidence interval, NS not significant, SMTK systematic mailing of the test kit, CPAM Caisse Primaire d'assurance Maladie, MGEN Mutuelle Générale de l'Éducation Nationale, RSI Régime Social des Indépendants, MFP Mutuelle de la Fonction Publique, RATP Régie Autonome des Transports Parisiens, SNCF Société Nationale des Chemins de Fer

*0.01 < p < 0.05; **0.001 < p ≤ 0.01; ***p ≤ 0.001

Promotion actions at national level such as awareness campaigns on the risks of colorectal cancer, local actions on the promotion of the new screening test and the invitation/recall letter are currently the only available tools to offer the CRCSP in this cosmopolitan population. However, studies report that printed materials with health messages are likely to be insufficient to overcome behavioral barriers in cancer screening [32]. In addition to e-mail invitation, a specific telephone message should be tested as it has been proven to increase motivation for post-screening colonoscopy [33]. This form of invitation/recall could reduce the difference in participation rates between people who change their residence and those who remained at the same address between two campaigns.

These movements between two campaigns likely influenced the high proportion of NLAI and lost to follow-up in this cohort. A strategy of involving local associations in the redistribution of undistributed invitation letters should also be considered to decrease NLAI. Similarly, e-mail contact, already experienced elsewhere [34] should be considered because the NLAI and lost to follow-up are often the consequence of the low inaccessibility of certain residential areas in the district.

This study has inherent deficiencies that are common to all follow-up and incidence studies. The observed incidences should be considered with caution because of logistical difficulties compromising the comprehensiveness of the collection of data on detected lesions and also because of lost to follow-up. Indeed, many people who had a positive test who were reported as unexplored by a colonoscopy at the time of the study have an unknown status.

CONCLUSION

Although it is still below the minimum acceptable European target of 45%, the participation rate has increased between the last gFOBT-campaign and the first FIT campaign in this cohort, justifying the acceptance of the new test by individuals and their GPs. To support this gain in terms of participation, the continuation of promotional actions to facilitate the introduction of the new test seems very necessary. In the population of Seine-Saint-Denis, which is probably the most cosmopolitan in France, these promotion actions should aim, first and foremost, to change people's behavior and attitude towards health prevention programs, notably the CRCSP.

A progressive decline in the incidence of lesions was observed between the initial and the fourth gFOBT-campaign. A rebound in incidences was observed, justifying the major impact of the screening test change between the fourth and fifth campaigns. This screening test change did not affect the predominance of tubulovillous components among the High-Risk-Polyps detected, but it allowed to increase the proportion of TIS.

DISCLAIMER

Before analysis, all data were anonymized. The database had a favorable opinion from the institution that oversees the ethics of data collection ("Commission nationale de l'informatique et des libertés": CNIL). According to the current French legislation, a

study that does not change the care of patients did not require the opinion of the Clinical Research Centers Ethics Committee.

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COMPLIANCE WITH ETHICAL STANDARDS

Guarantor of the article: Koivogui Akoï.

Specific author contributions: Koivogui Akoï and Le Mab Guillaume are the doctors in charge of coordinating the screening program in the department. Koivogui Akoï and Benamouzig Robert designed the project. Koivogui Akoï collected the field data. Koivogui Akoï and Benamouzig Robert analyzed the data and interpreted the results. Koivogui Akoï and Benamouzig Robert drafted the manuscript. All the authors read and approved the final version of this manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Controversies over the benefits of the screening program are currently fueling the scientific debate.
- ✓ Low participation rate in CRC screening program is a major handicap to its sustainability.
- ✓ The doctor-patient's communication breakdown is a contributing factor to the gradual decline in participation-rate.
- ✓ The screening test may have been a limiting factor since guaiac-fecal-occult-blood-test (gFOBT) identified only 50% of CRCs.
- ✓ The characteristics of fecal-immunochemical-test for hemoglobin (FIT) have not been described in large populations after several gFOBT-campaigns.

WHAT IS NEW HERE

- ✓ The participation rate increased after the fourth gFOBT-campaign when FIT was used, justifying the impact of promotional campaigns and the acceptance of the new test by people and GPs.
- ✓ The cumulative incidence of neoplasia increased between the fourth gFOBT-campaign and the first FIT-campaign, justifying the test change performance.

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