Original research

Does a long time to colonoscopy after a positive faecal immunochemical test result have a deleterious impact on colorectal cancer outcomes? A nationwide cohort study

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ABSTRACT

Background Depending on the colorectal cancer (CRC) screening programme, a colonoscopy should be performed within 1–3 months after a positive faecal immunochemical test (FIT) result. However, such short timescales may be difficult to meet and seem trivial when most CRCs take years to develop.

Objective To assess the impact of time to colonoscopy on CRC outcomes.

Design This French nationwide retrospective cohort study included individuals with a positive FIT result between 2016 and 2019 and a subsequent colonoscopy performed within 24 months. The risks of CRC, advanced-stage CRC and advanced adenoma (AA) according to time interval to colonoscopy were assessed and evaluated on individual and socio-geographic characteristics.

Results Overall, 374 113 FIT-positive individuals underwent post-FIT colonoscopy (86.6% compliance rate), with 21 616 CRCs and 122 359 AAs diagnosed. Compared with the 2–3 months interval class, no increased risk of CRC, advanced-stage CRC or AA was observed after 3 months up to 24 months, with adjusted odds ratio after 12 months at 0.93 (0.95 CI 0.83 to 1.03), 1.04 (0.85 to 1.25) and 0.88 (0.82 to 0.93), respectively. Individuals with high faecal haemoglobin concentrations (f-Hb ≥200 µg/g) were respectively eight, eleven and two times more likely to have a CRC, an advanced-stage CRC or an AA as compared with the 30–40 µg/g class.

Conclusion No increased risk of CRC, advanced-stage CRC or AA was observed up to 24 months. Our findings suggest that ensuring colonoscopy compliance after a positive FIT may take precedence over rigid adherence to interval. The higher the f-Hb, the sooner the colonoscopy should be performed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies have found an increased risk of colorectal cancer (CRC) in individuals with a time to colonoscopy after positive faecal immunochemical test (FIT) result greater than 3 to 13 months.

WHAT THIS STUDY ADDS

⇒ This nationwide cohort study—the largest ever reported—found no increase in the risk of CRC, advanced-stage CRC or advanced adenoma to 24 months as compared with the 2–3 months interval after adjustment for individual and sociogeographical characteristics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings do not support the previous consensus and suggest that the aim of health policies may no longer focus on an ideal 1–3-month time to colonoscopy after a positive FIT result, as recommended by most guidelines, but rather to ensure that every individual with a positive FIT result uptake colonoscopy.

INTRODUCTION

Colorectal cancer (CRC) is a widespread public health problem, affecting almost 1.9 million people a year and causing over 900 000 deaths.[1] CRC screening helps reduce both specific mortality and incidence of CRC, by detecting early-stage CRC or precancerous lesions, accessible to curative treatment.[2 3] Several countries have implemented national CRC-screening programmes based on repeated faecal occult blood tests (FOBTs). Quantitative faecal immunochemical tests (FITs) have replaced guaiac-based FOBTs (gFOBTs) in most countries.[3 4] In the event of a FIT result equal to or higher than the chosen f-Hb threshold (a positive result), which differs between countries, a colonoscopy is recommended, ideally within 31 days of referral (acceptable standard is >90%; >95% is desirable) according to French and European guidelines,[5] within 2 months according to Canadian and Veterans Health Administration recommendations,[6 7] and within 3 months after the positive FIT result in the Taiwanese CRC screening programme.[8] However, in the real world, the time to colonoscopy varies widely and often exceeds the recommended timescales. In the French CRC screening programme, the median time to colonoscopy was 80 days over the 2018–2019 period (before the COVID-19 pandemic), with significant inter-regional disparity (60 to 142 days).[9]

Previous retrospective studies have suggested that delays >3 months,[10] >9 months,[7 11] >12 months[6 8] or >13 months[12] from positive FIT result to colonoscopy were associated with an increasing incidence of CRC. Delays >3 months,[10] >6 months,[8 11] >7 months[7] or >16 months[12] were also associated with more advanced-stage CRCs. Furthermore, delays >3 months[10] or >12 months[7] were associated with an increase in the advanced adenoma (AA) incidence. However, all these studies suffered from significant biases, mainly large numbers of participants lost to follow-up, leading to an overestimation of the deleterious effect of a prolonged time to colonoscopy after a positive FIT result.[13]

Although the association of longer delays to colonoscopy with worse outcome seems intuitive, the magnitude of the effect depends on the duration of colorectal carcinogenesis. The mean overall time from normal tissue to progress to an adenoma and then to CRC ranges from 10.6 to 25.8 years, and the time from preclinical cancer development to symptomatic CRC detection is estimated to be around 1.6 to 4.0 years depending on the microsimulation model used.[14–16] Once an adenoma becomes advanced, the estimated rate for CRC transition is 1%–5% annually, whereas this rate is <1% for a sessile serrated lesion.[15–17] Overall, a few months' increase in time to colonoscopy seems trivial compared with the many years it takes for colorectal carcinogenesis. Further studies are needed to evaluate the impact of time to colonoscopy on CRC risk and define an evidence-based cut-off if CRC risk is really associated with longer delays.[18]

The aim of this study was to assess the association between time to colonoscopy after a positive FIT result and risk of CRC, advanced stage CRC and AA at diagnosis in the French nationwide CRC screening programme.

MATERIAL AND METHODS

Description of the French CRC screening programme

A national CRC screening programme has been conducted in France since 2009, based on a biennial gFOBT. It involves individuals aged 50 to 74 years, without personal or family history of colorectal neoplasia, hereditary cancer syndromes or inflammatory bowel disease. In 2015, a quantitative FIT (OC Sensor) replaced the gFOBT (Hemoccult).[4] The faecal haemoglobin (f-Hb) positivity threshold adopted is 30 µg Hb per gram faeces (µg/g): f-Hb concentration is communicated to the screening management structure (SMS) and to the general practitioner (GP), but not to the participant, and exceptionally communicated to an involved gastroenterologist. In the event of a positive test result, the patient is referred by the GP to a gastroenterologist to schedule a colonoscopy. If no colonoscopy is recorded after the positive test result, reminders are sent by the SMS, at the very least, to the GP after 4 months and to the participant after 12 months. All colonoscopies are performed by gastroenterologists, and almost all under general anaesthesia provided by an anaesthesiologist.

Study population

Participants with a positive FIT result within the French national CRC screening programme between 1 January 2016 and 31 December 2019 were included. Participants who did not comply with colonoscopy or underwent a colonoscopy >24 months after the positive FIT result were excluded. Colonoscopies with poor bowel preparation and incomplete colonoscopies with no visualised lesions were considered inconclusive. Participants with a final inconclusive colonoscopy or identification of a non-CRC cancer were included for colonoscopy compliance rate calculations but were excluded for the analysis of colonoscopy yield.

Data collected

Age, sex, place of residence of participants, date of the FIT, screening round, f-Hb, date of the colonoscopy, completeness of the colonoscopy, colonoscopy and pathological analysis results, location of the most advanced detected lesion and CRC stages were prospectively collected by the SMS. AA was defined as an adenoma or a serrated polyp measuring 10 mm or more, or the presence of high-grade dysplasia, or a villous or tubulo-villous component. In situ and intramucosal carcinomas ('Tis' in the TNM classification and American Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC) stage 0) were classified as high-grade dysplasia.[19] CRC classified as stage III or IV according to the AJCC/UICC classification was considered advanced-stage CRC.

