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Effect of aminosalicylates or thiopurines on the risk of colorectal cancer in inflammatory bowel disease: a propensity-adjusted case-control study nested in the CESAME cohort

Short title: aminosalicylates, thiopurines, and colorectal cancer in IBD

Fabrice Carrat (1), Philippe Seksik (2), Jean-Frédéric Colombel (3), Laurent Peyrin-Biroulet (4) and Laurent Beaugerie (2) for the CESAME study group

(1) Department of Public Health, Hôpital Saint-Antoine, Assistance Publique, Hôpitaux de Paris, and Sorbonne Universités, and Institut Pierre Louis d'épidémiologie et de Santé Publique, Paris, France

(2) Department of Gastroenterology, Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, and Université Pierre et Marie Curie Paris 06, Paris, France

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

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

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@aphp.fr

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Abbreviations used in this paper:

CRC, colorectal cancer;

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

CI, confidence interval;

IBD, inflammatory bowel diseases;

SD, standard deviation;

UC, ulcerative colitis;

ABSTRACT

Background: Whether aminosalicylates or thiopurines reduce the risk of colorectal cancer (CRC) in inflammatory bowel (IBD) disease is controversial.

Aim: To assess simultaneously the chemopreventive effect of aminosalicylates or thiopurines in a case-control study nested in the CESAME observational cohort that enrolled consecutive patients with IBD between May 2004 and June 2005. Patients were followed up to December 2007.

Methods: Study population comprised 144 case patients who developed CRC from the diagnosis of IBD (65 and 79 cases diagnosed respectively before and from 2004, starting year of the prospective observational period of CESAME) and 286 controls matched for gender, age, IBD subtype and year of diagnosis, and cumulative extent of colitis. Exposure to aminosalicylates or thiopurines was defined by an exposure to the treatment during the year of the diagnosis of cancer. The propensity of receiving 5-ASA and thiopurines was quantified by a composite score taking into account patient and IBD characteristics. The role of aminosalicylates or thiopurines was assessed by multivariate analysis. Propensity scores and the history of primary sclerosing cholangitis were entered into the multivariate model for adjustment.

Results: By multivariate analysis adjusted for propensity, a significant protective effect of exposure to drugs during the year of cancer was found for aminosalicylates (OR=0.587, 95%CI: 0.367-0.937, $P = 0.0257$), but not for thiopurines (OR=0.762, 95%CI: 0.432-1.343, $P = 0.3468$).

Conclusion: In a case-control study nested in the CESAME cohort, a significant decrease in the risk of CRC in IBD was associated with exposure to aminosalicylates, not to thiopurines.

Key words: aminosalicylates, thiopurines, inflammatory bowel disease, colorectal cancer, chemoprevention, CESAME.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world.¹ Patients with inflammatory bowel disease (IBD) may develop sporadic CRC and CRC complicating inflammation of colonic mucosa.² The resulting epidemiologic figure is that patients with IBD have an overall two-fold increase in the risk of CRC compared with age and gender-matched individuals from the general population.³ This relative risk is much more elevated (from 6 to 9) in patients suffering from IBD associated with primary sclerosing cholangitis,⁴ and in patients with longstanding extensive colitis, defined by IBD duration superior to ten years and an estimated cumulative extent of colonic inflammation of 50% or greater.⁵ Various markers of chronic histologically active colonic disease are also independently associated with an increased risk of CRC.⁶ Detecting and removing early neoplastic lesions during colonoscopy surveillance and the use of chemopreventive agents are the two theoretical approaches for reducing the risk of CRC in patients with IBD. Given the evidence for cases of inflammation-driven CRC in IBD, all anti-inflammatory drugs used on a long-term basis in IBD, including aminosalicylates, immune-modulators and biologics are candidates for chemoprevention. In addition, it has been suggested that aminosalicylates could have various specific inhibiting effects on CRC carcinogenesis at a molecular level.⁷ Aminosalicylates used in IBD, that include mesalazine, sulfasalazine, olsalazine and balsalazide, were first reported as potentially chemopreventive in individuals studies and in a first reference meta-analysis restricted to ulcerative colitis.⁸ This conclusion was confirmed later in two updated meta-analyses, one pooling patients with ulcerative colitis and Crohn's disease,⁹ and the other restricted to patients with ulcerative colitis,¹⁰ but not in a meta-analysis restricted to non-referral populations of patients with IBD.¹¹ Data on the effect of exposure to thiopurines on the risk of CRC

in IBD are more limited and conflicting. The first studies, published from 1990 to 2010 came mainly from referral centers and failed to demonstrate a chemopreventive effect,¹²⁻¹⁷ whereas the converse was true for the majority of more recent studies, including studies from medico-administrative databases,¹⁸ observational cohorts¹⁹ and referral centers.⁶ Two meta-analyses have been published up to now, one with negative results,²⁰ and the other suggesting a chemopreventive effect of thiopurines.²¹

We decided to assess simultaneously the chemopreventive effect of aminosalicylates (primary objective) or thiopurines (secondary objective) in the CESAME (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France) observational cohort. CESAME is a prospective national French observational cohort that included 19 486 patients who were enrolled between May 2004 and June 2005, and followed up to December 2007. History of prior CRC was part of the baseline data recorded at entry, and all cases of incident CRC were subsequently recorded. We had no details regarding exposure to aminosalicylates in the general CESAME project, so we performed a nested case-control study, with retrospective study of case and control source medical files, using a specific report form.

