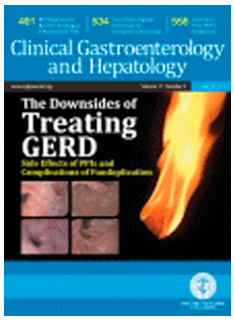
High Risk of Anal and Rectal Cancer in Patients With Anal and/or Perianal Crohn's Disease

Laurent Beaugerie, Fabrice Carrat, Stéphane Nahon, Jean-David Zeitoun, Jean-Marc Sabaté, Laurent Peyrin-Biroulet, Jean-Frédéric Colombel, Matthieu Allez, Jean-François Fléjou, Julien Kirchgesner, et al.

Accepted Manuscript



High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease

Laurent Beaugerie, Fabrice Carrat, Stéphane Nahon, Jean-David Zeitoun, Jean-Marc Sabate, Laurent Peyrin-Biroulet, Jean-Frédéric Colombel, Matthieu Allez, Jean-François Fléjou, Julien Kirchgesner, Magali Svrcek

PII: S1542-3565(17)31414-3
DOI: 10.1016/j.cgh.2017.11.041
Reference: YJCGH 55575

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 21 November 2017

Please cite this article as: Beaugerie L, Carrat F, Nahon S, Zeitoun J-D, Sabate J-M, Peyrin-Biroulet L, Colombel J-F, Allez M, Fléjou J-F, Kirchgesner J, Svrcek M, for the CESAME Study Group, High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease, *Clinical Gastroenterology and Hepatology* (2017), doi: 10.1016/j.cgh.2017.11.041.

High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease

Short title: Anorectal cancers in anal and/or perianal Crohn's disease

Laurent Beaugerie (1), Fabrice Carrat (2), Stéphane Nahon (3), Jean-David Zeitoun (1,4)), Jean-Marc Sabate (5), Laurent Peyrin-Biroulet (6), Jean-Frédéric Colombel (7), Matthieu Allez (8), Jean-François Fléjou (9), Julien Kirchgesner (1) and Magali Svrcek (9), for the CESAME Study Group.

(1) Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine F-75012 and GRC-UPMC 03, UPMC Univ Paris 06 F-75005, Paris, France

(2) Department of Public Health, Hôpital Saint-Antoine, Assistance Publique, Hôpitaux de Paris, and Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), Paris, France

(3) Department of Gastroenterology, Groupe Hospitalier Intercommunal Le Raincy-Montfermeil, Montfermeil, France

(4) Department of Surgical Proctology, Croix Saint-Simon Hospital, Paris, France

(5) Department of Gastroenterology, APHP, Hôpital Avicenne and Sorbonne Paris Cité, Univ Paris Diderot, Paris, France

(6) Inserm U954 and Department of Hepato-Gastroenterology, University Hospital of Nancy, Lorraine University, Vandoeuvre-lès-Nancy, France

(7) The Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, USA

(8) APHP, Hôpital Saint Louis, Department of Gastroenterology, INSERM UMRS 1160, Paris Diderot, Sorbonne Paris-Cité University, Paris, France

(9) Department of Pathology, AP-HP, Hôpital Saint-Antoine F-75012; UPMC Univ Paris 06 F-75005, Paris, France

The list of the CESAME Study Group appears in the Supplementary Material

Funding: The CESAME project was supported by grants from Programme Hospitalier de Recherche Clinique National (AOM05157), Association François Aupetit, Délégation Inter-régionale de la Recherche clinique Ile de France-AP-HP, Ligue contre le Cancer, and Fonds de Recherche de la Société Nationale Française de Gastro-entérologie.

Abbreviations used in this paper:

CD, Crohn's disease ;

CESAME, Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France;

HPV, Human Papilloma Virus

IBD, Inflammatory Bowel Disease

IRR, Incidence Rate Ratio

SCC, Squamous-Cell Carcinoma

SD, Standard Deviation

Corresponding author: Prof. Laurent Beaugerie, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris CEDEX 12, France. Tel: +33 1 49 28 31 71, Fax: +33 1 49 28 31 88

E-mail: laurent.beaugerie@sat.aphp.fr

Disclosures: The authors disclose the following**:**

Laurent Beaugerie has received consulting fees from Janssen, Pfizer and Allergan, lecture fees from Abbvie, Janssen, MSD, Ferring Pharmaceuticals, Mayoly-Spendler, Takeda, and research support from Abbott, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD and Takeda. Stéphane Nahon has received consulting fees from Abbvie, MSD, Hospira-Pfizer and lecture fees from Abbvie, MSD, Takeda, Pfizer, Ferring Pharmaceuticals and Mayoli. Jean-David Zeitoun reports being an advisor for several consulting firms in link with pharmaceutical industry (Cepton, Oliver Wyman, Roland Berger, McCann Healthcare, Omnicom, Grey Healthcare, Saatchi and Saatchi Healthcare, Sudler& Hennessey, TBWA, Havas, Nextep). He also reports speaking fees from a manufacturers' professional association, consulting fees from Mayoly-Spindler, Ferring, Merck, Teva, Pierre Fabre, Johnson & Johnson, and Menarini, consultancy for EY, and being invited to a French medical congress by AbbVie. He is a personal investor in approximately 20 digital companies, medtech companies or biotech companies. He is also a shareholder and advisory board member in several medtech companies. He reports being cofounder and shareholder of Inato, a digital company involved in clinical research and whose customers are pharmaceutical companies. Jean-Marc Sabaté has received consulting fees from Biogaran and travel fees from Abbvie. Laurent Peyrin-Biroulet has reveived consulting fees from Merck, Abbvie, Janssen,

Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Pharmacosmos, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, and lecture fees from Merck, Abbvie, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Mitsubishi, HAC-pharma. Jean-Frederic Colombel has served as consultant, advisory board member or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, Theravance Biopharma. He has served as speaker for AbbVie, Ferring, Pfizer, Takeda, Shire, speaker's bureau for Amgen. He owns stock options from Intestinal Biotec Development, Genfit, and has received research Grants from AbbVie, Takeda, and Janssen and Janssen. Matthieu Allez has received honorarium from Abbvie, MSD, Janssen, Takeda, Pfizer, Celgene, Ferring Pharmaceuticals, Tillots, Novartis and Mayoli. Magali Svrcek has received consulting fees from BMS and lecture fees from Novartis.