The French deprivation index (FDep 2015)[20] and the French APL index (Potential Localized Accessibility)[21] were associated with the city of residence at the time of the FIT (see details in online supplemental methods). The FDep index reflects socioeconomic deprivation. The APL index reflects the accessibility of the patients to a GP. Overall colonoscopy rate by county in 2018 was used to reflect accessibility to colonoscopy (see details in online supplemental methods).

Statistical analysis

The main outcome was the detection rate of CRCs. Secondary outcomes were the detection rates of advanced-stage CRCs and AAs. Colonoscopy compliance rate was defined as the number of individuals with a positive FIT result who had undergone a colonoscopy within 24 months, regardless of the quality of the bowel preparation or the completeness of the colonoscopy. The time to colonoscopy variable was divided into monthly classes up to 24 months and considering delays over 9 months and delays over 12 months overall. The proportions of patients with CRC, advanced-stage CRC or AA, by each monthly class were assessed.

Univariate and multivariate logistic regression models were performed to analyse the impact of the time to colonoscopy and other potential confounding factors on the risk of having a CRC, an advanced-stage CRC or an AA at colonoscopy. Multivariate models were constructed following a two-step method, including first individual variables (age class, sex, round of FIT, metrological season and year of the FIT, f-Hb class, time to colonoscopy class) and then socio-geographical variables (FDep class, APL class, colonoscopy rate per 100 000 inhabitants' class). The 2–3 months' time to colonoscopy (ie, 60 to 90 days) was selected as the reference class, since it was the most frequent class and permitted to provide results on both shorter and longer delays to colonoscopy. The collinearity of the variables was assessed before their inclusion in the logistic regression model by measuring the variance inflation factor (VIF). If VIF >5, the variable was not included.

Sensitivity analyses were performed by: (1) considering only first round of FIT or subsequent round of FIT; (2) considering only patients with a high (≥ 150 µg/g) or a low (< 150 µg/g) f-Hb; (3) including Tis carcinomas in the CRC rather than the AA group; (4) modelling the risk of right-sided CRC (from caecum to transverse colon), left-sided CRC (from splenic flexure to rectosigmoid junction) and rectal cancer, respectively; and (5)

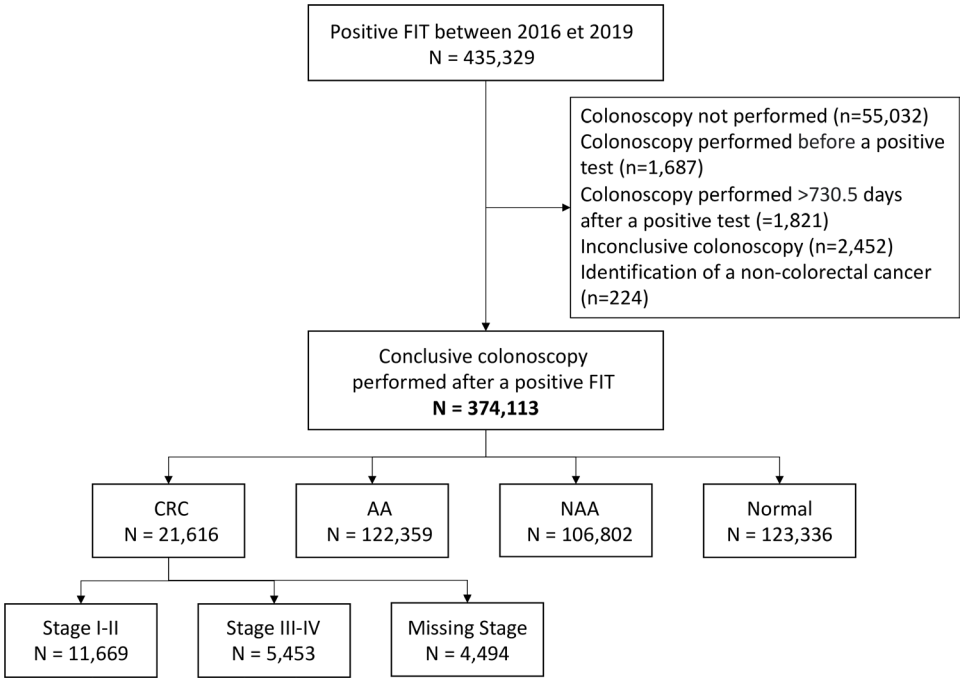


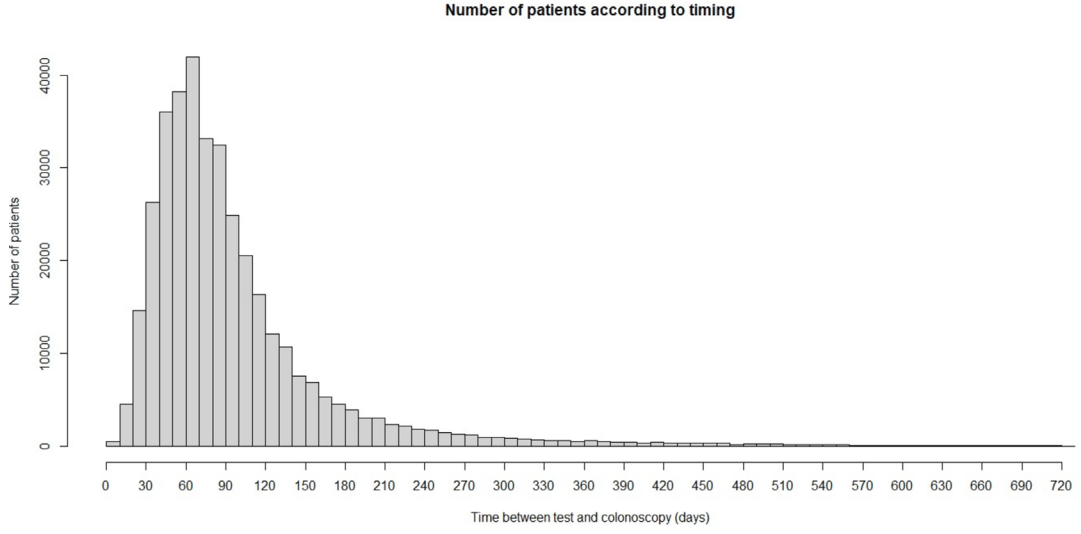
Figure 1 Flow chart of the study. AA, advanced adenoma; CRC, colorectal cancer; FIT, faecal immunochemical test; NAA, non-advanced adenoma.

excluding counties with a rate of unknown CRC stage greater than 30%. Furthermore, to test the robustness of our analyses to exclusion of subjects with no colonoscopy within 24 months, CRC prevalence in these subjects was modelled by applying f-Hb class specific CRC detection rates observed in patients with late colonoscopy (delay after 9 months, or after 12 months). All analyses were performed with R statistical software (*V.4.2, The R Foundation for Statistical Computing, Vienna, Austria*).