Methods

CESAME cohort design and population

Details on the design and demographics of the cohort are available elsewhere.²² In brief, from May 2004 to May 2005, 680 French gastroenterologists (38.4% with a full-time hospital practice, 24.3% with a mixed 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) for 588 cases (3.0%), and non-existent for 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.

Selection of cases and controls

We used a matched case-control study to assess the link between exposure to salicylates and thiopurines and the risk of colorectal cancer in patients with IBD, with propensity scores to adjust for measured confounding factors related to exposure to treatment. Patients of the case-control study were recruited between May 2004 and December 2007. Cases were patients who had a history of colorectal cancer at entry in the cohort or who subsequently developed a colorectal cancer during the follow up. Colorectal cancer was defined as malignant colorectal lesions not limited to the epithelium (i.e. excluding high-grade dysplasia). The date of colorectal cancer was considered as the date on which histological proof of colorectal cancer was obtained. We excluded eight patients who developed colorectal cancer before the diagnosis of IBD. We aimed to select 2 controls for every case from the same source population who had no prior or current diagnosis of colorectal cancer on the date of the colorectal cancer in the case. Controls were individually matched to cases by age (up to 10 years older or younger), gender, IBD (Crohn's disease on one side, ulcerative colitis or IBD unclassified on the other), duration of disease (up to 5 years longer or shorter) and presence of an extensive colitis (estimated cumulative proportion of mucosal area macroscopically or microscopically affected by IBD >50%). The selection of controls in the cohort was realized by an independent statistician using the greedy matching algorithm which minimized a global distance criteria between cases and potential controls.²³ Matching criteria were checked by a trained monitor

on the basis of source medical files. Eligible controls who underwent a proctocolectomy during the exposure study period (n=13) were secondarily excluded from the study, and replaced by the same number of controls according to the same selection rules.

Definition of exposures

In the specific case-control report form filled-in according to data of the source medical files, we recorded treatment intake on at least one occasion during a period from IBD onset to the date when colorectal cancer was ascertained in case and their matched controls, the years of first and last intake (from which we derived exposures to treatment the year when cancer was diagnosed), and the proportion of time under treatment during the five years preceding colorectal cancer diagnosis. Demographic characteristics, smoking status, and history of primary sclerosing cholangitis were noted. Number of IBD flares, surgical procedures and medical visits over the last 5 years preceding cancer occurrence in cases and their matched controls were recorded on a semi-quantitative scale and then dichotomized according to pre-defined threshold in the analyses. Medical data of the specific case-control report form were systematically reviewed by two senior gastroenterologists (LB & PS).

Statistical analysis.

We estimated that 120 cases and 240 controls would be necessary to confirm, with more than 80% power, a decrease of 50% of the risk of colorectal cancer with salicylates, assuming that the exposure to salicylates in the control group was between 40% and 80%. Assuming exposure to thiopurine therapy of 20% in the control group, we estimated that 200 cases and 400 controls would be necessary to

confirm, with more than 80% power, a decrease of 50% of the risk of colorectal cancer with thiopurines.

We used univariate conditional logistic regression model and the Wald Chi-Square test to compare patients with colorectal cancer with their matched controls. In order to address confounding by indication, we adjusted our analyses of treatment exposures on the propensity scores, i.e. the probability of being treated with salicylates or thiopurines according to the observed covariates. To account for temporal change in the indication of treatments, we built two separate logistic models for the propensity score according to the date of cancer, before 2004, or in 2004 or after. The propensity score for receiving a treatment was the predicted probability obtained from the logistic equation given the covariates values. Covariates tested in the propensity models were age, sex, IBD type, duration of IBD, extensive colitis, active smoking, ≥ 1 surgical procedure over the 5 years preceding the cancer date. Among several methods for taking into account propensity, adjustment, matching, stratification (most often by quintiles) or weighting (i.e. inverse probability treatment weighting, IPTW) can be used. In our particular case, we chose to use propensity predicted probabilities as adjustment covariates rather than matching, stratification or weighting, because our analysis was already matched (with strata defined by a case and matched controls).

We first explored the univariate association between exposure to treatments or other covariates with colorectal cancer using conditional logistic regression with adjustment on propensity scores. A multivariate conditional logistic regression model was then built by entering exposure to treatments, propensity scores and all covariates with a *P*-value < 0.20 in univariate analysis. All analyses were performed with SAS v9.4 software (SAS institute Inc, Cary, NC).

