MICI ET CANCERS

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25/03/2016

MICI et cancers

- I- Cancers associés aux MICI
- II- Cancers liés aux traitements des MICI

Enseignement de la cohorte CESAME

- Cohorte prospective observationnelle française « Cancers Et Sur-risque Associé aux Maladies inflammatoires intestinales En France »
- 19486 patients, 680 gastroentérologues
- Inclusion sur 1 an de 05/04-06/05 >> suivi jusqu'au 31/12/2007
- 60.3% MC / 39.7% RCH

Beaugerie, Lancet 2009

Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study

Laurent Beaugerie, Nicole Brousse, Anne Marie Bouvier, Jean Frédéric Colombel, Marc Lémann, Jacques Cosnes, Xavier Hébuterne, Antoine Cortot, Yoram Bouhnik, Jean Pierre Gendre, Tabassome Simon, Marc Maynadié, Olivier Hermine, Jean Faivre, Fabrice Carrat, for the CESAME Study Group

GASTROENTEROLOGY 2011;141:1621–1628

Increased Risk for Nonmelanoma Skin Cancers in Patients Who Receive Thiopurines for Inflammatory Bowel Disease

LAURENT PEYRIN–BIROULET,* KIARASH KHOSROTEHRANI,‡ FABRICE CARRAT,§ ANNE–MARIE BOUVIER,‖ JEAN–BAPTISTE CHEVAUX,* TABASSOME SIMON,¶ FRANK CARBONNEL,# JEAN–FRÉDÉRIC COLOMBEL,** JEAN–LOUIS DUPAS,‡‡ PHILIPPE GODEBERGE,§§ JEAN–PIERRE HUGOT,‖‖ MARC LÉMANN,¶¶ STÉPHANE NAHON,## JEAN–MARC SABATÉ,*** GILBERT TUCAT,‡‡‡ and LAURENT BEAUGERIE§§§ for the Cesame Study Group

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Inflamm Bowel Dis. 2012 Nov;18(11):2063-71. doi: 10.1002/ibd.22889. Epub 2012 Jan 23.

Excess primary intestinal lymphoproliferative disorders in patients with inflammatory bowel disease.

Sokol H, Beaugerie L, Maynadié M, Laharie D, Dupas JL, Flourié B, Lerebours E, Peyrin-Biroulet L, Allez M, Simon T, Carrat F, Brousse N; CESAME Study Group.

GASTROENTEROLOGY [illegible] 21–1628

GASTROENTEROLOGY 2013;145:166–175

Increased Risk for Nonmelanoma Skin Cance[illegible] Thiopurines for Inflammatory Bowel Dise[illegible]

LAURENT PEYRIN–BIROULET,* KIARASH KHOSROTEHRA[illegible]
JEAN–BAPTISTE CHEVAUX,* TABASSOME SIMON,[¶] F[illegible]
JEAN–LOUIS DUPAS,[‡‡] PHILIPPE GODEBERGE[5e]
JEAN–MARC SABATÉ,[***] GILBERT TUCAT[‡‡]

Lymphoproliferative d[illegible] thiopurines for in[illegible] observatio[illegible]

Laurent P[illegible]
A[illegible]

Risk of Colorectal High-Grade Dysplasia and Cancer in a Prospective Observational Cohort of Patients With Inflammatory Bowel Disease

LAURENT BEAUGERIE,[1] MAGALI SVRCEK,[2] PHILIPPE SEKSIK,[1] ANNE–MARIE BOUVIER,[3] TABASSOME SIMON,[4]
MATTHIEU ALLEZ,[5] HEDIA BRIXI,[6] JEAN–MARC GORNET,[5] ROMAIN ALTWEGG,[7] PHILIPPE BEAU,[8] BERNARD DUCLOS,[9]
ARNAUD BOURREILLE,[10] JEAN FAVRE,[3] LAURENT PEYRIN–BIROULET,[11] JEAN–FRANÇOIS FLÉJOU,[2] and
FABRICE CARRAT,[12] for the CESAME Study Group

Infl[illegible]

Exc[illegible] disorders in patients with inflammatory bowel disease.

Sokol H[illegible] Flourié B, Lerebours E, Peyrin-Biroulet L, Allez M, Simon T, Carrat F, Brousse N; CESAME Study Group.

GASTROENTEROLOGY [illegible] 21–1628

Inflamm Bowel Dis. 2013 Aug;19(9):1823-6. doi: 10.1097/MIB.0b013e31828c84f2.

Incidence, presentation, and prognosis of small bowel adenocarcinoma in patients with small bowel Crohn's disease: a prospective observational study.

Elriz K[1], Carrat F, Carbonnel F, Marthey L, Bouvier AM, Beaugerie L; CESAME study group.

Thiopurines for Inflammatory Bowel Dis[illegible]

LAURENT PEYRIN–BIROULET,* KIARASH KHOSROTEHRA[illegible]
JEAN–BAPTISTE CHEVAUX,* TABASSOME SIMON,[illegible]
JEAN–LOUIS DUBAS,‡‡ PHILIPPE GODEBERGE,[illegible]

[illegible] in a Prospec[illegible]
[illegible]el Disease
[illegible] SIMON,[4] [illegible] DUCLOS,[9]

Inflammatory bowel disease

ORIGINAL ARTICLE

Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer

Laurent Beaugerie,[1] Fabrice Carrat,[2] Jean-Frédéric Colombel,[3] Anne-Marie Bouvier,[4] Harry Sokol,[1] Abdenour Babouri,[5] Franck Carbonnel,[6] David Laharie,[7] Jean-Luc Faucheron,[8] Tabassome Simon,[9] Aimery de Gramont,[10] Laurent Peyrin-Biroulet,[5] for the CESAME Study Group

[illegible]udy

LAUR[illegible]
MATTHIEU [illegible]
ARNAUD BOUH[illegible]
FABRICE CARRAT,[illegible]

GASTROENTEROLOGY ... 45:166–175 ...21–1628

Inflamm Bowel Dis. 2013 Aug;19(9):1823-6. doi: 10.1097/MIB.0b013e31828c84f2.

Increased Risk of Acute Myeloid Leukemias and Myelodysplastic Syndromes in Patients Who Received Thiopurine Treatment for Inflammatory Bowel Disease

Anthony Lopez,* Morgane Mounier,‡ Anne-Marie Bouvier,§ Fabrice Carrat,|| Marc Maynadié,‡ Laurent Beaugerie,|| and Laurent Peyrin-Biroulet,* for the CESAME Study Group

AP&T Alimentary Pharmacology and Therapeutics

Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study

A. Bourrier*,†, F. Carrat‡,§, J.-F. Colombel¶, A.-M. Bouvier**, V. Abitbol††,‡‡, P. Marteau§§,¶¶, J. Cosnes*,†, T. Simon***,†††, L. Peyrin-Biroulet‡‡‡, L. Beaugerie*,† & the CESAME study group

MA
ARNAUD
FABRICE CARR

Recommandations

ECCO Guideline/Consensus Paper

European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies

Vito Annese,[a] Laurent Beaugerie,[b] Laurence Egan,[c] Livia Biancone,[d] Claus Bolling,[e] Christian Brandts,[f] Daan Dierickx,[g] Reinhard Dummer,[h] Gionata Fiorino,[i] Jean Marc Gornet,[j] Peter Higgins,[k] Konstantinos H Katsanos,[l] Loes Nissen,[m] Gianluca Pellino,[n] Gerhard Rogler,[o] Franco Scaldaferri,[p] Edyta Szymanska,[q] Rami Eliakim; on behalf of ECCO

Journal of Crohn's and Colitis, 2015, 945–965
doi:10.1093/ecco-jcc/jjv141
Advance Access publication August 20, 2015
ECCO Guideline/Consensus Paper

MICI et cancers

- Cancers associés aux MICI

- Cancers et traitement des MICI

MICI et cancers

- Cancers associés aux MICI
  - Cancer des voies biliaires (cholangiocarcinome)
  - Cancer de l'intestin grêle
  - Cancer colo-rectal
  - Autres cancers

Cholangiocarcinome et CSP

- Concerne les patients atteints d'une inflammation chronique des voies biliaires (cholangite sclérosante primitive=CSP)
- Incidence CSP : 1/100 000
- <5% patients vivant avec une MICI

	Hepatobiliary tract cancers (155)					
Autoimmune disease	Cases	Deaths	SIR	95% CI	HR	95% CI
Digestive tract involvement						
Ankylosing spondylitis	17	16	1.50	0.87–2.41	1.25	0.76–2.04
Celiac disease	16	16	**2.72**	1.55–4.42	1.26	0.77–2.05
Crohn's disease	72	61	**2.63**	2.06–3.31	1.10	0.86–1.42
Discoid lupus erythematosus	4	4				
Immune thrombocytopenic purpura	9	7	**3.18**	1.44–6.06	1.39	0.66–2.91
Localized scleroderma	3	3				
Pernicious anemia	38	38	**1.68**	1.19–2.30	1.23	0.90–1.70
Polyarteritis nodosa	7	7	**2.90**	1.15–6.01	**2.13**	1.01–4.47
Sarcoidosis	35	34	**1.47**	1.02–2.05	1.20	0.86–1.68
Sjögren syndrome	6	5	1.85	0.67–4.05	**3.05**	1.28–7.28
Systemic lupus erythematosus	31	29	**2.70**	1.83–3.83	**1.54**	1.07–2.22
Systemic sclerosis	30	29	**2.42**	1.63–3.46	0.99	0.69–1.43
Ulcerative colitis	188	163	**4.51**	3.89–5.20	0.96	0.82–1.12

Castro, Clinical Gastroenterology and Hepatology 2014

Cholangiocarcinome et CSP

	ECC Cases (n=549)			ICC Cases (n=535)		
	OR	95% Confidence Interval	p-value	OR	95% Confidence Interval	p-value
Bile duct diseases						
Cholecochal cysts	47.1	30.4-73.2	<0.001	36.9	22.7 - 59.7	<0.001
Cholangitis	45.7	32.9-63.6	<0.001	64.2	47.7 - 86.5	<0.001
Biliary cirrhosis	11.8	3.7-38.2	<0.001	19.8	7.8 - 49.9	<0.001
Cholelithiasis	11.0	9.1-13.2	<0.001	13.5	11.3 - 16.1	<0.001
Choledocholithiasis	34.0	26.6-43.6	<0.001	22.5	16.9 - 30.0	<0.001
Cholecystitis	5.9	4.0-8.6	<0.001	8.5	6.1 - 11.7	<0.001
Cholecystectomy	12.0	9.5-15.3	<0.001	5.4	3.9 - 7.5	<0.001
Liver Flukes	-	-	-	-	-	-
Chronic liver diseases						
Alcoholic liver disease	4.5	2.2-9.1	<0.001	3.1	1.3 - 7.5	0.01
Nonspecified cirrhosis	5.4	2.9-10.2	<0.001	10.0	6.1 - 16.4	<0.001
Hemochromatosis	1.3	0.3-5.2	0.73	2.6	1.0 - 7.0	0.06
Non-alcoholic liver disease	2.4	0.9-6.5	0.08	3.0	1.2 - 7.3	0.02
HCV infection	1.5	0.2-11.0	0.67	4.4	1.4 - 14.0	0.01
Endocrine disorders						
Diabetes mellitus type II	1.5	1.3-1.8	<0.001	1.8	1.5 - 2.1	<0.001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Digestive disorders						
IBD	2.1	1.1-4.0	0.02	4.0	2.5 - 6.4	<0.001
Crohn's Disease	2.8	1.3-6.4	0.01	2.4	1.0 - 5.9	0.05
Ulcerative Colitis	1.7	0.7-4.0	0.27	4.5	2.6 - 7.9	<0.001
Duodenal ulcer	1.9	1.2-3.0	0.005	3.4	2.4 - 4.8	<0.001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Miscellaneous conditions						
Smoking	1.7	1.0-3.0	0.07	1.8	1.0 - 3.2	0.04
Obesity	1.1	0.7-1.8	0.71	1.7	1.1 - 2.6	0.01

Welzel, Clinical Gastroenterology and Hepatology 2007

Cholangiocarcinome et CSP

Table 2 Cholangiocarcinoma in patients with inflammatory bowel disease (IBD) and in population controls

	IBD		Population controls		Incidence rate ratio**
	No.	Incidence rate*	No.	Incidence rate*	
Overall	27	7.6 (5.2–11.0)	69	1.9 (1.5–2.4)	4.0 (2.5–6.4)
Years after IBD diagnosis/index date					
<1	5	12.9 (5.4–30.9)	9	2.3 (1.2–4.4)	5.6 (1.5–18.7)
1–4.9	6	4.9 (2.2–11.0)	21	1.7 (1.1–2.6)	2.9 (0.97–7.5)
5–9.9	8	8.5 (4.3–17.1)	17	1.7 (1.1–2.8)	4.9 (1.8–11.9)
≥10	8	7.8 (3.9–15.5)	22	2.1 (1.4–3.1)	3.8 (1.4–8.8)
Ulcerative colitis	22	8.2 (5.4–12.5)	55	2.0 (1.5–2.6)	4.1 (2.4–6.8)
Crohn's disease	5	4.3 (1.8–10.3)	17	1.4 (0.88–2.3)	3.0 (0.9–8.6)

Erichsen, Eur J Epidemiol 2009

Cholangiocarcinome et CSP

Table 1. IBD as a Potential Risk Factor for Cholangiocarcinoma

First Author	Country	Study Dates	Study Design	Risk Factor	CC Type	Cases (% With Risk Factor)	Controls (% With Risk Factor)	Risk Estimate (95% CI)	Selected Adjusted Variables
Welzel[48]	Denmark	1978-1991	Case-control	IBD	ICC	764 (0.92%)	3056 (0.20%)	4.67 (1.6-13.9)	Age, sex
Erichsen[49]	Denmark	1978-2003	Cohort	UC	ECC/ICC	Incidence rate 8.2	Incidence rate 2.0	4.1 (2.4-6.8)	Age, sex
				Crohn's disease	ECC/ICC	Incidence rate 4.3	Incidence rate 1.4	3.0 (0.9-8.6)	
Shaib[47]	United States	1993-1999	Case-control	UC	ICC	625	90,834	2.2 (1.2-3.9)	Age, sex, race, geographic location
				Crohn's disease	ICC	625	90,834	2.0 (0.6-6.3)	
Welzel[28]	United States	1993-1999	Case-control	UC	ICC	535 (2.4%)	102,782 (0.6%)	4.5 (2.6-7.9)	Age, sex, race, geographic location
				Crohn's disease	ICC	535 (0.9%)	102,782 (0.4%)	2.4 (1.0-5.9)	
				UC	ECC	549 (0.9%)	102,782 (0.6%)	1.7 (0.7-4.0)	
				Crohn's disease	ECC	549 (1.1%)	102,782 (0.4%)	2.8 (1.3-6.4)	

