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# Chimioprévention de la carcinogénèse colique

Pauline Wils- Lille

# Introduction

## CHIFFRES

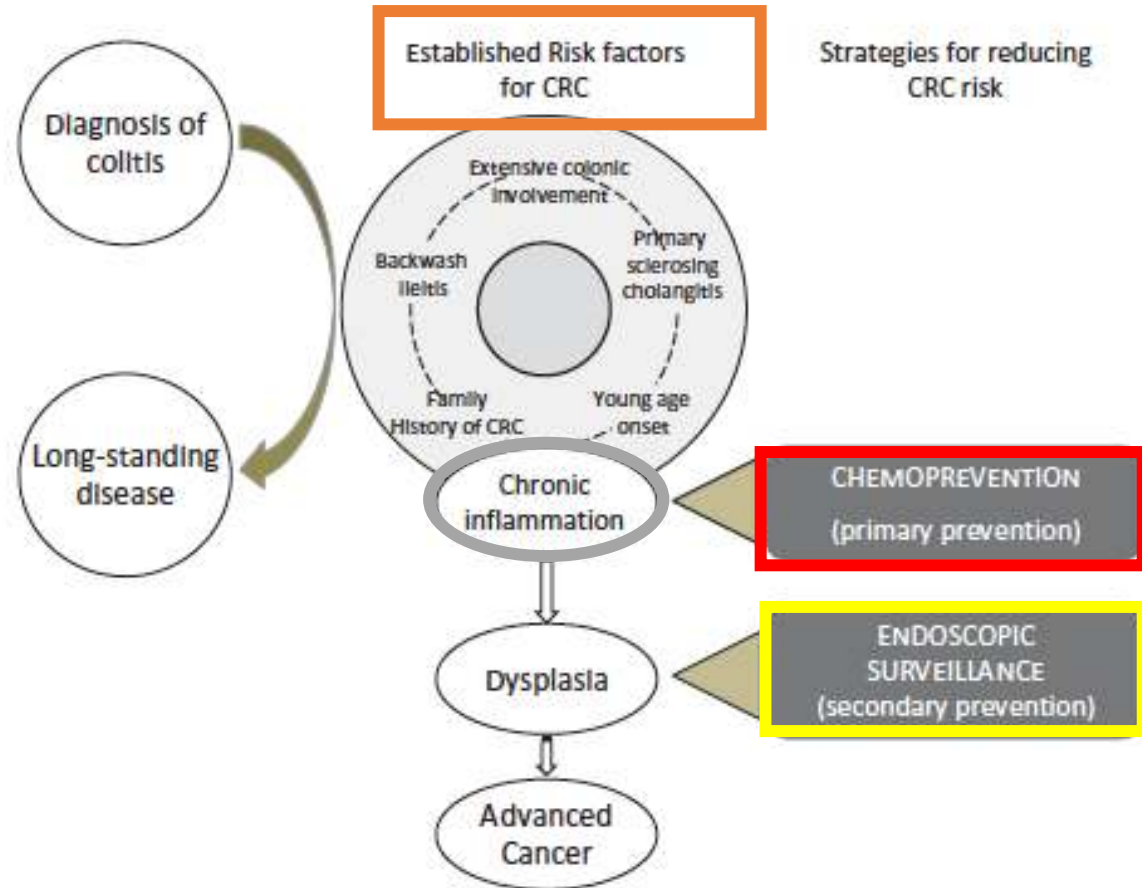
- 3ème cancer en terme de fréquence
- 2ème cause de décès par cancer dans le monde
- Baisse de l'incidence du CCR chez les patients atteints de MICI, mais risque estimé à 1.7 x supérieur

## FACTEURS de RISQUE de CCR dans la MICI colique

Disease-related factor	Patient-related factors
Extensive colitis	Prior history of dysplasia
Duration of disease	Family history of CRC in FDR, especially if <50 years old
Severity of inflammation	Primary sclerosing cholangitis
Cumulative inflammatory burden	Possible: earlier age of disease onset, male sex, and patient compliance with medication/follow-up
Structural alterations as a consequence of chronic inflammation	
Pseudopolyps*	
Stricture	
Shortened lead pipe colon	

**Comment prévenir la survenue du CCR chez les patients atteints de MICI ?**

# Current strategies for reducing risk of CCR



La chimioprévention du cancer = administration chronique d'un agent synthétique, naturel ou biologique dans le but de réduire ou retarder l'apparition d'une tumeur maligne.

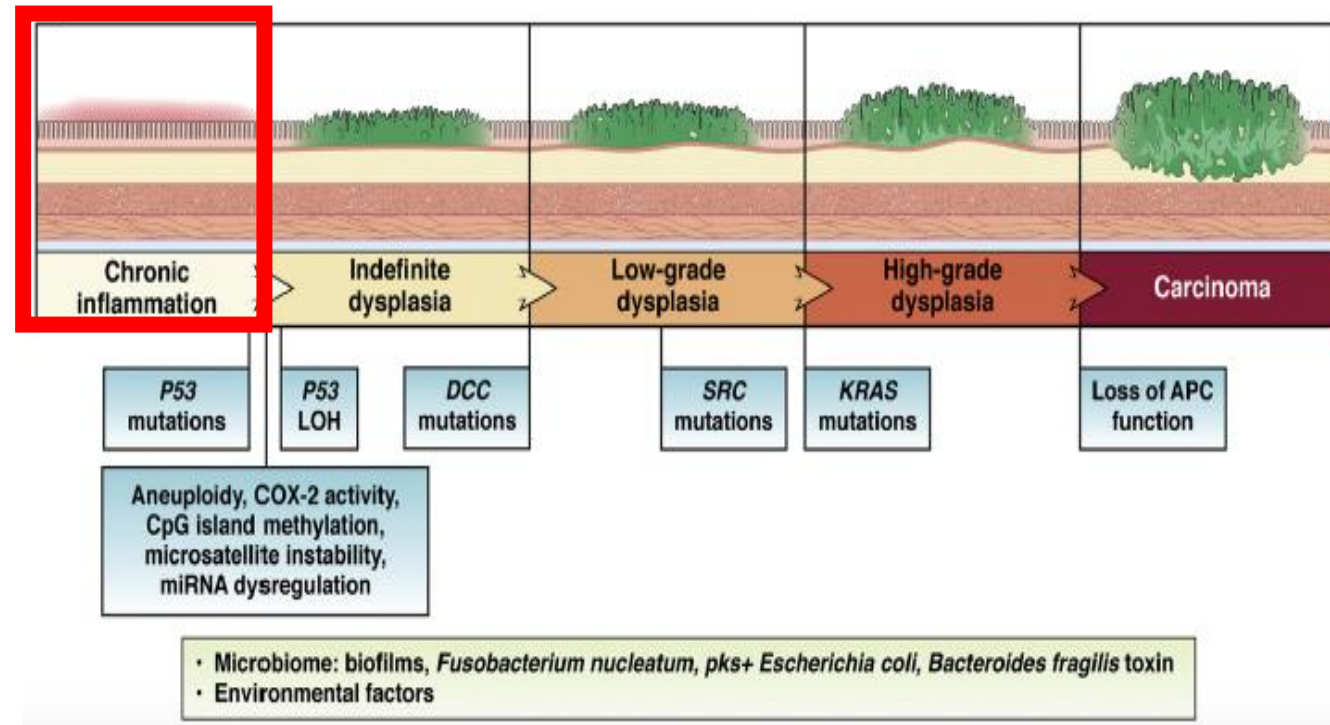
Effet chimiopréventif d'une molécule est suggéré par des études épidémiologiques, basé sur des arguments biologiques puis doit être confirmé par un essai RCT.

