



12 year study of the prevalence, risk factors and characteristics of Interval colorectal cancers after negative colonoscopy performed for a positive gFOBT in a screening programme in Isère (France) from 2002 - 2013

Paul Jennings

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UNIVERSITE GRENOBLE ALPES

FACULTE DE MEDECINE DE GRENOBLE

Année : 2017

N°

**12 year study of the prevalence, risk factors and characteristics of Interval colorectal
cancers after negative colonoscopy performed for a positive gFOBT in a screening
programme in Isère (France) from 2002 - 2013**

THESE

PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE

DIPLÔME DE L'ETAT

Paul JENNINGS

[Données à caractère personnel]

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12 year study of the prevalence, risk factors and characteristics of Interval colorectal cancers after negative colonoscopy performed for a positive gFOBT in a screening programme in Isère (France) from 2002 - 2013

P Jennings, A Seigneurin, C Exbrayat

Abstract

Introduction:

The objective of our study was to describe and analyse the PCCRCs (Post-Colonoscopy Colorectal Cancers) and endoscopist performance-related risk factors in our regional screening programme.

Method:

This was a population-based retrospective cohort study from 2002-2013. PCCRC was defined as colorectal adenocarcinoma diagnosed between six and sixty months post colonoscopy. We analysed the endoscopist performance-related PCCRC risk factors of the 62 gastroenterologists who had carried out at least 30 colonoscopies during this period.

Results

During this period there were 10,557 negative colonoscopies performed. 15 PCCRCs were diagnosed from 2002-2013 with an average age of 67.1, men comprised 73% of the cases, 53% of the PCCRCs were in the distal colon. PCCRCs comprised 1.1% (0.7% - 1.8%) of all Colorectal Cancers (CRCs) diagnosed in the screening programme, with an incidence rate of 0.41 (0.21 - 0.71) per 1000 person years.

The breakdown of PCCRC aetiology was as follows: 41% related to missed cancers, 29% new cancers, 24% failed biopsy detection, and 6% incomplete removal.

Gastroenterologists' ADRs (adenoma detection rate) were an average of 30% but large heterogeneity was present, ranging from 11% to 49%.

An inverse linear trend was noted between ADR and the number of PCCRCs per gastroenterologist, which was not statistically significant.

Conclusion

The PCCRC prevalence and incident rate were low relative to the literature. However significant ADR heterogeneity was present. Decreasing this heterogeneity by establishing a national benchmark ADR, regular performance feedback and training modules should homogenise ADRs and decrease the number of interval cancers in the region.

Key Words: Colorectal Cancer; Population Screening Programme, Interval cancer, Guaiac Faecal Occult Blood Test; Colonoscopy; Diagnosis

Résumé

Introduction

L'objectif de cette étude est de décrire les caractéristiques des PCCRCs (cancer d'intervalle post coloscopie) et les facteurs de risques liés aux performances de l'endoscopiste.

Méthode

L'étude a porté sur les coloscopies faites après un test de dépistage positif entre 2002 et 2013 dans le département de l'Isère. Les PCCRCs étaient définis comme des adénocarcinomes diagnostiqués entre six et soixante mois après coloscopie. Les facteurs de risque liés à la performance de l'endoscopiste ont été analysés parmi les 62 gastroentérologues ayant réalisé au moins 30 coloscopies.

Résultat

10 557 coloscopies négatives ont été réalisées. 15 PCCRCs ont été diagnostiqués entre 2002-2013, l'âge moyen était 67,1 ans, 73% ont touché les hommes, 53% étaient localisés dans le colon distal.

1.1% (0.7%, 1.8%) des cancers diagnostiqués en dépistage étaient des PCCRCs avec un taux d'incidence de 0.41 (0.21, 0.71) pour 1 000 personnes-années.

L'étiologie des PCCRC était: 41% cancers ratés, 29% nouveaux cancers, 24% échecs de détection à la biopsie et 6% prélèvement incomplet.

Les TDAs (taux de détection des adénomes) étaient hétérogènes et variaient de 11% à 49% (moy : 30 %). On observait une tendance linéaire inverse entre des TDA et le nombre de PCCRs qui n'était pas statistiquement significative.

Conclusion

La prévalence des PCCRCs et le taux d'incidence étaient bas par rapport à la littérature. Une forte hétérogénéité était présente. Une homogénéisation des TDAs par l'établissement d'un seuil national de

TDA, l'information des praticiens sur leurs résultats et des formations, devraient homogénéiser les TDAs et diminuer le nombre de cancer d'intervalle dans la région.

Mots clés : Cancer colorectal; Programme de Dépistage, cancer d'intervalle, Test Hemocult, Coloscopie; Diagnostique

Résumé Détaillé

Introduction

Le cancer colorectal est le troisième cancer le plus souvent diagnostiqué chez les hommes et le deuxième chez les femmes, avec 1.4 million de nouveaux cas et 693 000 décès en 2012 dans le monde.

En France, le dépistage du cancer colorectal est basé sur un test de recherche de saignement occulte dans les selles et une coloscopie est réalisée en présence d'un test positif. La coloscopie n'a pas une sensibilité de 100% et le taux d'incidence de cancer d'intervalle post coloscopie (PCCRC) varie entre 0,22 et 2,2 cas pour 1 000 personnes-années et un sur 27 cancers colorectaux étant diagnostiqué entre 6 et 36 mois après une coloscopie.

Les objectifs de cette étude sont :

- De décrire les caractéristiques des PCCRCs.
- De calculer l'incidence de PCCRC en Isère, et de la comparer à l'incidence des autres régions.
- De classer les PCCRCs par étiologie (prélèvement incomplet, échec de détection par biopsie, cancer raté, nouveau cancer)
- D'étudier les facteurs de risques de PCCRC liés à l'endoscopiste.

Méthodes

L'étude a porté sur les coloscopies faites après un test de dépistage positif entre 2002 et 2013 dans le département de l'Isère. Les PCCRCs étaient définis comme des adénocarcinomes diagnostiqués entre six et soixante mois après coloscopie. Le croisement des participants au programme départemental de dépistage des cancers colorectaux entre 1^{er} janvier 2002 et 31 décembre 2013 avec la base de données du Registre du cancer de l'Isère a permis d'identifier les PCCRCs et de comparer leurs caractéristiques avec : les cancers d'intervalle post hemocult (CI gFOBT), les cancers dépistés (SC) et les cancers hors dépistage (NPC) pour cette période.

117 gastroentérologues ont réalisé 10557 coloscopies négatives. Les facteurs de risque liés à l'endoscopiste ont été analysés parmi les 62 gastroentérologues ayant réalisé au moins 30 coloscopies pendant la période.

Résultats

Au total, 10 557 coloscopies négatives ont été réalisées. La répartition des cancers colorectaux au cours de cette période était la suivante : 6 249 NPC (cancer hors dépistage), 620 SC (cancer dépisté), 15 PCCRC, 711 CI gFOBT. Parmi les PCCRCs l'âge moyen était 67,1 ans, 73% ont touché les hommes, 53% étaient localisés dans le colon distal.

1.1% (IC 95% 0.7% à 1.8%) de tous les cancers diagnostiqués dans le programme de dépistage étaient des PCCRCs avec un taux d'incidence de 0.41 (IC 95% 0.21 à 0.71) pour 1 000 personnes-années. Il y avait 1.8 (IC 95% 1.0-3.2) PCCRCs pour 1 000 coloscopies.

L'étiologie des PCCRCs était la suivante : 41% cancers ratés, 29% nouveaux cancers, 24% échecs de détection à la biopsie et 6% prélèvement incomplet.

Les TDAs (taux de détection des adénomes) étaient très hétérogènes et variaient de 11% à 49% (moy : 30 %). On observait une diminution des TDAs quand le nombre de PCCRCs augmentait mais cette tendance n'était pas statistiquement significative.

Discussion et Conclusion

La prévalence des PCCRC (1,1 %) et le taux d'incidence (0,41 pour 1 000 personnes-années) sont très bas contre respectivement : 1.8% à 9% et 0.2 à .2.2 cas pour 1 000 personnes-années dans la littérature. Ce résultat semble indiquer un bon niveau de qualité des endoscopies réalisées dans notre département. La comparaison reste cependant difficile compte tenu de l'hétérogénéité des études publiées.

Comparativement à la littérature, les PCCRCs du département de l'Isère étaient plus jeunes, touchaient majoritairement des hommes et présentaient une distribution égale des lésions entre proximal et distal. Les méta-analyses ont montré que les patients âgés sont plus touchés par les PCCRCs, sans différence entre les sexes, et avec une fréquence 2,4 fois supérieure des cancers proximaux.

L'augmentation du risque de PCCRC avec une diminution des TDAs a été montrée dans la littérature, le TDA étant un indicateur de qualité reconnu des coloscopies. Le faible effectif des cancers d'intervalle post coloscopie n'a pas permis de retrouver de tendance significative dans notre département. L'établissement d'un seuil de TDA dans les recommandations du programme de dépistage français et l'information des praticiens sur leurs résultats devrait permettre d'homogénéiser les TDAs et diminuer ainsi le nombre de cancers d'intervalle. Des formations pourraient être organisées et proposées aux gastroentérologues ayant des résultats inférieurs au seuil déterminé. Une étude plus large incluant d'autres départements avec des Registres de cancer pourrait permettre de consolider ces résultats dans le programme français de dépistage des cancers colorectaux.