Table 2. Cholangitis and Choledocholithiasis as Potential Risk Factors for Cholangiocarcinoma

First Author	Country	Study Dates	Study Design	Risk Factor	CC Type	Cases (% With Risk Factor)	Controls (% With Risk Factor)	Risk Estimate (95% CI)	Selected Adjusted Variables
Welzel[48]	Denmark	1978-1991	Case-control	Cholangitis	ICC	764 (1.3%)	3056 (0.23%)	6.32 (2.3-17.5)	Age, sex
				Choledocholithiasis	ICC	764 (0.79%)	3056 (0.03%)	23.97 (2.9-198.9)	
Shaib[47]	United States	1993-1999	Case-control	Cholangitis	ICC	625 (3.4%)	90,834 (0.2%)	8.8 (4.9-16.0)	Age, sex, race, geographic location
				Choledocholithiasis	ICC	625 (1.1%)	90,834 (0.3%)	4.0 (1.9-8.5)	
Welzel[28]	United States	1993-1999	Case-control	Cholangitis	ICC	535 (12.5%)	102,782 (0.2%)	64.2 (47.7-86.5)	Age, sex, race, geographic location
				Choledocholithiasis	ICC	535 (11%)	102,782 (0.5%)	22.5 (16.9-30.0)	
				Cholangitis	ECC	549 (9.1%)	102,782 (0.2%)	45.7 (32.9-63.6)	
				Choledocholithiasis	ECC	549 (15.8%)	102,782 (0.5%)	34.0 (26.6-43.6)	

Tyson and El-Serag, Hepatology 2011

Cholangiocarcinome: Prévention

- Lors du diagnostic d'une CSP
  - Indication à une coloscopie +++
  - Puis coloscopie **annuelle quand association CSP-RCH +++**
  - **Surveillance CCK :** Bio/6 mois, cholangio-IRM annuelle

- Chémoprévention par acide urso-désoxycholique?
  - Uniquement pour CSP – 25 mg/kg/jour

Talwalkar, Inflamm Bowel Dis 2005

Cholangiocarcinome et CSP

Association RCH et CSP

- Risque de cholangiocarcinome 0,5-1% /an
- ↑ risque de CCR chez les patients CSP-RCH

Cancer de l'intestin grêle

Population générale

- Adénocarcinome
- Cancer rare
- 60 X moins fréquent que le cancer colo-rectal

Population MICI

- Adénocarcinome
- Concerne patient **MC**
- Evolution moyenne de plus de 15 ans
- Séquence: inflammation-dysplasie-cancer

	Incidence rate (/1000 patient-years)	Standardized incidence radio
Small bowel CD	**0.235**	**34.9**
Small bowel disease > 8 years	**0.464**	**46.0**

Palascak-Juif, Inflamma Bowel Dis 2005
Canavan, Aliment Pharmacol Ther 2006
Elriz K, Inflamm Bowel Dis 2013 (CESAME study group)

Cancer de l'intestin grêle

- **<u>Facteurs de risque connus :</u>**
  - Atteinte jéjunale
  - Maladie pénétrante et délabrante du grêle avec inflammation chronique
  - Durée d'évolution
  - Sexe masculin

Elriz K, Inflamm Bowel Dis 2013 (CESAME study group)
Annese V, Beaugerie L, et al. ECCO Guideline, JCC 2015

Cancer de l'intestin grêle : prévention ?

Table 3. Univariate Analysis of Treatment Variables Associated With SBA During CD

	Cases (N = 21)	Controls (N = 63)	OR*	95% CI
≥2 yr of salicylates, N (%)	6 (29)	36 (57)	0.29	0.10–0.82
≥6 months of steroids, N (%)	15 (71)	32 (51)	1.94	0.71–5.34
Azathioprine/6-mercaptopurine, N (%)	6 (29)	17 (27)	1.02	0.33–3.17
Methotrexate, N (%)	1 (5)	1 (2)	3.61	0.22–59.12
Infliximab, N (%)	0	1 (2)	Not calculable	
Small bowel resection, N (%)	5 (24)	46 (73)	0.07	0.01–0.32

*Odds ratio estimated from a conditional logistic regression including the matching factors and the individual characteristic listed.

Table 4. Final Multivariate Model of Significant Factors Independently Associated With SBA in CD

	OR*	95% CI
≥2 yr of salicylates	0.16	0.03–0.79
Small bowel resection	0.04	0.01–0.28

*Odds ratio based on a backward elimination conditional logistic regression model.

Piton G, Cosnes J, et al. Am J Gastroenterology 2008

Cancer de l'intestin grêle : Conclusion

PAS DE STRATEGIE DE SURVEILLANCE, mais…

- **Vigilance chez les patients MC avec atteinte iléale**
  - Signes évocateurs :
    - Symptômes digestifs alors que le patient est en rémission
    - Antériorité d'atteinte sévère du grêle
    - Non réponse au traitement médical optimisé de lésions du grêle
  - Entéro-IRM
  - VCE et entéroscopie: diagnostic ++

- **Chémoprévention ?**
  - Rôle de la cicatrisation muqueuse?
  - Dérivés du 5-ASA? (niveau de preuve : grade C)

Elriz K, Inflamm Bowel Dis 2013 (CESAME study group)
Annese V, Beaugerie L, et al. ECCO Guideline, JCC 2015

Cancer colo-rectal

Population générale

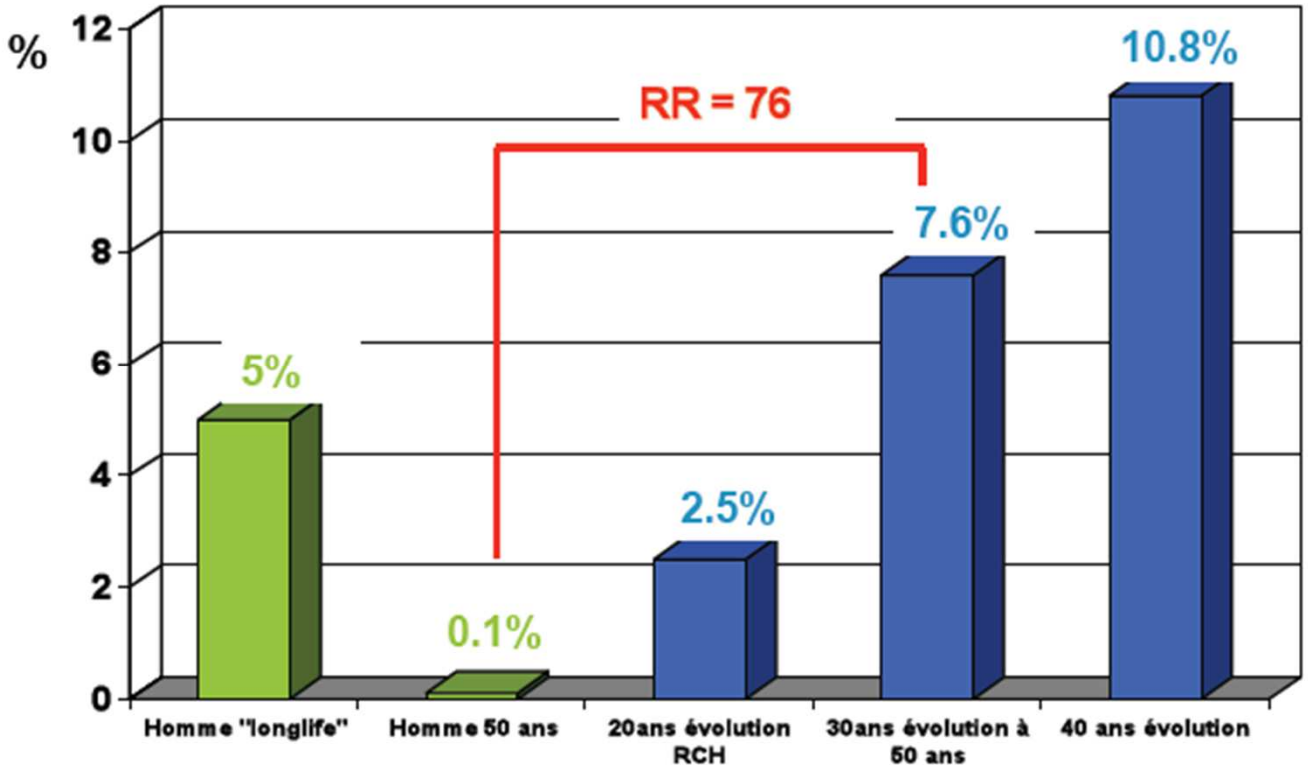
- 43 000 nouveaux cas/an
- 17 500 décès
- Risque cumulé au long de la vie : 4 à 5%
- Surtout > 50 ans

MICI

- Risque identique **RCH = MC**
- 1% de tous les cas de CCR, FDR majeur
- Risque ↑ lors **atteinte pancolique/CSP**
- Pathogénèse spécifique
- Transformation lente de lésions inflammatoires chroniques
- Séquence: inflammation – dysplasie –K

Institut National du Cancer 2015

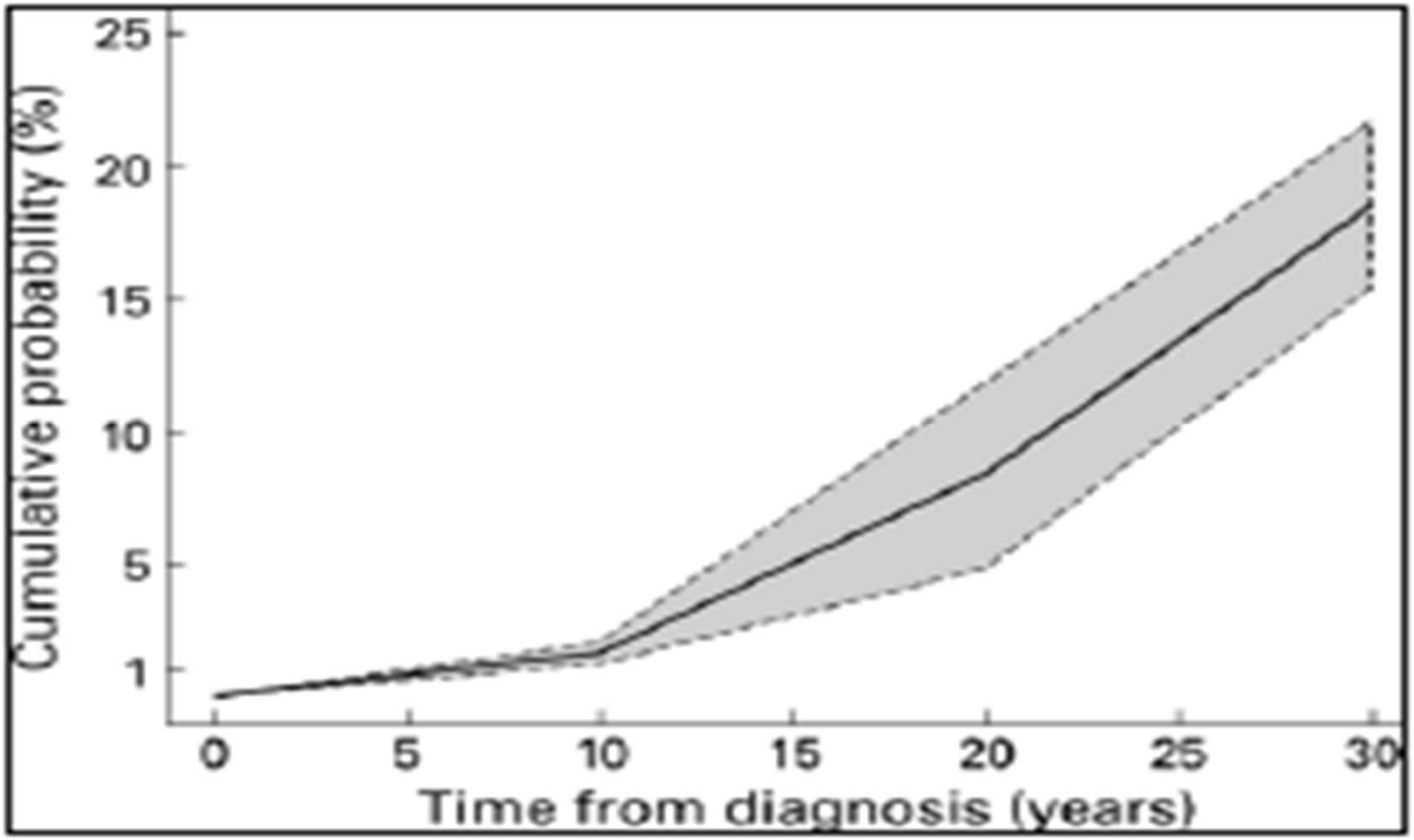
Risque cumulé de CCR dans les MICI



Bouvier, Rapport collectif « Incidence et mortalité par cancer en France 1978-2000 », 2003

Rutter, Gastroenterology 2006

Risque cumulé de CCR dans les MICI

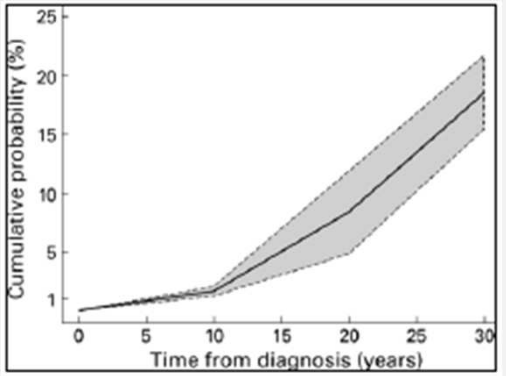


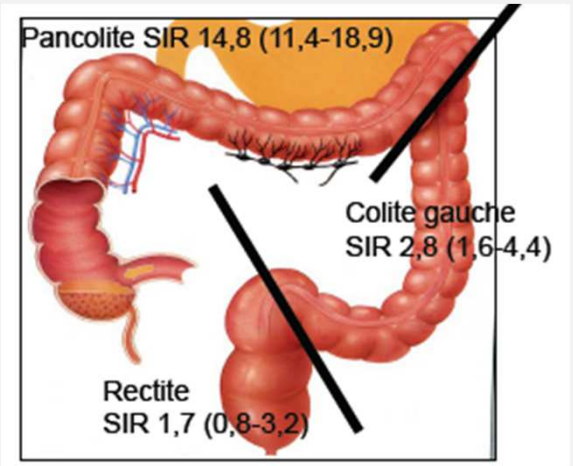
Itzkowitz, Gastroenterology 2004

CCR et MICI: Facteurs de Risque

- Durée d'évolution de la maladie +++
  - À 10 ans: 2%
  - À 20 ans: 8%
  - À 30 ans: 18%
- Étendue de la maladie: atteinte pancolique
- Antécédents familiaux de CCR au 1er degré < 50 ans
- Cholangite Sclérosante Primitive
  - RR X 3-10 /RCH
- Activité inflammatoire chronique

Après 7-10 ans d'évolution RCH, le risque est supposé augmenter de 0.5 à 1% chaque année





Itzkowitz, Gastroenterology 2004
Eaden, Gut 2001
Ekbom, NEJM 1990

CCR et MICI: risque identique entre RCH et MC?