Results

Study population

The study recruited 144 cases and 286 controls, since two cases were matched with only one control. Baseline characteristics of cases and their matched controls are presented in Table 1. Mean age of patients was 52.5 (standard deviation (SD) = 15.7) years, 178 (41%) were female, 161 (37%) had Crohn's disease, 337 (78%) had an extensive colitis and IBD duration was on average 15.2 (SD = 10.7) years. Sixty-five cases occurred before 2004 (range 1961 – 2003) and 79 cases occurred in 2004 or after (range 2004-2007). A primary sclerosing cholangitis was found more frequently in cases (12%) than in matched controls (2% - $P < 0.001$). Over the 5 years preceding the date of cancer, there was no difference between cases and controls regarding the proportion of patients with more than one flare per year or the proportion of patients with at least one medical visit per year, however, the proportion of patients with history of at least one surgical procedure was lower in cases (17%) than in controls (25%, $P = 0.0327$)

Exposure to IBD drugs and propensity scores

Based on source medical files, exposure to salicylates or thiopurines the year of cancer was missing in 4 (3%) cases (3 < 2004, 1 \geq 2004) and 6 (2%) controls (5 < 2004, and 1 \geq 2004), so comparisons were made between 140 cases and 280 controls (Table 2). Exposure to salicylates treatment during the year of cancer did not differ between cases and their respective controls (51% vs. 58%, $P = 0.1369$). The mean duration of exposure to salicylates was 8.8 ± 9 (mean \pm standard deviation) years in cases and 10.7 ± 8 years in controls ($P = 0.07$). Among patients exposed to

salicylates the year of cancer, 135 controls (83%) and 56 cases (80%) had been exposed for more than two years before the year of cancer. No difference was found for exposure to thiopurines during the year of cancer (22% vs 23%, $P = 0.7978$).

However, exposure to thiopurines at any moment preceding the cancer was lower in cases (31% vs. 41%, $P = 0.0356$). No difference was found between cases and controls for anti-TNF therapy or other immune-suppressive therapy, including corticosteroids, during the year of cancer. Eleven cases and three controls – all with primary sclerosing cholangitis – were treated with ursodeoxycholic acid.

Among case and control patients exposed or non-exposed to aminosalicylates in the year of cancer, 97% and 95% respectively underwent a colonoscopy within the 5 years preceding the diagnosis of cancer in cases (and the corresponding index date in controls). These percentages were 83% and 75% for the 2-year period preceding the diagnosis of cancer, and 14% and 20% for the 5 to 2-year period before the diagnosis of cancer. Exploration of factors associated with exposure to salicylates during the year of cancer (Table S1) showed that, before 2004, the probability of being treated with salicylates was lower in men (OR= 0.494, 95%CI 0.263-0.927, $P = 0.0282$). In 2004 or after, treatment with salicylates was positively associated with age (OR = 1.034 per one year increase, 95%CI 1.015-1.054, $P < 0.001$), and negatively associated with Crohn's diseases (OR = 0.412, 95%CI 0.222-0.765, $P = 0.0049$) and with history of colonic surgery (OR = 0.373, 95% CI 0.183-0.763, $P = 0.0068$). Association of salicylates treatment with primary sclerosing cholangitis did not reach statistical significance either before 2004 (OR = 2.364, 95%CI 0.556-10.053, $P = 0.2442$) or in 2004 or after (OR = 4.813, 95%CI 0.923-25.11, $P = 0.0623$). When this analysis was repeated for thiopurine therapy (Table S2), we found that, before 2004, the probability of being treated with thiopurine was

negatively associated with history of colonic surgery (OR = 0.231, 95%CI 0.063-0.838, $P = 0.0258$) and positively associated with Crohn's disease (OR = 8.343, 95%CI 3.236-21.50, $P < 0.001$). In 2004 or after, propensity score for thiopurine therapy was negatively associated with age (OR = 0.963 per one year increase, 95%CI 0.942-0.984, $P < 0.001$), and with history of colonic surgery (OR = 0.350, 95%CI 0.152-0.804, $P = 0.0134$) and positively associated with Crohn's disease (OR = 5.129, 95%CI 2.487-10.58, $P < 0.001$).

The derived propensity scores for salicylate treatment were higher in cases than their respective matched controls (58.3% vs. 54.3%, $P < 0.001$) but no significant difference was found as regards propensity score for thiopurines (24.0% vs. 22.4%, $P = 0.0721$).