RESULTS

Individuals' characteristics

Among 435 329 participants with a positive FIT result, 376 789 (86.6%) had a colonoscopy within 24 months, and 374 113 were included in the study (figure 1). A total of 21 616 CRCs (5.8%), 5453 advanced-stage CRCs (1.5%) and 122 359 AAs (32.7%) were diagnosed. The distributions of time to colonoscopy and monthly delay classes are shown in figure 2. Overall,



Class	(0,30]	(30,60]	(60,90]	(90,120]	(120,150]	(150,180]	(180,210]	(210,240]	(240,270]	(270,300]	(300,330]	(330,360]	(360,540]	(540,730]
n	19,748	100,550	107,624	61,804	30,484	16,778	10,126	6,404	4,588	3,264	2,441	1,869	6,351	2,082
%	5.3	26.9	28.8	16.5	8.1	4.5	2.7	1.7	1.2	0.9	0.7	0.5	1.7	0.6

Figure 2 Frequency of individuals according to time to colonoscopy after positive FIT result. FIT, faecal immunochemical test.

19 748 participants (5.3%) had their colonoscopy performed ≤1 month, 227 922 (60.1%) ≤3 months and 37 305 (10.0%) >6 months. The median time to colonoscopy was 77 days (IQR: 55–119 days).

Participants' characteristics according to colonoscopy results are detailed in table 1. CRCs were significantly more frequent in older participants, men, first screening round and in highest f-Hb. CRCs were significantly more frequent in 2016–2017, which corresponds to the first screening round using FIT replacing gFOBT, than in 2018–2019 (6.1% vs 5.3%, p <0.001). Although statistically significant, there were no clinically significant differences according to socioeconomic status (French Deprivation Index (FDep)), accessibility to GP (Localised Potential Accessibility (APL)) or colonoscopy rate per 100 000 inhabitants. Characteristics among participants diagnosed with CRC, according to stage at diagnosis, are detailed in online supplemental table 1S. CRC stage was not documented for 20.8% of participants. Advanced-stage CRCs were significantly more frequent in women, first screening round and in highest f-Hb.

Impact of the time to colonoscopy on the risk of CRC, advanced-stage CRC and AA

After 3 months and up to 24 months, the proportions of participants diagnosed with CRC, advanced-stage CRC and AA were constant according to the time to colonoscopy (figure 3).

Table 2 presents the results of univariate and multivariate logistic regression models assessing CRC versus no CRC, advanced-stage CRC versus no advanced-stage CRC and AA versus no AA or CRC.

The multivariate logistic regression model showed no increase in CRC risk when the time to colonoscopy was >3 months, up to 24 months after the FIT result. The adjusted OR (aOR) for CRC risk was 0.91 (95% (0.84–0.99) after 9 months and 0.93 (0.83–1.03) after 12 months, as compared with the 2 to 3 months class. The risk of CRC was significantly greater for the 0 to 1 month class (aOR=1.57 (1.48–1.66)) and 1 to 2 months class (aOR=1.09 (1.05–1.13)). Results for advanced-stage CRC were similar, with an over-risk for the 0 to 1 month class (aOR=1.91 (1.72–2.11)) and 1 to 2 months class (aOR=1.09 (1.01–1.17)), but no over-risk after 3 months up to 24 months. The aOR for advanced-stage CRC was 0.99 (0.85–1.14) after 9 months and 1.04 (0.85–1.25) after 12 months. No increasing risk of AA was found after 3 months, and in contrast, a decreasing risk was observed after 9 months (aOR=0.90; CI95% (0.86–0.95)) and after 12 months (aOR=0.88; CI95% (0.82–0.93]). aOR for CRC, advanced-stage CCR and AA detection is summarised in online supplemental figure 1S.

Impact of other variables on the risk of CRC, advanced CRC and AA

There was no association between the f-Hb and the time to colonoscopy (online supplemental figure 2S). Individuals with f-Hb ≥200 µg/g were, respectively, eight times, 11 times and two times more likely to have a CRC, an advanced-stage CRC and an AA as compared with the 30–40 µg/g class (online supplemental figure 3S).

In multivariate analyses, no increased risk of CRC, advanced-stage CRC and AA was observed after 3 months when focusing on first-round or subsequent rounds of FIT, when focusing on participants with f-Hb ≥150 µg/g or <150 µg/g or when considering Tis carcinomas as CRCs instead of AAs (see figure 4 and online supplemental table 2S to 6S). No influence of the time to colonoscopy on risk of CRC was observed depending on CRC location (online supplemental table 7S). No influence of time to colonoscopy on advanced-stage CRC risk was observed when excluding counties with a rate of unknown CRC stage greater than 30% (data not shown). The characteristics of participants with no colonoscopy at 24 months were similar to those of participants with later colonoscopy (after nine or 12 months) (online supplemental table 8S). Applying f-Hb-specific CRC detection rates observed in late colonoscopy to participants with no colonoscopy had little effect on estimated CRC detection rates and univariate association between late colonoscopy and CRC detection.

DISCUSSION

Our nationwide population-based study, including nearly 375 000 FIT positive participants, has found no increased risk of CRC, advanced-stage CRC and AA associated with the time to colonoscopy after a positive FIT result, up to 2 years, both overall and by location. In contrast, there was a significantly higher risk of CRC and advanced-stage CRC in participants undergoing colonoscopy within 60 days of the positive FIT result. There was no association between social deprivation, access to the GP or access to colonoscopy with the colonoscopy result.

These results conflict with those of previous studies[6–8 10–12 22] (online supplemental table 9S) that reported increased risks of CRC and advanced-stage CRC when time to colonoscopy exceeded a delay from 3 to 18 months after the positive FIT result.[6–8 10–12] Regarding AA risk, two out of three studies found a significantly increased risk associated with time to colonoscopy exceeding 3 or 12 months.[7 10 11] The existence of an increased risk of advanced neoplasia associated with a few months' delay between a positive FIT result and colonoscopy; its magnitude and the very short delays reported in some studies seem disproportionate in the light of current knowledge about the extremely slow process of colorectal carcinogenesis.[14] Further, thresholds for supposedly clinically deleterious delays ranged from 3 months (almost impossible) to 18 months (biologically more plausible regarding results of simulation studies[14 17]), depending on the study. Conceptually, if there were to be a detrimental effect of the delay between FIT result and colonoscopy in such a short period of time as 12–18 months, it would be as a continuum rather than a precise threshold (the longer the delay, the greater the risk). A deleterious effect of prolonged time to colonoscopy could be biologically more plausible for CRCs following the serrated pathway of colorectal carcinogenesis, which is faster than the adenoma pathway.[23] However, serrated lesions do not bleed and are poorly detected by FIT.[24 25]

The absence of increased risk of advanced neoplasia associated with time to colonoscopy up to 2 years in our study could be explained either by a lack of statistical power—despite this being the study with the largest number of colonoscopies performed at 12 months or more—or by the fact that the actual duration of colorectal carcinogenesis is close to the slowest scenarios in modelling studies.[14]

Methodological issues in the evaluation of the association of time to colonoscopy and risk of colorectal neoplasms have been discussed earlier.[13 18 26] Overestimation of this association results from two main issues: (1) the number of participants lost to follow-up without any colonoscopy and 2) the indication for delayed colonoscopies.