**TABLE 1** Requirements of chemopreventive agents

1. Low toxicity
2. Few or no side-effects
3. Easy to take
4. Easy to administer
5. Cost-effective

# inflammation-induced carcinogenesis

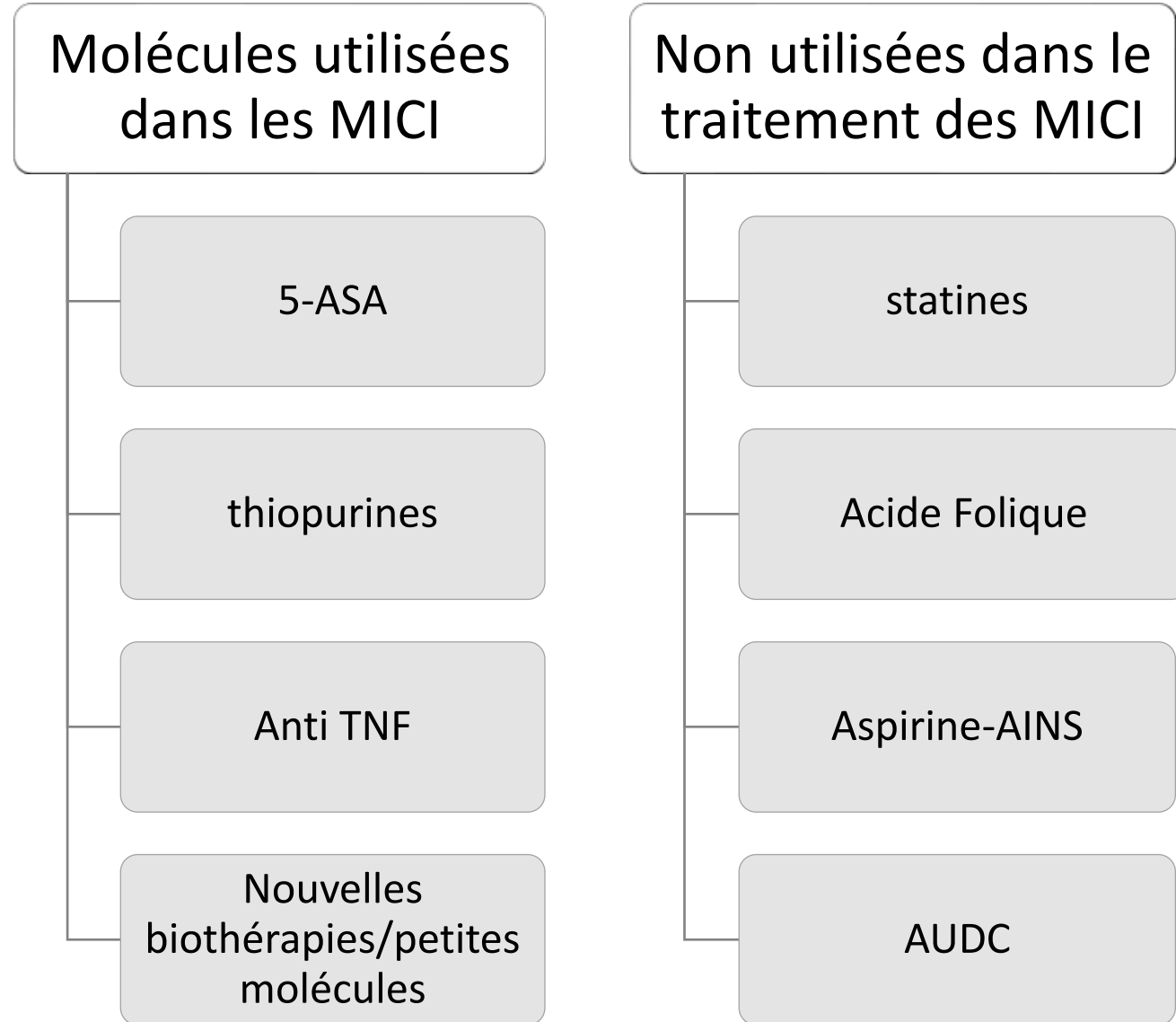
Colonic inflammation: a key player in colorectal cancer development



Théoriquement: traiter l'inflammation chronique =  risque de CCR

MAIS aucun essai RCT ne l'a démontré  Données à partir d'études observationnelles  
Cohortes, Cas-control, Méta-analyses

# Molécules avec effet chimiopréventif potentiel



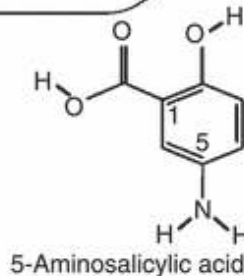
# 5 ASA= propriétés anti-inflammatoires et antitumorales intrinsèques