Effect of salicylates and thiopurines

By univariate analysis adjusted on the propensity score for receiving salicylates treatment, a protective effect of exposure to salicylates during the year of cancer was found (OR = 0.567, 95%CI 0.359-0.896, $P = 0.0150$). Detailed analyses stratified by year of cancer (<2004, ≥ 2004), by IBD subtype and according to presence of longstanding extensive colitis (Figure 1) showed that the most protective effect was found in patients with longstanding extensive colitis before 2004 (OR=0.345, 95%CI 0.148-0.801, $P = 0.0133$) and in patients with ulcerative colitis and longstanding extensive colitis (OR=0.302, 95%CI 0.135-0.675, $P = 0.0036$). There was no significant preventive effect in the subset of patients with Crohn's disease (OR=0.736, 95%CI 0.348-1.556, $P = 0.4223$).

By univariate analysis adjusted on the propensity score for receiving thiopurines, no association was observed between thiopurines treatment and colorectal cancer (OR

= 0.828, 95%CI 0.488-1.403, $P = 0.4826$). This was also the case for all stratified analyses (Figure 2).

Multivariate analysis adjusted on propensity scores for receiving salicylates or thiopurines confirmed the independent association of salicylates treatment with cancer (OR = 0.587, 95%CI: 0.367-0.937, $P = 0.0257$), and the increased risk associated with primary sclerosing cholangitis (OR = 8.321, 95%CI: 1.172-59.10, $P = 0.0342$); no other covariate met the statistical level of significance (Table 3).

Discussion

Using a propensity-adjusted case-control study nested in the CESAME cohort, covering the 1961-2007 period, we confirmed the overall chemopreventive effect of exposure to salicylates in the risk of CRC in IBD, but we failed to confirm this effect for thiopurines.

In 1994 was published the first individual case-control study suggesting a chemopreventive effect of sulfasalazine on the risk of colorectal cancer.²⁴ In 2004 was presented during the Digestive Disease Week the results of the first meta-analysis of case-control and cohort studies in ulcerative colitis, suggesting a halving of the risk of CRC in patients with a regular exposure to salicylates, at an average daily dose of 1.2 g mesalamine equivalents or more.⁸ In this context, it is plausible that gastroenterologists were progressively more prone from the late 90s to prescribe salicylates in patients with ulcerative or Crohn's colitis at high risk of CRC, partly or purely for the purpose of chemoprevention, and particularly after communication of results of the first positive meta-analysis. This propensity bias could lead to an over-representation of exposure to salicylates in patients at higher intrinsic risk of CRC, that could in turn mask the real chemopreventive effect of aminosalicylates in case-control and cohort studies.

Therefore, in our case-control study, we decided to adjust the main analyses on the propensity for receiving aminosalicylates. In addition, in order to account for temporal change in the behaviour of prescribers, we used two separate logistic models for building the propensity score before 2004 and from 2004. We observed that, before adjustment on propensity, the crude percentages of patients were not different between cases and controls, whatever the expression of the exposures to salicylates (ever use, percentage of time of use within the 5-year period before cancer or any

use in the year of diagnosis of cancer). There was a change in the main result regarding aminosalicylates after adjustment on propensity and other prognosis factors, with a final significant 41% reduction in the risk of CRC in patients with IBD exposed to aminosalicylates in the multivariate model. We believe that this observation is of methodological interest and should be taken into account in further case-control or cohort studies exploring the impact of drugs that are known or suspected candidates for decreasing a risk.

The impact of exposure to aminosalicylates on the risk of CRC was clear in patients with ulcerative colitis, particularly in those with longstanding extensive colitis. This result is in line with most individual studies and meta-analyses that addressed the question of the chemopreventive effect of aminosalicylates and included patients with ulcerative colitis. One individual population-based study, covering a relatively recent historical period (1995-2008) had a negative result, but in this study there was not stratification for the extent of colitis, and there was no use of methods to control indication bias no adjustment for propensity.²⁵ A meta-analysis coming from the same group distinguished referral and non-referral populations, and found no chemopreventive signal in the non-referral populations.¹¹ However, in this meta-analysis, CESAME data were classified as coming from a referral population. Two-third of the CESAME investigators were gastroenterologists with partial or pure private practice outside the hospital, and the observed incidences of CRC in CESAME were identical to those reported in meta-analyses from population-based studies.² So we believe that the CESAME design is much closer to that of population-based studies than that of referral-centre studies.

It can be speculated that patients who have a good adherence to treatment with aminosalicylates also have a better adherence to endoscopic surveillance, this latter

phenomenon representing the real cause of decrease in colorectal cancer incidence. However, in our study, almost all patients exposed or non-exposed to aminosalicylates underwent at least one colonoscopy within the 5 years preceding the index date, which excludes this bias.