1. In our study, 58 540 (13.4%) participants had no colonoscopy within 24 months of the positive FIT result. The proportion of advanced neoplasia (AA or CRC) in these individuals remains unknown, and these participants were excluded

Table 1 Main characteristics of included participants according to colonoscopy result

		Normal colonoscopy n=1 23 336		Non advanced adenoma n=1 06 802		Advanced adenoma n=1 22 359		Colorectal cancer n=21 616		P value*
Age	49–54 years	27 878	40.8%	18 210	26.7%	19 752	28.9%	2442	3.6%	**<0.001**
	55–59 years	23 346	35.6%	18 500	28.2%	20 716	31.6%	2942	4.5%	
	60–64 years	24 064	31.1%	22 120	28.6%	26 654	34.5%	4499	5.8%	
	65–69 years	26 127	29.5%	26 006	29.3%	30 403	34.3%	6078	6.9%	
	70–75 years	21 921	29.5%	21 966	29.5%	24 834	33.4%	5655	7.6%	
Sex	Male	55 387	26.0%	64 335	30.2%	79 890	37.5%	13 151	6.2%	**<0.001**
	Female	67 949	42.1%	42 467	26.3%	42 469	26.3%	8465	5.2%	
Screening round	1	35 175	33.1%	27 948	26.3%	35 961	33.9%	7037	6.6%	**<0.001**
	≥2	88 161	32.9%	78 854	29.4%	86 389	32.2%	14 578	5.4%	
Season of performance of the FIT	Winter	38 352	32.6%	33 405	28.4%	39 144	33.2%	6879	5.8%	**<0.001**
	Spring	33 558	33.3%	29 264	29.1%	33 262	32.7%	5649	5.6%	
	Summer	29 768	32.8%	25 638	28.2%	30 096	33.2%	5263	5.8%	
	Autumn	21 658	33.4%	18 495	28.5%	20 856	32.2%	3825	5.9%	
Year of performance of the FIT	2016	41 561	31.6%	36 156	27.5%	45 679	34.7%	8169	6.2%	**<0.001**
	2017	25 874	32.7%	22 312	28.2%	26 067	33.0%	4758	6.0%	
	2018	33 980	34.0%	29 317	29.4%	31 171	31.2%	5403	5.4%	
	2019	21 921	34.4%	19 017	29.9%	19 442	30.5%	3286	5.2%	
Location of the detected lesion†	Right colon			36 081	51.4%	28 592	*40.7%*	5516	*7.9%*	**<0.001**
	Left colon			46 295	35.3%	74 623	*56.9%*	10 262	*7.8%*	
	Rectum			17 062	43.8%	16 467	*42.3%*	5445	*14.0%*	
	Unknown			7364	70.6%	2677	*25.7%*	393	*3.8%*	
Time to colonoscopy (days)	Mean	100.4		101.1		99.8		93.9		
	0, 30	7108	36.0%	5192	26.3%	5744	29.1%	1704	8.6%	**<0.001**
	30–60	33 209	33.0%	28 427	28.3%	32 706	32.5%	6208	6.2%	
	60–90	34 930	32.5%	30 867	28.7%	35 719	33.2%	6108	5.7%	
	90–120	20 110	32.5%	17 771	28.8%	20 576	33.3%	3347	5.4%	
	120–150	9838	32.3%	8866	29.1%	10 261	33.7%	1519	5.0%	
	150–180	5596	34.5%	4250	26.2%	5525	34.1%	832	5.1%	
	180–210	3346	33.0%	3000	29.6%	3262	32.2%	518	5.1%	
	210–240	2170	33.9%	1778	27.8%	2119	33.1%	337	5.3%	
	240–270	1564	34.1%	1331	29.0%	1482	32.3%	211	4.6%	
	270–300	1085	33.2%	966	29.6%	1051	32.2%	162	5.0%	
	300–330	800	32.8%	710	29.1%	794	32.5%	137	5.6%	
	330–360	629	33.7%	581	31.1%	566	30.3%	93	5.0%	
	360–540	2211	34.8%	1881	29.6%	1927	30.3%	332	5.2%	
	540–730	740	35.5%	607	29.2%	627	30.1%	108	5.2%	
f-Hb (µg/g)	Mean	88.1		85.6		105.6		146.3		
	30–40	31 484	37.4%	28 397	33.8%	22 509	26.8%	1733	2.1%	**<0.001**
	40–50	18 413	35.7%	16 695	32.4%	15 033	29.2%	1378	2.7%	
	50–60	12 083	35.4%	10 674	31.3%	10 294	30.1%	1104	3.2%	
	60–80	14 778	34.6%	12 835	30.0%	13 663	32.0%	1483	3.5%	
	80–100	9122	33.7%	7613	28.1%	9196	34.0%	1148	4.2%	
	100–150	11 749	31.6%	9962	26.8%	13 521	36.3%	2005	5.4%	
	150-200	5198	29.7%	4297	24.6%	6811	39.0%	1177	6.7%	
	≥200	20 463	25.7%	16 260	20.4%	31 281	39.3%	11 578	14.5%	
	Unknown	46	26.1%	69	39.2%	51	29.0%	10	5.7%	
FDep (social deprivation)	Q1 (the least)	21 612	33.9%	17 595	27.6%	20 930	32.8%	3654	5.7%	**<0.001**
	Q2	24 227	32.7%	21 132	28.5%	24 491	33.0%	4258	5.7%	
	Q3	25 012	32.4%	22 174	28.7%	25 552	33.1%	4448	5.8%	
	Q4	25 929	32.2%	23 433	29.1%	26 392	32.8%	4767	5.9%	
	Q5 (the most)	25 927	33.9%	21 814	28.5%	24 321	31.8%	4365	5.7%	
	Unknown	629	30.2%	654	31.4%	673	32.4%	124	6.0%	

Continued

Table 1 Continued

		Normal colonoscopy n=1 23 336		Non advanced adenoma n=1 06 802		Advanced adenoma n=1 22 359		Colorectal cancer n=21 616		P value*
APL (accessibility to GP)	[0, 2.8] (less)	23 849	31.7%	21 986	29.2%	25 242	33.5%	4217	5.6%	**<0.001**
	2.8–3.5	26 178	32.5%	22 703	28.2%	26 870	33.4%	4607	5.7%	
	3.5–4.1	23 033	32.7%	20 084	28.5%	23 146	32.9%	4149	5.9%	
	4.1–4.9	23 328	33.3%	19 931	28.4%	22 694	32.4%	4121	5.9%	
	4.9–12.7	22 220	34.5%	18 004	28.0%	20 573	31.9%	3598	5.6%	
	Unknown	4728	35.1%	4094	30.4%	3834	28.4%	825	6.1%	
Colonoscopy rate per 100 000 inhabitants	1480–1770	24 843	32.3%	21 672	28.2%	25 985	33.8%	4423	5.7%	**<0.001**
	1770–1940	29 548	34.5%	23 329	27.2%	27 935	32.6%	4932	5.8%	
	1940–2040	24 414	33.9%	20 434	28.4%	23 018	32.0%	4059	5.6%	
	2040–2150	20 918	31.7%	19 820	30.0%	21 295	32.2%	4001	6.1%	
	2150–2910	23 609	32.1%	21 547	29.3%	24 124	32.8%	4200	5.7%	

**Pearson's $\chi 2$ tests have been performed between the four groups*
†For the location variable, the denominator used to calculate percentages corresponds to the number of participants with an identified lesion (non-advanced adenoma (NAA), AA or CRC).
APL, the French APL index (see supplementary data); CRC, colorectal cancer; FDep, the French deprivation index; f-Hb, faecal haemoglobin concentration; FIT, faecal immunochemical test.

from our analysis. However, the characteristics of participants with no colonoscopy at 24 months were similar to those of participants with late colonoscopy. Including these participants in the analysis by assuming that they would have the same risk of CRC as those with late colonoscopy and similar f-Hb did not change our results and conclusions.