## Cell cycle (Ref)

S-phase arrest (19,21)  
 Chk1 & Rad17 upregulation (19)  
 Improvement of DNA replication fidelity (19,21)  
 Phosphorylation Ser15p53 (19)  
 SH-PTP2 activation, EGFR downregulation (25)  
 Appearance of abnormal mitotic cells, apoptosis (19)  
 Caspase 3 activation, PARP cleavage (27-30)  
 Suppression of c-Myc, c-Met, cyclin D1 (15,33)  
 Negative regulation of Cdc25A (37)

## TNF- $\alpha$ , TGF- $\beta$ and NF- $\kappa$ B pathway (Ref)

Inhibition of active NF- $\kappa$ B (14,57)  
 Downregulation of IL-1 $\beta$ , NF- $\kappa$ B, I $\kappa$ B kinase (57,58)  
 Inhibition of MMPs (60)  
 Inhibition of TNF- $\alpha$ , and COX-2 (12,45)  
 Reduction of TGF- $\beta$ 1 signalling (63,64)



## Interference with Wnt/ $\beta$ -catenin signalling

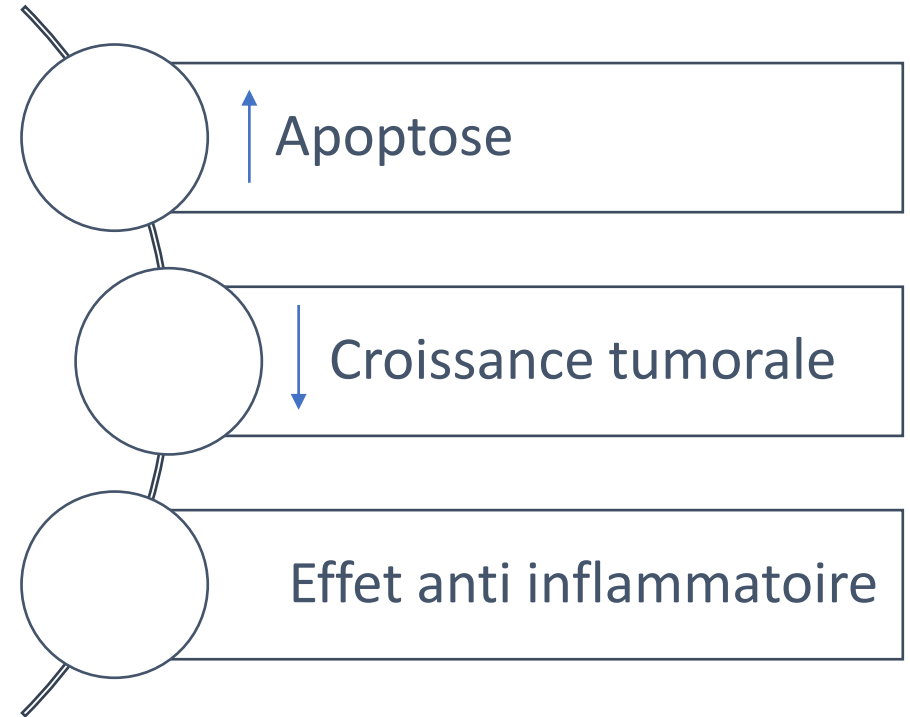
Interferes with Wnt/ $\beta$ -catenin signalling via PP2A (15)  
 Increases  $\beta$ -catenin phosphorylation (15)  
 Upregulation of PPAR- $\gamma$  (69,70)

## ROS and RNS scavenging (Ref)

Inhibition of free radicals, antioxidant (39,43)  
 ROS scavenger (21)  
 Regeneration after oxidative stress (42)  
 Reduction of nitrates and suppression of iNOS (45,50)  
 Stimulation of heme oxygenase activity (46)  
 Radioprotection against ROS and free radicals (47)  
 Decrease of myeloperoxidase activity, NO<sub>2</sub>/NO<sub>3</sub> (50)  
 Dissipation of mitochondrial membrane potential (27)

## Antimicrobial activity

Implication in antimicrobial activity (73)  
 Inhibition of mucosal *E. coli*-triggered IL-8 release (79)  
 Downregulation of bacterial genes transcription (80)



**Table 2.** Meta-analyses: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease

Author meta-analysis	Studies, n Total (hospital-based/ population-based)	Total cases	CRC cases	Dysplasia cases	Colonic neoplasia risk and 5-ASA exposure and other findings
Velayos et al. [20]	9 (3/6) UC	474	334	140	CRC/Dys: OR = 0.51; 95% CI 0.37–0.69 <i>Significant reduction for CRC</i> ★
Nguyen et al. [21]	13 (9/4)	1,259	Nr	Nr	CRC/Dys population based: OR = 0.95; 95% CI 0.66–1.38 CRC/Dys hospital based: OR = 0.58; 95% CI 0.45–0.75
Zhao et al. [22]	17 (9/8)	1,508	Nr	Nr	CRC/Dys: OR = 0.63; 95% CI 0.48–0.84 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>5-ASA dose effect &gt;1.2 g/d and sulfasalazine ≥2 g/d</i> ★
O'Connor et al. [23]	8 (4/4)	867	724	143	CRC/Dys: OR = 0.6; 95% CI 0.4–0.9 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>No protective effect of sulfasalazine</i>
Qui et al. [25]	26 (17/9)	1,958	Nr	Nr	CRC/Dys: OR = 0.58; 95% CI 0.45–0.75 <i>Significant reduction in the hospital based but not in the population-based studies</i> <i>Significant reduction for CRC alone but not dysplasia</i> <i>5-ASA 1.2 g greater effect than ≤1.2 g, sulfasalazine not effective</i> <i>5-ASA effective in UC for CRC prevention but not for dysplasia and not for CD</i> ★
Bonovas et al. [24]	31 (19/12)	2,137	Nr	Nr	CRC/Dys: RR: 0.57, 95% CI 0.45–0.71 <u><i>Significant reduction in the hospital – and population-based studies</i></u> <u><i>Significant reduction for both CRC and dysplasia</i></u> <i>No effect of 5-ASA on CD CRC prevention</i> <i>5-ASA dose effect &gt;1.2 g/d, sulfasalazine not effective</i> ★

Données poolées d'études en population ou de centres de référence:

➔ 50% du risque de CRC ou de dysplasie

Mesalamine  
dose-effect > 1.2g/j ★

Mais preuve scientifique FAIBLE  
-études hétérogènes  
-Résultats parfois différents lorsque pris séparément entre centres de référence et études en population  
-biais: caractère rétrospectif, facteurs confondants

# Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease

S. Bonovas<sup>\*</sup>, G. Fiorino<sup>\*</sup>, T. Lytras<sup>†,‡,§</sup>, G. Nikolopoulos<sup>¶</sup>, L. Peyrin-Biroulet<sup>\*\*</sup> & S. Danese<sup>\*††</sup>

**Table 2 | Meta-analysis results**

	No. of studies	Pooled effect estimate <sup>‡</sup> RR (95% CI)	Tests of homogeneity			Tests of publication bias	
			Q value (d.f.)	P-value	I-squared	Begg's P-value	Egger's P-value
All studies	31	0.57 (0.45–0.71)	66.2 (30)	<0.001	55%	0.39	0.01
Cohort studies	10	0.65 (0.43–0.99)	16.0 (9)	0.07	44%	0.28	0.02
Case-control studies	21	0.53 (0.40–0.70)	48.5 (20)	<0.001	59%	0.57	0.02
Population-based studies	12	0.70 (0.52–0.94)	29.9 (11)	0.002	63%	0.73	0.12
Hospital-based studies	19	0.46 (0.34–0.61)	22.7 (18)	0.20	61%	0.55	0.37
Studies rated as low risk of bias (i.e. high-quality) <sup>*</sup>	24	0.61 (0.48–0.78)	50.5 (23)	<0.001	54%	0.82	0.03
Studies rated as high risk of bias, or not assessed	7	0.42 (0.24–0.74)	11.7 (6)	0.07	49%	0.55	0.21
Studies adequately controlled for confounding <sup>†</sup>	8	0.66 (0.38–1.14)	15.1 (7)	0.035	54%	0.71	0.82
Studies not adequately controlled for confounding	23	0.54 (0.42–0.70)	50.8 (22)	<0.001	57%	0.41	<0.01
Studies published in full-text form	27	0.63 (0.51–0.79)	50.6 (26)	0.003	49%	0.83	0.03
Studies published as short reports or abstracts	4	0.26 (0.13–0.54)	4.8 (3)	0.19	37%	0.31	0.39
Data for ulcerative colitis	21	0.50 (0.38–0.64)	32.8 (20)	0.035	39%	0.22	0.13
Data for Crohn's disease	5	0.76 (0.43–1.33)	1.4 (4)	0.85	0%	0.46	0.38
Data for colorectal cancer	21	0.58 (0.45–0.74)	40.4 (20)	0.005	50%	0.53	<0.01
Data for colorectal dysplasia	5	0.54 (0.35–0.84)	1.0 (4)	0.91	0%	0.81	0.66
Data for mesalamine	9	0.70 (0.51–0.94)	14.6 (8)	0.07	45%	0.47	0.13
Data for sulfasalazine	11	0.72 (0.51–1.01)	21.2 (10)	0.020	53%	0.99	0.12

RR, relative risk; CI, confidence interval; d.f., degrees-of-freedom.

Tests of interaction: Cohort vs. Case-control studies,  $P = 0.41$ ; Population- vs. Hospital-based studies,  $P = 0.04$ ; Low vs. High risk of bias,  $P = 0.23$ ; Studies adequately controlled vs. not adequately controlled for confounding,  $P = 0.52$ ; Studies published in full-text form vs. Short reports or abstracts,  $P = 0.02$ ; Ulcerative colitis vs. Crohn's disease,  $P = 0.19$ .

Réduction du risque en population et en centre de référence

Chez UC mais pas CD

# Résultats de CESAME

case-control study nested in the CESAME observational cohort patients with IBD enrolled between May 2004 and June 2005 and followed up to December 2007