Mots clés : Cancer colorectal; Programme de Dépistage, cancer d'intervalle, Test Hémocult, Coloscopie; Diagnostique

Introduction:

Background/Rationale:

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in males and the second in females with an estimated 1.4 million new cases and 693,000 deaths occurring in 2012¹.

In 2012, in France; Colorectal Cancer was the fourth most commonly diagnosed cancer behind, Prostate, Breast and Lung. In 2012 40,825 new cases were diagnosed, and 17,148 people died as a result of colorectal cancer in France².

Colonoscopy is widely used as part of colorectal cancer screening³⁻⁵. Colonoscopy can be used directly as a first line screening tool, or second line, after a positive gFOBT (guaiac positive faecal occult blood test) or FIT (faecal immunochemical test). Colonoscopy is not however an infallible test with incidence of post-colonoscopy colorectal cancer (PCCRC) ranging from 0.2/1000 person-years⁶ to 2.2 cases / 1000 person years⁷ and 1 in 27 colorectal cancers being diagnosed between 6 and 36 months of colonoscopy⁸.

Following an endoscopist working group, an interval cancer was defined as “a colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam”⁹.

For the purposes of our research we focused solely on Interval Colorectal Cancer after Colonoscopy performed following a positive Guaiac Faecal Occult Blood Test (gFOBT) in the Isère regional screening programme from 2002 – 2013.

Significant research has been done on Interval Colorectal Cancer. Several recent studies have estimated the risk of PCCRCs. There is a wide range of heterogeneity relating to study setting, study design, patient characteristics, age, comorbidities, and definition of PCCRC, with most being performed outside of a screening context (see appendix 2). Those performed in a screening context either used colonoscopy as a primary screening tool or else used FIT as opposed to gFOBT as the

primary screening tool. In the Isère region, the sensitivity of gFOBT has already been studied¹⁰. To date however; there has been no study that has examined the risk of PCCRC following a positive gFOBT in a colorectal cancer screening programme.

Describing the characteristics of the PCCRCs in the region, would enable us to identify certain particularities that may pertain to the region, and how the screening programme could be modified in the future to better handle such particularities.

To better understand how we could decrease the risk of PCCRCs in the future in our screening programme, we analysed the characteristics of each of the 17 cases and divided them up by aetiology.

Finally we investigated endoscopist related PCCRC risk factors with particular attention paid to adenoma detection rate, and what modifications could be made to minimise these risks.

Objectives

The objectives of our study were:

- Calculate the risk of PCCRC in the Isère region, and to compare it to the levels of risk of PCCRC in other regions.
- Describe and compare the characteristics of the PCCRCs to all the colorectal cancers in the region
- Define the PCCRC by type (Incomplete Removal, Failed Biopsy Detection, Missed Cancer, New Cancer) according to the algorithm proposed by Pabby et al ⁷,
- Investigate Endoscopist performance-related risk factors relating to these PCCRCs

Methods:

Study Design:

This is a population-based retrospective cohort study.

Screening Procedures

The Colorectal cancer screening programme exists in the Isère region since 2002. The screening programme was based on a biennial Guaiac Faecal Occult Blood Test (gFOBT), targeting men and women from age 50 to 74, with a colonoscopy for positive gFOBT cases. Since 2015 the gFOBT has been replaced by a Faecal Immunochemical Test (FIT).

Data Collection:

1. Data relating to the PCCRC was obtained from the Office de Lutte contre le Cancer (ODLC) screening programme database. Data relating to all the colorectal cancers in the Isère region was obtained from the InVS Régistre des cancers de l'Isère.

Inclusion Criteria

- All subjects between the ages of 50-74 living in the Isère department who had a colonoscopy between the dates of 1st January 2002 to 31st December 2013 following a positive Guaiac Faecal Occult Blood Test screening test.

Exclusion Criterion

- All colonoscopies outside the period of 1st January 2002 to 31st December 2013 following a positive Guaiac Faecal Occult Blood Test .
- All colonoscopies which found an invasive colorectal cancer.

2. Three different time periods were used in our analysis 2002-2013, 2002-2014 and 2002-2009. Data from the Isère Cancer Registry identifying all cancers diagnosed in the region was only available up to 2013. Data relating to all endoscopists pertained to colonoscopies performed from 2002-2013. Meanwhile using the data from the ODLC we were able to identify all PCCRCs diagnosed up to 2014.

Therefore in analysing the performance of the endoscopists or comparing our results with results from the Isère Cancer Registry we used data up to 2013 (15 PCCRCs).

When analysing the characteristics of the PCCRCs in isolation we used the 2002-2014 data (17 PCCRCs). We used the 2002-2009 period when calculating the incidence rate and the number of PCCRCs per colonoscopy, to allow possible PCCRCs to be diagnosed up until 2014)

3. The results of all the patients that underwent colonoscopy after a positive gFOBT are communicated to the ODLC by general practitioners, patients and the gastroenterologists that carry out the colonoscopies in the screening programme in the region. By cross-referencing this information with the Isère Cancer Registry we were able to identify all persons who were diagnosed with an invasive colorectal cancer (In-situ cancers and anal cancers were not included) diagnosed between 6 months and 60 months after their colonoscopy, who could potentially be defined as having a PCCRC. Colorectal cancers diagnosed between 0 and 6 months post-colonoscopy are considered as screened cancers.

4. The list of potential PCCRCs is compared where possible with data from the relevant healthcare providers in order to collate as much information as possible. This enabled us to: 1) identify that the cases were indeed confirmed PCCRCs (by analysing; circumstances of the diagnosis of the CRC, Colonoscopy report, Surgical Operation Report, Pathology report, Location, Stage pTNM of the CRC and Index Colonoscopy Report following the positive Guaiac Faecal Occult Blood Test test.) and 2) identify the PCCRC by type (Incomplete Removal, Failed Biopsy Detection, Missed Cancer, New Cancer) according to the algorithm proposed by Pabby et al ⁷ Incomplete colonoscopies were classified as Missed Lesions.

5. The adenoma detection rate (ADR) and all other data relating to each gastroenterologist are recorded and calculated by the ODLIC. The ADR is based on all colonoscopies performed as a result of a positive gFOBT in the period from 2002-2013 by a given gastroenterologist. The ADR is defined as the proportion of screening colonoscopies that detect at least one adenoma. All colonoscopies where the gastroenterologist had performed less than thirty colonoscopies for gFOBT positive patients during the study period were excluded for the purpose of ADR analysis. They were however included for the purposes of the calculation of the incidence rate of PCCRC.

To analyse the ADR between 2002-2007 and 2008-2013, we again included only those gastroenterologists who had performed > 30 in the period.

Variables of Interest:

Patient: Sex, Age.

Colonoscopy: time interval between positive gFOBT and index Colonoscopy, the number of previous gFOBT performed, result of their index colonoscopy (type of lesion, location of lesion, caecal intubation achieved), result of diagnostic colonoscopy (date of colonoscopy, location of lesion, staging of lesion, size of lesion)

Gastroenterologist: number of colonoscopies performed in the context of the screening programme in the study period, ADR, bowel preparations and caecum intubation rate.

PCCRC / Screened Cancers / Non-Screened Cancers: Location of the cancer: recto sigmoid, descending colon, transverse colon, ascending colon and caecum/appendix.

Statistical analysis

The incidence rate was calculated as:

$$\frac{\sum_{2002-2009} \text{all study participants PCCRC}}{\min\left(\frac{\text{period of time between initial colonoscopy and PCCRC} - 0.5}{\text{or}}\right)}$$

$$\sum_{2002-2009} \text{all study participants} \min(\text{period from initial colonoscopy and 31 Dec 2003 ; 5 years}) - 0.)$$

The initial six months were subtracted and people were observed up to a maximum of 4.5 years, (as patients were only at risk of PCCRC after the first six months following their initial colonoscopy until five years later). We included all patients who had their index colonoscopy up to the end of 2009, and correspondingly all PCCRCs diagnosed until the end of 2014.

A Kaplan Meier survival analysis was used to analyse the time post colonoscopy until diagnosis of the PCCRC.

A poisson regression model was utilised to analyse the relationship between a gastroenterologist's number of PCCRCs (independent variable), and their ADR, controlling for the number of colonoscopies they had performed. We examined other possible confounding factors variables including percentage of satisfactory bowel preparations and caecum intubation rate.

All analyses were conducted using STATA data analysis and statistical software (Stata Corp. LP, College Station, TX, USA).

Results:

The 10,557 negative colonoscopies from January 2002 to December 2013, came from a cohort of 590,912 gFOBT tests carried out by participants between the ages of 50-74 who underwent a gFOBT as part of the Isère regional screening programme. Participation rates varied over time, from 23% in 2002 to 45% in 2009. 12,281 (2.1%) positive gFOBT were recorded, which led to 11,177 (90.5%) colonoscopies being performed. 620 participants who underwent colonoscopy were diagnosed with a cancer (Screening Cancer). The 10,557 negative colonoscopies (findings: normal, hyperplastic polyp,

adenoma or carcinoma in situ), were followed for an interval of five years (up to a maximum of 31st December 2013). During this follow up period 15 PCCRCs arose from this group.