Growing evidence suggests that epidemiology and carcinogenesis of CRC in ulcerative colitis and Crohn's colitis are the same.² However, we failed in our study to reproduce in patients with Crohn's disease the favourable effect of exposure to salicylates demonstrated in patients with ulcerative colitis. We must be prudent before drawing a negative conclusion in Crohn's disease because of methodological limitations. Patients with Crohn's disease who are at high risk of CRC and good candidates for chemoprevention are those with longstanding extensive colitis. These patients represent a small subset of patients with Crohn's disease, and their separate analysis leads to underpowered and uncertain multiple sub-stratifications. In addition, few patients with Crohn's disease are now chronically exposed to salicylates, and aminosalicylates are often prescribed for the sole purpose of chemoprevention in patients at highest risk of colorectal cancer, leading to a high propensity bias. Finally, we have limited global view in this field because, to date, there is no meta-analysis on the chemopreventive effect of aminosalicylates restricted to Crohn's disease or Crohn's colitis.

We also failed to confirm a chemopreventive effect of thiopurines in this case-control study that covered the 1961-2007 period, while we reported in a previous study a reduction of the risk in patients with longstanding extensive colitis exposed to thiopurines in the 2004-2007 period.⁵ First, our case-control study was adequately powered for salicylates, but not for thiopurines. Second, we can speculate that, if thiopurines act via their anti-inflammatory effect, the efficacy signal would become

apparent if patients exposed to thiopurines have a milder 'mean' colonic inflammation than the patients who are not exposed. The use of thiopurines has been restricted up to the early 2000s to a subset of patients with the most severe inflammation. In the study by Matula et al, patients exposed to 6-mercaptopurine were more often exposed to corticosteroids than those non exposed, suggesting that chronic inflammation was not lower, but greater, in patients treated with thiopurines than in those not treated with thiopurines.¹² Following the diffusion of thiopurines, it is plausible that this figure has been inverted and opens an historical window more favourable to demonstrate the efficacy of thiopurines.^{5, 18, 19} Unfortunately, we have no tool to validate this hypothesis in the absence of markers of intestinal inflammation in exposed vs. non-exposed patients in most studies.

We must point out some limitations of our study. The assessment of exposure to drugs was mainly retrospective. The cases of CRC that were diagnosed before the prospective observational period of the CESAME cohort did not provoke death by the enrolment in the cohort, leading to an over-representation of relatively benign cases of CRC within this period. Finally, in our multivariate model, we were not able to adjust for some lifestyle factors that are established risk factors for CRC (such as alcohol consumption or lack of physical exercise), and for chronic histological activity of colonic inflammation.

In conclusion, our study is confirmative of the favourable impact of chronic exposure of salicylates on the risk of CRC in IBD, with a maximal magnitude in patients with longstanding extensive ulcerative colitis.

FIGURE LEGEND

Figure 1. Multivariate-adjusted exploratory analyses of the association between exposure to aminosalicylates and colorectal cancer in various subgroups of patients. CD refers to Crohn's disease. UC refers to Ulcerative colitis or inflammatory bowel disease, unclassified. LEC refers to longstanding extensive colitis, defined by IBD duration superior to ten years and an estimated cumulative extent of colonic inflammation of 50% or greater. Years refer to the year of colorectal cancer diagnosis

Figure 2. Multivariate-adjusted exploratory analyses of the association between exposure to thiopurines and colorectal cancer in various subgroups of patients. CD refers to Crohn's disease. UC refers to Ulcerative colitis or inflammatory bowel disease, unclassified. LEC refers to longstanding extensive colitis, defined by IBD duration superior to ten years and an estimated cumulative extent of colonic inflammation of 50% or greater. Years refer to the year of colorectal cancer diagnosis

Supporting Information

Table S1. Propensity for being treated with aminosalicylates the year of cancer according to covariates and calendar periods

Table S2. Propensity for being treated with thiopurines the year of cancer according to covariates and calendar periods

Appendix S1. List of collaborators of the CESAME Study Group

AUTHORSHIP

Guarantor of the article: Fabrice Carrat. Author contributions: LB and FC were jointly responsible for the study concept, design and implementation. LB and FS were responsible for the reviewing of medical data extracted from source patient files. FC

was responsible for all statistical analyses. LB and FC were jointly responsible for the writing of the first draft of the report. All authors took part in the revision of the manuscript and approved the final version of the manuscript.

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Collaborators of the CESAME Study group are listed in Supporting information, Appendix S1

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Table 1. Patient baseline characteristics

	Cases (n=144)	Controls (n=286)	P - value
Age – years (mean ± SD)	52.6 ± 15.8	52.5 ± 15.7	*
Sex female -	60 (42)	118 (41)	*
Crohn's disease – no. (%)	55 (38)	106 (37)	*
Ulcerative colitis or IBD unclassified – no. (%)	89 (62)	180 (63)	
Duration of IBD – years (mean ± SD)	15.6 ± 10.9	15.0 ± 10.7	*
Extensive colitis	114 (79)	223 (78)	*
BMI	23.7 ± 4.6	23.7 ± 3.7	0.6755
Primary sclerosing cholangitis	17 (12)	6 (2)	<0.001
Active smoking**	10 (7)	33 (12)	0.1303
Status over 5 years preceding cancer			
> 1 flare / year***	22 (17)	35 (13)	0.3587
>= 1 medical visit /year	106 (74)	218 (76)	0.5403
>= 1 Surgical procedure	25 (17)	75 (26)	0.0327