- CCR sur colite ancienne étendue
  - MC: RR/pop gén: 18.2, risque cumulé CCR: 8% à 22 ans
  - RCH: RR/pop gén: 19.2, risque cumulé CCR: 7% à 20 ans

  → risque RCH = MC en cas de colite étendue

- Importance du type d'atteinte inflammatoire colique dans MC
  - MC pancolique **sans** intervalle de muqueuse saine: risque 10.6% à 25 ans
  - MC pancolique **avec** intervalle de muqueuse saine: risque 1.5% à 25 ans

Gillen, Gut 1994
Bergeron, Am J Gastroenterology 2010

CCR et MICI: cohorte CESAME

- CESAME observational cohort : incidence of high-grade dysplasia and colorectal cancer :
  - SIR for all IBD patients : 2.2 (1.5-3.0)
  - SIR for patients with long-standing extensive colitis : 7.0 (4.-10.5)
  - SIR for patients without long-standing extensive colitis : 1.1 (0.6-1.8)
- Risque = pancolite depuis 7-10 ans
- Dans les autres cas: risque = population générale

Beaugerie, Gastroenterology 2013

CCR et MICI + CSP = risque élevé

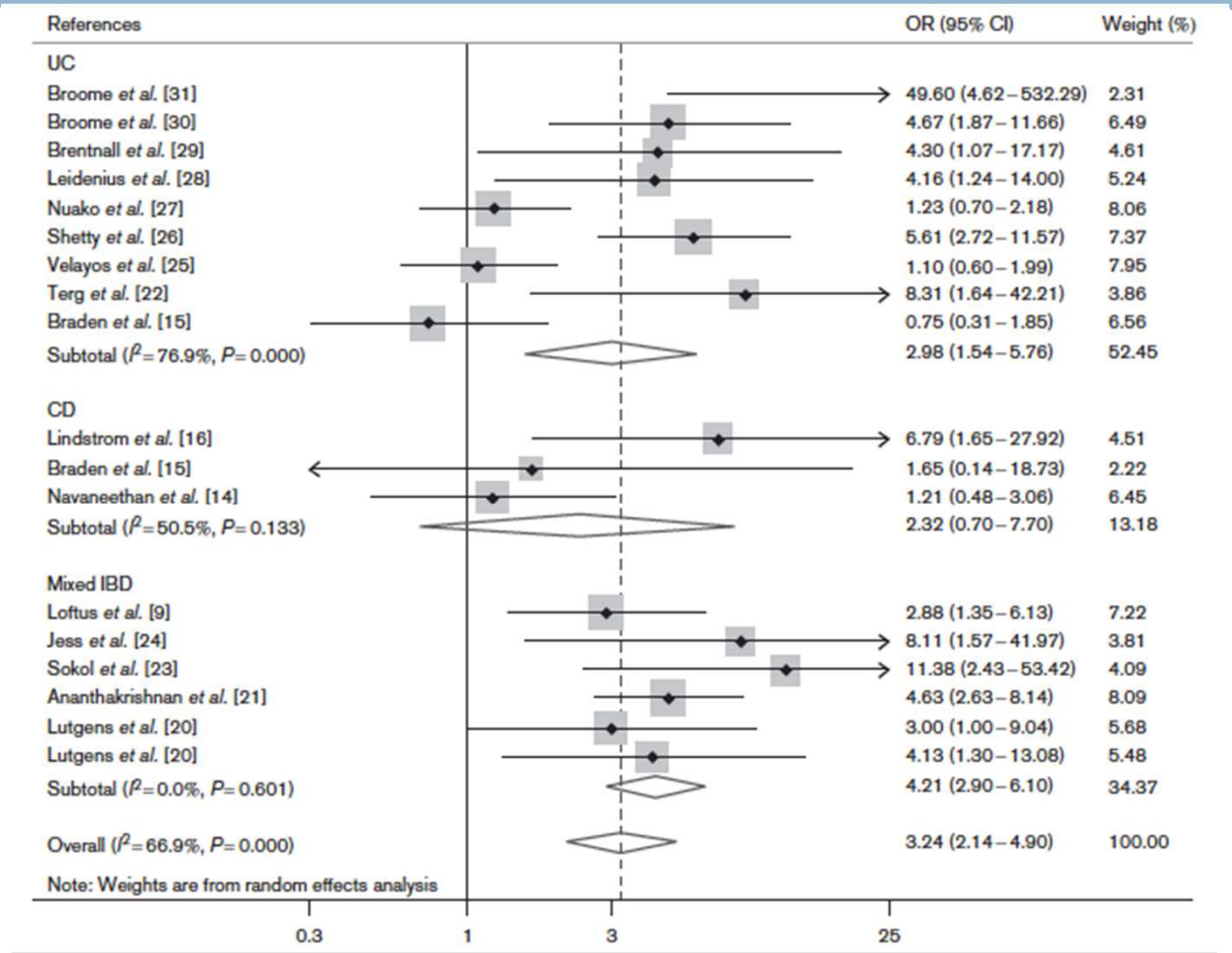


Fig. 2. Effect of PSC on the risk of development of colorectal neoplasia in patients with IBD. CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

OR 3.24 (2.14-4.90)

Zheng, Eur Journal Hepatol Gastroenterol 2016

CCR et MICI: Prévention

Personnes concernées

- Lésions s'étendant à un moment donné au-delà du rectum
- Surtout colite au dessus de l'angle gauche
- Evoluant depuis 7 à 10 ans
- Dès le diagnostic en cas de CSP

Moyens de prévention

• Chémoprévention

• Surveillance endoscopique

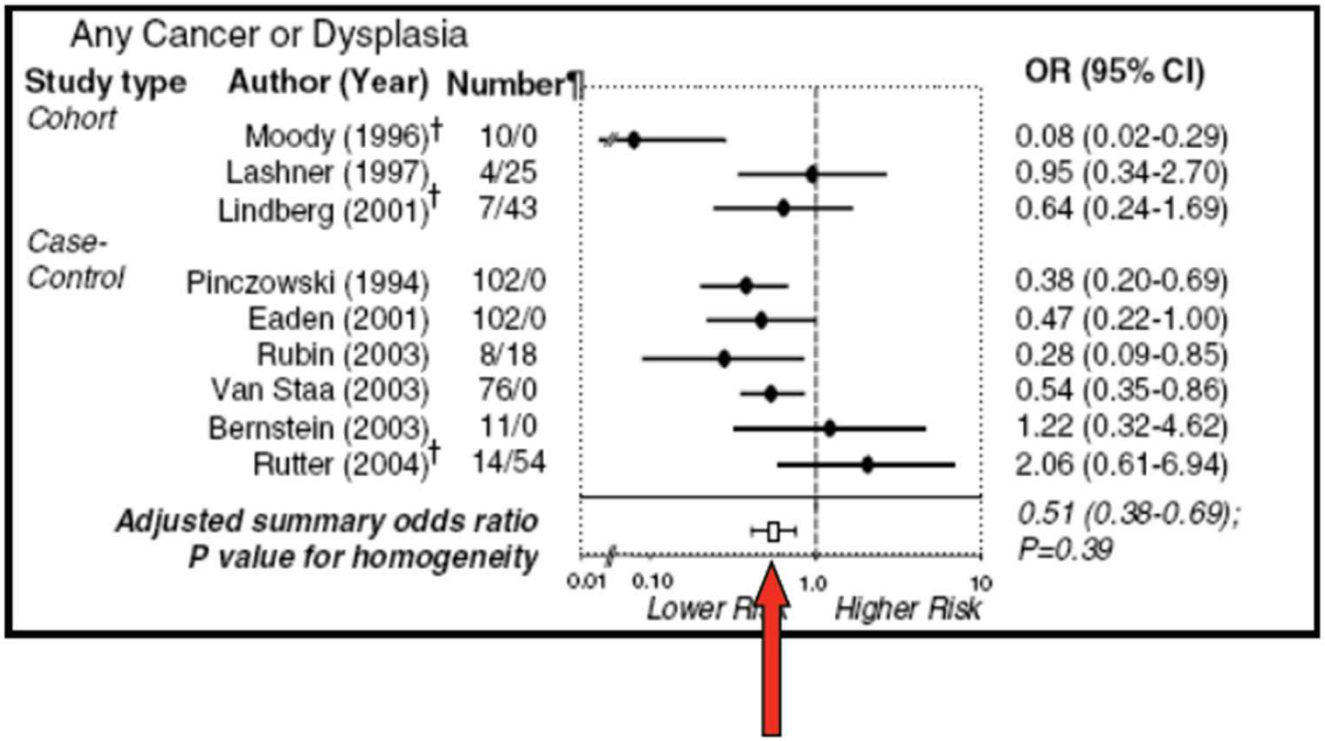
CCR et MICI: Prévention

Moyens de prévention

- **Chémoprévention**
- Surveillance endoscopique

Chémoprévention du CCR

Dérivés salicylés : méta-analyse dans la RCH



OR 0.51 (IC 0.37-0.69)

Velayos, Am J Gastro 2005

Chémoprévention du CCR

Dérivés salicylés

Mécanismes de prévention

- Cicatrisation muqueuse dans la RCH?
- Diminution du stress oxydatif
- Effet pro-apoptotique: Activation des récepteurs PPARγ
- Diminution des erreurs de réplication de l'ADN

Modalités d'administration

- Prise régulière
- Dès les 1ers mois de traitement
- Pour un temps indéterminé
- Dose: > 1g/j
- En plus des autres traitements anti-inflammatoires

Dubuquoy, Gut 2006
Gasche, Aliment Pharmacol Ther 2004

Chémoprévention du CCR

Dérivés salicylés

DONC,
RCH AVEC INDICATION DE TRAITEMENT = 5-ASA A VIE

- Dose: > 1g/j
- En plus des autres traitements anti-inflammatoires

Dubuquoy, Gut 2006
Gasche, Aliment Pharmacol Ther 2004

Chémoprévention du CCR

Acide urso-désoxycholique (AUDC)

Mécanismes de prévention

- Diminution de la concentration colique en ac désoxycholiques biliaires, carcinogènes
- Modulation protéine kinase C et réduction phospholipase A2
- Anti-oxydant

Efficacité <u>chez les patients RCH-CSP</u>

- Etude prospective randomisée Mayo Clinic
- AUDC vs placebo (n=52)
- Durée 42 mois, détection CCR/adénome en dysplasie sur coloscopies de surveillance
- 3 dysplasies vs 2 cancers + 6 dysplasies

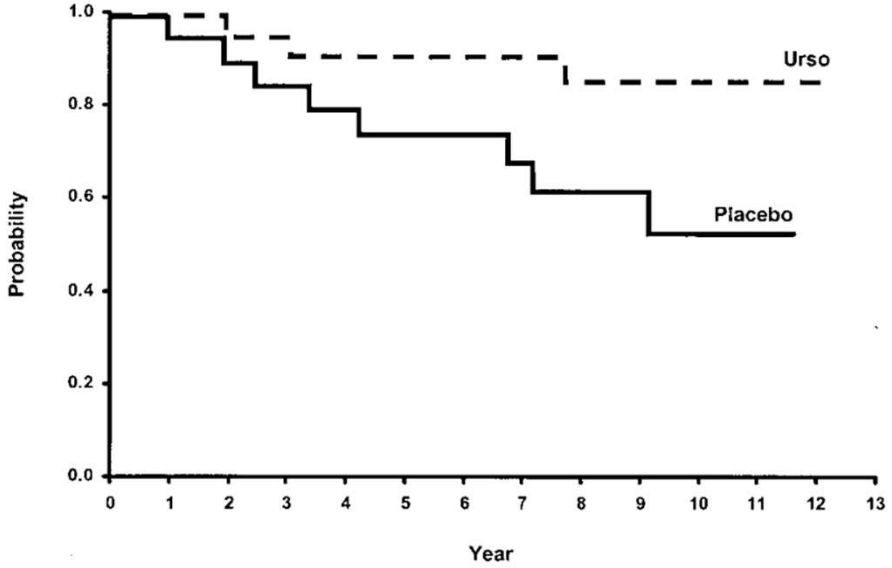


Figure 1. Kaplan–Meier estimates of proportion of patients free of dysplasia or cancer according to initial treatment assignment.

OR 0.26 (0.06-0.92), p=0.034

Pardi, Gastroenterology 2003

Chémoprévention du CCR

Azathioprine

Efficacité débattue

- Effet neutre?
- Réduction du risque de néoplasie avancé >5-ASA, cohorte hollandaise
- Réduction du risque de CCR? Cohorte CESAME

Multivariée FDR adénomes avancés dans les colites anciennes étendues (n=2841)

	HR	95% CI	
Exposition aux thiopurines	0.28	[0.09-0.89]	p=0.03
Sexe masculin	1.64	[0.77–3.47]	NS
Age (par an)	1.02	[0.99-1.05]	NS
Crohn (vs. RCH+IBDU)	1.00	[0.44-2.34]	NS

Fraser, Aliment Pharmacol Ther 2002
Beaugerie, JCC 2009
Van Schaik, Gut 2011

Chémoprévention du CCR

Par la cicatrisation muqueuse?