Amongst the 578,631 negative gFOBT tests that were recorded, 711 interval cancers were diagnosed in the following two years (IC gFOBT).

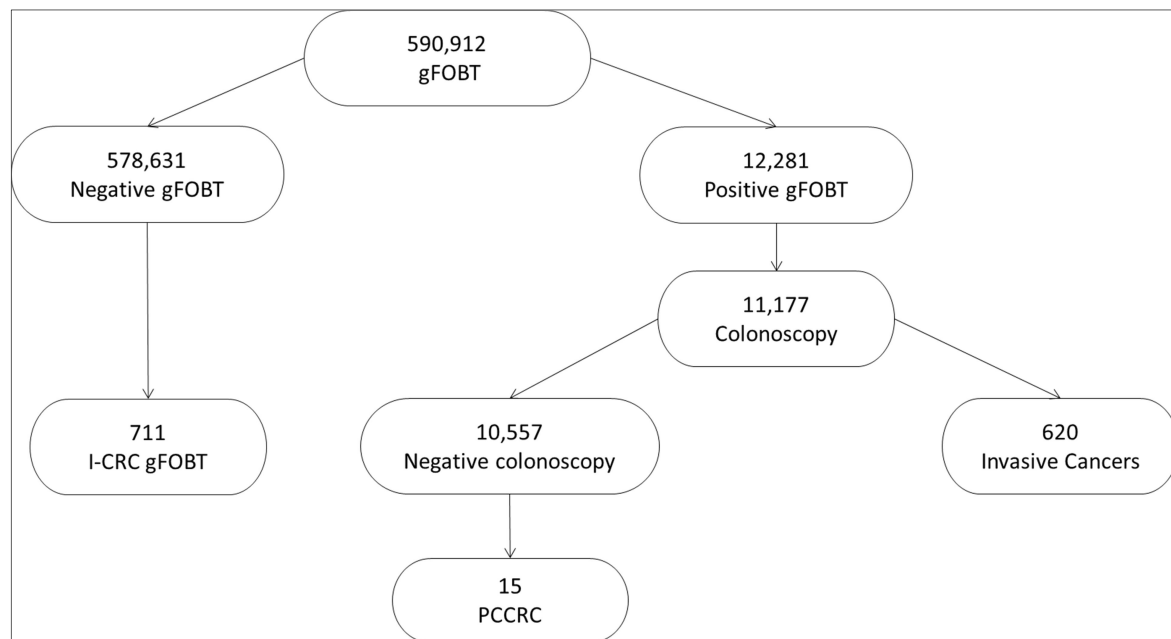


Figure 1: Flowchart of study participants 2002-2013

The risk of PCCRC in the Isère region

During the study period 2002-2013, in the Isère Colorectal Cancer screening programme, 1,346 CRCs were identified. PCCRC accounted for 1.1 % (15/1346) of newly diagnosed CRCs.

Amongst the 2002-2013 period 10,557 negative colonoscopies were performed, 6,143 of these colonoscopies were performed between 2002-2009, 11 PCCRCs emerged up to 2014, which equates to 1.8 interval cancers for every 1000 colonoscopies (95% Confidence Interval (Wilson) : 1.0-3.2 interval cancers for every 1000 colonoscopies).

From the 2002 to 2009 cohort of patients, 11 PCCRCs were diagnosed during 26,983 person-years of follow-up, which amounts to an incidence rate of 0.41 cases per 1,000 person-years (95% Confidence Interval 0.21 to 0.71 per 1,000 person years).

Characteristics of the Colorectal Cancers in the region 2002-2013

	NPC		SC		IC gFOBT		PCCRC	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
50-54	737	11.8%	48	7.7%	50	7.0%	0	0.0%
55-59	447	7.2%	83	13.4%	100	14.1%	1	6.7%
60-64	523	8.4%	136	21.9%	151	21.2%	5	33.3%
65-69	602	9.6%	159	25.6%	160	22.5%	4	26.7%
70-74	3,940*	63.1%	194	31.3%	250	35.2%	5	33.3%
Total	6,249	100%	620	100%	711	100%	15	100%

Table 1: Distribution of type of colorectal cancer by age category from 1 January 2002 to 31 December 2013

*>70 years old

Our study showed patients diagnosed with PCCRCs to be older (average age = 67.1) than those with Screened CRCs (average age = 65.2), however younger than those who did not participate in the screening programme (NPC) (average age 72.0). The age of those diagnosed with PCCRCs had a larger standard deviation (1.5 years).

	Male		Female		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
NPC	3,433	54.9	2,816	45.1	6,249	100
SC	421	67.9	199	32.1	620	100
IC gFOBT	386	54.3	325	45.7	711	100
PCCRC	11	73.3	4	26.7	15	100
Total	4,251		3,344		7,595	

Table 2: Comparison of Gender distribution by PCCRC and all other Colorectal Cancers in the Isère region from 2002-2013.

All the patient populations showed a predominance of male patients. PCCRCs had the highest male proportion of 73.3%.

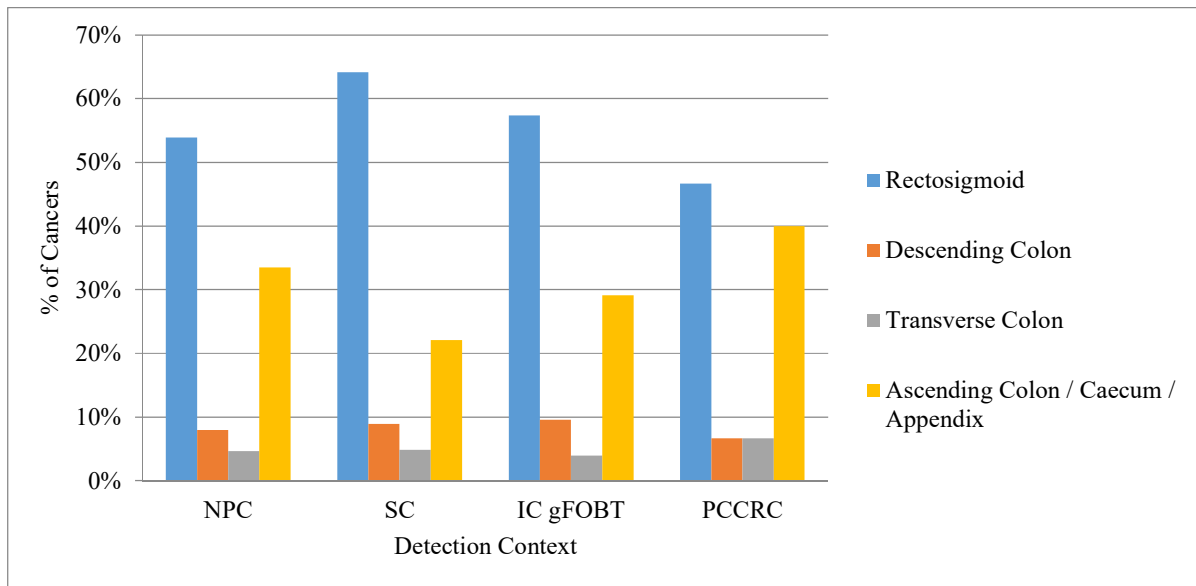


Figure 2: Cancer location by type of Colorectal Cancer diagnosed in the Isère region from 1 January 2002 to 31 December 2013

Colorectal cancers were categorised as proximal (caecum/appendix, right colon and transverse colon) and distal (left colon, sigmoid colon and rectum)⁸.

All the groups of cancers showed a predominance of distal versus proximal location. PCCRCs had an almost equal distal / proximal distribution (53% / 47%), the SCs had the most extreme distal / proximal distribution (73% / 27%).

Specific PCCRC case analysis

To better understand how we could decrease the risk of PCCRCs in the future in our screening programme, we analysed the characteristics of each of the 17 PCCRCs diagnosed between 2002 and 2014 and divided them up by aetiology.

PCCRCs have been categorized as (i) those arising because of missed lesions, either owing to inadequate examination (poor bowel preparation, incomplete colonoscopy) or because of incomplete visualisation (or failure to recognize a polyp despite visualisation of bowel segment), (ii) arising from incomplete resection of a recognized dysplastic polyp, (iii) arising de novo, as new, rapidly forming cancers, and (iv) arising as a result of failure of biopsy to identify a lesion as a CRC⁸. By dividing them by aetiology, special attention could be paid to the procedural factors (missed or incompletely resected lesions) as these are potentially avoidable¹¹.

Below are the key pieces of information of each of the PCCRCs, along with the type of PCCRC according to the Pabby algorithm (see appendix. A). Commentary for each case is included below.

Table 3 describes the characteristics of these 17 PCCRCs. Preparation was “good” in 64.7% 11/17 of colonoscopies, “sufficient” in 29.4% (5/17), and unknown in one case. The caecum was intubated in all but two cases. In these two cases CT colonography was performed in one instance and in the other, a barium enema confirmed an indication for a sigmoidectomy due to a “fixed macro diverticulosis”, which was performed.