Fabrice Carrat, Jean-François Fléjou and Julien Kirchgesner disclose no conflicts.

Author contributions: LB and FC were jointly responsible for the study concept, design and implementation. LB was responsible for the writing of the first draft of the report. FC and JK were responsible for statistical analyses. All authors took part in the revision of the manuscript.

Word count: 3000

ABSTRACT

Background and Aims: Little is known about the magnitude of the risk of anal and rectal cancer in patients with anal and/or perineal Crohn's disease. We aimed to assess the risk of anal and rectal cancer in patients with Crohn's perianal disease followed in the Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (CESAME) cohort.

Methods: We collected data from 19,486 patients with Inflammatory Bowel Disease (IBD) enrolled in the observational CESAME study in France, from May 2004 through June 2005; 14.9% of participants had past or current anal and/or perianal Crohn's disease. Subjects were followed for a median time of 35 months (interquartile range, 29-40 months). To identify risk factors for anal cancer in the total CESAME population, we performed a case-control study in which participants were matched for age and sex.

Results: Among the total IBD population, 8 patients developed anal cancer and 14 patients developed rectal cancer. In the subgroup of 2911 patients with past or current anal and/or perianal Crohn's lesions at cohort entry, 2 developed anal squamous-cell carcinoma, 3 developed perianal fistula-related adenocarcinoma, and 6 developed rectal cancer. The corresponding incidence rates were 0.26/1000 patient-years for anal squamous-cell carcinoma, 0.38/1000 patient-years for perianal fistula-related adenocarcinoma, and 0.77/1000 patient-years for rectal cancer. Among the 16,575 patients with ulcerative colitis or Crohn's disease without anal or perianal lesions, the incidence rate of anal cancer were 0.08/1000 patient-years and of rectal cancer was 0.21/1000 patient-years. Among factors tested by univariate conditional regression (IBD subtype, disease duration, exposure to immune-suppressive therapy, presence of past or current anal and/or perianal lesions), the presence of past or current anal and/or

perianal lesions at cohort entry was the only factor significantly associated with development of anal cancer (odds ratio, 11.2; 95%CI, 1.18-551.51) (*P* = .03).

Conclusion: In an analysis of data from the CESAME cohort in France, patients with anal and/or perianal Crohn's disease have a high risk of anal cancer, including perianal fistula-related cancer, and a high risk of rectal cancer.

Key words: carcinogenesis; inflammation; HPV

Summary

The magnitude of the risk of anorectal cancer in patients with anal/perianal Crohn's disease was unknown. Using data of the CESAME cohort, we show that patients with anal and/or perianal Crohn's disease are at high risk of both anal and rectal cancer

The risk of anal squamous-cell carcinoma (SCC) is low in general population[1]. A mild increase in this risk has been reported in patients with Crohn's disease in a meta-analysis of inflammatory bowel disease (IBD) referral center series,[2] possibly attributable to Human Papilloma Virus (HPV) infection and chronic inflammation of anal mucosa.[3,4] Patients with perianal fistulizing Crohn's disease are also at risk of perianal fistula-related SCC and adenocarcinoma.[5] Since anal and/or perianal Crohn's disease is associated in most cases with chronic inflammation of rectal mucosa, patients with chronic anal and/or perianal Crohn's disease are also theoretically at increased risk of rectal cancer. To date, the magnitude of these risks was unknown at a population level because IBD phenotype is a missing data in national registries and medico-administrative databases. We could assess specifically the risks of any malignancy in patients with anal and/or perianal Crohn's disease in the French nationwide CESAME observational cohort (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France) because the presence of past or current anal and/or perianal lesions was noted at entry into the prospective observational period. In this study, we report the magnitude of the risk of anal and rectal cancer in the subgroup of patients with Crohn's perianal disease followed in the CESAME observational cohort.

METHODS

Experimental design of the CESAME cohort

From May 2004 to June 2005, 680 French gastroenterologists (38.4% with a full-time hospital practice, 24.3% with a mixed with public/private practice, and 37.3% with a full-time private practice) enrolled, on an unpaid basis, 19,486 consecutive IBD patients from their individual practices. There were no exclusion criteria.

Data were collected on an electronic case report form. The patients' demographic characteristics, IBD type, date of diagnosis, cumulative disease location (small bowel, colon (more or less than 50% of the total mucosal area affected, estimated from macroscopic or microscopic findings), or anus), previous history of cancer, and exposure to immune-suppressive therapy were recorded at the time of inclusion in the cohort. The gastroenterologists were asked to report all cases of high grade dysplasia, cancer or death among their patients during the follow-up period, and to provide information on each surviving patient, obtained during a final visit between 1 January and 31 December 2007. They were also asked to record all changes in immune-suppressive treatment status at interim visits. The follow-up period ended on 31 December 2007. Follow-up was complete (i.e. included the final visit) in 16,459 cases (84.5%), partial (interim visits but no final visit) in 588 cases (3.0%), and non-existent in 2439 cases (12.5%). The median follow-up of the overall population was 35 months (inter-quartile range [IQR], 29-40].

The protocol was approved by the institutional review boards of the French National Society of Gastroenterology, Association François Aupetit (the French IBD patient association), and Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID). The study was authorized by the French Data Protection Agency (CNIL, registration number #04-1239, dated 6 July 2004). The patients' specific written informed consent was not required for this observational study.

Characterization of the cases of anal cancer and rectal cancer in patients with anal/perianal Crohn's disease

Clinical characteristics of patients with Crohn's disease and past or current anal and/or perianal lesions at entry into the observational period of the CESAME cohort, and who developed anal cancer or rectal high-grade dysplasia or cancer during the follow-up, were reviewed by a senior gastroenterologist (LB). Pathological reports of biopsy and/or surgical specimens were reviewed jointly by a senior gastroenterologist (LB) and a senior pathologist (MS).

Statistical analysis

To identify risk factors for anal cancer in the total CESAME population, we used a nested case-control (four controls for one case) study matched for age and sex. We tested by univariate exact conditional regression the following item: IBD subtype, disease duration, any exposure to immune-suppressive therapy at cohort entry, presence of past or current anal and/or perianal lesions at cohort entry

RESULTS

Demographics of the CESAME cohort

Of the 19,486 CESAME patients, 45.1% were male, 60.3% had Crohn's disease, and 39.7% had ulcerative colitis or IBD,unclassified. Details of patient characteristics and exposure to various immune-suppressive drugs at cohort entry according to the IBD subtype are shown in Table 1 and 2. Most (83%) of the patients receiving any immune-suppressive drug were receiving thiopurines, either alone or in combination with anti-TNF agents in 90.2% and 9.8% of the cases, respectively.