Arguments en faveur

- **Physiopathologie du CCR sur MICI**
  - Séquence inflammation – dysplasie – cancer
- **Risque CCR selon l'inflammation muqueuse**
- Inflammation en cours
  - Inflammation endoscopique: OR 2.54 [1.45-4.4]
  - Inflammation histologique: OR 5.13 [2.36-11.14]
- Inflammation passée
  - Pseudo-polypes OR 2.29 [1.28-4.11]
  - Sténose OR 4.62[1.03-20.8]
- Aspect endoscopique normal
  - Risque CCR à 5 ans = population générale

Rutter, Gastroenterology 2004
Rutter, Gut 2004

Chémoprévention du CCR

SYSTEMATIC REVIEWS AND META-ANALYSES

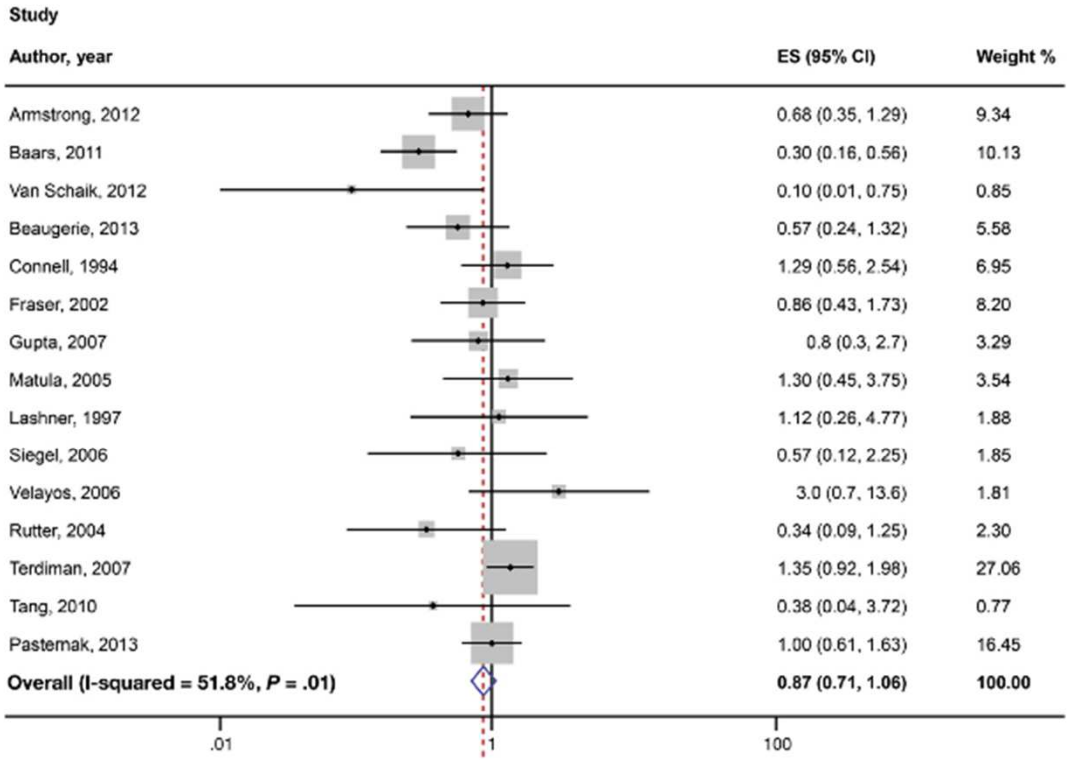
Fasiha Kanwal, Section Editor

Thiopurines and Risk of Colorectal Neoplasia in Patients With Inflammatory Bowel Disease: A Meta-analysis

Tine Jess,* Anthony Lopez,‡ Mikael Andersson,* Laurent Beaugerie,§ and Laurent Peyrin-Biroulet‖

OR 0.87 (0.71-1.06)

AZT non protecteur

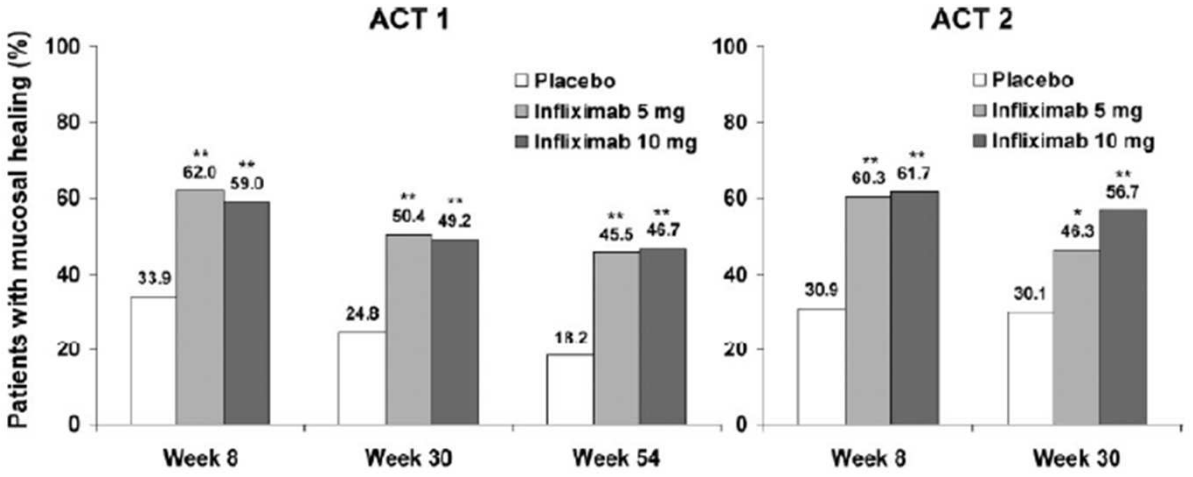


Jess, Clinical Gastroenterology and Hepatology 2014

Chémoprévention du CCR

Les anti-TNF alpha? Méthotrexate ? Anti-intégrine ?

- Pas de données disponibles sur CCR
- Données d'efficacité des anti-TNF à court terme



Chémoprévention du CCR

Intérêt des statines?

- **Etude de population sur 11 001 patients avec MICI**
- **Dont 1376 ont un traitement par statines**
- **Pop statine : 2% CRC**
- **Pop sans statine : 3% CRC**
- **Résultat à confirmer**

Table 4. Results of Stratified Analysis Between Statin Use and Risk of Colorectal Cancer in Inflammatory Bowel Diseases

	Adjusted odds ratio	95% Confidence interval
By type of inflammatory bowel disease		
Ulcerative colitis	0.57	0.35–0.93
Crohn's disease	0.15	0.06–0.35
By sex		
Female	0.36	0.18–0.75
Male	0.35	0.21–0.59
Smoking status		
Never-smoker	0.20	0.05–0.87
Ever-smoker	0.44	0.29–0.67

OR 0.42 (0.28-0.62)

Ananthakrishnan, Clinical Gastroenterology and Hepatology 2016

Chémoprévention du CCR

CONCLUSION :

- **Recto-colite hémorragique avec atteinte colique = traitement par 5-ASA à vie**
- **AUDC, statines : faible niveau de preuve. Pas de recommandation de prescription.**
- **Azathioprine : pas d'effet propre**
- **Autres traitements, antiTNF alpha : pas d'étude spécifique**
- **Rôle probable de la cicatrisation muqueuse et donc effet indirect des immunosuppresseurs.**

CCR et MICI: Prévention

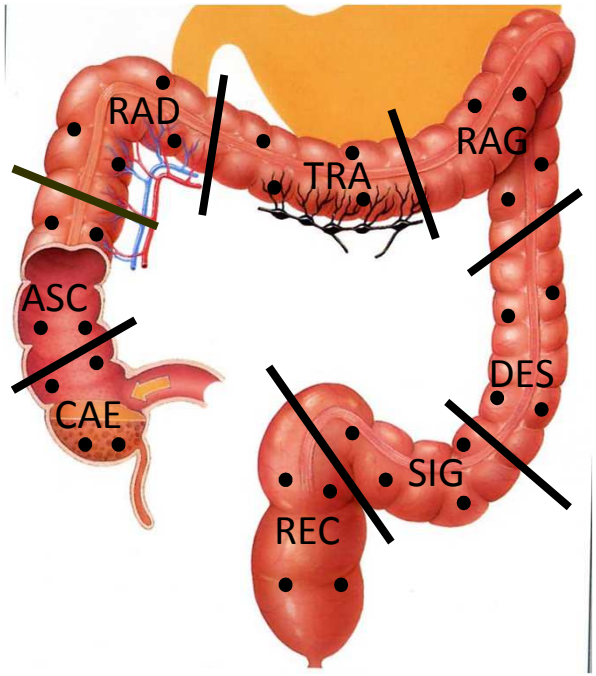
Moyens de prévention

- Chémoprévention
- **Surveillance endoscopique**

Dépistage endoscopique du CCR : quelles techniques?

Qualité de la préparation colique
Coloscopie en période quiescente

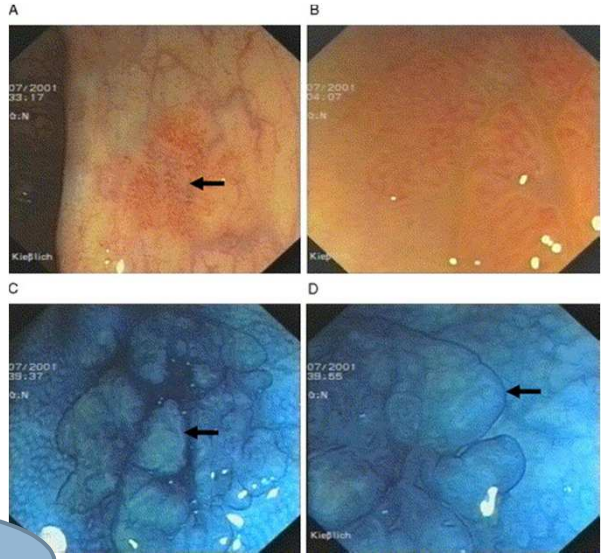
Biopsies multiples aléatoires



2-4 biopsies/ 10 cm, Pots séparés

Chromoendoscopie + Biopsies ciblées

- Coloration à indigo carmin
- Biopsies ciblées sur zone anormale
- ↑ détection de foyers dysplasiques?



Absence RCT

Dépistage endoscopique du CCR : quelles techniques?

Biopsies systématiques versus chromo-endoscopie

- Etude prospective longitudinale
- 68 patients (55 RCH, 13 MC) avec colite > colon gauche
- 1) biopsies systématiques par segment + LB 2) chromo-endoscopie
- 44 lésions dysplasiques détectées : 6 par biopsies systématiques, 11 en LB, 27 par CE

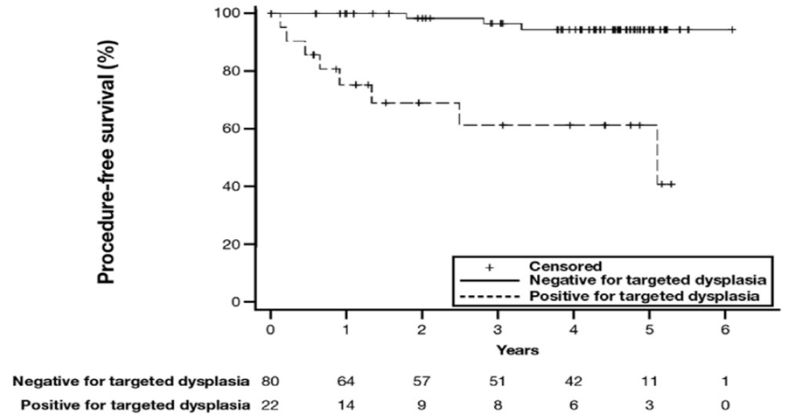


Figure 3. Kaplan-Meier. Negative targeted (white light or methylene blue) examination on index examination and follow-up.

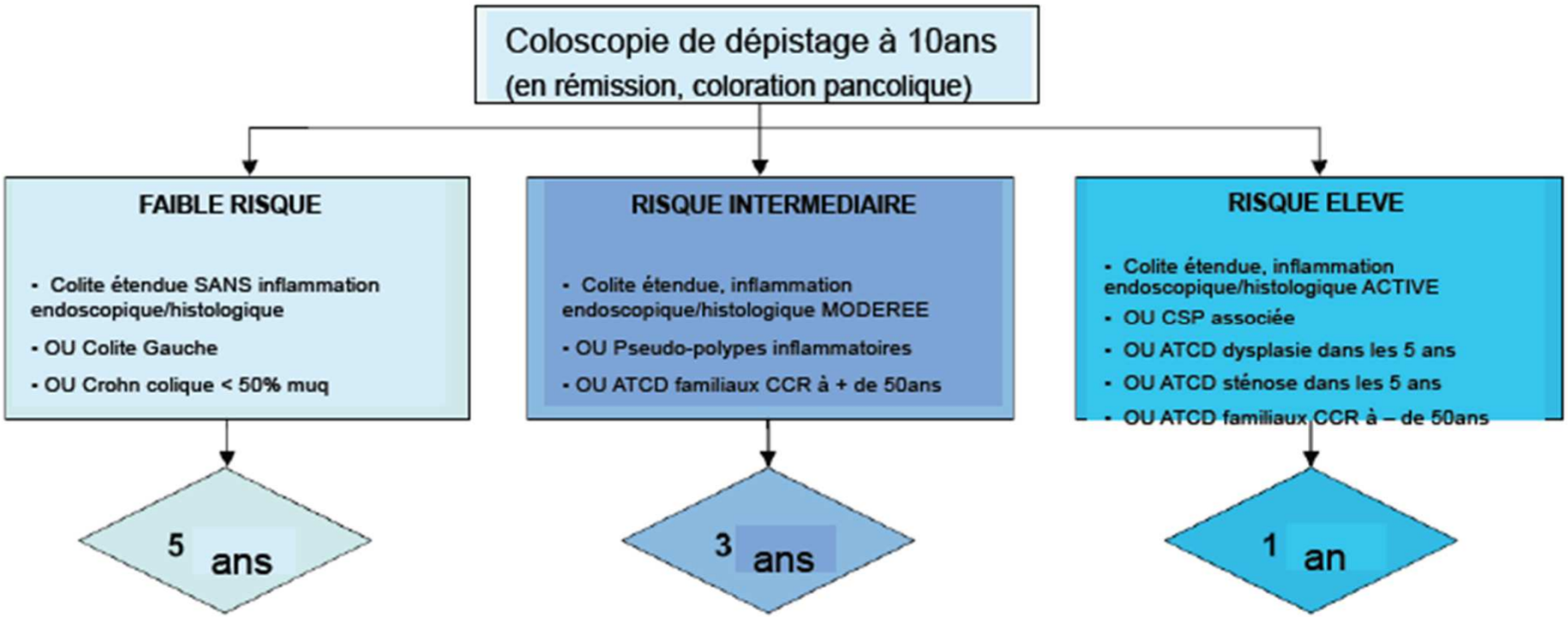
Table 2. GEE Model: Positive Findings and Different Methods of Specimen Examination Over Time

Predictor	OR	95% CI	*P* value
Dye targeted vs random biopsy	5.43	2.9–9.9	<.001
No-dye targeted vs random biopsy	2.28	0.9–5.3	.054
Dye targeted vs no-dye targeted	2.38	1.4–4.0	.001
Time (1 mo)	0.99	0.99–1.004	.219

Marion, Clinical Gastroenterology and Hepatology 2016

Dépistage endoscopique du CCR : quel rythme?

Recommandations internationales pour le dépistage de la dysplasie dans les MICI



Cairns, Gut 2010

Dépistage endoscopique du CCR : quel rythme?