IBD, inflammatory bowel disease; SD, standard deviation; * matching criteria, ** 1 missing value, ***

32 missing values,

Table 2. Exposure to IBD drugs in cases and controls

	Cases (n=140)	Controls (n=280)	P - value
<u>Salicylates</u>			
Mesalazine			
Ever exposed (n (%))	103 (74)	221 (79)	0.1603
YoC exposed*	57 (41)	115 (41)	0.8565
% 5 years**	40.0 +/- 44.0	39.6 +/- 42.7	0.9451
Olsalazine			
Ever exposed	4 (3)	27 (10)	0.0232
YoC exposed*	1 (1)	10 (4)	0.1249
% 5 years**	0.2 +/- 1.2	2.5 +/- 13.8	0.1923
Sulfasalazine			
Ever exposed	52 (38)	117 (42)	0.3071
YoC exposed*	12 (9)	39 (14)	0.0717
% 5 years**	7.8 +/- 24.9	11.2 +/- 29.1	0.2716
Any salicylate			
Ever exposed	121 (86)	256 (91)	0.0977
YoC exposed*	72 (51)	162 (58)	0.1369
% 5 years**	48.3 +/- 44.6	53.7 +/- 45.0	0.2876
Propensity score to receive salicylates (during the YoC) (m +/- SD)	58.3 +/- 17.5	54.3 +/- 18.0	<0.001
<u>Thiopurines</u>			
Azathioprine			
Ever exposed	43 (31)	111 (40)	0.0418
YoC exposed*	31 (22)	63 (23)	0.9308
% 5 years**	16.6 +/- 32.6	17.0 +/- 32.7	0.9492
Mercaptopurine			
Ever exposed	4 (3)	7 (3)	0.8313
YoC exposed*	1 (1)	3 (1)	0.7256
% 5 years**	0.5 +/- 4.5	0.4 +/- 4.8	0.7511
Thioguanine			
Ever exposed	0 (0)	3 (1)	0.9906
YoC exposed*	0 (0)	0 (0)	—
% 5 years**	0 +/- 0	0.3 +/- 3.2	0.9892
Any thiopurines			
Ever exposed	44 (31)	114 (41)	0.0356
YoC exposed*	31 (22)	65 (23)	0.7978
% 5 years**	17.1 +/- 33.2	17.7 +/- 32.9	0.9272
Propensity score to receive thiopurines (during the YoC)	24.0 +/- 19.0	22.4 +/- 17.5	0.0721

<u>Anti-TNF therapy</u>			
Ever exposed	13 (9)	23 (8)	0.7552
YoC exposed	9 (6)	14 (5)	0.5911
% 5 years**	2.0 +/- 10.2	1.6 +/- 7.8	0.6426
<u>Methotrexate</u>			
Ever exposed	7 (5)	16 (6)	0.7578
YoC exposed*	4 (3)	7 (3)	0.8232
% 5 years**	1.2 +/- 8.3	1.2 +/- 8.6	0.9754
<u>Others (cyclosporine, cyclophosphamide, FK-506)</u>			
Ever exposed	3 (2)	8 (3)	0.6709
YoC exposed*	0 (0)	1 (0)	0.9917
% 5 years**	0.3 +/- 3.4	0.2 +/- 1.8	0.6793
<u>Any immune-suppressive therapy</u>			
Ever exposed	46 (33)	115 (41)	0.0642
YoC exposed*	35 (25)	77 (28)	0.5372
% 5 years**	18.4 +/- 34.6	20.0 +/- 34.8	0.5755
<u>Corticosteroids</u>			
Ever exposed	92 (66)	208 (74)	0.0331
YoC exposed*	31 (22)	55 (20)	0.6549
% 5 years**	13.8 +/- 26.7	14.0 +/- 24.5	0.9752
<u>Ursodeoxycholic acid</u>			
Ever exposed	13 (9)	4 (1)	0.0011
YoC exposed*	11 (8)	3 (1)	0.0025
% 5 years**	5.0 +/- 19.6	0.9 +/- 8.9	0.0239
<u>Folinic acid</u>			
Ever exposed	3 (2)	20 (7)	0.0409
YoC* exposed	1 (1)	11 (4)	0.0783
% 5 years**	0.4 +/- 3.2	1.9 +/- 11.3	0.1897

SD, standard deviation; YoC, year of cancer; * any exposure during the calendar year when cancer was diagnosed in cases; ** percentage of time under treatment during the five years preceding the date of colorectal cancer diagnosis

Table 3. Multivariate analysis of factors associated with colorectal cancer, adjusted on propensity scores for receiving salicylates or thiopurines.