Characteristics of CESAME patients with anal and/or perianal Crohn's disease and incidence of anal and rectal cancers in this population

Among the 11,759 patients with Crohn's disease enrolled in the CESAME cohort, 2911 (24.8%) had previous or current anal and/or perianal lesions at entry into the observational period. In this subgroup, 1178 (40.5%) were males, mean (standard deviation (SD)) age of patients was 36.8 (14.6) years. Mean (SD) disease duration from diagnosis to entry into the observational period was 10.6 (2.1) years. No past or current involvement of rectum and colon at cohort entry was noted in 475 (16.3%) patients. An estimated cumulative proportion of mucosal colorectal area macroscopically or microscopically affected by IBD at cohort entry <50 % or >=50% was observed in 950 (32.6%) and 1486 (51.1%) patients, respectively.

Among the 2911 patients with Crohn's disease and previous or current anal and/or perianal lesions at entry into the observational period, followed for a total 7830 patient-years, two patients were diagnosed with anal SCC, three with perianal fistula-related anal adenocarcinoma and six with rectal adenocarcinoma. Incidence rates (Figure 1) were 0.26/1000 patient-years (95% confidence interval [CI], 0.03-0.92) for anal SCC, 0.38/1000 patient-years (95% CI, 0.08-1.12) for perianal fistula-related adenocarcinoma, and 0.77/1000 patient-years (95% CI, 0.28-1.67) for rectal adenocarcinoma (Table 3). The total incidence rate of anorectal cancers was 1.40/1000 patient-years (95% CI, 0.70-2.51). For the purpose of comparison between risk levels, the risk of colon cancer in patients with anal and/or perianal Crohn's disease (0.13/1000 patient-years (95% CI, 0.003-0.711) was also plotted in Figure 1.

Incidence of anal and rectal cancer in patients with ulcerative colitis, IBD,unclassified or Crohn's disease without anal or perianal lesions

The remaining 16,575 individuals of the CESAME cohort population comprised 7727 patients with ulcerative colitis (n=7044) or IBD,unclassified (n=683), and 8848 patients with Crohn's disease without previous or current anal or perianal lesions at entry into the observational period. In this population, three patients were diagnosed with anal SCC and eight with rectal adenocarcinoma. Corresponding incidence rates were respectively 0.08/1000 patient-years (95% CI, 0.02-0.23) and 0.21/1000 patient-years (95% CI, 0.09-0.42).

Risk factors for anal cancer in the total CESAME

To identify risk factors for anal cancer in the total CESAME population, we used a nested case-control (four controls for one case) study matched for age and gender. Among the factors tested by univariate exact conditional regression (IBD subtype, disease duration, any exposure to immune-suppressive therapy at cohort entry, presence of past or current anal and/or perianal lesions at cohort entry), presence of past or current anal and/or perianal lesions at cohort entry was the sole factor significantly predictive for anal cancer (odds ratio, 11.2; 95%CI, 1.18-551.51) (*P* = .03).

Incidence of anal or rectal high-grade dysplasia

No case of incident anal high-grade dysplasia was reported in the CESAME population. Incident rates of rectal high-grade dysplasia by IBD phenotype are indicated in Table 3.

Incidence Rate Ratios (IRR) of anorectal cancers in patients with Crohn's disease and anal and/or perianal lesions

The IRR of subtypes of anorectal cancers diagnosed in patients with with Crohn's disease and anal and/or perianal lesions, compared to patients with Crohn's disease without anal or perianal lesions, and to patients with ulcerative colitis or IBD,unclassified, are listed in Table 4.

Characteristics of incident cases of anal cancer and rectal high-grade dysplasia or cancer in patients with Crohn's disease and anal and/or perianal lesions

Ten out of the 12 patients who developed anal or rectal high grade dysplasia or cancer had active local mucosal inflammation at diagnosis of cancer (Table 5). The nine patients who were diagnosed with perianal fistula-related adenocarcinoma (n=3) or rectal adenocarcinoma (n=6) during the follow-up had a median age of 46 years at diagnosis of cancer (range, 28-55 years), and a median disease duration of 14 years at diagnosis of cancer (range, 9-26 years). One of the three patients diagnosed with perianal fistula-related adenocarcinoma had a recto-vaginal fistula, and another one a pre-existing chronic anorectal stricture. The three patients diagnosed with perianal fistula-related adenocarcinoma had mucinous adenocarcinomas, defined according to the World Health Organization as tumors having pools of mucus with either disrupted tubules and/or interstitial mucus in more than 50% of the neoplasm.[6] This was also the case for two out of the six cases of rectal adenocarcinoma.

DISCUSSION

To our knowledge, our study provides the first estimation of the risk of anal and rectal cancer in patients with Crohn's disease and anal and/or perianal lesions. We show a high incidence rate of anorectal cancer, exceeding that of sporadic colorectal cancer in general population[7] and in total IBD population[8,9] Patients who develop perianal fistula-related or rectal adenocarcinoma are typically young patients with longstanding anorectal inflammation.

Our study has several limitations. The study population, defined as patients with any anal and/or perianal lesions from diagnosis of Crohn's disease to cohort entry included patients with chronic anal and/or perianal lesions and patients with transient sporadic primary anal lesions or suppurative perianal lesions. Excluding these latter patients from analysis would lead to higher incidence of cancers and reinforce the global alarming result of our study. Another limitation is that CESAME is a nationwide cohort, but not a population-based one. However, two-thirds of the CESAME investigators were gastroenterologists with partial or pure private practice, and the observed incidences of colorectal cancer in CESAME[8] were identical to those reported in the literature.[9,10] By contrast to previous CESAME studies on organ malignancies[8,11,12], we could not provide here standardized incidence ratios because, in The French network of cancer registries, anal squamous cell carcinomas are pooled with skin cancers and rectal cancers are not individualized among colorectal cancers. From a methodological point of view, we acknowledge that the low absolute number of events in the study population may lead to imprecise estimates of incidence rate ratios. Finally the mucosal HPV status of our patients was unknown and we were unable to address the role of smoking habits and family history of colorectal cancer since these data were not recorded at cohort entry. In the ongoing European cohort study I-CARE (Ibd CAncer and seRious infections in

Europe, https://clinicaltrials.gov/ct2/show/NCT02377258), these factors will be taken into account.