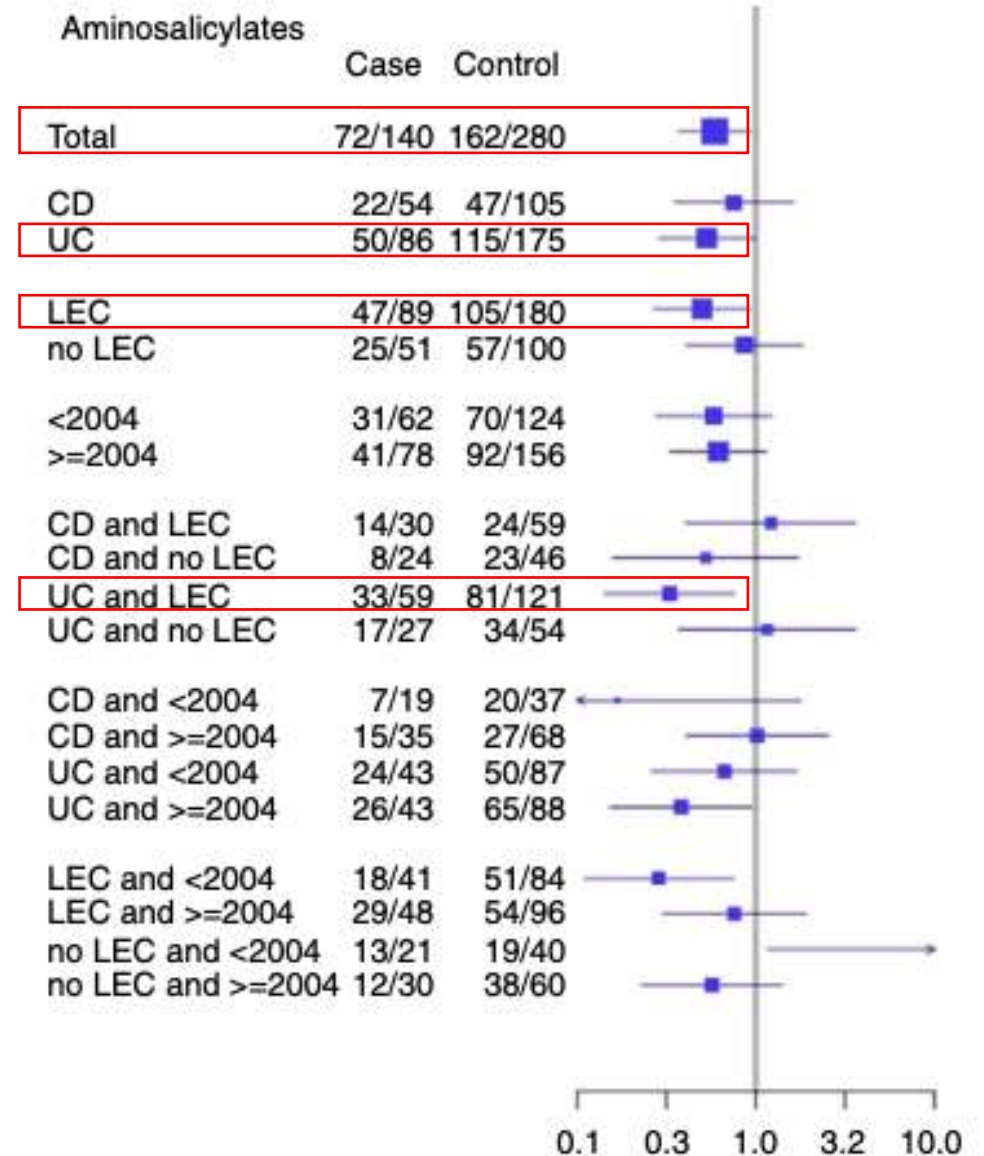
144 cases of CCR

**Protective effect with 5ASA:**

**OR = 0.587, 95% CI: 0.367–0.937, P = 0.0257**

**In patients with UC and LEC OR= 0.30 (95%CI: 0.14-0.68)**

On patients with risk factors: long-standing [ $> 10$  years] and extensive [ $> 50\%$  of colonic mucosa at any time] colitis



# Thiopurines et chemoprevention du CCR

**Table 3.** Meta-analyses: use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease

Author meta-analysis	Studies, n Total (hospital-based/ population-based)	Total cases	CRC cases	Dysplasia cases	Colonic neoplasia risk
Gong et al. [32]	19	Nr	Nr	Nr	RR = 0.71, 95% CI 0.54–0.94, result significant for heterogeneity Analysis separated by case-control (RR = 0.46, 95% CI 0.29–0.74, result significant for heterogeneity) and cohort study (RR = 0.96, 95% CI 0.94–0.98)
Jess et al. [33]	15	1,574	1,344 CRC/ high- or low-grade Dys	Nr	OR = 0.87, 95% CI 0.59–1.29 (but significant heterogeneity) In subgroup analysis separation in clinical based ( $n = 13$ ; OR = 0.87, 95% CI 0.59–1.09), case-control ( $n = 8$ ; OR = 0.83, 95% CI 0.65–1.08, and cohort study ( $n = 7$ ; OR = 0.93, 95% CI 0.67–1.28)
Lu et al. [34]	24	8,698	6,954 CRC 1,744 (CRC and/or high-grade Dys)	Nr	OR = 0.63, 95% CI 0.46–0.86 Colonic neoplasia risk decreases significant for UC (OR = 0.67, 95% CI 0.45–0.98), but not for CD patients (OR = 1.06, 95% CI 0.54–2.09) Decrease of risk significant for CRC (OR = 0.65, 95% CI 0.45–0.96) and advanced colorectal neoplasia (CRC and/or high-grade Dys) (OR = 0.62, 95% CI 0.44–0.89), but not dysplasia alone (OR = 0.90, 95% CI 0.37–2.21) Protective effect of thiopurines distinct in clinic based (OR = 0.59, 95% CI 0.42–0.82) and case-control studies (OR = 0.40, 95% CI 0.26–0.62), but not in population-based studies (OR = 0.95, 95% CI 0.55–1.62) and cohort studies (OR = 0.98, 95% CI 0.81–1.18)
Zhu et al. [35]	27	Nr	Nr	Nr	Analyses separated by case-control (OR = 0.49, 95% CI 0.34–0.70, result significant for heterogeneity) and cohort study (OR = 0.96, 95% CI 0.94–0.98) In subgroup analysis separation in hospital based ( $n = 12$ ; OR = 0.37, 95% CI 0.26–0.52) and population based ( $n = 4$ ; OR = 0.80, 95% CI 0.58–1.12), results significant for heterogeneity

Méta-analyses: résultats contradictoires

limitations :  
Hétérogénéité dans la dose utilisée, le temps d'exposition et pris en compte de potentiels facteurs confondants

Pas de dose minimale ou de durée minimale de traitement retrouvée pour obtenir un effet chimioprotecteur