Hyperplastic polyps were found in 4/17 (23.5%) index colonoscopies, 4/17 (23.5%) found no lesion, and 9/17 (52.9%) colonoscopies found adenomas. Out of the 9 adenomas 6/9 (66.6%) were in the same location as the PCCRC, 2/9 (22.2%) were in a different location, and 1/9 (11.1%) was unknown.

Table 3: Characteristics of the 17 PCCRCs diagnosed in the Isère Screening Programme, 2002-2014

Colo; No.	Age	Sex	Prep	Colo Comp leted	Further Exam	Result Further Exam	Interval Betw Colos (years)	Index Colo Finding	Location Adenoma	Location PCCRC	PCCRC Stage	Size* (cm)	Probable aetiology
1	79	M	Good	Yes	-	-	4.8	Hyperplastic Polyp	-	Caecum / Appendix	I	?	New Cancer
2	74	F	Suffic ient	No	CT Scan	Normal	1.3	No Lesion	-	Sigmoid	Ila	4	Missed Cancer
3	74	F	Good	Yes	Control 3 years	-	3.0	Adenoma	Right Colon	Left Colon	IIlc	?	Missed Cancer
4	72	M	Suffic ient	Yes	-	-	1.9	No Lesion	-	Caecum / Appendix	IIlb	?	Missed Cancer
5	71	M	Suffic ient	Yes	Control 1 mth	-	2.4	Adenoma	Rectum, Sigmoid, Right Colon	Rectum	?	?	Failed Biopsy Detection
6	68	F	Good	Yes	-	-	2.2	Hyperplastic Polyp	-	Right Colon	Ila	0.6	New Cancer
7	68	M	Good	Yes	-	-	2.04	No Lesion	-	Transverse Colon	IIlb	2.5	Missed Cancer
8	64	M	Good	Yes	Control 2 mths	-	0.8	Adenoma	Sigmoid	Sigmoid	I	?	Failed Biopsy Detection
9	66	M	Good	Yes	-	-	2.6	Adenoma	Sigmoid	Sigmoid	?	3	Failed Biopsy Detection
10	65	M	Good	No	Barium Enema	Fixed Macro Diverticulo sis and Sigmoid Polyp.	1.0	Adenoma	Sigmoid	Left Colon(anas tomosis site)	?	3	Missed Cancer

Colo; No.	Age	Sex	Prep	Colo Comp leted	Further Exam	Result Further Exam	Interval Betw Colos (years)	Index Colo Finding	Location Adenoma	Location PCCRC	PCCRC Stage	Size* (cm)	Probable aetiology
11	64	F	?	?	-	-	1.5	Adenoma	Sigmoid	Sigmoid	I	3.3	Failed Biopsy Detection
12	61	M	Good	Yes	-	-	0.8	Hyperplastic Polyp	-	Right Colon	IV	-	Missed Cancer
13	64	M	Suffic ient	Yes	-	-	4.2	Adenoma	Sigmoid	Rectum	I	1.8	New Cancer
14	61	M	Suffic ient	Yes	-	-	2.2	No Lesion	-	Sigmoid	IIIb	3	Missed Cancer
15	63	F	Good	Yes	-	-	4.7	Hyperplastic Polyp	-	Caecum / Appendix	IIIb	1.2	New Cancer
16	62	M	Good	Yes	Control in 3 years	-	4.8	Adenoma	?	Rectum	Ila	3.5	New Cancer
17	59	M	Good	Yes	Control in 3mths	-	2.8	Adenoma	Right, Transverse, Left, Sigmoid	Right Colon	I	4	Incomplete Resection

**Age at diagnosis of PCCRC*

Table 4: Summary of Colonoscopy findings and cancer characteristics of the 17 PCCRCs diagnosed in Isère Screening Programme from 2002-2014

Colo No.	Colonoscopy findings and cancer characteristics
1	Index colonoscopy found a hyperplastic polyp in rectum. 4.8 years later stage I cancer found in Caecum Appendix
2	Colonoscopy performed, difficult to visualise sigmoid due to insufficient bowel preparation, CT scan performed which was normal. Hospitalised 1.33 years later for occlusive syndrome, stage IIa sigmoid tumour found.
3	Index colonoscopy found advanced polyp in right colon. Colonoscopy repeated 3 years later, stage IIc cancer of left colon.
4	Index colonoscopy was normal, 1.8 years later stage IIb cancer found in caecum.
5	Index colonoscopy found an advanced polyp in right colon and rectum, Colonoscopy 1 month later: sigmoid adenoma (not fully resected as difficult position) and Carcinoma in-situ of rectum, resected with clear margins. Rectal Cancer (Lieberkuhnian adenocarcinoma) diagnosed July 2010
6	Index Colonoscopy: 2 hyperplastic polyps. 2.2 years later: 6mm, Stage IIa cancer found in right colon
7	Index colonoscopy normal. 2.0 years later 2.5cm stage IIb tumour found in transverse colon
8	Index colonoscopy : adenoma in the sigmoid removed with diathermy , NOT clear margins, colonoscopy repeated 2 months later showed the remnant of the sigmoid sessile polyp which was resected with clear margins. Colonoscopy 7.5 months later: stage I sigmoid adenocarcinoma (Thermal Artefact?)
9	Index colonoscopy found sigmoid adenoma, resected with clear margins. 2.6 years later, a neuroendocrine tumour of the sigmoid.
10	Index colonoscopy not completed due to fixed macro diverticulosis and voluminous sigmoid polyp. Barium enema confirmed this, therefore surgical indication for sigmoidectomy, which was performed and found a carcinoma in-situ. 6 weeks later a control colonoscopy was performed which was normal. 9 months later another colonoscopy was performed which found a 3cm adenocarcinoma at the anastomosis site.
11	Index colonoscopy found a carcinoma in situ in the sigmoid, resected via colonoscopy 3 weeks later with clear margins. 1.5 years later a control colonoscopy found a Lieberkuhnian adenocarcinoma in the sigmoid
12	Index colonoscopy found 3 hyperplastic polyps of the sigmoid colon. During a routine work-up for an abdominal eventration, 0.8 years later a voluminous lieberkuhnian adenocarcinoma of right colon complicated with peritoneal carcinomatosis and metastatic lung lesions were found.

13	Index colonoscopy found an adenoma in the sigmoid. 4.2 years later colonoscopy finds a rectal adenocarcinoma, stage I
14	Index colonoscopy normal. 2.2 years later, colonoscopy finds sigmoid adenocarcinoma, 3cm and stage IIIb
15	Index colonoscopy found hyperplastic polyp in caecum. 4.2 years later in a work-up for GI motility disorder, a Stage IIIb caecal adenocarcinoma is found.
16	Index colonoscopy: 10 polyps in transverse and sigmoid colon, 9 of which were hyperplastic, one showed severe dysplasia (location not mentioned), resected with clear margins. 4.8 years later, during a work-up for an anal fistula a rectal adenocarcinoma was found. Stage IIa, 3.5cm.
17	Index colonoscopy: 12 polyps removed, 1 sessile polyp in the right colon 4mm resected by cold excision, right transverse colon: 3 sessile polyps 5-6mm each resected by hot excision, left colon: 3 sessile polyps 8-10mm polypectomy, Sigmoid: 3 polyps resected by polypectomy. Pathology found low grade dysplasia in the 2 lesions in the right colon (i.e. the pathology report interpreted one of the transverse polyps as a right colon polyp, does not mention clear margins), 1 transverse left, 1 left and 3 sigmoid. Control 3mths later never performed. 2.8 years later in the work-up for an Iron deficiency Anaemia: Lieberkuhnian adenocarcinoma of the right colon, stage I, 4cm.

The aetiology of the 17 PCCRCs in our study were as follows: 7 (41%) missed cancers, 5 (29%) new cancers, 4 (24%) failed biopsy detection, 1 (6%) incomplete removal.

In theory 47% (incomplete removal and missed cancer) of our PCCRCs could have been avoided.

Time to PCCRC diagnosis post index colonoscopy

The time to diagnosis of PCCRC was as follows. (By definition there were no PCCRCs in the first 6 months).