Localisation et ancienneté

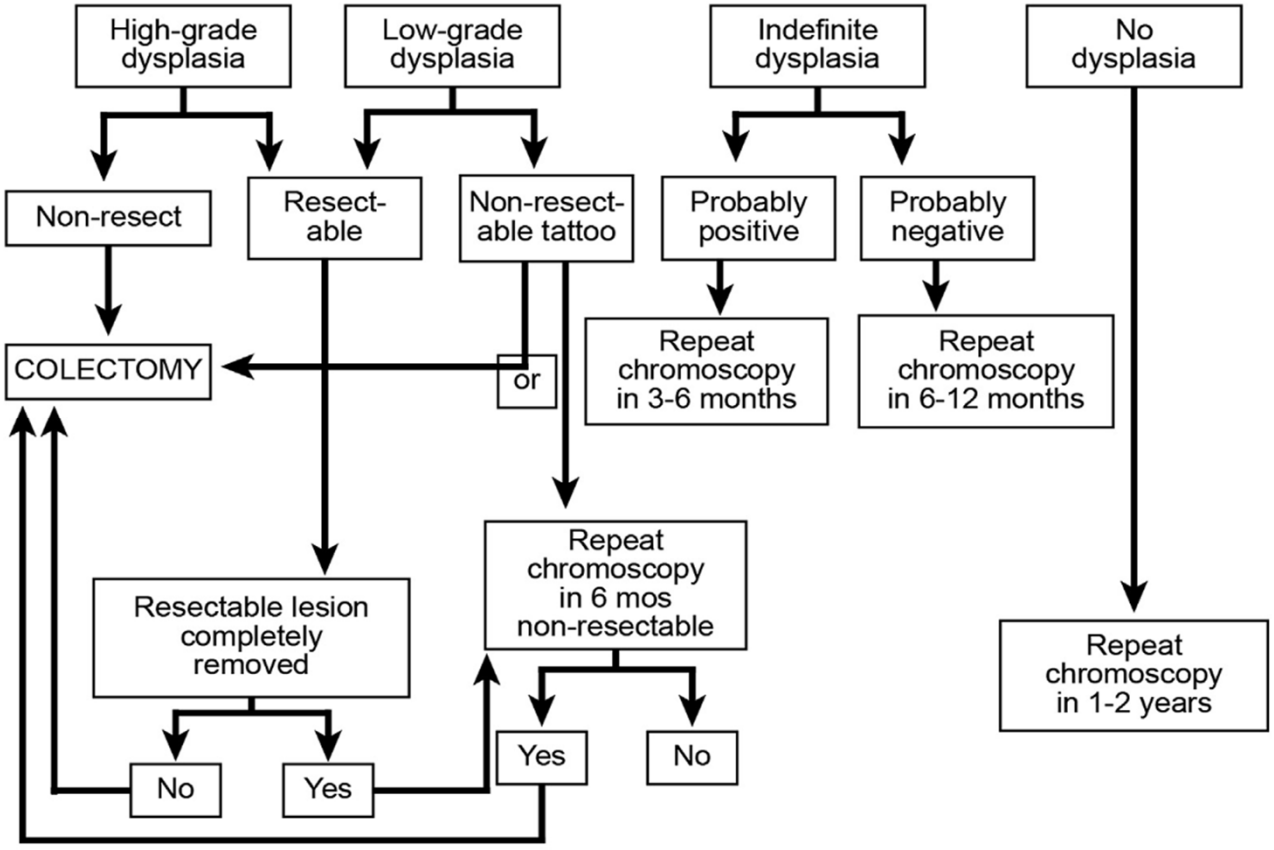
- Pancolite : à partir de 8 ans
- Colite gauche : à partir de 15 ans
- Rectite : identique à la population générale

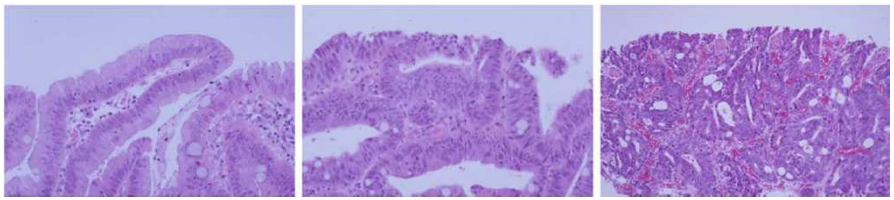
Rythme

- De 10 à 20 ans : tous les 3 ans
- De 20 à 30 ans : tous les 2 ans
- Après 30 ans : tous les ans
- Surveillance **annuelle** en cas de CSP

Recommandations de la SFED 2004

Dépistage endoscopique du CCR : dysplasie





Itzkowitz, Gastroenterology 2004

Efficacité de la surveillance endoscopique?

- Velayos, Gastroenterology 2006
  - Analyse multivariée des facteurs de risques de CCR sur RCH
  - Coloscopie de surveillance: OR 0.4 [0.2-0.7]

- Lutgens, Br J cancer 2009
  - Etude cas témoins: CCR sur MICI, surveillés vs non surveillés
  - Amélioration survie groupe surveillance
  - Par détection tumorale à stade plus précoce

- Revue Cochrane, 2008
  - Stratégies de surveillance IBD

> There is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. There is evidence that cancers tend to be detected at an earlier stage in patients who are undergoing surveillance, and these patients have a correspondingly better prognosis, but lead-time bias could contribute substantially to this apparent benefit. There is indirect evidence that surveillance is likely to be effective at reducing the risk of death from IBD-associated colorectal cancer and indirect evidence that it may be acceptably cost-effective.

→ recommandation grade B ou C

MICI et CCR : conclusion

- **MC colique et RCH = population à risque de CCR**
- **Risque élevé : atteinte colique étendue, durée d'évolution, ATCD familiaux, CSP**
- **Prévention : 5-ASA**
- **Prévention : coloscopie à partir de 7-10 ans d'évolution, rythme selon étendue, durée d'évolution et FDR**
- **Chromo-endoscopie +++**

Autres cancers : cancer du canal anal

- Cancer de l'anus et du canal anal : complication rare d'évolution d'atteinte périnéale dans la MC.
- En cas de fistule anale de MC : incidence reste rare : 0.2/1000 personnes/années.
- Après au moins 10 ans d'évolution de la fistule.
- Prévention = examen clinique régulier en cas d'atteinte périnéale, et biopsie de toute lésion suspecte.

Annese, ECCO guideline JCC 2015

Autres cancers : cancer du réservoir

- Après colo-proctectomie totale et AIA avec réservoir, il existe une risque résiduel de cancer du réservoir.

- Incidence : entre 1,8 et 5,3%

- Facteur de risque :
  - Dysplasie sur la colectomie : x 4
  - CCR sur la colectomie : x 25

- Surveillance :
  - Annuelle si FDR, avec biopsies du réservoir
  - Sinon indéfinie (/2-3 ans?)

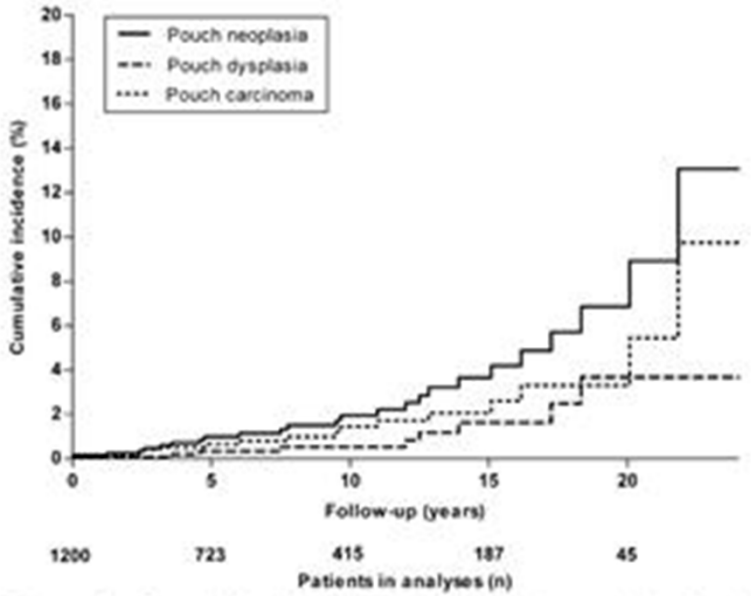


Figure 2. Cumulative incidences of pouch neoplasia (both carcinoma and dysplasia), pouch carcinoma, and pouch dysplasia.

Karive , Gastroenterology 2010
Derikx, Gastroenterology 2014
Annese, ECCO guideline JCC 2015

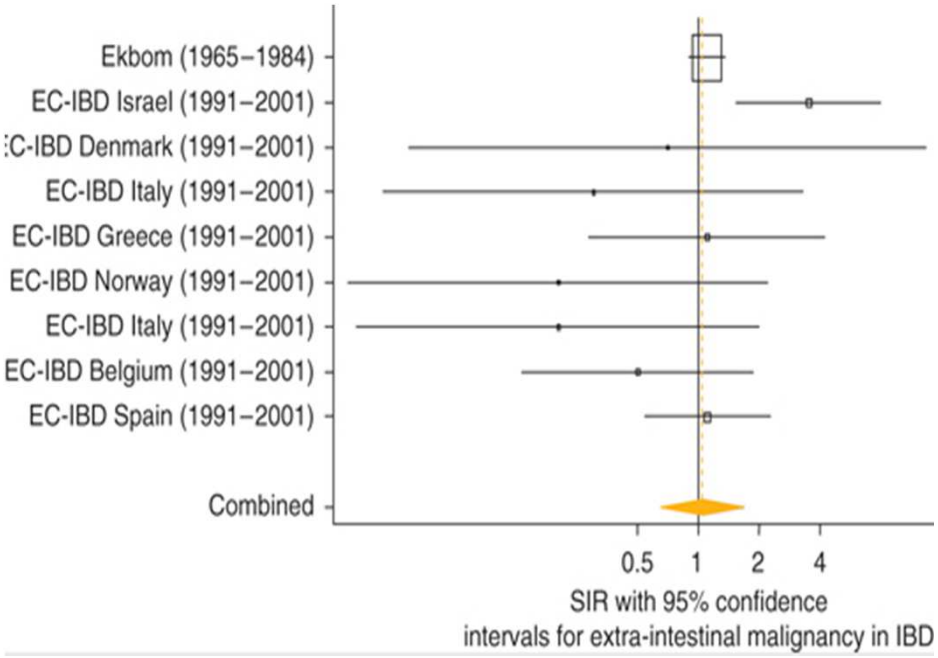
Autres tumeurs digestives ?

- Tumeurs neuroendocrines : identique population générale
- GIST : identique population générale

Annese, ECCO guideline JCC 2015

Autres cancers solides

Risque global a priori non augmenté … mais ….



OR 1.10 (0.96-1.27)

WHAT IS CURRENT KNOWLEDGE

- ✓ The risk of intestinal cancer in inflammatory bowel disease (IBD) has been analyzed thoroughly, presumably because of the fact that IBD primarily affects the small and large intestine.
- ✓ The risk of extra-intestinal cancer (EIC) in patients with IBD remains uncertain, despite knowledge of a relatively high frequency of extra-intestinal manifestations among patients with Crohn's disease (CD) and ulcerative colitis (UC).

WHAT IS NEW HERE

- ✓ This is to our knowledge the first meta-analysis assessing the risk of overall and site-specific EIC in patients with CD and UC based exclusively on population-based studies.
- ✓ We observed a higher overall risk of developing EIC among patients with CD than among patients with UC, whose risk was similar to that of the background population.
- ✓ More specifically, CD patients were at an increased risk of developing upper gastrointestinal cancer, lung, urinary bladder, and squamous cell cancer.
- ✓ On the other hand, UC patients had an increased risk of developing liver–biliary cancer and leukemia counter-weighted by a decreased risk of lung cancer.

Pedersen, Am J Gastroenterol 2010

MICI et cancers

- Cancers associés aux MICI

- Cancers et traitement des MICI

MICI et onco-hématologie

Table 3. SIRs of site-specific cancers in 1,437 patients with ulcerative colitis, compared with the general population, North Jutland County, Denmark, 1978–2010

Cancer (ICD-10)	Observed, *n*	Expected, *n*	SIR (95% CI)
All	207	185.12	1.12 (0.97–1.28)
Upper GI (C00–C17)	9	7.46	1.21 (0.55–2.29)
Colorectal (C18–C20)	15	17.28	0.85 (0.48–1.41)
Liver, bile ducts, pancreas (C22–C25)	9	5.47	1.65 (0.75–3.13)
Lung (C30–C39, C45)	16	18.22	0.88 (0.50–1.43)
Malignant melanoma and other skin cancer excluding basal cell carcinoma (C43–C44)	9	9.15	0.98 (0.45–1.87)
Breast (C50)	17	16.83	1.01 (0.59–1.62)
Female organs (C51–C58)	8	7.92	1.01 (0.44–1.99)
Cervical dysplasia including carcinoma *in situ* (N87, D06)	19	26.69	0.71 (0.43–1.11)
Male organs (C60–C63)	25	14.94	**1.67 (1.08–2.47)**
Urinary tract (C64–C68)	12	11.09	1.08 (0.56–1.89)
Lymphoma (C81–C90)	8	5.66	1.41 (0.61–2.78)
Leukemia (C91–C96)	5	3.05	1.64 (0.53–3.82)
Other (remaining cancer codes)	55	41.84	**1.31 (1.01–1.71)**

CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; SIR, standardized incidence ratio.
Bold text in this table reflects statistically significant results.

Table 5. SIRs of site-specific cancers in 774 patients with Crohn's disease, compared with the general population, North Jutland County, Denmark, 1978–2010

Cancer (ICD-10 code)	Observed, *n*	Expected, *n*	SIR (95% CI)
All	129	83.29	**1.55 (1.29–1.84)**
Upper GI (C00–C16)	5	2.81	1.78 (0.58–4.14)
Small intestine (C17)	2	0.13	**15.18 (1.84–54.8)**
Colorectal (C18–C20)	12	6.99	1.72 (0.89–3.00)
Liver, bile ducts, pancreas (C22–C25)	1	2.18	0.46 (0.01–2.56)
Lung (C30–39, C45)	15	7.04	**2.13 (1.19–3.52)**
Malignant melanoma and other skin cancer (excluding basal cell carcinoma (C43–C44))	7	4.02	1.74 (0.70–3.59)
Breast (C50)	13	8.34	1.56 (0.83–2.66)
Female organs (C51–C58)	5	4.14	1.21 (0.39–2.81)
Cervical dysplasia including carcinoma *in situ* (N87, D06)	29	17.61	**1.65 (1.10–2.37)**
Male organs (C60–C63)	4	4.96	0.81 (0.22–2.06)
Urinary tract (C64–C68)	7	4.13	1.69 (0.68–3.49)
Lymphoma (C81–C90)	7	2.32	**3.01 (1.21–6.19)**
Leukemia (C91–C96)	1	1.20	0.83 (0.02–4.63)
Other (remaining cancer codes)	21	17.41	**1.21 (0.75–1.84)**

CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; SIR, standardized incidence ratio.
Bold text in this table reflects statistically significant results.