2. None of the studies (including ours) did account for high-risk symptoms (ie, iron-deficiency anaemia or haematochezia) at the time of colonoscopy.[7 13 27] A late colonoscopy after a positive FIT result could be more motivated by the onset of symptoms rather than by a positive FIT result performed many months earlier. Two studies included colonoscopies performed >2 years after the positive FIT, which is not in conformity with European guidelines and increased the proportion of colonoscopies motivated by the onset of symptoms and the proportion of advanced-stage CRCs.[10 12] There are several participant-, provider- and system-related barriers that contribute to a delayed or lack of colonoscopy follow-up after a positive FIT result.[28] The fact that the risk of CRC remains high and stable over time is an argument for regularly reminding non-compliant participants to undergo a colonoscopy up to 2 years after the FIT result. To this end, it seems to us that the GP's involvement would be an advantage. Moreover, participant- and provider-directed reminders, as used in the French CRC screening programme, might help improve colonoscopy compliance rates[29]. Most studies did not report the way participants who did not comply >6 months after the positive FIT were managed.[6–8 10 11 22] Early colonoscopies may also be motivated by symptoms. Although symptomatic participants are theoretically excluded from

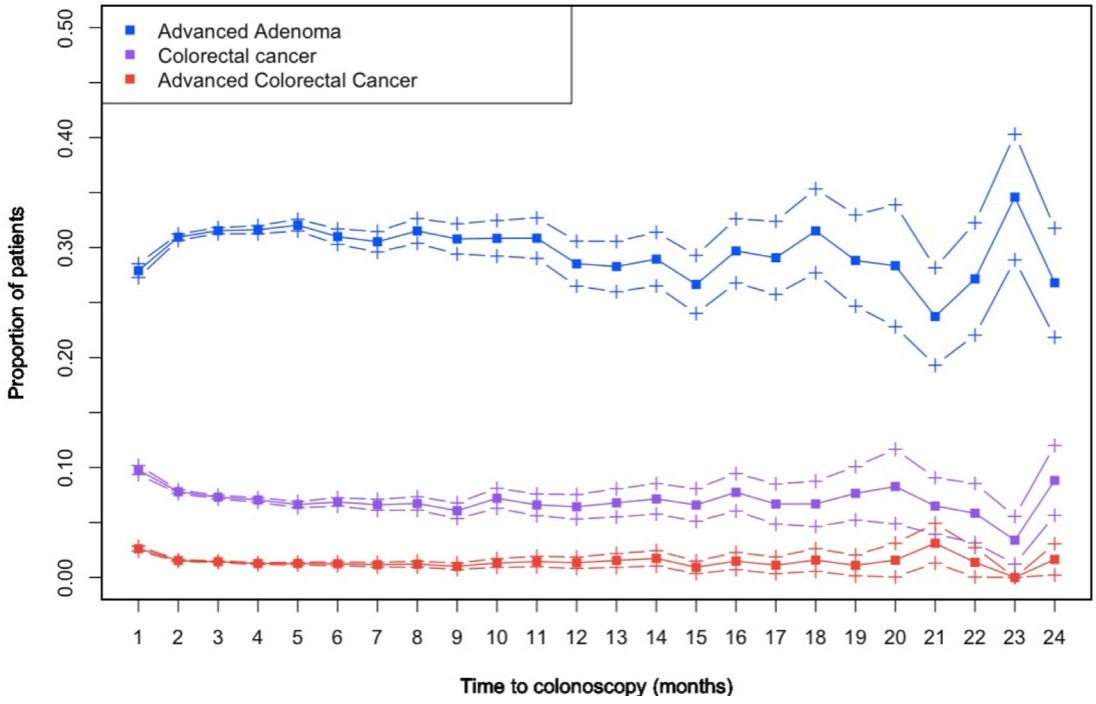


Figure 3 Proportion of CRC, advanced-stage CRC and advanced adenoma according to time to colonoscopy in months. CRC, colorectal cancer.

Table 2 Logistic regression assessing impact of time interval to colonoscopy after positive FIT on colonoscopy result

Characteristics		Advanced adenoma				Colorectal cancer†				Advanced colorectal cancer‡			
		Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value	Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value	Univariate OR (CI 95%)	P value	Multivariate OR (CI 95%)	P value
Age	49–55 years	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**
	55–59 years	1.16 (1.13 to 1.18)		1.27 (1.24 to 1.31)		1.27 (1.20 to 1.34)		1.51 (1.42 to 1.60)		1.19 (1.07 to 1.32)		1.43 (1.28 to 1.59)	
	60–64 years	1.35 (1.32 to 1.38)		1.50 (1.47 to 1.54)		1.67 (1.58 to 1.75)		2.04 (1.93 to 2.15)		1.60 (1.45 to 1.76)		1.95 (1.76 to 2.16)	
	65–69 years	1.36 (1.33 to 1.39)		1.55 (1.51 to 1.59)		1.99 (1.89 to 2.08)		2.52 (2.39 to 2.66)		1.84 (1.68 to 2.02)		2.34 (2.12 to 2.59)	
	70–75 years	1.32 (1.29 to 1.35)		1.53 (1.49 to 1.57)		2.22 (2.11 to 2.33)		2.95 (2.79 to 3.11)		1.92 (1.75 to 2.11)		2.54 (2.29 to 2.82)	
Sex	Male	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**0.001**	1	0.7
	Female	0.58 (0.57 to 0.58)		0.59 (0.58 to 0.60)		0.84 (0.82 to 0.86)		0.91 (0.88 to 0.94)		0.92 (0.87 to 0.97)		1.01 (0.96 to 1.07)	
Round of screening	1	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**
	≥2	0.91 (0.89 to 0.92)		0.82 (0.80 to 0.83)		0.81 (0.79 to 0.83)		0.69 (0.67 to 0.71)		0.74 (0.70 to 0.78)		0.67 (0.63 to 0.71)	
Season of performance of the FIT	Winter	1	**<0.001**	1	**<0.001**	1	**0.045**	1	**<0.001**	1	**0.046**	1	**0.002**
	Autumn	0.94 (0.92 to 0.96)		0.96 (0.95 to 0.98)		0.96 (0.92 to 0.99)		0.99 (0.95 to 1.02)		0.96 (0.89 to 1.03)		0.99 (0.92 to 1.06)	
	Spring	1.00 (0.98 to 1.01)		1.01 (0.99 to 1.03)		0.99 (0.96 to 1.03)		1.03 (0.99 to 1.07)		1.03 (0.96 to 1.11)		1.07 (1.00 to 1.15)	
	Summer	0.95 (0.93 to 0.97)		1.00 (0.98 to 1.02)		1.01 (0.97 to 1.05)		1.10 (1.05 to 1.14)		1.07 (0.99 to 1.15)		1.14 (1.05 to 1.24)	
Year of performance of the FIT	2016	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	0.079
	2017	0.92 (0.90 to 0.94)		0.92 (0.91 to 0.94)		0.97 (0.93 to 1.00)		0.96 (0.92 to 0.99)		0.99 (0.92 to 1.06)		0.97 (0.90 to 1.04)	
	2018	0.84 (0.82 to 0.85)		0.85 (0.84 to 0.87)		0.86 (0.83 to 0.90)		0.90 (0.86 to 0.93)		0.89 (0.83 to 0.95)		0.93 (0.87 to 1.00)	
	2019	0.81 (0.79 to 0.82)		0.82 (0.81 to 0.84)		0.82 (0.79 to 0.86)		0.86 (0.83 to 0.90)		0.85 (0.79 to 0.92)		0.91 (0.84 to 0.99)	