We observed an incident rate of SCC higher than in general population,[1] but close to that reported in meta-analyses in Crohn's disease population.[2] This excess incidence is attributed to a conjunction of HPV infection and chronic local inflammation,[3,4,13] The resulting incidence remains low, but could be attenuated in the future by the impact of HPV vaccination,[14] and does not justify now per se surveillance programs.[3] By contrast, the burden of anal cancers that are diagnosed in patients with Crohn's anal and/or perianal disease raises challenging questions of clinical practice. We also observed a high rate of rectal cancer in patients with anal and/or rectal Crohn's lesions, exceeding that observed in patients with ulcerative colitis at highest risk of colorectal cancer, i.e. those with longstanding extensive colitis.[10] Overall, in patients with anal and/or perianal Crohn's disease, the risk of anorectal cancer was eleven times greater than the risk of colon cancer.

Thus, there is now a solid epidemiologic and pathogenesis rationale (dysplasia-cancer sequence in chronically inflamed lesions and fistula tracts)[15] for building surveillance programs in order to detect premalignant dysplastic lesions and early anorectal cancers in patients with longstanding anal and/or perianal Crohn's disease. At this time, optimal frequency and modalities of surveillance are unknown.[3,16] In addition, the frequent presence of anorectal impassable strictures,[17] and initial location of malignant lesions in inaccessible fistula tracts make the surveillance difficult, if not, in some cases, impossible.[18,19] Dedicated consensus and guidelines regarding detection of advanced anorectal neoplasia in patients with anal and/or perianal Crohn's disease are now eagerly awaited.

Acknowledgments

The list of CESAME Study Group collaborators appears in the Supplementary Material

Figure legends

Figure 1: Incidence rates of anal squamous-cell carcinoma, perianal fistula-related adenocarcinoma, rectal adenocarcinoma and colon carcinoma, in 2911 patients of the CESAME cohort with Crohn's disease and past or current anal and/or perianal lesions at entry into the observational period, followed for 7830 patient-years.

References

1. Shiels MS, Kreimer AR, Coghill AE, et al. Anal Cancer Incidence in the United States, 1977-2011: Distinct Patterns by Histology and Behavior. Cancer Epidemiol Biomark Prev 2015;24:1548–56.

2. Slesser AA, Bhangu A, Bower M, et al. A systematic review of anal squamous cell carcinoma in inflammatory bowel disease. Surg Oncol 2013;22:230–7.

3. Wisniewski A, Fléjou J-F, Siproudhis L, et al. Anal Neoplasia in Inflammatory Bowel Disease: Classification Proposal, Epidemiology, Carcinogenesis, and Risk Management Perspectives. J Crohns Colitis 2017;11:1011–1018.

4. Ruel J, Ko HM, Roda G, et al. Anal Neoplasia in Inflammatory Bowel Disease Is Associated With HPV and Perianal Disease. Clin Transl Gastroenterol 2016;7:e148.

5. Laukoetter MG, Mennigen R, Hannig CM, et al. Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg 2011;15:576–83.

6. Bosman, F T; World Health Organization; International Agency for Research on Cancer. *WHO classification of tumours of the digestive system*. IARC Press; 2010.

7. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2014.

8. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. Gastroenterology 2013;145:166–175.e8.

9. Lutgens MWMD, Oijen MGH van, Heijden GJMG van der, et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19:789–799.

10. Beaugerie L, Itzkowitz SH. Cancers Complicating Inflammatory Bowel Disease. N Engl J Med 2015;373:195.

11. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374:1617–1625.

12. Bourrier A, Carrat F, Colombel J-F, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther 2016;43:252–261.

13. Shah SB, Pickham D, Araya H, et al. Prevalence of Anal Dysplasia in Patients With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2015;13:1955–61 e1.

14. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2014;8:443–68.

15. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011;140:1807–16.

16. Annese V, Beaugerie L, Egan L, et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis 2015;9:945–965.

17. Brochard C, Siproudhis L, Wallenhorst T, et al. Anorectal stricture in 102 patients with Crohn's disease: natural history in the era of biologics. Aliment Pharmacol Ther 2014;40:796–803.

18. Ky A, Sohn N, Weinstein MA, et al. Carcinoma arising in anorectal fistulas of Crohn's disease. Colon Rectum 1998;41:992–6.

19. Korelitz BI. Carcinoma arising in Crohn's disease fistulae: Another concern warranting another type of surveillance. Am J Gastroenterol 1999;94:2337–2339.

Table 1. Characteristics of the CESAME patient population

	Thiopurine therapy at entry						
	Ongoing (N=5867)		Discontinued (N=2809)		Never received (N=10,810)		Total (N=19,486)
Age (years)	37.0	(14.3)	39.5	(14.4)	42.3	(16.3)	40.3 (15.6)
Male sex	2592	(44.2%)	1142	(40.7%)	5046	(46.7%)	8780 (45.1%)
Age at onset of disease (years)	28.6	(13.2)	29.0	(13.4)	34.9	(15.1)	32.1 (14.6)
Duration of disease (years)	8.4	(7.2)	10.5	(7.8)	7.4	(8.4)	8.2 (8.0)
Crohn's disease	4452	(75.9%)	2154	(76.7%)	5153	(47.7%)	11,759 (60.3%)
Disease location							
Ileum	3082	(52.5%)	1543	(54.9%)	3597	(33.3%)	8222 (42.2%)
Colon (<50%)*	1358	(23.1%)	627	(22.3%)	1876	(17.4%)	3861 (19.8%)
Colon (>50%)	2079	(35.4%)	1085	(38.6%)	1426	(13.2%)	4590 (23.6%)
Anal/Perianal	1384	(23.6%)	740	(26.3%)	787	(7.3%)	2911 (14.9%)
Ulcerative colitis or inflammatory bowel disease unclassified	1415	(24.1%)	655	(23.3%)	5657	(52.3%)	7727 (39.7%)
Colon (<50%)*	578	(9.9%)	237	(8.4%)	3883	(35.9%)	4698 (24.1%)
Colon (>50%)	837	(14.3%)	418	(14.9%)	1774	(16.4%)	3029 (15.5%)
Past history of cancer	83	(1.4%)	77	(2.7%)	302	(2.8%)	462 (2.4%)
Follow-up (months)	35.7 (31.1-40.1)		35.4 (29.9-40.0)		34.3 (27.7-39.1)		35.0 (29.2-39.5)