MC >> RR x 3 pour LNH

Jess, Am J Gastroenterol 2013

MICI et onco-hématologie

ECCO Statement 3A

IBD patients show a trend toward higher risks of developing haematological malignancies. Compared with the general population, UC patients are significantly more likely to develop leukaemia, whereas those with CD are at higher risk for lymphoma, especially non-Hodgkin lymphoma [EL1]

ECCO Statement 3B

Early disease onset, male gender, and age >65 are risk factors for haematological malignancies in IBD patients [EL 3]

ECCO Statement 3C

The possibility of haematological malignancies should be considered for any IBD patient with persistent haematological changes that are unresponsive to treatment, unexplained fever, adenopathy, or hepatosplenomegaly. A complete workup and haematological consultation are advised [EL 3]

able 5. SIRs of site-specific cancers in 774 patients with rohn's disease, compared with the general population, North utland County, Denmark, 1978–2010

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olorectal (C18–C20)	12	6.99	1.72 (0.89–3.00)
		2.18	0.46 (0.01–2.56)
		7.04	**2.13 (1.19–3.52)**
		4.02	1.74 (0.70–3.59)
		8.34	1.56 (0.83–2.66)
		4.14	1.21 (0.39–2.81)

Lung (C30–C39, C45)			
Malignant melanoma and other skin cancer excluding basal cell carcinoma (C43–C44)			
Breast (C50)			
Female organs (C51–C58)			
Cervical dysplasia including carcinoma *in situ* (N87, D06)			
Male organs (C60–C63)	25	14.94	**1.67 (1.08–2.4**
Urinary tract	12	11.09	1.08 (0.56–1.89
Lymphoma (C81–C90)	8	5.66	1.41 (0.61–2.78
Leukemia (C91–C96)	5	3.05	1.64 (0.53–3.82
cancer codes)			

CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; SIR, standardized incidence ratio.
Bold text in this table reflects statistically significant results.

MC >> RR x 3 pour LNH

Jess, Am J Gastroenterol 2013
Annese, ECCO guideline JCC 2015

MICI et onco-hématologie

- Rôle de l'exposition aux thiopurines?
  - Cytotoxicité pour NK, et LT
  - Prolifération cellules EBV+
  - Immortalisation LB

- Données de la transplantation et IS

Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study

- Cohorte CESAME (60% MC/40% RCH)
- N=23 lymphome dont 15 groupe AZA/6-MP
  - EBV, LB, 2 cas (décès) de post MNI-LB
  - exposition AZA/6-MP: 1-16 ans

↑ risque lors exposition AZA/6-MP

	Hazard ratio (95% CI)	p value
Age (per 1-year increase)	1·06 (1·03–1·09)	<0·0001
Duration of inflammatory bowel disease (per 1-year increase)	1·04 (1·00–1·08)	0·0359
Sex		
Female*	..	..
Male	2·32 (0·95–5·64)	0·0648
Thiopurine therapy†		
Never received*	..	..
Discontinued	1·02 (0·20–5·11)	0·9839
Continuing	5·28 (2·01–13·9)	0·0007

*Reference group. †Time-dependent thiopurine therapy was coded with two dummy variables: continuing therapy was equal to zero when thiopurines were not used, and one from the start of therapy to discontinuation (if any); discontinued therapy was equal to zero when thiopurines were used or if thiopurines were never used, and one from treatment interruption to reintroduction (if any). The hazard ratio between patients with continuing thiopurine therapy (or patients who discontinued therapy) and patients who had never received thiopurines represents the relative risk for an individual on therapy (or who has discontinued therapy) compared with a never-treated individual.

Table 2: **Independent risk factors for lymphoproliferative disorder**

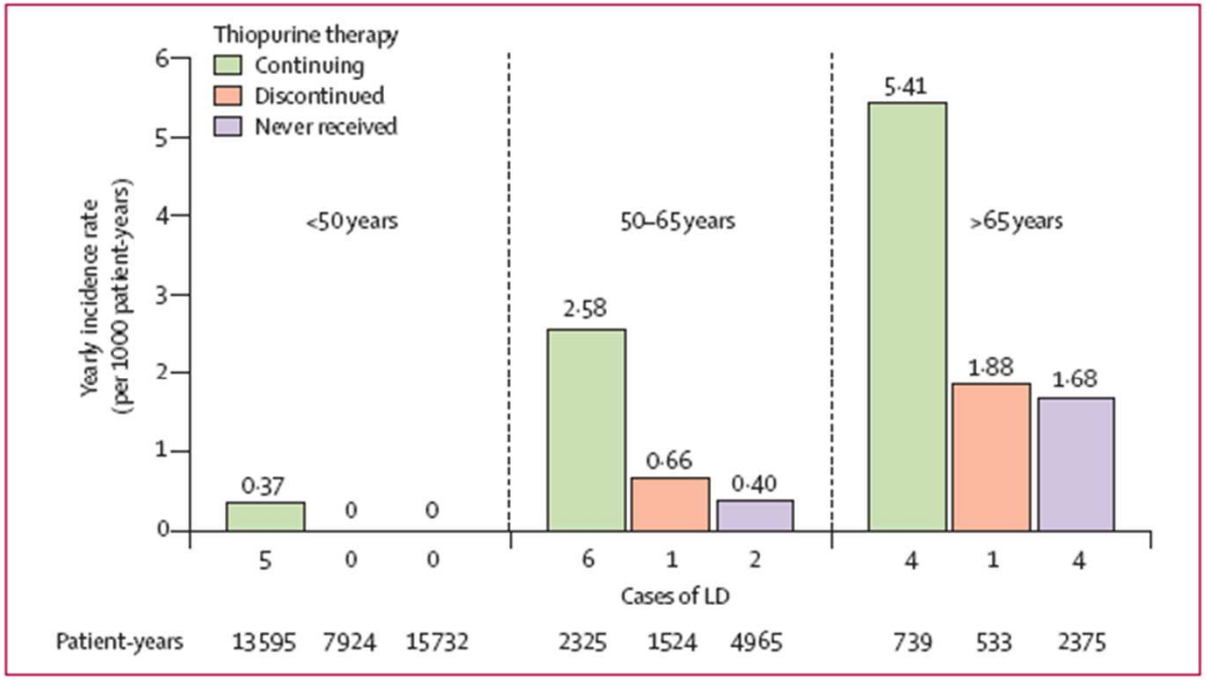
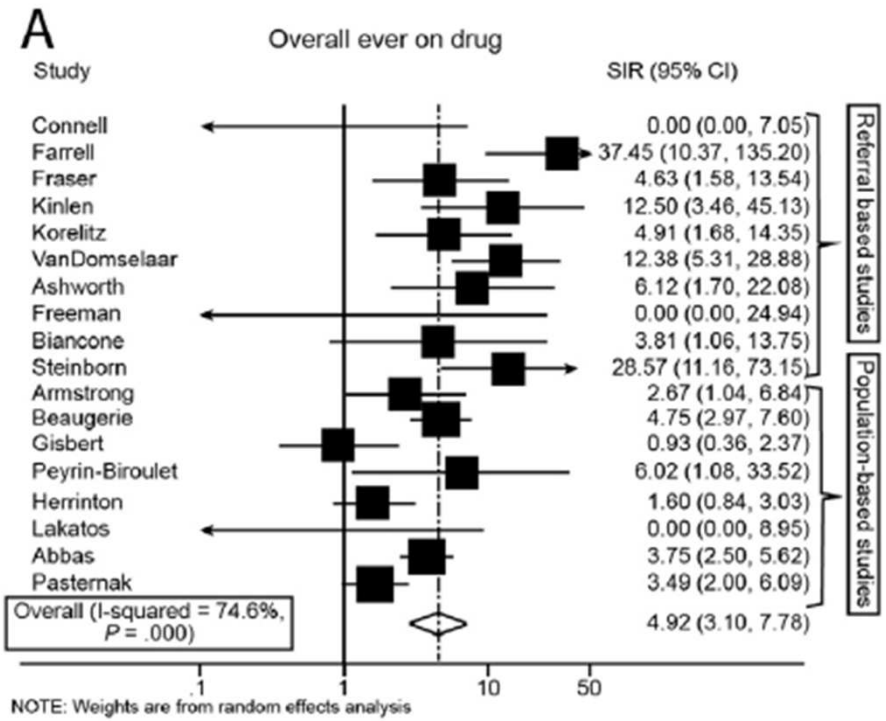
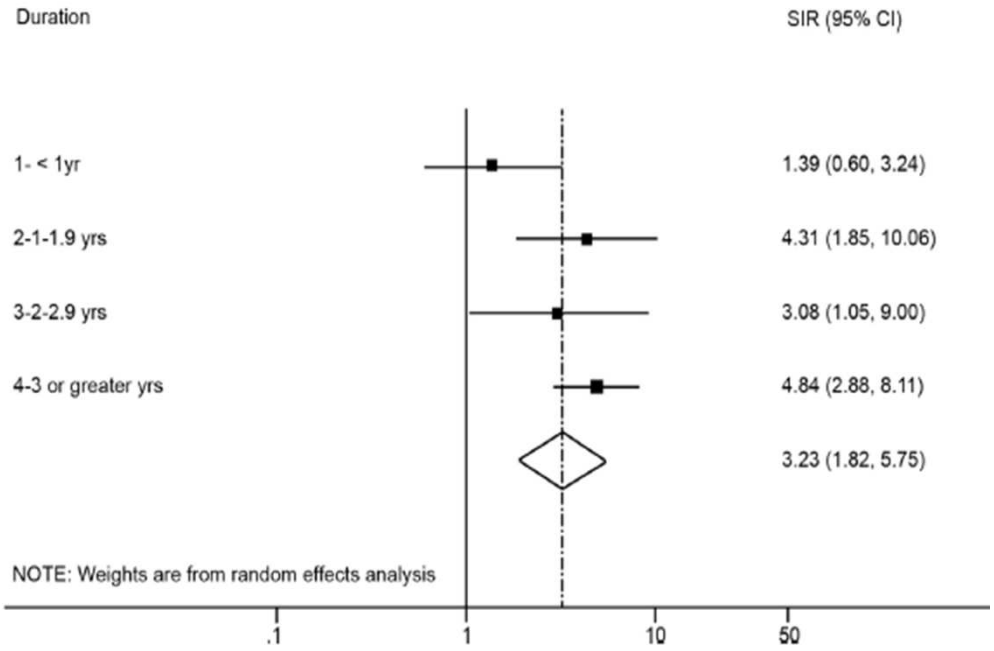


Figure: **Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort**

Beaugerie, Lancet 2009

Risk of Lymphoma in Patients With Inflammatory Bowel Disease Treated With Azathioprine and 6-Mercaptopurine: A Meta-analysis





SIR for lymphoma: 4.92 (3.10-7.78)
SIR for **current users: 5.71 (3.72-10.1**)
SIR for **former users: 1.42 (0.86-2.34)**

SIR for men: 4.50 (3.71-5.40)
SIR for <30 years: 6.99 (2.99-16.4)

Kotlyar, Clinical Gastroenterology and Hepatology 2015

Lymphome T hépato-splénique?

- Reporté depuis quelques années (1er cas 1990)
  - 37 cas avec MC dans une revue systématique de 2013
  - 79% AZA+anti-TNF

-Homme jeune

-Utilisation combinée AZA/6-MP + anti-TNF

-Lymphoprolifération rapide et fatale

Table 2 Demographic and clinical characteristics of reported Crohn's disease patients with hepatosplenic T-cell lymphoma (HSTCL)

	Unique cases (n = 37)	Cases with insufficient reporting[a] (n = 9)
Age at HSTCL diagnosis, years	**n = 36**	**n = 0**
Mean	30	-
Median	26	-
Range	12 to 79	-
Disease duration, years	**n = 16**	**n = 0**
Mean	10	-
Median	6	-
Range	4 to 35	-
Sex, n (%)	**n = 36**	**n = 6**
Female	5 (14%)	1 (17%)
Survival, n (%)	**n = 26**	**n = 4**
Died	24 (92%)	4 (100%)
Survived	2 (8%)	0 (0%)
Physical examination and laboratory abnormalities at time of HSTCL diagnosis, n (%)	**n = 19**	**n = 1**
Hepatosplenomegaly or splenomegaly	19 (100%)	1 (100%)
Fever	9 (47%)	-
Cytopenia of any type	11 (58%)	-
Altered liver enzymes and/or LDH	5 (26%)	-

Shale, Gut 2008

Selvaraj, Syst Rev 2013

Lymphome post-EBV

- Lymphome lié à la primo-infection EBV (XRL = X-related lymphoproliferation)
- Cas rapportés : patients 20-30 ans EBV-négatif

  + exposition aux thiopurines

>> Sérologie EBV systématique avant thiopurines

>> Si négatif : EVITER THIOPURINES

Sokol, Gut 2009

Increased Risk of Acute Myeloid Leukemias and Myelodysplastic Syndromes in Patients Who Received Thiopurine Treatment for Inflammatory Bowel Disease

- Leucémie aigue myéloide et myélodysplasie:
- Cohorte CESAME :
  - Patients en cours de traitement par thiopurines :
    - SIR 1.54 (0.05-8.54)
  - Patients ayant eu un traitement par thiopurines :
    - SIR 6.98 (1.44-20.36)

Lopez, Clinical Gastroenterology and Hepatology 2014

Cancers solides et anti-TNF?

Table 2. Rate Ratios for Incident Overall Cancer Among 56 146 Patients With Inflammatory Bowel Disease Exposed and Unexposed to TNF-α Antagonists[a]

	TNF-α Antagonist Exposure				Rate Ratio (95% CI)		
	Exposed		Unexposed				
	Person-years	Cases	Person-years	Cases	Crude[b]	Adjusted[c]	Adjusted[d]
Total	18 440	81	469 874	3465	1.07 (0.86-1.33)	1.25 (1.00-1.58)	1.07 (0.85-1.36)
Female	10 665	43	258 706	1803	1.01 (0.75-1.37)	1.12 (0.82-1.54)	0.96 (0.69-1.33)
Male	7776	38	211 168	1662	1.12 (0.82-1.85)	1.40 (1.00-1.96)	1.20 (0.85-1.69)

Abbreviation: TNF-α, tumor necrosis factor α.

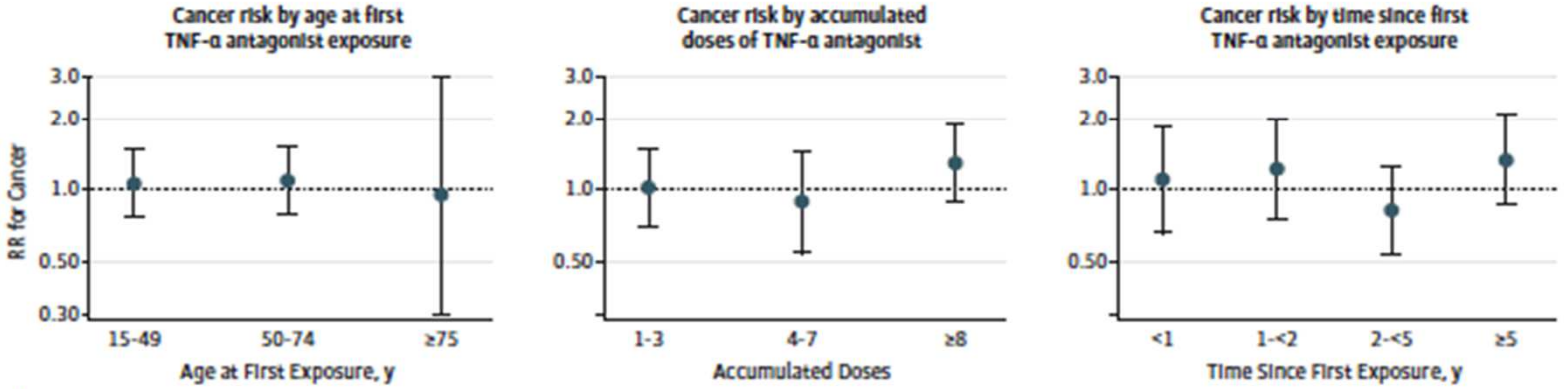
[a] Analyses were restricted to 3 months or more following first TNF-α antagonist exposure.