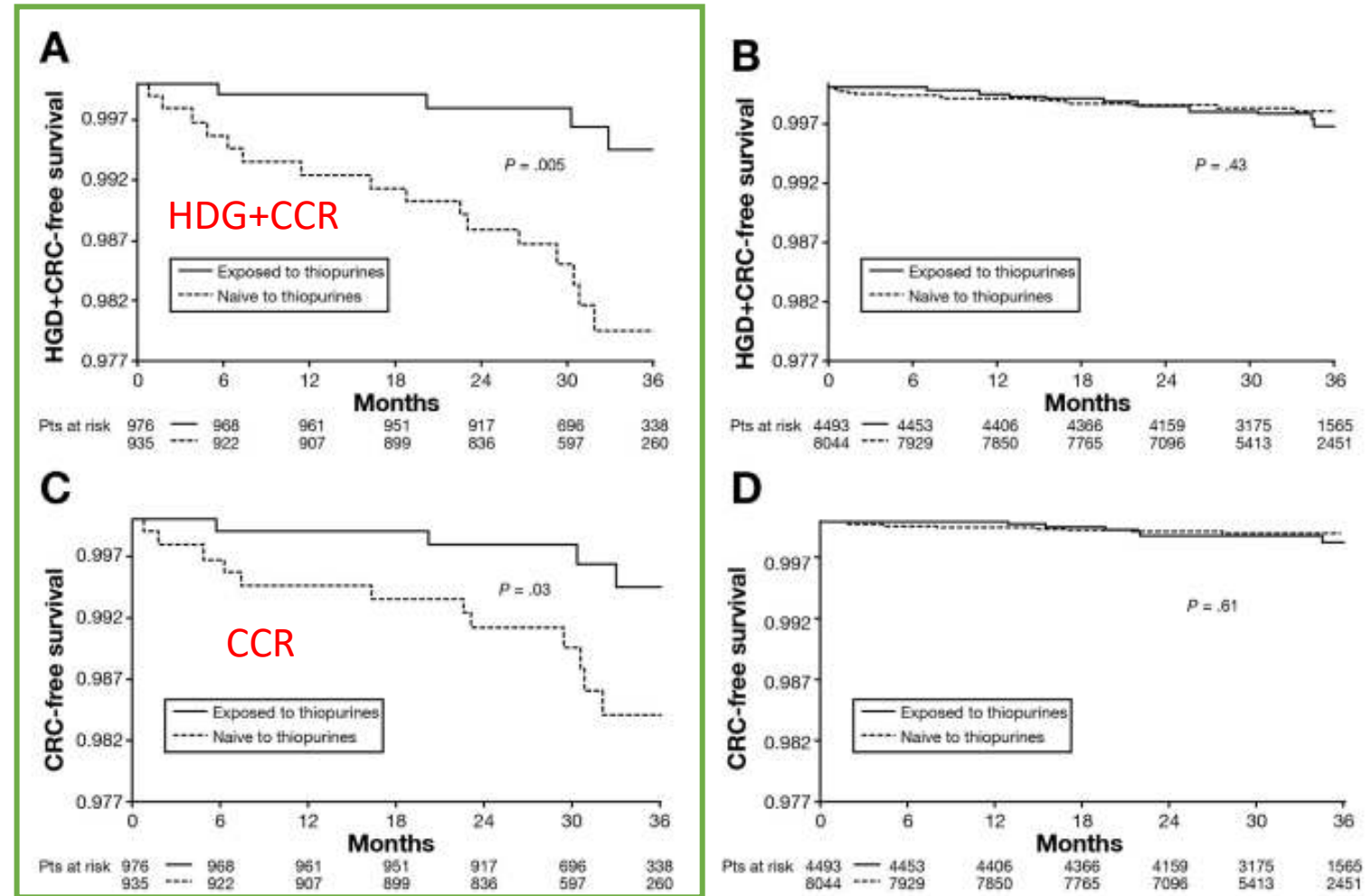
# Protective effect of thiopurine with long-standing (>10y) and extensive colitis

With LEC

Risk on CRC among IBD patients enrolled in the observational cohort CESAME

19,486 patients with IBD:

- 30.1% receiving thiopurine therapy)
- 2841 patients (14.6%) were characterized as having long-standing extensive colitis (ie, >10 years and involving 50% of the colon)
- 37 CCR+ 20 HGD
- Expo thiopurines: Réduction du risque x 3.6



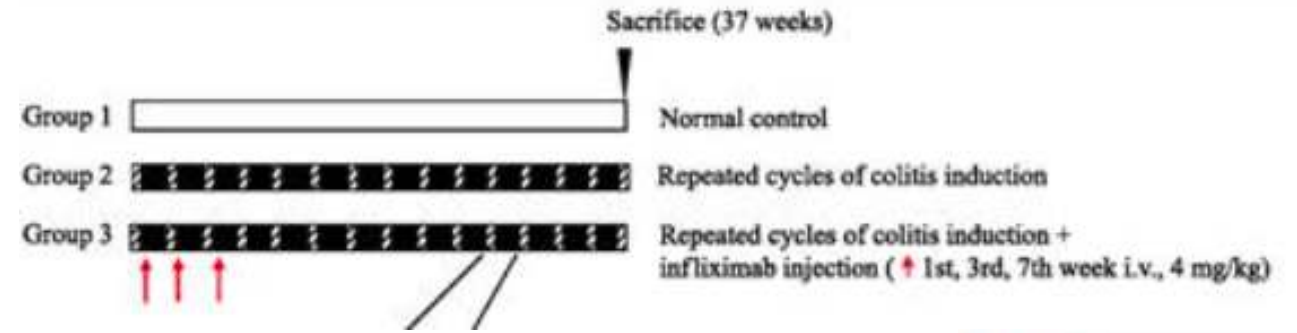
**Figure 2.** Probability of remaining free of colorectal advanced neoplasia (HGD or cancer) in patients with (A) or without (B) long-standing extensive colitis according to thiopurine exposure status at the time of entry into the cohort, and probability of remaining free of CRC in patients with (C) or without (D) long-standing extensive colitis according to thiopurine exposure status at the time of entry into the cohort.

# Anti TNF

Action chimiopréventive suggérée par des études sur la souris:

l'utilisation précoce d'un anti TNF réduirait le risque de CCR associé à la colite DSS induite:

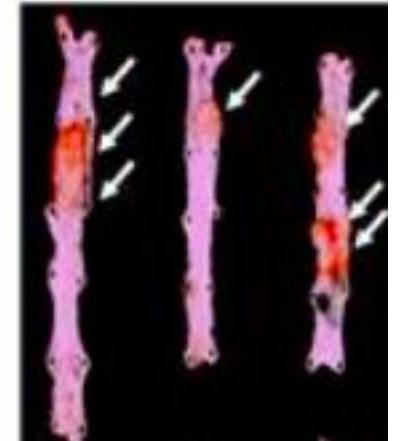
- induction de l'apoptose de cellules inflammatoires
- diminution du taux de TNFalpha
- inhibition de la voie de B cathe-nine



Tumor incidence and multiplicity according to group

Groups	Treatments	Tumor incidence (%)	Tumor multiplicity
Group 1	None	0/10 (0.0)	-
Group 2	Repeated DSS	9/12 (75.0)	1.57±0.55
Group 3	Repeated DSS + infliximab (1st, 3rd, 7th)	2/12 (16.7)*	1.00

\*  $P < 0.001$  (vs group 2)



# Anti TNF

Peu de donnée chez l'humain

Etude multicentrique cas-contrôle  
Néerlandaise (78 centres):

- 159 cas de CCR associés à MICI vs 392 MICI
- Après prise en compte des facteurs confondants, les immunosuppresseurs (OR 0.3; 95 %CI 0.16 – 0.56, P < 0.001) et anti-TNF (OR 0.09; 95 %CI 0.01 – 0.68, P < 0.02) semblaient protecteurs