	OR	95%CI	<i>P</i> - Value
Salicylates in the YoC	0.587	0.367-0.937	0.0257
Thiopurines in the YoC	0.762	0.432-1.343	0.3468
Primary sclerosing cholangitis	8.321	1.172-59.10	0.0342
Active smoking*	0.831	0.357-1.935	0.6678
>= 1 Surgical procedure over the 5 years preceding cancer	1.210	0.288-5.087	0.7950

OR, odds-ratio; CI, confidence interval; YoC: year of cancer, i.e. the year when cancer was diagnosed in cases.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 done	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 done	Explain the scientific background and rationale for the investigation being reported
Objectives	3 done	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 done	Present key elements of study design early in the paper
Setting	5 done	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 Done(a) Done(b)	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7 Done	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* done	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 Done	Describe any efforts to address potential sources of bias
Study size	10 done	Explain how the study size was arrived at
Quantitative variables	11 done	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 Done	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses

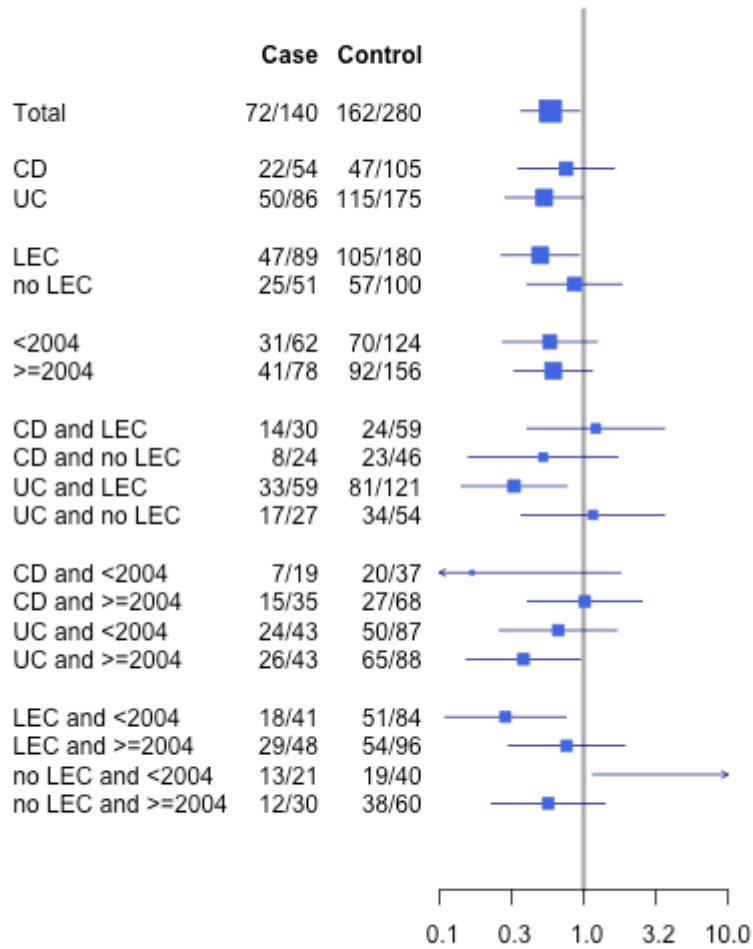
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Results		
Participants	13* N/A	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed <hr/> (b) Give reasons for non-participation at each stage <hr/> (c) Consider use of a flow diagram
Descriptive data	14 done*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <hr/> (b) Indicate number of participants with missing data for each variable of interest <hr/> (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15* done	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
Main results	16 done	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included <hr/> (b) Report category boundaries when continuous variables were categorized <hr/> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 done	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 done	Summarise key results with reference to study objectives
Limitations	19 done	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 done	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 N/A	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 done	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Salicylates