[b] Adjusted for age.

[c] Adjusted for age, calendar year, disease duration, baseline propensity scores, and use of 5-aminosalicylates/sulphasalazine, local and systemic corticosteroids, and methotrexate/cyclosporine/cyclophosphamide.

[d] Additionally adjusted for use of azathioprine.

Figure 2. Risk of Cancer According to Age at First Exposure to a TNF-α Antagonist, Accumulated Doses of TNF-α Antagonists, and Time Since First Dose of a TNF-α Antagonist, Comparing Exposed and Unexposed Patients With Inflammatory Bowel Disease



Exposed									
Person-years	15007	3261	149	6694	4664	7083	3115	3591	7190	4545
Cases, No.	38	40	3	31	18	32	16	19	23	23

Andersen, JAMA 2014

Cancers solides et anti-TNF?

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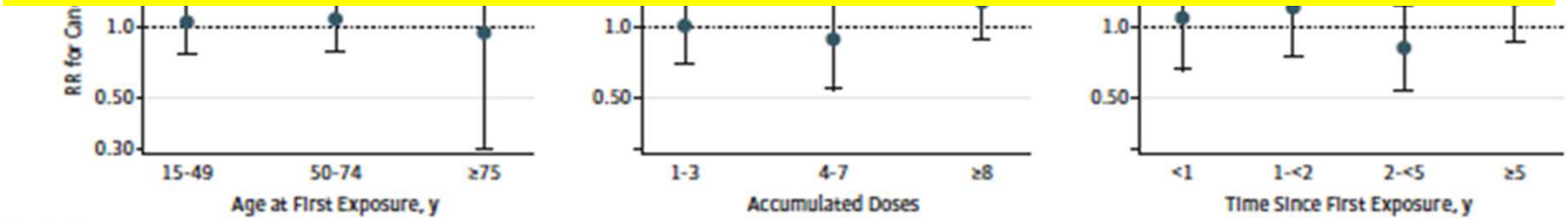
	Person-years	Cases	Person-years	Cases	Crude[b]	Adjusted[c]	Adjusted[d]

1) Pas d'augmentation du risque par les anti-TNF alpha
2) Peut-on traiter par anti-TNF alpha en cas d'antécédent de cancer dans les 5 ans ?



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Andersen, JAMA 2014

The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organisation: Safety

WCOG Statement 2.5
Overall risk of malignancy as a consequence of anti-TNF therapy

There is no consistent evidence of an increased overall risk of malignancy in patients with IBD treated with anti-TNF therapy [EL 2a]

WCOG Statement 2.6
Risk of non-Hodgkin's lymphoma as a consequence of anti-TNF therapy

Patients whose treatment includes anti-TNF therapy have a higher risk of non-Hodgkin's lymphoma compared with the general population (OR: 3.2, 95% CI: 1.5–6.9) [EL 2a], but it is unclear whether the risk is attributable to anti-TNF therapy, thiopurines, or the combination of both

Hepatosplenic T-cell lymphoma

WCOG Statement 2.7
Risk of hepatosplenic T-cell lymphoma as a consequence of anti-TNF therapy

Hepatosplenic T-cell lymphoma in patients with IBD is very rare, but young patients treated with a combination infliximab and thiopurines appear to be predisposed [EL 4]. It is not known whether all anti-TNF agents confer the same risk, or whether the risk is primarily attributable to the thiopurines in combination with anti-TNF therapy

Balance bénéfices-risques
Cas individuel

Van Assche, Am J Gastro 2011

Que faire en cas d'antécédent de cancer ?

Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer

Beaugerie, Gut 2013

- Cohorte CESAME : 405 pts **avec ATCD K** (20% colon, 20% sein)
- Etude de l'impact des IS sur survenue nouveaux K/récidive

Conclusion:

- **Pts avec ATCD de K: FDR indépendant (X2) de développer un K**
- **Autre FDR de développer K: âge, exposition IS (cohorte)**

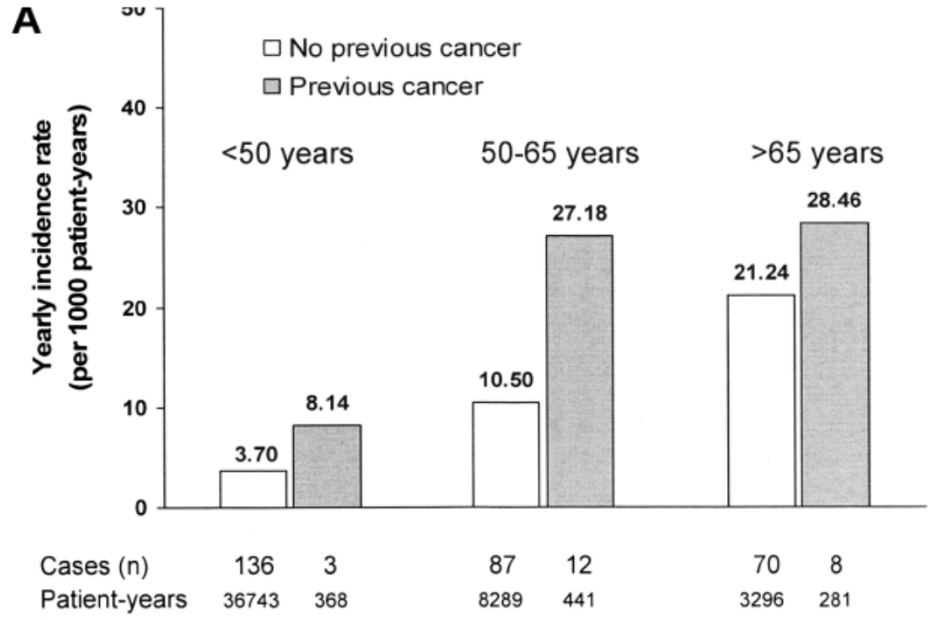


Table 4 Independent risk factors for incident cancer* in the total study population

Variable	Adjusted HR	95% CI	p Value
Age per 1-year increase*	1.05	1.04 to 1.05	<0.0001
Gender			
Female	ref	–	–
Male	1.15	0.92 to 1.44	0.22
IBD subtype			
Ulcerative colitis or IBDU	ref	–	–
Crohn's disease	1.03	0.81 to 1.30	0.82
Personal history of cancer†			
No	ref	–	–
Yes	1.92	1.25 to 2.97	0.003
Exposure to any immunosuppressant			
No	ref	–	–
Yes	1.68	1.34 to 2.13	<0.0001

*Defined as the first occurrence of cancer in patients without previous cancer, and a new or recurrent cancer in patients with previous cancer.
†At entry into the observational period.
IBDU, IBD, unclassified.

Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer

- Cohorte CESAME : 405 pts avec ATCD K
- Etude de l'impact des IS sur survenue nouveaux K/récidive

Conclusion:

- **Pts avec ATCD de K: FDR indépendant de développer un K**
- **Pts avec ATCD de K: développement nouveau K > récidive**
- **Pts avec ATCD de K: exposition aux IS, pas d'impact majeur sur survenue nouveau ou récidive K**

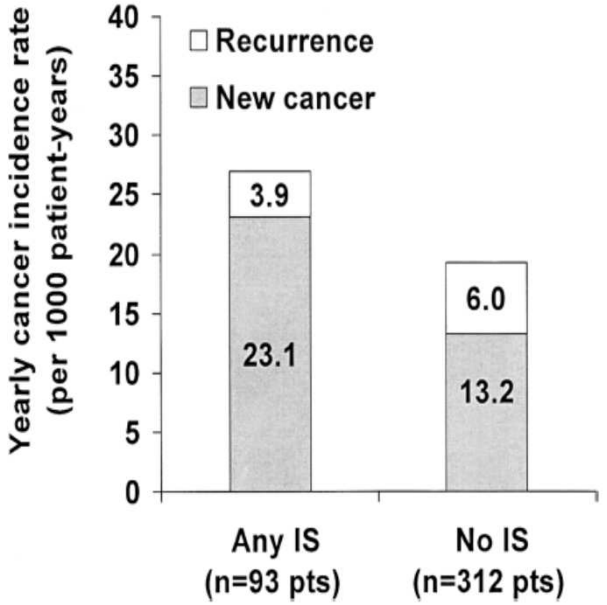
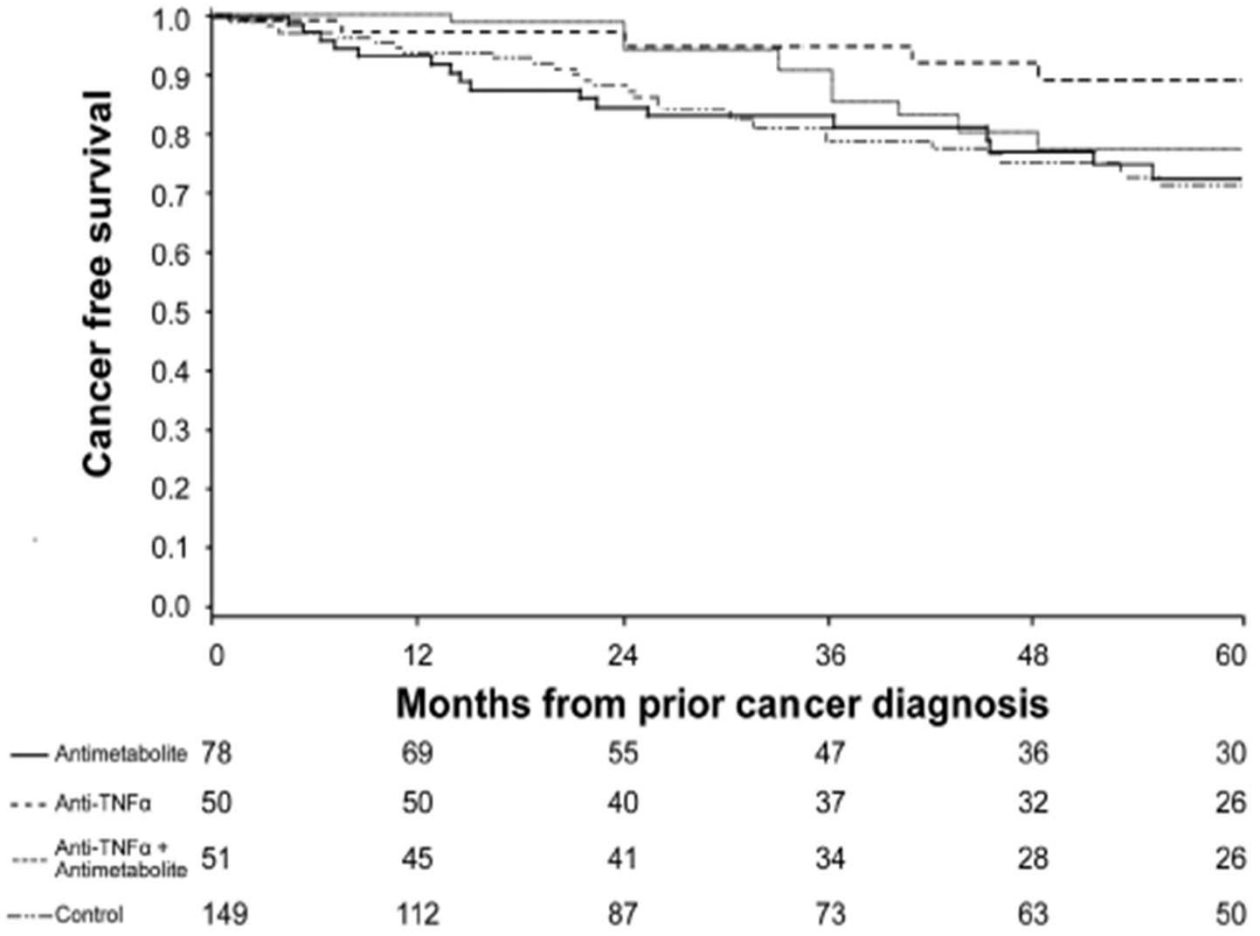


Figure 2 Rate of new and recurrent cancer in patients (pts) with previous cancer according to immunosuppressant (IS) status at entry.