**Table 3.** Results of univariate cox regression analysis for medication use

	Cases	Controls	Odds ratio (95% CI)	P value
<i>No. of patients</i>	159 (%) <sup>a</sup>	392 (%)	—	
None	11 (6.9)	4 (1)	—	—
<i>5-ASA</i>				NS
Yes	137 (86)	351 (89)	0.73 (0.42–1.27)	
No	22 (14)	41 (11)	1.0	
<i>Thiopurines</i>				<0.001
Yes	36 (23)	216 (55)	0.36 (0.16–0.86)	
No	123 (77)	176 (45)	1.0	
<i>Corticosteroids</i>				0.001
Yes	102 (64)	326 (83)	0.36 (0.24–0.55)	
No	57 (36)	66 (17)	1.0	
<i>MTX</i>				0.03
Yes	2 (1)	23 (6)	0.2 (0.48–0.88)	
No	157 (99)	369 (94)	1.0	
<i>Anti-TNF</i>				<0.001
Yes	4 (3)	75 (19)	0.11 (0.04–0.3)	
No	155 (97)	317 (81)	1.0	
<i>NSAIDS</i>				NS
Yes	7 (4)	9 (2)	1.96 (0.72–5.36)	
No	152 (96)	383 (98)	1.0	
<i>Folic acid</i>				NS
Yes	16 (10)	42 (11)	0.93 (0.51–1.71)	
No	143 (90)	350 (89)	1.0	

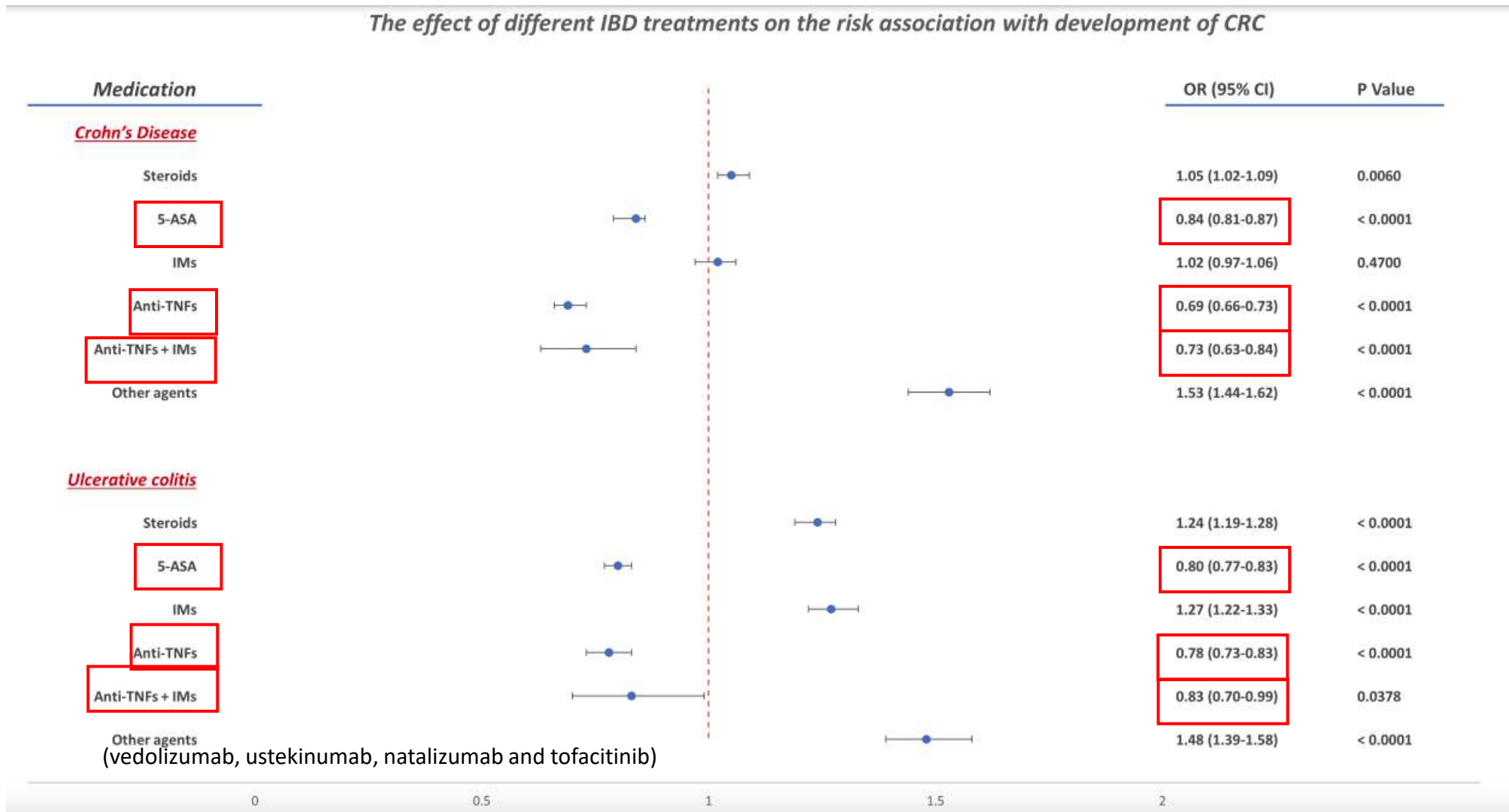
Baars JE. The Risk of Inflammatory Bowel Disease-Related Colorectal Carcinoma Is Limited: Results From a Nationwide Nested Case – Control Study Am J Gastroenterol 2011

# Database multicentrique américaine (Explorys)

Cohorte de de 225 000 patients avec CD et 188 000 avec UC (1999-2020)

Effet de differents traitements sur le risque de CCR: 16% sous anti TNF, 3% sous "other agents"

Montre une association inverse entre utilisation des anti TNF et survenue d'un CCR



# Diminution du risque de CCR avec les anti TNF

- Nationwide population-based study
- French health insurance database
- 32 403 patients with UC, 15 542 [48.0%] were exposed to anti-TNF.  
During a median follow-up of 6.1 years

risk of CRC associated with anti-TNF exposure was not decreased in the overall group of patients with UC (hazard ratio [HR], 0.85; 95% CI, 0.58-1.26),