Data are Mean (SD) or number (%) or Median (IQR)
* estimated cumulative proportion of mucosal area macroscopically or microscopically involved

Table 2. Immune-suppressive drug exposure status of the CESAME population at entry to the cohort

	Exposure to immune-suppressive therapy		
	Crohn's disease (n=11,759)	Ulcerative colitis or IBDU (n=7727)	All (n=19486)
Thiopurines			
Ongoing, n (%)	4452 (37.9)	1415 (18.3)	5867 (30.1)
Discontinued, n (%)	2154 (18.3)	655 (8.5)	2809 (14.4)
Never received, n (%)	5153 (44.8)	5657 (73.2)	10810 (55.5)
Methotrexate			
Ongoing, n (%)	600 (5.1)	94 (1.2)	694 (3.6)
Discontinued, n (%)	617 (5.3)	82 (1.1)	699 (3.6)
Never received, n (%)	10542 (89.6)	7551 (97.7)	18093 (92.8)
Anti-TNF agents			
Ongoing, n (%)	877 (7.5)	48 (0.6)	925 (4.7)
Discontinued, n (%)	929 (7.9)	85 (1.1)	1014 (5.2)
Never received, n (%)	9953 (84.6)	7594 (98.3)	17547 (90.1)
Other immunosuppressants[a]			
Continuing, n (%)	77 (0.7)	119 (1.5)	197 (1.0)
Discontinued, n (%)	179 (1.5)	301 (3.9)	480 (2.5)
Never received, n (%)	11503 (97.8)	7307 (94.6)	18809 (96.5)

IBDU, Inflammatory Bowel Disease Unclassified.
[a] Ciclosporin, mycophenolate mofetil or cyclophosphamide.

Table 3. Incident rates of rectal high-grade dysplasia and rectal cancer in the CESAME cohort by IBD phenotype

	Patient-years	Rectal high-grade dysplasia (n/1000 PY (95% CI))	Rectal cancer (n/1000 PY (95% CI))
Crohn's disease			
All (n=11759)	27,828	0.072 (0.009-0.260)	0.323 (0.148-0.614)
With anal and/or perianal lesions[a] (n=2911)	7830	0.128 (0.003-0.711)	0.766 (0.281-1.667)
Without anal or perianal lesions[a] (n=8848)	19,998	0.050 (0.001-0.279)	0.150 (0.031-0.438)
Ulcerative Colitis or IBD,unclassified			
All (n=7727)	17,666	0.170 (0.035-0.496)	0.283 (0.092-0.660)
With longstanding extensive colitis[b] (n=1083)	2571	0.778 (0.094-2.807)	0.389 (0.010-2.165)
Without longstanding extensive colitis (n=6644)	15,095	0.066 (0.002-0.369)	0.265 (0.072-0.678)

CI, Confidence interval; IBD, Inflammatory Bowel Disease; PY, Patient-years;
[a] at entry into the observational period of the CESAME cohort
[b] defined as IBD duration greater than 10 years and an estimated cumulative proportion of mucosal area macroscopically or microscopically effected by IBD or greater than or equal to 50%

Table 4. Incidence Rate Ratios of anorectal cancers in patients with Crohn's disease and anal and/or perianal lesions compared to other IBD subgroups

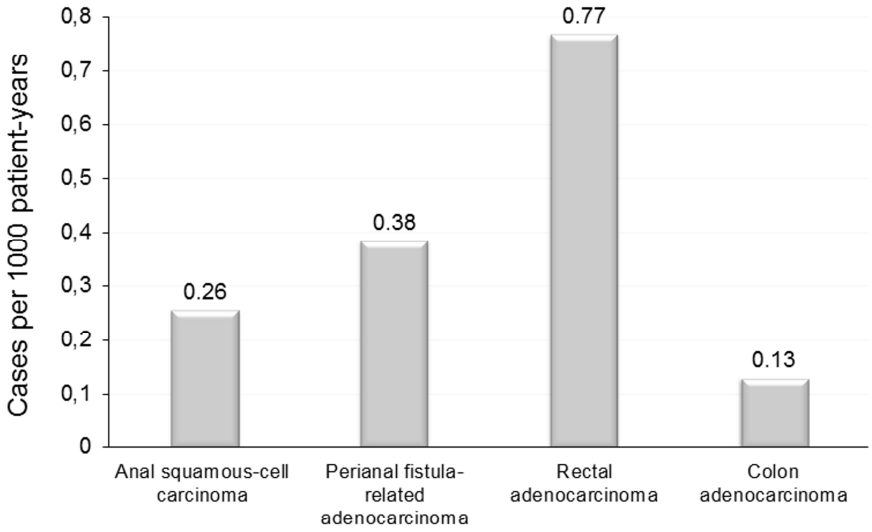
	Compared to patients with Crohn's disease without anal and/or perianal lesions (IRR (95% CI))	Compared to patients with ulcerative colitis or IBD,unclassified (IRR (95% CI)
Anal cancers		
Anal squamous cell carcinoma	—[a]	1.50 (0.25-9.00)
Perianal fistula-related anal adenocarcinoma	—[a]	—[b]
All anal cancers	—[a]	3.76 (0.90-15.73)
Rectal cancers	5.11 (1.28-20.42)	2.71 (0.83-8.87)
All anorectal cancers	9.36 (2.61-33.54)	3.10 (1.25-7.71)

IRR, Incidence Rate Ratio; IBD, Inflammatory Bowel Disease; CI, Confidence interval;
[a] No case was diagnosed in patients with Crohn's disease without anal or perianal lesions
[b] No case was diagnosed in patients with ulcerative colitis or IBD,unclassified

Table 5. Characteristics of incident cases of anal cancer and rectal high-grade dysplasia or cancer in patients with Crohn's disease and past or current anal and/or perianal lesions at entry into the CESAME cohort (7830 patient-years).