Beaugerie, Gut 2013

Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents

- 333 patients from 8 academic centers with prior cancer and subsequent therapies
- No difference with control arm, whatever type of treatment (p=0.14)



Axelrad, Clinical Gastroenterology and Hepatology 2016

Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents

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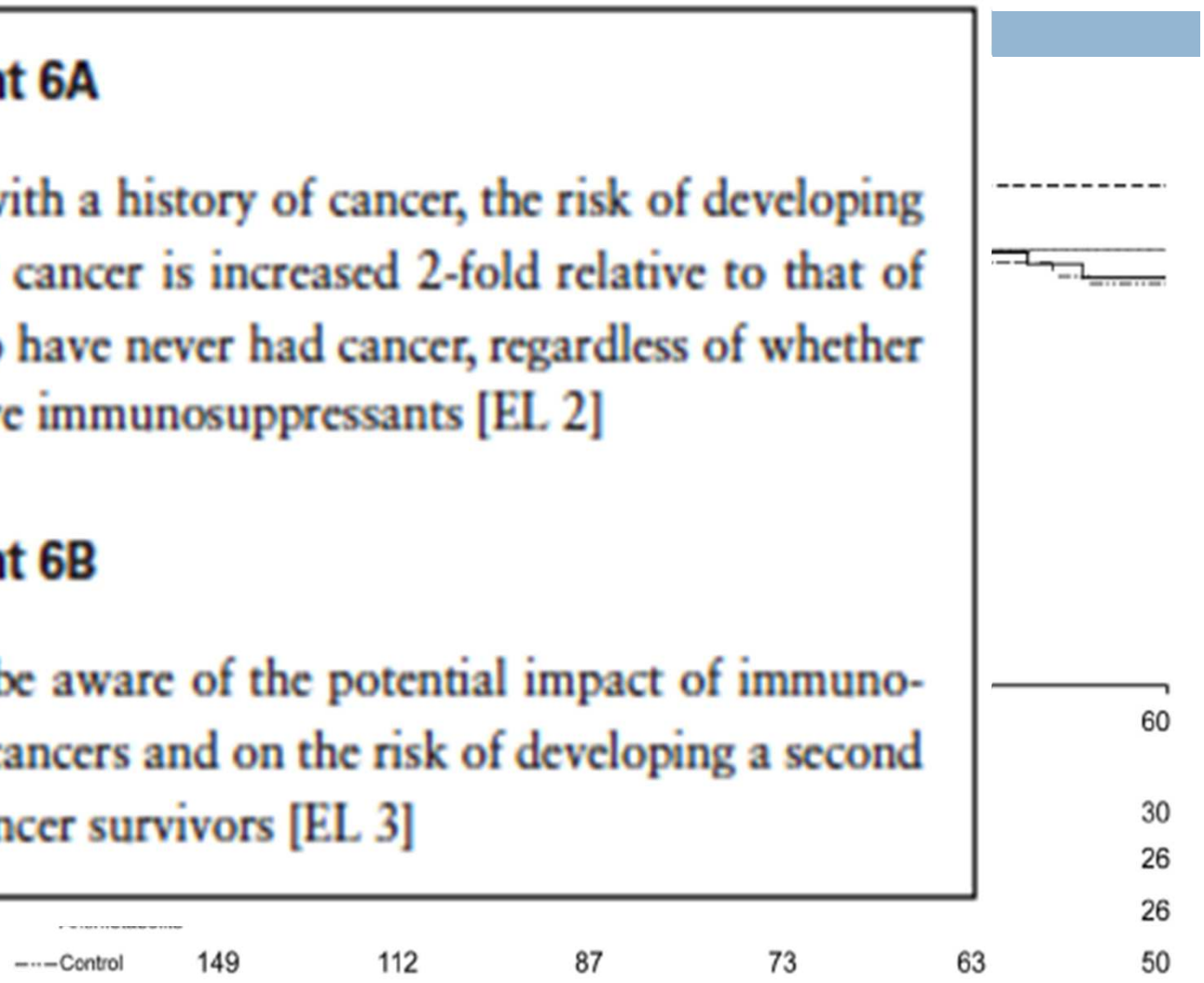
ECCO Statement 6A

In IBD patients with a history of cancer, the risk of developing new or recurrent cancer is increased 2-fold relative to that of IBD patients who have never had cancer, regardless of whether or not they receive immunosuppressants [EL 2]

ECCO Statement 6B

Physicians must be aware of the potential impact of immuno-suppressants on cancers and on the risk of developing a second malignancy in cancer survivors [EL 3]



Axelrad, Clinical Gastroenterology and Hepatology 2016

ECCO Statement 6C

Preliminary data on immune-mediated inflammatory diseases and IBD demonstrate no obvious excess risk of developing a second [new or recurrent] cancer while being treated with anti-TNF therapy [EL 4]

ECCO Statement 6D

All cases of cancer in IBD should be managed with multidisciplinary support. In general, thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped at least until cancer therapy is completed [EL 5]

ECCO Statement 6E

Thiopurines should be withdrawn in IBD patients who develop squamous-cell carcinomas, aggressive forms of basal-cell carcinomas, and multiple synchronous or sequential lesions. In patients with sporadic non-aggressive basal cell carcinoma, thiopurines can be continued if no satisfactory therapeutic alternatives are available [EL 5]

ECCO Statement 6F

In patients with active IBD and a history of malignancy, 5-aminosalicylates, nutritional therapies, and local corticosteroids can be safely used [EL 3]. In more severe flares that do not respond to these treatments, the use of anti-TNF, methotrexate, short-term systemic corticosteroids, and/or surgery should be considered on a case-by-case basis [EL 5]

ECCO Statement 6G

Based on data in transplant recipients, physicians should consider delaying the resumption of immunosuppressant therapy for IBD in patients being treated for cancer, because of the risk of recurrent neoplastic disease, for 2 years following the completion of cancer treatment [EL 3]. The delay can be extended to 5 years if the cancer is associated with an intermediate or high risk of recurrence [EL 3]

ECCO Statement 6H

Limited evidence indicates that IBD can be aggravated by hormonal therapy, chemotherapy-induced mucositis, or immune system-activating therapy, alone or in combination [EL 4]. In patients with active disease at cancer diagnosis, remission can be induced and maintained thanks to the immunosuppressant effects of cancer treatment [despite withdrawal of immunosuppressant therapy for IBD] [EL 4]. The impact of targeted anticancer therapy on IBD remains unknown [EL 5]

Annese, ECCO guideline JCC 2015

Que faire en cas d'antécédent de cancer ?

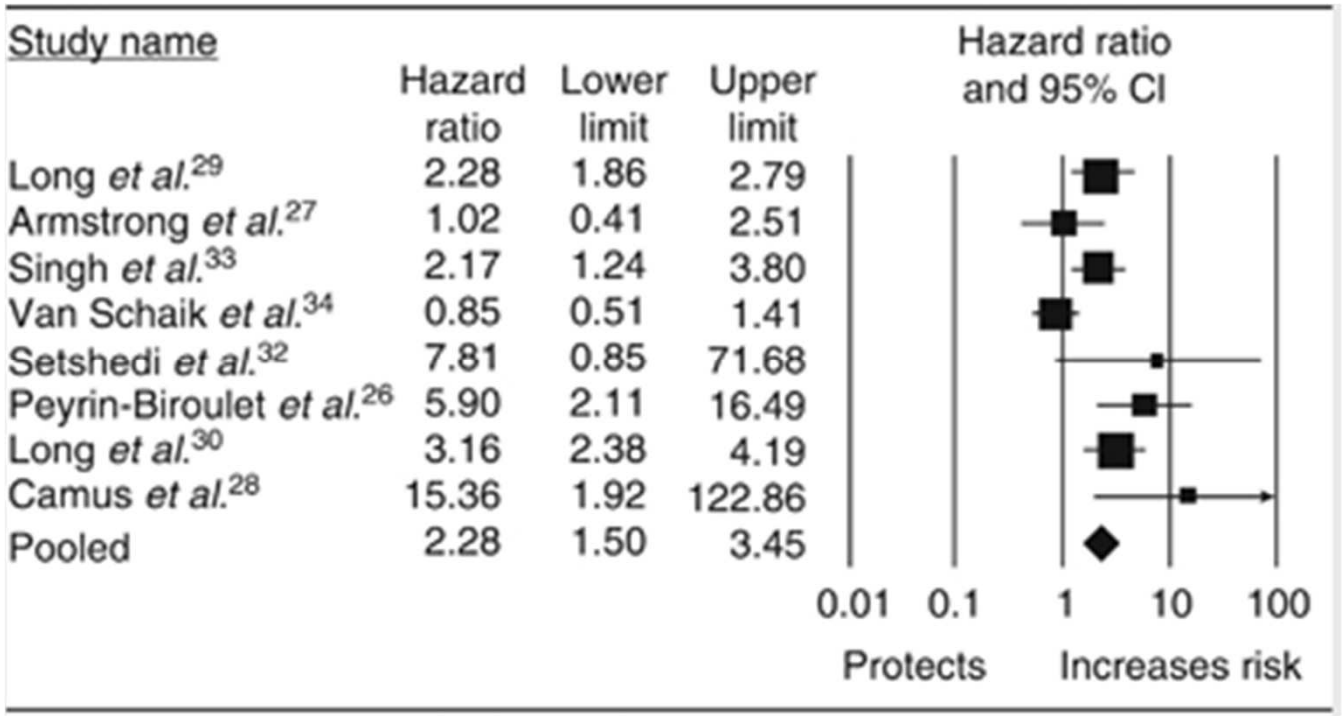
- **Conclusion :**
- **ATCD K + MICI = Risque nouveau K x 2 mais faible risque de récidive**
- **Thiopurines et antiTNF ne semblent pas augmenter le risque de cancer solide, MAIS…**
- **Ces traitements doivent être stoppés jusqu'à la fin du traitement du cancer**
- **Eviter IS dans les 2 ans après traitement du cancer, voire 5 ans si risque de rédivie estimé élevé**
- **Attention aux pathologies malignes onco-hématologiques**

Non-melanoma skin cancers NMSC?

- Rapporté avec traitement par thiopurines
  - ↑mutagénèse des cellules épithéliales, induite par UVA (6-TGN)
  - ↑ photosensibilité aux UVA
  - Données de la transplantation et IS
- MICI: peu données, cohorte CESAME
  - exposition active ou passée AZA/6-MP
  - ↑ risque NMSC, même avant 50 ans

Peyrin-Biroulet, Gastroenterology 2011

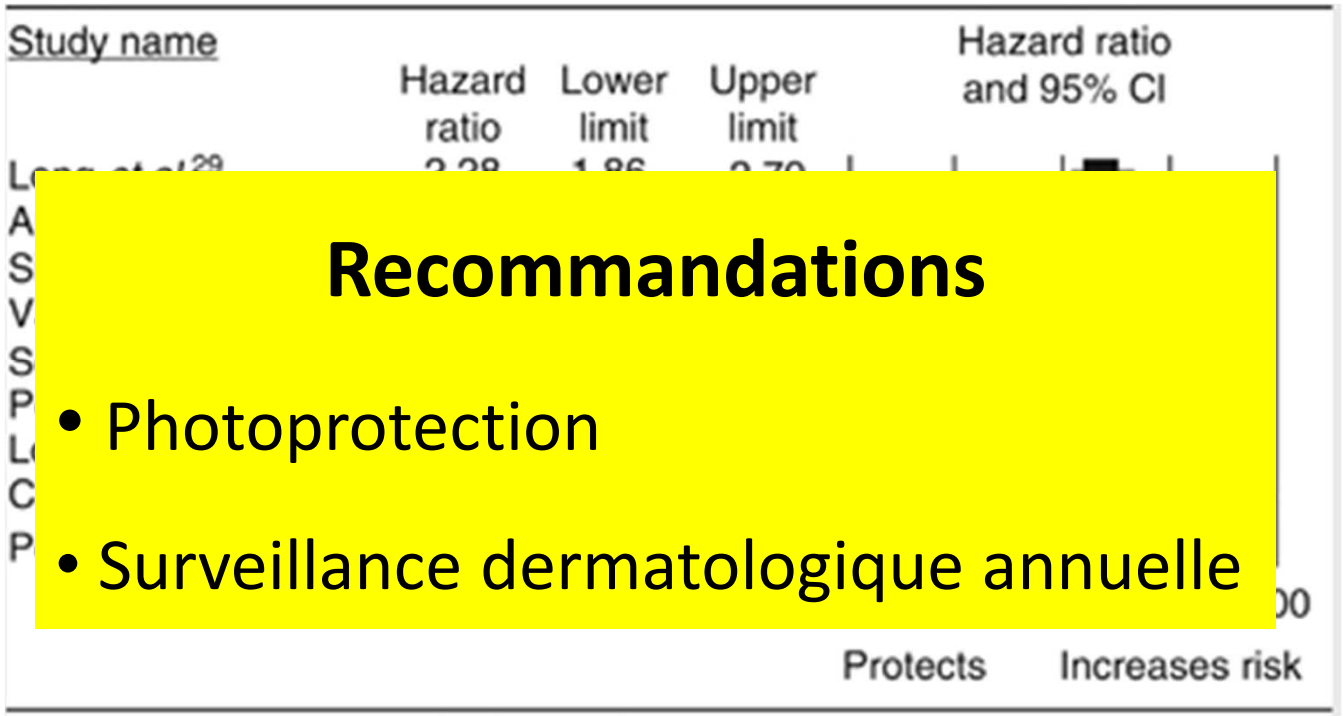
Non-melanoma skin cancers NMSC?



Risque augmenté chez les patients traités
par thiopurine pour une MICI

Ariyaratnam, Am J Gastroenterol 2014

Non-melanoma skin cancers NMSC?



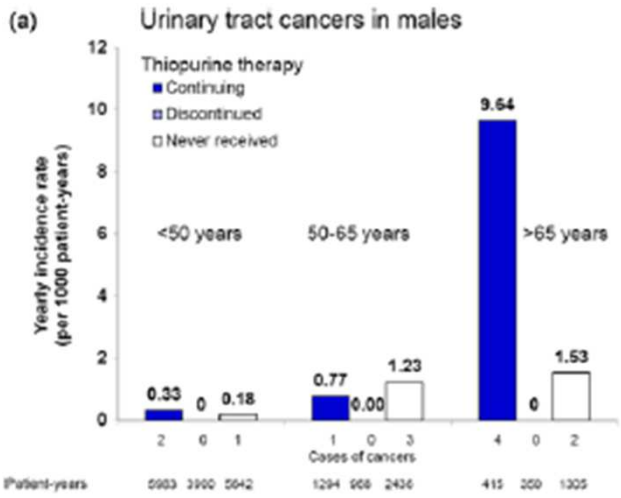
Risque augmenté chez les patients traités par thiopurine pour une MICI

Ariyaratnam, Am J Gastroenterol 2014

Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study

Table 3 | Standardised incidence ratios (SIRs) of urinary tract cancers according to thiopurine therapy status* in the 19 486 patients with IBD of the CESAME cohort followed prospectively for a median period of 35 months

	Patient-years	Reported cases	Expected cases	SIR	95% CI	*P* value
Urinary tract cancers (all)	49 731	16	9.87	1.62	0.93–2.63	0.09
Ongoing thiopurine therapy	16 657	8	2.35	3.40	1.47–6.71	0.006
Discontinued	9985	1	1.56	0.64	0.01–3.56	0.92
Never received	23 088	7	5.96	1.17	0.47–2.42	0.78
Kidney cancers (all)	49 733	10	4.87	2.05	0.98–3.77	0.06
Ongoing thiopurine therapy	16 658	5	1.22	4.11	1.34–9.60	0.02
Discontinued	9985	1	0.80	1.26	0.03–6.99	0.91
Never received	23 090	4	2.86	1.40	0.38–3.58	0.64
Bladder cancers (all)	49 742	6	5.00	1.20	0.44–2.61	0.77
Ongoing thiopurine therapy	16 664	3	1.13	2.65	0.55–7.76	0.21
Discontinued	9988	0	0.76	0.00	0.00–4.83	0.94
Never received	23 091	3	3.10	0.97	0.20–2.82	0.95



Cohorte CESAME

Bourrier, Aliment Pharmacol Therap 2016

MICI et cancers: points clés

- Règles générales
  - Protection solaire et suivi dermatologique
  - Arrêt du tabac (MC et RCH)
  - Surveillance gynécologique (FCV)
- Dépistage endoscopique
  - Inflammation colique ancienne (>7-10 ans)
  - Dès le diagnostique en cas de CSP
  - Apport de la chromo-endoscopie
- Chémoprévention: 5-ASA ++ - Cicatrisation muqueuse? AUDC? Statines?
- Vigilance sur l'immunosuppression induite (AZA, anti-TNF): EBV
- Attente des bénéfices de la cicatrisation muqueuse?