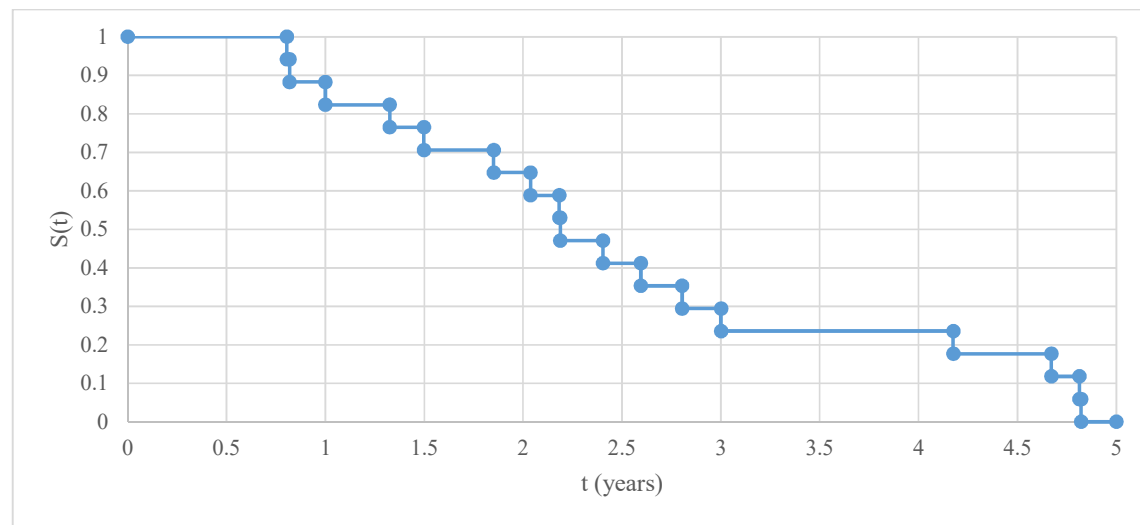


Figure 3. Kaplan Meier curve; Time to Interval Colorectal Cancer diagnosis following negative colonoscopy from 2002-2014.

It was seen that after the first six months the time from Index Colonoscopy to PCCRC diagnosis follows a relatively uniform distribution. The average interval between index colonoscopy and diagnosis of PCCRC was 2.5 years.

Endoscopist performance related PCCRC Risk factors.

Finally we investigated endoscopist performance-related PCCRC risk factors. We paid particular attention to the adenoma detection rate ADR (a metric defined as the proportion of colonoscopy examinations that detects ≥ 1 adenomas¹²).

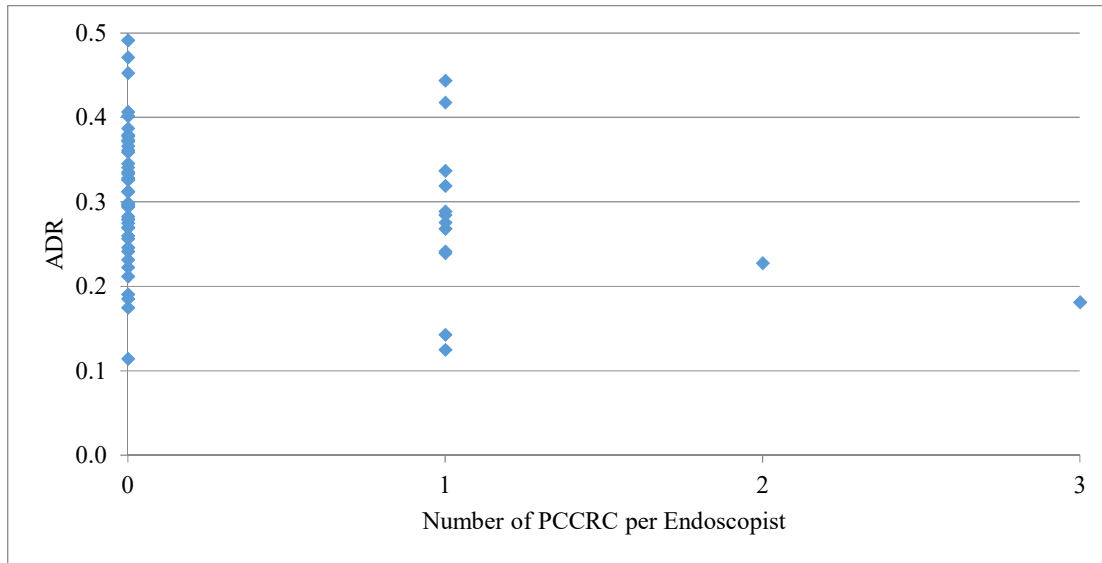


Figure 4: Relationship of ADR to Number of PCCRCs per endoscopist diagnosed between 2002-2014

There was an average ADR of 30.1% for our entire group of endoscopists. For the endoscopists who had performed the index colonoscopy for zero PCCRCs there was an average ADR of 31.0%, for the endoscopists who had performed the index colonoscopy for one PCCRC there was an average ADR of 28.2%, the endoscopist who had performed the index colonoscopy for two PCCRCs had an ADR of 22.8%, and the endoscopist who had performed the index colonoscopy for three PCCRCs had an ADR of 18.1%.

A large degree of variability was noted in the ADRs, ranging from 11% to 49% with a standard deviation of 8.2%.

A poisson regression model was used to analyse the relationship between the number of PCCRCs per gastroenterologist (dependent variable), and ADR (independent variable). ADR was found to be statistically significant ($p=0.03$). However when the model was adjusted to take into account the number of colonoscopies per gastroenterologist, ADR was no longer statistically significant explanatory variable ($p=0.109$).

We compared the ADR of endoscopists from the period 2002-2007 to 2008-2013. The average ADRs were 29.1% compared to 31.4%, with no statistical difference between the periods.

Caecal intubation rate was a very satisfactory 96.4%.

Discussion:

Risk of PCCRC

PCCRC had a prevalence of 1.1%, an incident rate of 0.41 cases per 1,000 person-years and a rate of

It is difficult to compare these results with other studies due to the wide range of heterogeneity relating to patient characteristics, age, comorbidities, study setting, study design, definition of PCCRC (see appendix 2). Our study has a prevalence and incidence rate that are low relative to other studies. Other studies had prevalence rates ranging from 1.8% - 9% and an incidence rate ranging from 0.2-2.2 per 1000 person years. Amongst all the literature it had the lowest prevalence rate and the second lowest incidence rate, however the study with the lowest incident rate was in a study carried out by Kaminski et al⁶ where the participants were aged between 40-66 and colonoscopy was used as a primary screening tool, both of these factors would significantly lower the incidence rate.

The lower level of risk may be attributable to the fact that all our colonoscopies are carried out by gastroenterologists. Colonoscopies performed by gastroenterologists are more effective at colorectal cancer prevention¹³, and thereby decrease the number of PCCRCs.

Secondly participants in our study had a maximum age of 75, whereas in many other studies patients of all ages were included. The annual transition rate from adenoma to carcinoma may not be constant over a lifetime, may increase with age and be as high as 5% per year in men over the age of 70¹⁴.

Finally, the fact that our population relates to a screening population that had an uptake rate of between 23-45% may bias our results. People who agree to participate in a screening programme may be more health conscious and therefore in better health, with less comorbidities than those who had a colonoscopy performed for symptomatic reasons. Green et al¹⁵ showed that non-participants in Colorectal Cancer Screening programs had behaviours that can negatively affect cancer outcomes (less

continuity of care with one physician, fewer preventive visits, less use of recommended screening tests, and were current or past smokers.)

Characteristics of the PCCRC Colorectal Cancers in the region

Age

Our study showed patients diagnosed with PCCRCs to be older (average age = 67.1) than those with screened CRCs (average age = 65.2), however younger than those who did not participate in the screening programme (average age 72.0). Our patients tended to be younger than those in the literature, Singh et al showed that older patients (>65-70) had a higher risk of PCCRCs than younger individuals (<65-70), adjusted OR = 1.15. As referenced above, the annual transition rate from adenoma to carcinoma may not be constant over a lifetime, may increase with age and be as high as 5% per year in men over the age of 70¹⁴.

The reason the patients who developed a PCCRC in our study were younger than the literature is most likely due to the maximum age limit of 75 in our screening programme.

Our patients' ages had a large standard deviation (1.5 years) relating to the small number of cases.

Gender

Our study found that out of the 17 PCCRCs, 12 of them were male. Meta-analysis has not shown a clear relationship between gender and PCCRCs, however some individual studies found a higher prevalence of PCCRCs in females as compared with males¹⁶⁻¹⁹. This is thought to be due to the female colon being longer and more redundant, leading to more discomfort, longer insertion times and lower completion rates²⁰. The gender distribution in our study may be due to the small number of cases.

Location

A meta-analysis carried out by Singh et al⁸ showed that PCCRCs were 2.4 times more likely to be proximal than distal (which equates to 70.6% of lesions being proximal with 29.4% being distal). All 12 studies included in his meta-analysis, had more proximal than distal lesions.

The site of PCCRC in our population shows an almost equal distribution between distal (53%) and proximal (47%). Our result is therefore quite unusual.

The hypotheses for the greater frequency of proximal versus distal PCCRCs are as follows: failure of endoscopists to intubate the cecum, even when they believe they have reached the cecum, or the likelihood that inadequate bowel preparations affect the right side more than the rest of the colon²¹. Furthermore, there are differences in gene expression and molecular characteristics between right-sided and left-sided CRCs²² with microsatellite instability and CpG island methylator phenotypes being more common in right-sided tumours^{23,24}. These characteristics have been linked with more rapid carcinogenesis²⁵. Moreover, depressed adenomatous lesions, which are more difficult to detect endoscopically, may occur more often in the right side of the colon,^{26,27} and these lesions may be more likely to rapidly progress to adenocarcinoma²⁸.

Possible explanations for the difference in distribution of lesions in our study include the following: Research has shown that colonoscopies performed by gastroenterologists are more effective at colorectal cancer prevention¹³. As only gastroenterologists perform colonoscopies, there should be a decreased risk of “failure of endoscopists to intubate the cecum, even when they believe they have reached the cecum”. This greater proficiency theory was supported by the fewer number of “missed cases” in our study compared to other studies.