	Age (years) at diagnosis of neoplasia	Sex	Cumulative location of Crohn's lesions at cohort entry	Crohn's disease duration diagnosis of neoplasia (years)	Active local mucosal inflammation at diagnosis of neoplasia	History of chronic perianal fistulas at diagnosis of neoplasia	History of chronic anorectal stricture at diagnosis of neoplasia	Exposure to immune-suppressive therapy at diagnosis of neoplasia
Patients with anal squamous-cell carcinoma								
1	49	M	Colon <50%[a], anus[b]	2	Yes[c]	No	No	AZA
2	73	F	Anus	3	No	No	No	0
Patients with perianal fistula-related adenocarcinoma								
3[e]	37	F	Small bowel, colon >50%,	9	Yes[c]	Yes (rectovaginal)	No	0
4[e]	38	M	Anus	22	Yes[c]	Yes	Yes	0
5[e]	46	M	Colon >=50%, anus Small bowel, colon >=50%, anus	28	Yes[c]	Yes	No	AZA
Patients with rectal adenocarcinoma								
6[e]	28	M	Colon >=50%, anus	10	Yes[d]	Yes	No	AZA + IFX
7	28	M	Colon>=50%, anus	9	Yes[d]	No	No	MTX + IFX
8[e]	48	F	Colon>=50%, anus	14	Yes[d]	No	No	MTX
9	48	F	Anus	19	No	Yes	No	0
10	51	M	Colon>=50%, anus	26	Yes[d]	No	Yes	0
11	55	M	Colon>=50%, anus	10	Yes[d]	No	No	0
Patients with rectal high-grade dysplasia								
12	54	M	Colon>=50%, anus	24	Yes[d]	Yes	No	IFX

IBD, inflammatory bowel disease; M, male; F, female; AZA, azathioprine; IFX, infliximab; MTX, methotrexate
[a] Estimated cumulative proportion of mucosal colorectal area macroscopically or microscopically affected by IBD
[b] Anal and/or perianal lesions.
[c] Inflammation of anal canal mucosa
[d] Inflammation of rectal mucosa
[e] Mucinous adenocarcinoma



List of collaborators of the CESAME Study Group

The following investigators participated in the Study, listed from highest to lowest number of patients enrolled in the cohort: Jean-Frédéric Colombel; Jacques Cosnes; Jean-Pierre Gendre; Marc Lémann; Xavier Hébuterne; Antoine Cortot; Yoram Bouhnik; David Laharie; Jean Louis Dupas; Bernard Flourié; Eric Lerebours; Laurent Beaugerie; Laurent Peyrin-Biroulet; Matthieu Allez; Bernard Messing; Guillaume Cadiot; Philippe Marteau; Jean- Claude Soulé; Jean-Marc Gornet; Michel Veyrac; Bernard Duclos; Philippe Beau; Arnaud Bourreille; Philippe Baumer; Franck Carbonnel; Denis Heresbach; Etienne-Henry Metman; Christian Florent; Antoine Blain; Jean-Luc Faucheron; Bruno Bonaz; Xavier Roblin; Pascal Potier; Christian Boehm; Thierry Kurtz; Hervé Lamouliatte; Isabelle Nion-Larmurier; Jean-Charles Delchier; Stanislas Chaussade; Anne Marie Weiss; Jean Pierre Cézard; Laurent Siproudhis; Stéphane Nahon; Daniel Sondag; Raymond Jian; Jean-Christophe Souquet; Pierre Bord; Benoit Coffin; Hélène D'almagne; Patrick Delasalle; Régis Fournier; Maryan Cavicchi; Marc-Henry Souffran; Luc Vandromme; Claire Guedon; Philippe Seksik; Christophe Michiels; Pascal Renard; Patrice Rogier; Sylvie Gouilloud; André Rotenberg; Guillaume Savoye; Alain Thevenin; Laurent Mallet; Franck Brazier; Francois Jean; Anne-Marie Justum; Jean-Paul Latrive; Jean-Luc Gerbal; Robert Pierrugues; Gérard Chardonnal; Laurence Picon; Nicole Reix; Nicolas Drouët D'aubigny; Hervé Uettwiller; Anne Courillon Mallet; Alain Palacci; Raoul-Jacques Bensaude; Pierre Bonniaud; Olivier Empinet; Andrée Nisard; Alain Rudelli; Bernard Tubiana; Philippe Capelle; Alain Dabadie; Daniel Evard; Pierre-Emile Julien; Magali Picon-Coste; Stéphane Schneider; Denis Goldfain; Jérôme Bellanger; Jean-Pierre Blondelot; Philippe Lamy; Sébastien Lemière; Jean Francois Mockly; Benoit Pellat; Gilles Gatineau-Sailliant; Bernard Nalet; Stéphane Nancey; Daniel

Kusielewicz; Patrick Loison; Jean-Michel Popot; François Merite; Jean-Pol Roux; Pauline Afchain; Alain Blanquart; Laurent Heyries; Marc Reville; Dominique Viron; Frank Zerbib; Christophe Claviere; Didier Léostic; Philippe Pouderoux; Alain Moitry; Hervé Hagège; Jean-Pierre Hugot; Benoit Humeau; Jean-Marc Sabate; Emmanuel Lederman; Dominique Lescut; Fabrice Luneau; Bruno Mesnard; Lionel Smadja; Michel Steinberg; Marc Brun; Gilles Macaigne; Jean Luc Marchal; Stéphane Ollivier; Dominique Ouvry; Jean Paul Perche; Serge Rambaud; Robert Benamouzig; Jean Louis Cazenave; Jean-Charles Coffin; Martine Blazquez; Marion Lagneau; Bruno Person; Christian Wittersheim; Bertrand Napoleon; Israël Cemachovic; Franck Iglicki; Mehran Howaizi; Eric Leprince; Bruno Leurent; Thierry Morin; Riad Darsouni; Alain Attar; Philippe Baron; Anne Breton; Jean Marie Gillion; Jean-Marc Guemene; Claude Jouffre; Xavier Moreau; Pierre Claude; André Quinton; Vered Abitbol; Jean Michel Brichard; Benoit Desaint; Martin Bouygues; Philippe Chatrenet; Marcelo Salmeron; Jean Silvie; Bruno Waldner; Yves Emery; Armand Moraillon; Daniel Kunkel; Philippe Dubois; Patrick Faure; Christian L'Hirondel; Jean-Eric Labérenne; Pierre Moreau; Adelino Pereira; Genevieve Plihon; Thierry Wolff; Yann Ngo; Arnaud Boruchowicz; Béatrice Jost; Jean Pierre Gotlib; Odile Danne; Philippe Raoux; Marie-José Ramond-Bouhali; Andre Baetz; Bruno Veyres; Christian Chapoutot; Gérard Le Dréau; Jérôme Filippi; Jean Mudry; Philippe Kalt; Sophie Minault; Pierre-André Bounin; Tony Andréani; Jacky Charneau; Didier Reijasse; Jean-Louis Bolze; Jean Luc Thaunat; Christian Le Couteulx; Chantal Maurage; Robert Bader; Philippe Codjovi; Jean-Luc Migairou; Alain Morali; Philippe Rey; Bruno Richard Molard; Richard Petit; Stéphane Koch; Philippe Cassan; Jean-Paul Deschamps; Christine Meicler Caby; Jean-Jacques Meurisse; Philippe Prades; James Boulant; Michel Diacono; Jean-Marie Monsch; J-François Dupuy; Guy Bellaiche; Martine Guegan; Jean-Marc Comte;