Continued

Table 2 Continued

		Advanced adenoma		Colorectal cancer†		Advanced colorectal cancer‡					
f-Hb (µg/g)	30-40	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**	1	**<0.001**
	40–50	1.14 (1.11 to 1.17)		1.14 (1.11 to 1.17)		1.31 (1.22 to 1.40)		1.30 (1.20 to 1.39)		1.30 (1.10 to 1.52)		1.28 (1.08 to 1.51)	
	50–60	1.20 (1.17 to 1.24)		1.20 (1.16 to 1.23)		1.59 (1.47 to 1.71)		1.57 (1.46 to 1.70)		1.61 (1.35 to 1.91)		1.60 (1.34 to 1.90)	
	60–80	1.32 (1.28 to 1.35)		1.32 (1.29 to 1.36)		1.71 (1.59 to 1.83)		1.71 (1.59 to 1.83)		1.83 (1.56 to 2.13)		1.81 (1.55 to 2.12)	
	80–100	1.46 (1.42 to 1.51)		1.45 (1.41 to 1.50)		2.10 (1.95 to 2.27)		2.08 (1.92 to 2.25)		2.04 (1.72 to 2.42)		2.05 (1.72 to 2.43)	
	100–150	1.66 (1.61 to 1.70)		1.66 (1.61 to 1.70)		2.71 (2.53 to 2.89)		2.69 (2.51 to 2.87)		3.04 (2.64 to 3.51)		3.03 (2.63 to 3.50)	
	150–200	1.91 (1.84 to 1.98)		1.91 (1.84 to 1.98)		3.43 (3.18 to 3.70)		3.43 (3.18 to 3.71)		4.20 (3.58 to 4.92)		4.20 (3.58 to 4.94)	
	≥200	2.27 (2.22 to 2.32)		2.23 (2.19 to 2.28)		8.09 (7.69 to 8.52)		8.00 (7.59 to 8.44)		11.2 (10.0 to 12.6)		10.9 (9.73 to 12.2)	
FDep (social deprivation)	Q1 (the least)	1	**<0.001**	1	**<0.001**	1	0.4	1	0.2	1	0.2	1	0.6
	Q2	1.01 (0.99 to 1.03)		0.96 (0.96 to 1.01)		1.00 (0.96 to 1.05)		1.02 (0.98 to 1.08)		1.04 (0.95 to 1.14)		1.00 (0.91 to 1.10)	
	Q3	1.01 (0.99 to 1.04)		0.99 (0.97 to 1.01)		1.01 (0.96 to 1.05)		1.02 (0.97 to 1.08)		1.04 (0.95 to 1.14)		1.00 (0.91 to 1.10)	
	Q4	1.00 (0.98 to 1.02)		0.97 (0.94 to 0.99)		1.04 (0.99 to 1.08)		1.05 (1.00 to 1.11)		1.07 (0.98 to 1.17)		1.03 (0.94 to 1.13)	
	Q5 (the most)	0.95 (0.93 to 0.98)		0.92 (0.90 to 0.95)		1.00 (0.95 to 1.04)		1.01 (0.96 to 1.06)		1.11 (1.02 to 1.21)		1.06 (0.97 to 1.16)	
APL (accessibility to GP)	(0, 2.8)(the least)	1	**<0.001**	1	**<0.001**	1	**0.015**	1	**0.027**	1	0.3	1	0.5
	2.8–3.5	1.00 (0.98 to 1.02)		1.01 (0.98 to 1.03)		1.05 (1.00 to 1.09)		1.04 (1.00 to 1.09)		1.06 (0.97 to 1.15)		1.05 (0.96 to 1.14)	
	3.5–4.1	0.97 (0.95 to 1.00)		0.99 (0.97 to 1.01)		1.06 (1.01 to 1.10)		1.05 (1.00 to 1.10)		1.02 (0.94 to 1.11)		1.01 (0.93 to 1.10)	
	4.1–4.9	0.95 (0.93 to 0.97)		0.97 (0.94 to 0.99)		1.05 (1.01 to 1.10)		1.04 (0.99 to 1.08)		1.02 (0.93 to 1.11)		1.01 (0.92 to 1.10)	
	4.9–12.7 (the most)	0.93 (0.91 to 0.95)		0.95 (0.92 to 0.97)		1.00 (0.95 to 1.04)		0.99 (0.94 to 1.03)		0.96 (0.88 to 1.05)		0.96 (0.88 to 1.06)	
Colonoscopy rate per 100 000 inhabitants	1480-1770	1	**<0.001**	1	**<0.001**	1	**0.013**	1	**<0.001**	1	**0.002**	1	**<0.001**
	1770–1940	0.95 (0.93 to 0.97)		0.95 (0.93 to 0.97)		1.00 (0.96 to 1.04)		0.99 (0.94 to 1.03)		1.05 (0.97 to 1.14)		1.05 (0.96 to 1.14)	
	1940–2040	0.92 (0.90 to 0.94)		0.93 (0.90 to 0.95)		0.98 (0.94 to 1.02)		0.96 (0.92 to 1.01)		0.93 (0.85 to 1.01)		0.91 (0.84 to 1.00)	
	2040–2150	0.94 (0.91 to 0.96)		0.98 (0.95 to 1.00)		1.06 (1.01 to 1.10)		1.03 (0.99 to 1.09)		0.98 (0.90 to 1.07)		1.05 (0.96 to 1.15)	
	2150–2910	0.96 (0.94 to 0.98)		0.95 (0.93 to 0.97)		0.99 (0.95 to 1.04)		0.94 (0.90 to 0.98)		0.90 (0.83 to 0.98)		0.86 (0.79 to 0.94)	