The difference in distribution may also just be a statistical anomaly due to the small number of PCCRCs in our study.

Definition of PCCRC by type

The aetiology of PCCRC in our study was divided up as follows: Missed Cancer 7 (41%), New Cancer 5 (29%), Failed Biopsy Detection 4 (24%), and Incomplete Removal 1 (6%).

We compared our results with the results of Robertson et al²⁹ and Le Clerq¹¹.

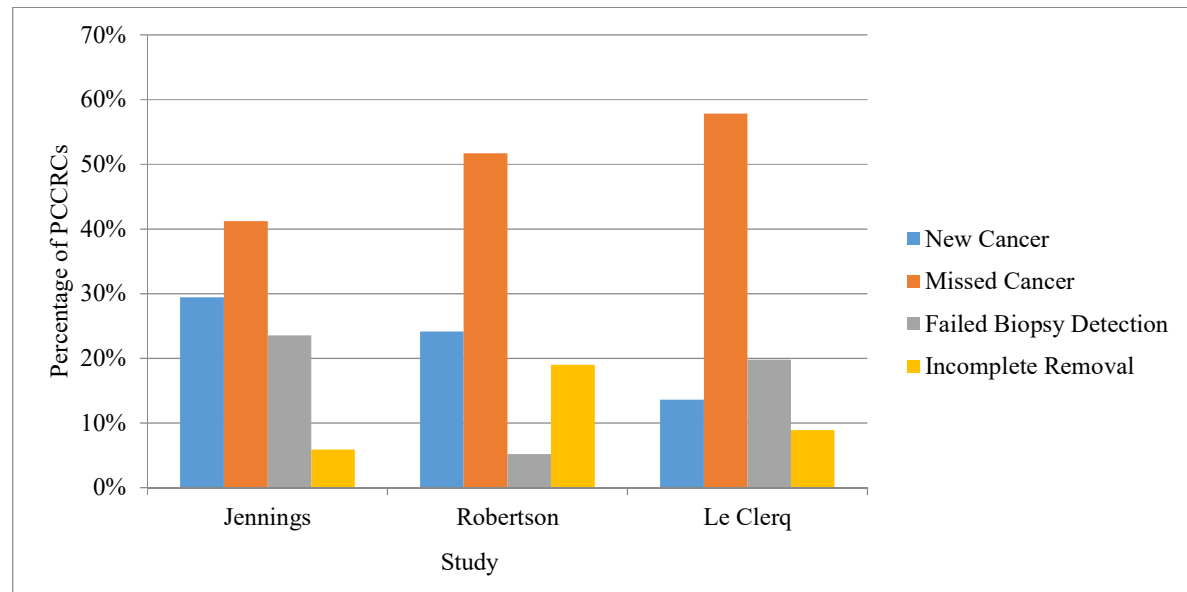


Figure 5: Comparison of aetiology of PCCRCs by study.

Our study contained proportionally more New Cancers and Failed Biopsy Detections and less Missed Cancers and Incomplete Removals than other studies.

As previously mentioned only gastroenterologists performed the colonoscopies in our study, their great proficiency¹³ may result in a decreased percentage of missed cancers and incomplete removals.

Endoscopist performance related PCCRC Risk factors.

Endoscopists also have an important role to play in avoiding PCCRCs. There are many different endoscopist performance related factors which affect the risk of PCCRCs. Certain factors were not relevant for our study e.g. non-gastroenterologists being more likely than gastroenterologists to have carried out the index colonoscopy⁸. In our region all the colonoscopies are carried out by gastroenterologists. Particular attention was paid to the ADR.

Heterogeneity in ADR is particularly important given that it is associated inversely with the risk of

interval colorectal cancer⁶ and colorectal cancer deaths³⁰. ADR is therefore a key quality indicator and has been identified as a target for intervention in terms of quality control^{31–33}. Kaminski et al⁶ in a screening programme setting demonstrated that endoscopists with an ADR <20% significantly increased the risk of PCCRC as compared with those with ADR>20%. Corley et al³⁰ in a study of all colonoscopies in patients aged > 50, showed that the risk of advanced stage PCCRC and fatal PCCRC were reduced by 57% and 62% respectively, with ADRs >33% compared with ADRs < 19%. Although not statistically significant, our data showed a similar trend that as ADR decreased the number of PCCRCs increased.

There was an average ADR of 30% for our entire group of endoscopists. Our data did however come from a screening population who had a positive gFOBT, which would be at greater risk of adenomas than a general population. Participants presenting for colonoscopy following a positive guiac-based FOBT have a 35% risk of detection of adenoma and a nearly 11 % risk of cancer³⁴. This compares with a 15%–25% risk of detection of benign adenoma by ad hoc case finding^{3,4,35}. In the UK NHS bowel cancer screening programme the benchmark ADR rate is 35%.

Within the Isere region; significant levels of heterogeneity within the ADRs were noted. To reduce this heterogeneity and thereby reduce the number of PCCRCs a benchmark ADR rate should be included in the French Colorectal Cancer Screening Guidelines and gastroenterologists should be informed of their current ADR. Kaminski et al³³ showed that performance feedback improved ADR by 1.8%. Training programs could be offered to those who have ADRs below the benchmark level. Studies have shown that ADR can be improved by further training^{31,33} and these improvements in ADR are associated with a reduced risk of interval colorectal cancer and death³⁶. Kaminski et al³³ demonstrated that training programmes had a greater effect on ADR than performance feedback, with an absolute improvement of 3.9% (OR 1.25) over performance feedback alone.

Caecal intubation rate was a very satisfactory 96.4%. Current US guidelines recommend a caecal intubation rate of 95% for routine screening exams³⁷, whereas EU guidelines³⁸ do not differentiate between screening and non-screening colonoscopies and recommend a caecal intubation rate of 90%.

Out of the 62 gastroenterologists who had performed > 30 colonoscopies, 87.5% of all the colonoscopies had a preparation level that ranged from sufficient to good. Amongst our cases of PCCRC, 94.1% (16/17) had between good to sufficient bowel preparation, with one case unknown. Inadequate colonic cleansing has been shown in the literature to account for a significant proportion of missed lesions and often results in longer, more difficult, and incomplete exams^{39,40}.

Limitations and Strengths of our Study

Limitations:

We did not have access to information regarding certain variables which would have enabled a more complete description of the PCCRCs in the region, such as family history of colorectal cancer, presence of diverticular disease, comorbidities, smoker status, and molecular phenotype of PCCRC.

Our results may slightly underestimate the incidence of PCCRCs in Isère due to people either entering or leaving the region. It was not possible to identify PCCRCs amongst the patient population who had positive gFOBT followed by negative colonoscopies but who then left the region. Neither was it possible to identify PCCRCs in the patient population who moved to the region following a positive gFOBT as these people were not included in our database either. It was not possible to address these two sources of bias, but we assume the effect to be quite small. Out of all the regions in France, Isère has one of the smallest levels of migration among this age bracket, ranked 15th lowest out of the 96 French regions with a net migration rate of -0.90 per 1000 people per annum⁴¹.

Another source of bias in our study is that we were unable to definitively identify all PCCRCs for patients who had positive gFOBT near the end of the study period of 31 December 2013, as we were unable to follow the patients for the required 5 years. We identified all the PCCRCs which occurred up to and including the 31 December 2014.

Strengths:

We had complete, exhaustive data on all cancers over a lengthy study period due to the input of data from the Régistre Du Cancer de l' Isere. Interval cancers were able to be identified by cross-referencing all the data from the ODLC with data from the Régistre Du Cancer de l' Isere.

We had extensive data on the endoscopists and their corresponding quality indicators.

(*) THESE SOUTENUE PAR : Mr Paul JENNINGS

(*) TITRE : 12 year study of the prevalence, risk factors and characteristics of Interval colorectal cancers after negative colonoscopy performed for a positive gFOBT in a screening program in Isère (France) from 2002 - 2013

Conclusion:

A very low PCCRC (post colonoscopy colorectal cancer) prevalence rate (1.1% of all cancers diagnosed amongst people who participated in the screening programme) and incidence rate (0.41 per 1000 person years) were found compared with those in the literature (1.8% - 9% and 0.2-2.2 per 1000 person years respectively). This result indicates that overall the gastroenterologists who carry out the colonoscopies do so, to a very high level. Comparison with the literature is however difficult due to the heterogeneity of the articles.

When compared with the literature, the cases of PCCRCs in our study were younger, with a majority of males and an equal distribution between proximal and distal lesions. Meta-analyses showed that PCCRCs generally affected older patients, with no difference by gender and proximal lesions being 2.4 times more frequent than distal ones.

The inverse relationship between PCCRC frequency and ADR (adenoma detection rate) has been shown repeatedly in the literature, with ADR being recognised as the main benchmark with regard to quality of colonoscopy. The same inverse linear tendency between ADR and PCCRC frequency was present in our data, although not statistically significant.