Jean-Michel Cayla; Francois Le Tallec; Franck Meurisse; Philippe Desurmont; Laurent Roget; Philippe Bouyssou; Bruno Le Gall; Francis Bloch; Loic Larvol; Monique Jullien; Jacques Moreau; Laurent Rebouissoux; Bruno Decroix; Nina Dib; Paul Dieterling; Frédéric Lenormand; Emmanuel Lagier; Philippe Fallourd; Serge Charpin; Hugues Bertrand; Gilles Bommelaer; Daniel Battistelli; Bernard Delon; Lionel Dentant; Etienne Dorval; Jérôme Dumortier; Eric Gaye-Bareyt; Yves Gerosa; Chantal Guez; Martine Mornet; Paul Benfredj; René Piperaud; Noel Stremsdoerfer; Eric Verdier; Alain Grinholtz; Georges Barjonet; Antoine See; Ramuntxo Arotçarena; Anne Baudet; Joel Broyer; Antoine Charachon; Hugues Blondon; Pascal Mouton; Hubert Claudez; Jacques Labat-Labourdette; Jacques Haëm; Patrick Estable; Patrick Levy; Alain Rosenbaum; Yvon Balavoine; Alain Blanchi; Pierre Coutarel; Nadege Delaperriere; Michel Dervichian; Francis Marois; Jacques Seroka; Laurent Michaud; Olivier Leroy; Emmanuel Meyran; Bernard Poilroux; Abdallah Tensaouti; Thierry Paupard; Dominique Agard; Sandrine Beaulieu; Kader Benfiguig; Patrice Capony; Jean Cottereau; Pierre Desreumaux; Jean-Michel Dramard; Mathieu Duché; Patrick Mamou; Isabelle Etienney; Gilles D'Abrigeon; Béatrice Godeberge; Gilbert Tucat; Jean Puech; Jean Roger; Marie-George Lapalus; Paul Bauret; Philippe Houcke; Béatrice Pornin; Bruno Champigneulle; Laurent Cuissard; Xavier-Richard David; Frédéric Lombard; Antoine Granveau; Jean-François Hamon; Olivier Ink; Fabienne Blondel; Alain Namias; Didier Pillon; Antoine Reignier; Gilles Tordjman; Christos Christidis; Simon Zirabe; Michel Audebert; Eric Bion; Claude Bourgeaux; Cécile Poupardin; Philippe Deplaix; Gérard Fratini; Thierry Garnier; Gerard Desseaux; Hervé Magois; Sylvain Lochum; Jean-Francois Vergier; Patrick Texereau; Christel Rat; Francoise Uzzan; Alain Vidal; Nadia Vinante; Bernard Watrin; Cécile Wurtz-Huckert; Bruno Barre; Dominique Chaslin Ferbus; Jean-François Contou; Dominique

Coupier; Benoit David; Dany Gargot; Denis Huc; Remy Barraya; Roger Faroux; Jean-Luc Fourgeaud; Hubert Grimprel; Jean Auroux; Jean-François Rey; Jean Pierre Arnoux; Franck Lentini; Ludovic Tardy; Olivier Mouterde; Claire Spyckerelle; Bruno Vacherot; Alain Weissman; Michel Alpérine; Anne Le Sidaner; Pierre-Olivier Bonnet-Eymard; Jean Louis Colson; Daniel Pellet; Bernard Deltombe; André Edouard; Henri Maechel; Jean-Claude Jaillet; Julien Genes; Anne-Marie Leveque; Damien Lucidarme; Philippe Maignan; Nathalie Mallier Gehrke; Jérôme Sanchez; Frank Tusseau; Alban Casteur; Jacques Bottlaender; Denis Constantini; Thierry Coton; Philippe Even; Francois Druart; François Riot; Jean-Michel Gauchet; Geneviève Hecquet; Gerard Henry; Patrick Hochain; Jean Pierre Arpurt; Abdelkrim Medini; Michele Dartois-Hoguin; Henri Moindrot; Philippe Emery; Pierre Periac; Annie Prunier; Pascal Renkes; Christine Tawil-Longreen; Edmond Vincent; René-Louis Vitte; Christian Loeb; Alain Carwana; Didier Barbereau; Philippe Bohon; Céline Corrieri-Baizeau; Daniel Sahy; Philippe Derreveaux; Dominique David; François Desbazeille; Patrick Fontenelle; Jean Luc Slama; Yvon Le Mercier; Michel Certin; Jean Jacques Reig; Isabelle Rosa; Thierry Helbert; Patrick Tounian; Luc Turner; Valéry Perot; Luc Aillet; Arnaud Pauwels; Philippe Barré; Bernard Nury; Claude Cazalbou; Franck Devulder; Alain Durget; Jeanne Dubroca; Daniele Gaudy; Michel Greff; Christian Jacques; Jocelyne Lafarge; Gilles Kezachian; Ronan Le Gall; Alex Pariente; Tiphaine Pinault; Michaël Bismuth; Nathalie Boyer-Darrigrand; Philippe Bretagnolle; Stephane Carpentier; Franck Cholet; Christian Theodore; Rémi Combes; Francois Combet; Christophe Delanoe; Stéphanie De Montigny; Denis Soudan; Olivier Fourdan; Gilles Minier; Jeanne Languepin; Jean Roche; Jean-Louis Ginies; Olivier Nouel; Philippe Petitgars; Edith Robin; Romain Hamm; Jean François Roques; Sylvie Roussin-Bretagne; Agnès Sénéjoux; Sophie Muron; Nicolas Bardoux;