Continued

Table 2 Continued

		Advanced adenoma		Colorectal cancer†		Advanced colorectal cancer‡	
Time to colonoscopy (days)	0–30	0.86 (0.83 to 0.89) **<0.001**	0.87 (0.84 to 0.91) **<0.001**	1.57 (1.48 to 1.66) **<0.001**	1.56 (1.47 to 1.65) **<0.001**	1.95 (1.76 to 2.15) **<0.001**	1.91 (1.72 to 2.11) **<0.001**
	30–60	0.98 (0.96 to 1.00)	0.98 (0.96 to 1.00)	1.09 (1.05 to 1.13)	1.09 (1.05 to 1.13)	1.09 (1.02 to 1.17)	1.08 (1.01 to 1.17)
	60–90	1	1	1	1	1	1
	90–120	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	0.95 (0.91 to 0.99)	0.96 (0.91 to 1.00)	0.89 (0.82 to 0.97)	0.89 (0.82 to 0.97)
	120–150	1.01 (0.98 to 1.04)	1.01 (0.98 to 1.03)	0.87 (0.82 to 0.92)	0.87 (0.82 to 0.92)	0.91 (0.81 to 1.02)	0.88 (0.79 to 0.99)
	150–180	0.98 (0.94 to 1.01)	0.97 (0.93 to 1.00)	0.87 (0.80 to 0.93)	0.84 (0.78 to 0.91)	0.81 (0.70 to 0.94)	0.78 (0.67 to 0.91)
	180–210	0.95 (0.91 to 0.99)	0.92 (0.88 to 0.97)	0.90 (0.82 to 0.98)	0.89 (0.81 to 0.98)	0.89 (0.74 to 1.06)	0.87 (0.72 to 1.04)
	210–240	0.99 (0.94 to 1.04)	0.97 (0.92 to 1.03)	0.92 (0.82 to 1.03)	0.91 (0.81 to 1.02)	0.85 (0.67 to 1.06)	0.82 (0.65 to 1.03)
	240–270	0.94 (0.88 to 1.01)	0.93 (0.87 to 0.99)	0.80 (0.69 to 0.92)	0.78 (0.67 to 0.90)	0.67 (0.49 to 0.90)	0.67 (0.48 to 0.89)
	270–300	0.94 (0.88 to 1.02)	0.94 (0.87 to 1.02)	0.87 (0.74 to 1.02)	0.83 (0.70 to 0.97)	0.91 (0.66 to 1.22)	0.86 (0.62 to 1.17)
	300–330	0.97 (0.89 to 1.06)	0.95 (0.87 to 1.04)	0.99 (0.83 to 1.17)	0.93 (0.77 to 1.11)	1.04 (0.73 to 1.43)	1.01 (0.71 to 1.40)
	330–360	0.86 (0.78 to 0.95)	0.83 (0.75 to 0.92)	0.87 (0.70 to 1.07)	0.84 (0.67 to 1.04)	0.87 (0.56 to 1.28)	0.86 (0.55 to 1.27)
	360–540	0.87 (0.82 to 0.92)	0.84 (0.79 to 0.89)	0.92 (0.82 to 1.03)	0.87 (0.77 to 0.98)	1.01 (0.81 to 1.25)	0.96 (0.77 to 1.18)
	540–730	0.86 (0.78 to 0.94)	0.82 (0.75 to 0.91)	0.91 (0.74 to 1.10)	0.86 (0.70 to 1.05)	1.05 (0.72 to 1.48)	1.01 (0.69 to 1.42)

P value relates to global comparison of all the objects/classes of a variable. Variance inflation factors of included variables in the three logistic regression models were all less than 1.3.
*Logistic regression model assessing the presence of advanced adenoma vs no advanced adenoma AA vs NAA on colonoscopy (patients with CRC have been excluded).
†Logistic regression model assessing the presence of CRC vs no CRC on colonoscopy.
‡Logistic regression model assessing the presence of advanced CRC vs no advanced CRC on colonoscopy (including patients without CRC, patients with no advanced CRC and patients with unknown stage CRC).
APL, the French APL index (see supplementary data); CRC, colorectal cancer; FDep, the French FDep index; f-Hb, faecal haemoglobin concentration; FIT, faecal immunochemical test; GP, general practitioner.

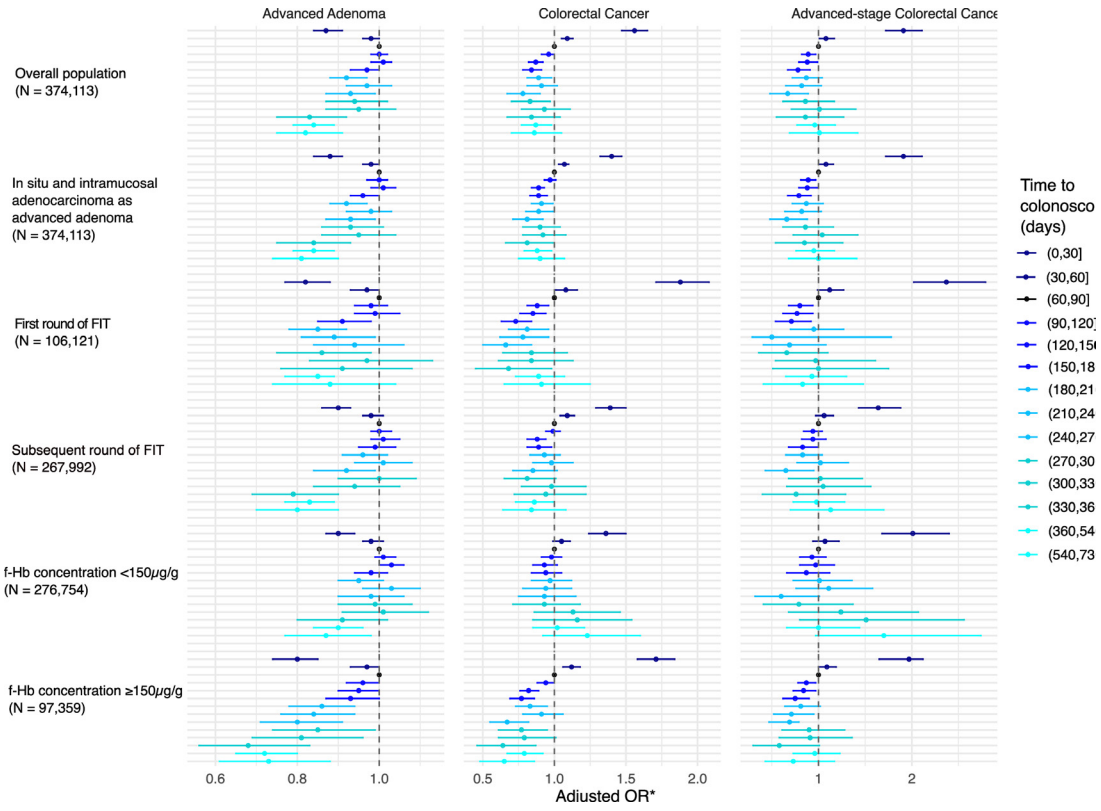


Figure 4 Overall population and subgroup analyses representing adjusted risks of CRC, advanced-stage CRC and advanced adenoma FIT. * Adjusted OR from multivariate logistic regression model including age, sex, year and season of the FIT, F-Hb concentration, FDEP, APL, colonoscopy rate per 100 000 inhabitants and time to colonoscopy level. APL, Localised Potential Accessibility; CRC, CRC, colorectal cancer; FDep, French Deprivation Index; F-Hb, faecal haemoglobin; FIT, faecal immunochemical test.

the French CRC screening programme, GPs are sometimes tempted to give a symptomatic patient a screening FIT to decide whether or not to refer the patient to a gastroenterologist for a colonoscopy. This probably explains the higher CRC detection rate in colonoscopies performed within 60 days after FIT result in our study, as in the study of Brenner et al .[6] Using the 2 to 3 months class as a reference makes our results comparable with studies which excluded early colonoscopies (within 7 to 30 days, depending on the study).[6–8 12] The decrease in risk of CRC and AA in participants with colonoscopy later than 9 and 12 months as compared to those with colonoscopy at 3 months suggests that colonoscopies motivated by symptoms may still be frequent in the 3 months group. However, no inflection point in the association between delay and risk of CRC or AA was found later, and the aOR remained stable with increasing delay, suggesting that the selection of reference class would have little impact (cf online supplemental figure 1S).