Thiopurines

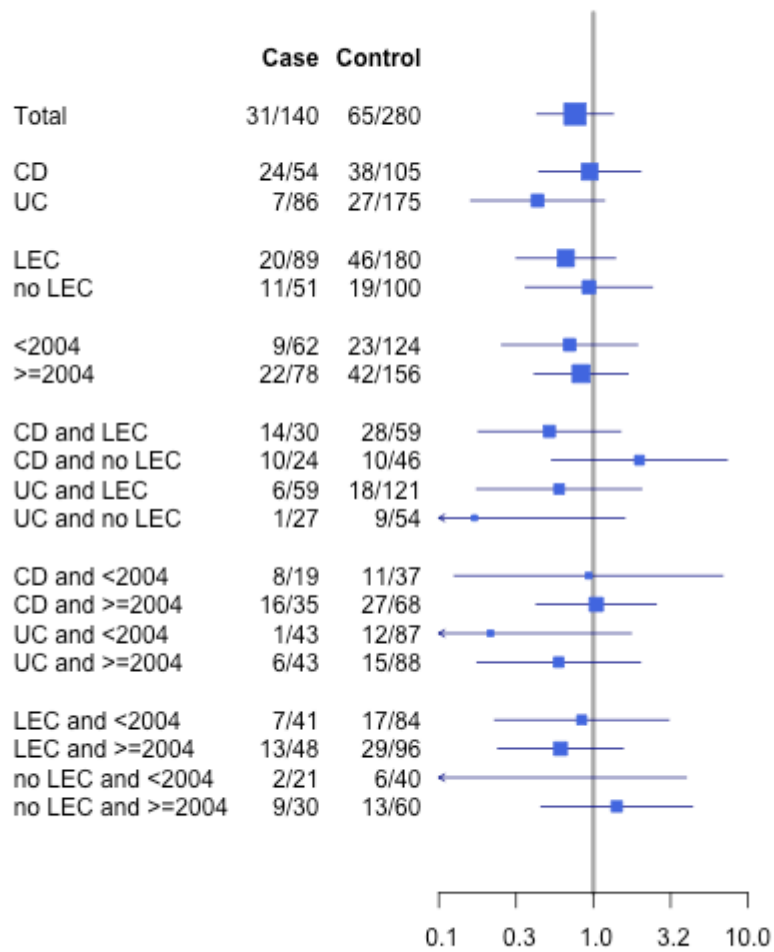


Table S1. Propensity for being treated with aminosalicylates the year of cancer according to covariates and calendar periods

Covariates	<2004		≥2004	
	OR	p-value	OR	p-value
Age (per yr increase)	1.02 (0.99-1.04)	0.19	1.03 (1.02-1.05)	<0.001
Male gender (vs female)	0.49 (0.26-0.93)	0.03	1.02 (0.55-1.88)	0.96
Crohn's disease (vs ulcerative colitis or IBD unclassified)	0.81 (0.42-1.56)	0.52	0.41 (0.22-0.77)	0.004
Duration of IBD (per year increase)	1.00 (0.96-1.03)	0.78	1.03 (0.99-1.07)	0.10
Extensive colitis	1.29 (0.63-2.67)	0.49	0.62 (0.30-1.31)	0.22
Primary sclerosing cholangitis (Yes vs No)	2.36 (0.56-10.1)	0.24	4.81 (0.92-25.1)	0.06
Active smoking (Yes vs No)	0.97 (0.29-3.27)	0.96	0.91 (0.37-2.25)	0.83
≥ 1 surgical procedure over the 5 years	0.64 (0.30-1.39)	0.26	0.37 (0.18-0.76)	0.007

IBD, inflammatory bowel disease; OR, odds ratio

Table S2. Propensity for being treated with thiopurines the year of cancer according to covariates and calendar periods

	<2004		≥2004	
Covariates	OR	p-value	OR	p-value
Age (per yr increase)	1.00 (0.97-1.03)	0.93	0.96 (0.94-0.98)	<0.001
Male gender (vs female)	0.44 (0.18-1.08)	0.07	1.08 (0.55-2.14)	0.82
Crohn's disease (vs ulcerative colitis or IBD unclassified)	8.34 (3.24-21.5)	<0.001	5.13 (2.49-10.6)	<0.001
Duration of IBD (per year increase)	1.04 (0.99-1.09)	0.13	1.01 (0.97-1.05)	0.56
Extensive colitis	2.07 (0.68-6.31)	0.20	1.58 (0.71-3.51)	0.27
Primary sclerosing cholangitis (Yes vs No)	0.23 (0.02-2.44)	0.22	0.55 (0.12-2.45)	0.44
Active smoking (Yes vs No)	0.96 (0.18-5.22)	0.96	0.81 (0.32-2.05)	0.66
≥ 1 surgical procedure over the 5 years	0.23 (0.06-0.84)	0.03	0.35 (0.15-0.80)	0.01

IBD, inflammatory bowel disease; OR, odds ratio

Appendix S1

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 Lemièrre; 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 Poudroux; 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 Igllicki; 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; 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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 Aurox; 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; 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Denis Soudan; Olivier Fourdan; Gilles Minier; Jeanne Languépin; 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 Maslah; 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 Ecuier; Arnaud Patenotte; 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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 Thieffin; 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'Abrevanel; Hélène Dall'Osto; Sophie Hervé; Jean Lefebvre; Damien Levoir; Philippe Lillo; Michel Rouch; Muriel Mathonnet; Mercedes De Lustrac; François-Jean Ramond; Bernard Roupret; Alain Soupison;

The following persons participated in the central Coordination of the Study: Djamila Ait-Ouadda, Yves Barbaza, Brice Bayart, Thomas Bottini, Franck Cochet, Isabelle Goderel, Orélien Maury, Léa Mbonyingo, Vanessa Pourtau, Elise Rasoanarivo, Laure Romain-Huttin, Anne-Violaine Sallé, Jonathan Trang (Unité UMR-S 707); Hakeem Admane, Elodie Drouet (Unité de Recherche Clinique de l'Est Parisien)