Philippe Berthelemy; Patrick Madonia; Bertrand Carles; Catherine Reynier; Emmanuel Cuillerier; Innocenti Dadamessi; Jacques Danis; Bernard Debenes; Nathalie Dubuc-Rey; Gilles Lesur; Pauline Jouet; Catherine Lenaerts; Marc Garret; Alexandra Mineur; Bernard Chabry; Francois Pigot; Valérie Rossi; Ruth Tennenbaum; Julien Salloum; Maurice Hakim Slaoui; Stéphane Mathieu; Valérie Papapietro; Sheila Viola; Alexis Bezet; Claude Altman; Alain Audan; Jean Calabet; Claude Masliah; Laurent Fayemendy; Marc Duruy; Benoit Gauffeny; Ludovic Helie; Kamran Imani; Raoul Janin-Manificat; Jean-Paul Galmiche; Anne Kerlirzin; Laurent Bedenne; Christophe Locher; Gilles Michaudel; Gilles Missonnier; Michel Rinaldi-Dovio; Jean-Michel Rouillon; Stéphane Ecuer; Arnaud Patenotte; Jean Ariel Bronstein; Vincent Baty; Michel Bougnol; Pierre Bourbon; Philippe Cerbelaud; Annick Chavaillon; Franck Boiffin; Béatrice Dubern; Isabelle Duval De Laguierce; Fernand Greco; Florence Bouhot; Philippe Godeberge; Brigitte Grandmaison; Pascal Gros; Guy Targues; Jacques Corallo; Jean Boutin; Jacques Guillan; Jean Pierre Barbieux; Isabelle Loury Lariviere; Henri Le Genissel; Henri Leroi; Marc Bellaiche; Marie-Claire Elie-Legrand; Michel Dapoigny; Philippe Denoyel; Patrice Pienkowski; Philippe Pouche; Marc Michel Saurfelt; Jean Marie Thorel; Thierry Piche; Bruno Travers; Patrick Tuvignon; Marc Zalcberg; Guy Boulay; Christophe Zamora; Joelle Samama; Etienne Ricotie; Patrice De Fleury; Francois Maille; Jean Louis Mougenel; Olivier Gonot; Jean Philippe Menat; Mehdi Kaassis; Francoise Lang; Laurent Abramowitz; Nathalie Ganne; Olivier Pecriaux; Jacques-Arnaud Seyrig; Iradj Sobhani; Thierry Parmentier; Antoine Van Nieuwenhuyse; Francois-Xavier Weber; André Glibert; Catherine Bineau; Bernard Canet; Catherine Collin; Frederic Cordet; David David Parlier; Dominique Carre; Annie Peytier; Francine Fein; Jerome Barouk; Jacques Dewannieux; Johannes Hartwig; Jean-Louis Jouve; Bertrand Laplane; Gilles Lascar;

Christophe Legrand; Pierre Le Marchand; Marie Pierre Liebaert; Michele Terdiman-Pire; Naceur Abdelli; Dominique Neveu; Philippe De La Lande; Patrick De Saint Louvent; Cécile Pelatan; Agnès Petit; Martial Richecoeur; Frederic Texier; Jean Brice Cazals; Bertrand Tissot; Christian Mourrut; Marie Doubremelle; Marc Foltz; Florence Gautier-Jubé; Jacques Martin; Elie Khouri; Thierry Lons; Martine Carlier-Bandu; Jean-Luc Monnin; Hervé Roche; Bernard Willemin; Xavier Houard; Abdelaziz Fatisse; Michèle Algard; Kamel Arab; Isabelle Borel; Cécile Lagarrigue; Ariane Chryssostalis; Dominique Boutroux; Jean-Pierre Dupuychaffray; Saïd Khaddari; François Mion; Thierry Puy-Montbrun; Jean-Philippe Girardet; Bruno Gury; Alain Landau; Monique Le Bihan; Sandrine Nieuviarts; Jean Ollivry; Philippe Le Bourgeois; Marie-Astrid Piquet; Michel -Pierre Escartin; Remi Systchenko; Franck Venezia; Michel Wantiez; Xavier Lesage; Elie Zrihen; Philippe Aygalenq; Barbara Dieumegard; Bernard Savarieau; Philippe Bulois; Stéphane Cattan; Jean-Lucien Diez; Olivier Fauchot; Eric Durous; Valérie Gazut; Christian Guilleminet; Jean-Marc Bories; Isabelle Joly Le Floch; Jean-Paul Vove; Stéphane Lelouch; Philippe Lévy; François Lhopital; Norma Marcato; Marianne Mozer-Bernardeau; Jean-Baptiste Nousbaum; Philippe Cattan; Alain Plane; Jean-Michel Raymond; Gilles Roseau; Gerald Rozental; Christian Boustière; Corinne Bonny; Mariepierre Cordier-Collet; Laurent Courat; Bernard Croguennec; Karine Delaunay- Tardy; Damien Labarriere; Edmond Geagea; Frédéric Gottrand; Eve Gelsi; Gerard Thiefin; Eric Wohlschies; Mathieu Miguet; Philippe Ponsot; Jean Suzanne; Yves Teste; Anne-Claire Dupont Gossart; Jean-Luc Baroni; Benabdallah Benchaa; Georges Blanc; Bernard Maroy; Philippe Bonjean; Catherine Brézault; Laure Bridoux-Henno; Claude Chayette; Dominique Auby; Robert Fiorucci; Georges Galindo; Gilles Hubert; Gilles Bonneau; Evelyne Marinier; Michele Pouteau; Afchine Alamdari; Bruno Delbende; Patrick Chamouard; Pascale

D'Abravanel; Hélène Dall'Osto; Sophie Hervé; Jean Lefebvre; Damien Levoir; Philippe Lillo; Michel Rouch; Muriel Mathonnet; Mercédes De Lustrac; François-Jean Ramond; Bernard Roupret; Alain Soupison;

The following persons participated in the Scientific Coordination of the Study: Anne-Marie Bouvier, Elodie Drouet, Tabassome Simon