Other methodological flaws in previous studies should also be considered. None of the other studies, except two,[8 22] included f-Hb, the strongest predictor of advanced neoplasia,[30 31] in the variables analysed. Contrary to the current recommendations, Tis carcinomas were considered CRCs in most (four of six) studies[6–8 22] so that the definition of CRC was a mix of CRC and AA. Including Tis carcinomas as CRCs has artificially increased the incidence of CRCs in these studies. In any case, adopting this definition did not change our results (online supplemental table 6S). Corley *et al* included only the villous component of adenomas in their definition of AA, but not size ≥10 mm nor high-grade dysplasia, the most important criteria in defining AA, and did not exclude incomplete (2.3%) colonoscopies or those with poor bowel preparation (8%).[7] Furthermore, the San Miguel study was a mix of gFOBT and FITs, the proportion of which was not specified.[12]

Our study has several strengths. To our knowledge, this is the largest and the second nationwide study on the subject,[8] carried out in an organised CRC screening programme, with proportion of first round of screening in line with previous studies.[6–8 10–12 22] Our study is the only one to consider several sociogeographical variables in multivariate analysis and to analyse the association of time to colonoscopy by location. Our study, with two other studies, is the only one to have included f-Hb in the variables analysed.[8 22] As previously demonstrated, the prevalence of advanced neoplasia was higher in participants with high f-Hb.[8 22] Although advanced neoplasia risk was not associated with time to colonoscopy, regardless of f-Hb, the higher prevalence of advanced neoplasia in participants with high f-Hb could justify prioritising these colonoscopies. The performance of French endoscopists exceeds acceptable standards for most indicators, including post-colonoscopy CRC rates (2.4% at 3 years).[32 33] Finally, we conducted sensitivity analyses to test the robustness of our results.

Our study has several limitations. Owing to the retrospective design, it was impossible to avoid unidentified confounding factors and missing data. As with all other studies, information on the possible presence of high-risk symptoms at the time of colonoscopy was lacking. Further, our study suffers from the same biases as previous studies, but ours are much smaller: (1) our 86.6% colonoscopy compliance rate is the highest of all published studies and the only one that meets European

recommendations (85% acceptable, >90% desirable)[5] since the 91.7% rate reported by Kaalby *et al* included colonoscopies performed as late as 4 years after the positive FIT-result, questioning the link between the FIT result and the reason for performing the colonoscopy.[6–8 10–12 22] (2) Our 20.8% rate of unknown CRC stages is the lowest of all published studies (21.0% to 35.2%).[10 11] (3) CIs of CRC risk increase with delay due to the low proportion of participants undergoing late colonoscopy; however, our study has the largest number of participants who underwent colonoscopy 6 months after a positive FIT result. (4) As in all previous studies, except one, information is lacking on the CRC outcomes in participants not complying with colonoscopy. Lee *et al* demonstrated that the relative risk of CRC was significantly lower in those participants than in those who did (relative risk (RR)=0.82 (0.77–0.86)) and significantly higher for the risk of advanced-stage CRC (RR=1.66 (1.49–1.85)).[8] (5) Our FIT positivity threshold was 30 µg/g, slightly higher than the 15[6] or 20 µg/g[7 8 10 11 22] in the other studies so that our neoplasia yield was slightly higher. However, this difference cannot explain the absence of influence of time to colonoscopy in our study. (6) Some might question the generalisability of our results, given that the French programme is unique in involving GPs in the first phase of screening invitations. Their role is to verify the eligibility of individuals (excluding those at high CRC risk and those with symptoms), encourage eligible individuals to undergo screening, inform them of the benefits and risks of screening and refer participants to a gastroenterologist after a positive test result. Another French peculiarity is that the f-Hb is notified to the GP. However, this has no impact on the time to colonoscopy after a positive FIT result, since there is no French recommendation specifying a threshold for urgent colonoscopy, unlike in the UK.[34]

Our study clearly does not provide a definitive answer to the question posed, but it undermines the current consensus based on previous studies. A definitive answer will be provided by a study of adequate size, with a colonoscopy compliance rate in line with recommendations (>85%), information on the eventual presence of high-risk symptoms at the time of colonoscopies, a follow-up of participants not complying with colonoscopy through cancer registries and the consideration of f-Hb.

Conclusion

Contrary to previous studies that suggested an increased CRC risk occurs when the time to colonoscopy after a positive FIT result exceeded 3–13 months, our nationwide cohort study, the largest ever performed, has found no increased risk of CRC, advanced-stage CRC and AA with time to colonoscopy up to 24 months. This is obviously not a reason to recommend waiting 2 years before performing a colonoscopy. For us, performing the colonoscopy within 1–3 months after the positive FIT result is too stringent a time target. Based on our results, we suggest that the priority in all CRC screening programmes is not to focus on the time to follow-up colonoscopy, but to ensure that every participant with a positive FIT result complies with colonoscopy. To this end, the use of participant- and/or provider-directed reminders or participant navigators has been shown to be effective. With regard to the optimal timeframe for colonoscopy, the higher the f-Hb, the greater the risk of advanced colorectal neoplasia and the shorter the time to colonoscopy should be. Moreover, the organisation of a fast-track approach dedicated to FIT-positive participants would be recommended to shorten the stressful period of waiting for the colonoscopy verdict.

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Contributors AG: conceptualisation, methodology, formal analysis, writing. BD: conceptualisation, methodology, writing. JP: data management, formal analysis. SVS: investigation, conceptualisation. MQ: investigation, conceptualisation. CQ: conceptualisation, methodology, supervision. LG: conceptualisation, methodology, supervision, writing. AG is the guarantor of this contributorship statement.

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Competing interests AG: board membership (Mercks) and travel reimbursement (Bayer, Roche, Servier). BD, JP, SVS, MQ, CQ and LG: no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was carried out using anonymous data extracted from a database set up by the French National Public Health Agency as part of its health monitoring mission. Under French law, the re-use of anonymous data does not require the approval of an ethics committee. Under French law, the approval of an ethics committee is required. For research involving the human person, a study based solely on the re-use of pre-existing data cannot be qualified as research involving the human person, as no act is performed on a human person (cf. L. 1121-1 and R1121-1 code de la santé publique). For certain processing of personal data relating to health, when carried out as part of research, studies or evaluations in the field of health and which do not involve human beings (cf. article 76, 2° loi n°78-17), the processing of anonymous data are therefore excluded from this obligation.

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Data availability statement Data are available upon reasonable request. Individual participant data will be shared upon reasonable request, and only after approval by the French Public Health Agency.

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