Despite the fact that we had a very low prevalence of PCCRCs in the region, there remains a lot of heterogeneity with regard to ADRs. To reduce this heterogeneity and thereby reduce the number of PCCRCs, a benchmark ADR rate should be included in the French Colorectal Cancer Screening Guidelines and gastroenterologists should be informed of their current ADR. Training programs could be offered to those who have ADRs below the benchmark level.

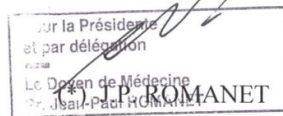
In the future it would be interesting to increase the study period and the number of regions studied to enable us to study a greater number of interval cancers and thereby perform a more in-depth statistical analysis.

It would also be interesting also to repeat this research in the future to examine the effect the new FIT (faecal immunochemistry test) test has had on PCCRC rates.

(*) VU ET PERMIS D'IMPRIMER

(*) Grenoble, le 26/10/2017

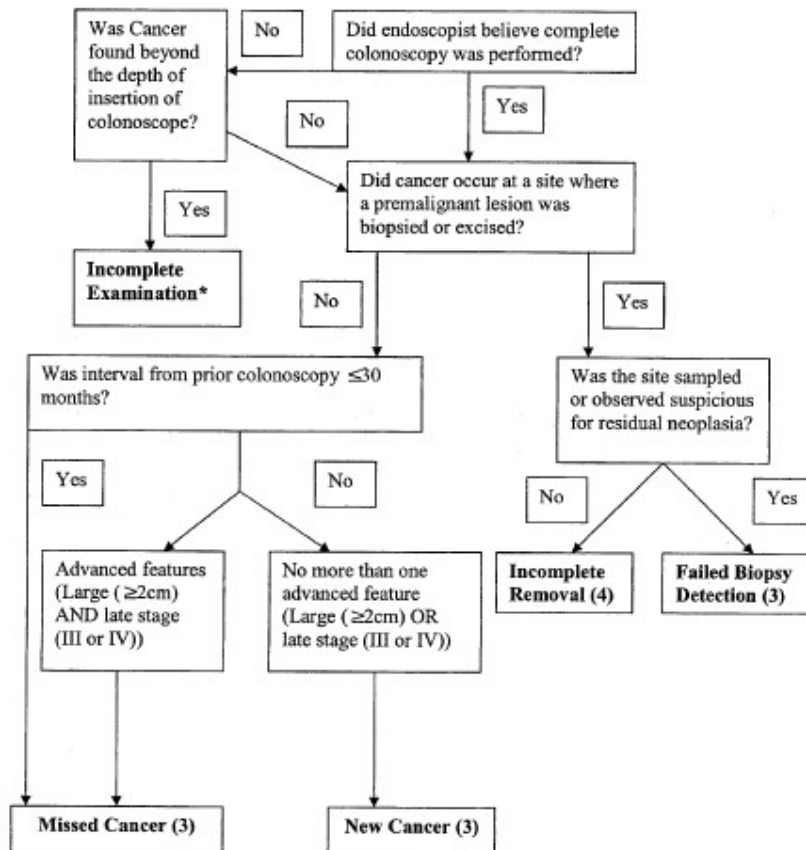
(*) LE DOYEN



(*) LE PRESIDENT DE LA THESE

PROFESSEUR Patrice FRANCOIS

Appendix 1 : Pabby Algorithm⁷



Appendix 2 : Description of other PCCRC articles

Study	Country	Time Period	Design	Population	Definition of I-CRC	PCCRC Prevalence
Brenner¹⁷	Germany	2003 – 2007	Prospective case – control,	Case : Patients first diagnosis of primary invasive colorectal cancer aged 30 or older whose cancer was NOT detected by screening Control : Community based control subjects randomly selected from population registers, employing frequency matching with respect to age, sex, and county of residence	Colonoscopy within 1 – 36 months of CRC diagnosis	1.8 %
Bressler¹⁸	Canada	1997 – 2002	Retrospective cohort; administrative database with record linkage	All patients (>20 years of age) in Canadian Institute for Health Information, the Ontario Health Insurance Program, and Ontario Cancer Registry databases with a new diagnosis of CRC.	Colonoscopy within 6 – 36 months of CRC diagnosis	3.4%
Cooper⁴²	United States	1994 – 2005	Retrospective cohort; administrative database with record linkage	Medicare-eligible patients aged > 68 years old diagnosed with CRC and reside in 1 of the geographic areas contained in the SEER registries	Colonoscopy within 6 – 36 months of CRC diagnosis	7.2 %
Erichsen¹⁹	Denmark	2000 – 2009	Retrospective cohort; population-based with record linkage	patients of all ages who were diagnosed with colorectal cancer from Danish Medical Registry	Colonoscopy within 12 – 60 months of CRC diagnosis	2.8%
Haseman⁴³	United States	1988 – 1993	Retrospective cohort; hospital based	Patients of all ages diagnosed with colorectal cancer in 20 central Indiana hospitals over a 5-year period	Colonoscopy within 1 – 36 months of CRC diagnosis	2.9%
Le Clerq¹¹	The Netherlands	2001 – 2010	Retrospective cohort; population-based with record linkage	Patients of all ages diagnosed with CRC in South-Limburg	Colonoscopy within 12 – 60 months of CRC diagnosis	2.9%
Nishihara⁴⁴	United States	1988 – 2010	Prospective cohort; self-report with medical record	2 sources: Nurses' Health Study : U.S. female nurses, 30 to 55 years of age at enrollment in 1976. Health Professionals Follow-up Study : U.S. male health professionals, 40 to 75 years of age at enrolment in	CRC diagnosed 1 – 60 months after colonoscopy (sensitivity analysis, 1 – 36 months)	7.1%

Study	Country	Time Period	Design	Population	Definition of I-CRC	PCCRC Prevalence
Samadder¹⁶	United States	1995 – 2009	review Retrospective cohort; population-based with record linkage	1986.. Utah residents of all ages who underwent colonoscopy examinations from 1995-2009	Colonoscopy within 6 – 36 months of CRC diagnosis	3.4%
Singh⁴⁵	Canada	1992 – 2008	Retrospective cohort; population-based with record linkage	Patients 50 – 80 years of age diagnosed with CRC between 1992 and 2008 from the province wide Manitoba Cancer Registry	Colonoscopy within 6 – 36 months of CRC diagnosis	7.9%
Baxter⁴⁶	Canada	2000-2005	Retrospective cohort; population-based with record linkage	All Individuals diagnosed with colorectal cancer in Ontario from 2000 to 2005 using the Ontario Cancer Registry.	Colonoscopy within 7 – 36 months of CRC diagnosis	9.0%
Arain⁴⁷	United States	1989-2004	Retrospective cohort; population-based with record linkage	All patients with a diagnosis of cancer at the Minneapolis Veterans Affairs Medical Center, excluding those with inflammatory bowel disease or familial adenomatous polyposis	Colonoscopy <60 months before CRC diagnosis	4.8%
Corley⁴⁸	United States	1998-2010	Prospective cohort with record linkage with medical record review	Patients >50 years of age undergone a colonoscopy between January 1, 1998, and December 31, 2010;	Colonoscopy within 6 – 120 months of CRC diagnosis	8.2%
Kaminski⁶	Poland	2000-2004	Prospective cohort with record linkage with medical record review	Large colonoscopy-based screening program, Patients aged eligible if they were 50 to 66 years of age and in good general health and colorectal cancer was not suspected; people 40 to 49 years of age were also eligible if they had a family history of cancer of any type	CRC diagnosed between the screening colonoscopy and the scheduled time of surveillance colonoscopy	Incidence Rate : 22.4 per 100,000 person years
Richter⁴⁹	United States	1998-2006	Retrospective Cohort	All individuals who had a colonoscopy at Massachusetts General Hospital. Individuals older than the age of 18, no history of inflammatory bowel disease	Colorectal carcinoma diagnosed less than five years after the index colonoscopy	3.1%
Portillo⁵⁰	Spain	2009-2015	Retrospective	Basque CRC screening programme : Patients 50-69	CRC detected prior to the	7.5%

Study	Country	Time Period	Design	Population	Definition of I-CRC	PCCRC Prevalence
			Cohort with record linkage	following a positive biennial FIT test.	scheduled follow-up: which varied between 1 year and 10 year depending on the findings of the index colonoscopy.*	

**Follow-up periods : 10 years with an invitation for a FIT in the case of a normal result/non-neoplastic polyps; 5 years with an invitation for a FIT in the case of a Low-Risk Adenoma (1-2 tubular adenomas and/or ≤ 10 mm and/or without high grade dysplasia); a colonoscopy after 3 years in the case of an Intermediate Risk Adenoma (3-4 adenomas and/or ≥ 10 mm and < 20 mm and/or a villous component and/or a high grade dysplasia; colonoscopy in < 1 year in the case of a detected High-Risk Adenoma (≥ 5 adenomas and/or ≥ 20 mm).*

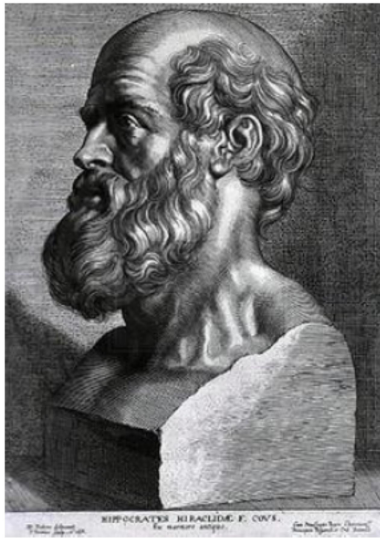
Bibliography

1. Torre, L. A. *et al.* Global cancer statistics, 2012: Global Cancer Statistics, 2012. *CA. Cancer J. Clin.* **65**, 87–108 (2015).
2. Ferlay, J. *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet].
3. Lieberman, D. A. *et al.* Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N. Engl. J. Med.* **343**, 162–168 (2000).
4. Schoenfeld, P. *et al.* Colonoscopic screening of average-risk women for colorectal neoplasia. *N. Engl. J. Med.* **352**, 2061–2068 (2005).
5. Zauber, A. G. *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N. Engl. J. Med.* **366**, 687–696 (2012).
6. Kaminski, M. F. *et al.* Quality indicators for colonoscopy and the risk of interval cancer. *N. Engl. J. Med.* **362**, 1795–1803 (2010).
7. Pabby, A. *et al.* Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. *Gastrointest. Endosc.* **61**, 385–391 (2005).
8. Singh, S., Singh, P. P., Murad, M. H., Singh, H. & Samadder, N. J. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. *Am. J. Gastroenterol.* **109**, 1375–1389 (2014).
9. Sanduleanu, S. *et al.* Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. *Gut* **64**, 1257–1267 (2015).
10. Gai, J. *et al.* Sensitivity of a colorectal cancer screening program based on a guaiac test: A population-based study. *Clin. Res. Hepatol. Gastroenterol.* **38**, 106–111 (2014).
11. le Clercq, C. M. C. *et al.* Postcolonoscopy colorectal cancers are preventable: a population-based study. *Gut* **63**, 957–963 (2014).
12. van Rijn, J. C. *et al.* Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am. J. Gastroenterol.* **101**, 343–350 (2006).

13. Baxter, N. N., Warren, J. L., Barrett, M. J., Stukel, T. A. & Doria-Rose, V. P. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **30**, 2664–2669 (2012).
14. Brenner, H., Altenhofen, L., Stock, C. & Hoffmeister, M. Natural History of Colorectal Adenomas: Birth Cohort Analysis Among 3.6 Million Participants of Screening Colonoscopy. *Cancer Epidemiol. Biomarkers Prev.* **22**, 1043–1051 (2013).
15. Green, B. B. *et al.* Nonparticipation in a Population-Based Trial to Increase Colorectal Cancer Screening. *Am. J. Prev. Med.* **42**, 390–397 (2012).
16. Samadder, N. J. *et al.* Characteristics of Missed or Interval Colorectal Cancer and Patient Survival: A Population-Based Study. *Gastroenterology* **146**, 950–960 (2014).
17. Brenner, H., Chang-Claude, J., Seiler, C. M. & Hoffmeister, M. Interval cancers after negative colonoscopy: population-based case-control study. *Gut* **61**, 1576–1582 (2012).
18. Bressler, B. *et al.* Rates of New or Missed Colorectal Cancers After Colonoscopy and Their Risk Factors: A Population-Based Analysis. *Gastroenterology* **132**, 96–102 (2007).
19. Erichsen, R. *et al.* Characteristics and Survival of Interval and Sporadic Colorectal Cancer Patients: A Nationwide Population-Based Cohort Study. *Am. J. Gastroenterol.* **108**, 1332–1340 (2013).
20. Chutkan, R. Colonoscopy Issues Related to Women. *Gastrointest. Endosc. Clin. N. Am.* **16**, 153–163 (2006).
21. Singh, H., Turner, D., Xue, L., Targownik, L. E. & Bernstein, C. N. Risk of Developing Colorectal Cancer Following a Negative Colonoscopy Examination: Evidence for a 10-Year Interval Between Colonoscopies. *JAMA* **295**, 2366 (2006).
22. Birkenkamp-Demtroder, K. Differential gene expression in colon cancer of the caecum versus the sigmoid and rectosigmoid. *Gut* **54**, 374–384 (2005).
23. Iacopetta, B. Are there two sides to colorectal cancer? *Int. J. Cancer* **101**, 403–408 (2002).
24. Chirieac, L. R., Shen, L., Catalano, P. J., Issa, J.-P. & Hamilton, S. R. Phenotype of microsatellite-stable colorectal carcinomas with CpG island methylation. *Am. J. Surg. Pathol.* **29**, 429–436 (2005).

25. Huang, C. S., Farraye, F. A., Yang, S. & O'Brien, M. J. The clinical significance of serrated polyps. *Am. J. Gastroenterol.* **106**, 229–240; quiz 241 (2011).
26. Konishi, K. *et al.* Clinicopathological differences between colonic and rectal carcinomas: are they based on the same mechanism of carcinogenesis? *Gut* **45**, 818–821 (1999).
27. Okamoto, M. *et al.* Flat-type early colorectal cancer preferentially develops in right-sided colon in older patients. *Dis. Colon Rectum* **48**, 101–107 (2005).
28. Soetikno, R., Friedland, S., Kaltenbach, T., Chayama, K. & Tanaka, S. Nonpolypoid (Flat and Depressed) Colorectal Neoplasms. *Gastroenterology* **130**, 566–576 (2006).
29. Robertson, D. J. *et al.* Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut* **63**, 949–956 (2014).
30. Corley, D. A. *et al.* Adenoma Detection Rate and Risk of Colorectal Cancer and Death. *N. Engl. J. Med.* **370**, 1298–1306 (2014).
31. Coe, S. G., Crook, J. E., Diehl, N. N. & Wallace, M. B. An endoscopic quality improvement program improves detection of colorectal adenomas. *Am. J. Gastroenterol.* **108**, 219–226; quiz 227 (2013).
32. Brenner, H. *et al.* Trends in Adenoma Detection Rates During the First 10 Years of the German Screening Colonoscopy Program. *Gastroenterology* **149**, 356–366.e1 (2015).
33. Kaminski, M. F. *et al.* Leadership training to improve adenoma detection rate in screening colonoscopy: a randomised trial. *Gut* **65**, 616–624 (2016).
34. UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. *BMJ* **329**, 133 (2004).
35. Regula, J. *et al.* Colonoscopy in Colorectal-Cancer Screening for Detection of Advanced Neoplasia. *N. Engl. J. Med.* **355**, 1863–1872 (2006).
36. Kaminski, M. F. *et al.* Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. *Gastroenterology* **153**, 98–105 (2017).
37. Rex, D. K. *et al.* Quality indicators for colonoscopy. *Gastrointest. Endosc.* **81**, 31–53 (2015).
38. Rembacken, B. *et al.* Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy* **44**, 957–968 (2012).

39. Froehlich, F., Wietlisbach, V., Gonvers, J.-J., Burnand, B. & Vader, J.-P. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest. Endosc.* **61**, 378–384 (2005).
40. Lebwohl, B. *et al.* The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest. Endosc.* **73**, 1207–1214 (2011).
41. Baccaini, B. & Levy, D. Recensement de la population de 2006 : Les migrations entre départements : le Sud et l'Ouest toujours très attractifs. *Insee Prem.* **1248**, (2009).
42. Cooper, G. S., Xu, F., Barnholtz Sloan, J. S., Schluchter, M. D. & Koroukian, S. M. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer* **118**, 3044–3052 (2012).
43. Haseman, J. H., Lemmel, G. T., Rahmani, E. Y. & Rex, D. K. Failure of colonoscopy to detect colorectal cancer: evaluation of 47 cases in 20 hospitals. *Gastrointest. Endosc.* **45**, 451–455 (1997).
44. Nishihara, R. *et al.* Long-Term Colorectal-Cancer Incidence and Mortality after Lower Endoscopy. *N. Engl. J. Med.* **369**, 1095–1105 (2013).
45. Singh, H., Nugent, Z., Demers, A. A. & Bernstein, C. N. Rate and Predictors of Early/Missed Colorectal Cancers After Colonoscopy in Manitoba: A Population-Based Study. *Am. J. Gastroenterol.* **105**, 2588–2596 (2010).
46. Baxter, N. N. *et al.* Analysis of Administrative Data Finds Endoscopist Quality Measures Associated With Postcolonoscopy Colorectal Cancer. *Gastroenterology* **140**, 65–72 (2011).
47. Arain, M. A. *et al.* CIMP Status of Interval Colon Cancers: Another Piece to the Puzzle. *Am. J. Gastroenterol.* **105**, 1189–1195 (2010).
48. Corley, D. A., Levin, T. R. & Doubeni, C. A. Adenoma detection rate and risk of colorectal cancer and death. *N. Engl. J. Med.* **370**, 2541 (2014).
49. Richter, J. M., Campbell, E. J. & Chung, D. C. Interval Colorectal Cancer After Colonoscopy. *Clin. Colorectal Cancer* **14**, 46–51 (2015).
50. Portillo, I. *et al.* Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). *World J. Gastroenterol.* **23**, 2731 (2017).



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.