**anti-TNF exposure was significantly associated with a decreased risk of CRC in patients with long-standing colitis [disease duration  $\geq 10$  years] [HR, 0.41; 95% CI, 0.20-0.86].**

# Maintien des 5 ASA sous anti TNF?

	All IBD (n)	Incident CRC (n)	Weighted percentage (95% CI)	P value
CRC diagnosed post-5ASA				
5ASA user	8379	226	3.2 (2.7, 3.6)	0.9685
Non-5ASA user	2528	65	3.2 (2.3, 4.0)	
CRC diagnosed after 1 year of 5ASA use				
5ASA user	8379	180	2.7 (2.2, 3.1)	0.2625
Non-5ASA user	2528	65	3.2 (2.3, 4.0)	
CRC diagnosed after 1 year of 5ASA use				
1. One-time user	556	10	2.0 (0.6, 3.4)	0.7412
2. Previous continuous user	1473	27	2.5 (1.5, 3.5)	
3. Persistent	1139	20	2.2 (1.2, 3.5)	
4. Intermittent user	5211	123	2.8 (2.3, 3.3)	
CRC diagnosed after 1 year of 5ASA use in 5ASA users who initiated anti-TNF				
Continued 5ASA	280	<6	1.6 (0, 3.5)	0.4046
Discontinued 5ASA	180	<6	3.2 (0, 7.2)	
CRC diagnosed after 1 year of 5ASA use in 5ASA users				
Initiated immunomodulator	1794	39	2.6 (1.7, 3.5)	0.9176
Not initiated-immunomodulator user	6585	141	2.7 (2.2, 3.1)	
CRC diagnosed after 1 year of 5ASA use in 5ASA users who initiated immunomodulator				
Continued 5ASA	1113	22	2.6 (1.4, 3.7)	0.8645
Discontinued 5ASA	681	17	2.7 (1.3, 4.1)	

Etude retrospective de cohorte en population (University of Manitoba IBD Epidemiologic Database, Canada) qui comparaient la survenue de différents outcomes selon poursuite ou non des 5ASA après initiation des anti TNF

60% des patients RCH (160/262) continuaient les 5 ASA après l'introduction des anti TNF

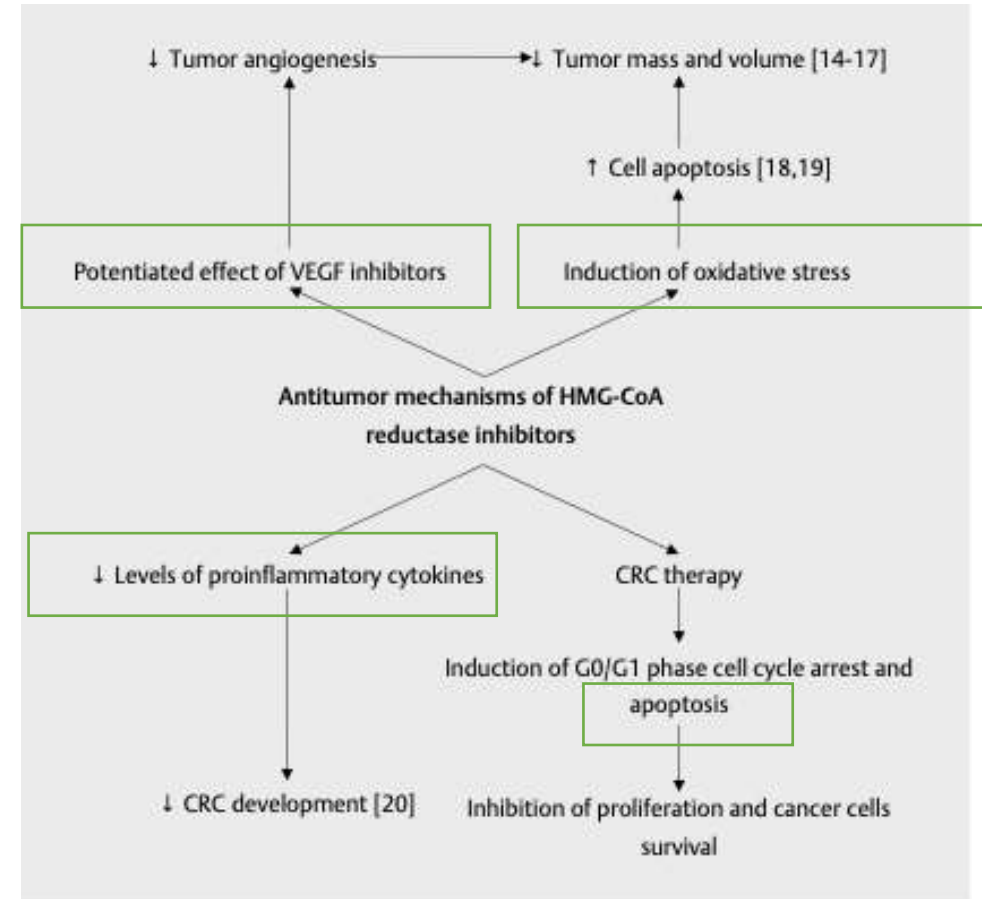
Il n'y avait pas de différence dans la survenue d'un CCR entre les patients qui continuaient et ceux qui arrêtaient les 5ASA

# Statines: effet chimiopréventif dans le CCR sporadique

Authors	Year	Study design	Study subjects	Results	Risk of CRC
Broughton et al.[41]	2012	Retrospective case-control	101 CRC, 132 controls	OR 0.43 (95% CI 0.25-0.80); P<0.01	Reduced
Clancy et al.[44]	2013	Retrospective cohort	266,109 statin users, 2,420 CRC	HR 0.79 (95% CI 0.69-0.90); P n/a	Reduced
Robertson et al.[49]	2010	Case-control	9,979 CRC, 99,790 controls	HR 0.95 (95% CI 0.80-1.12); P n/a	No effect
Cheng et al.[50]	2011	Case-control	1,156 CRC, 4,624 controls	aOR 1.09 (95% CI 0.91-1.30); P n/a	No effect
Björkhem-Bergman et al. [51]	2014	Case-control	21,143 CRC, 105,715 controls	OR 1.04 (95% CI 1.00-1.08); P n/a	No effect
Limburg et al. [52]	2011	Multicenter RCT	22 patients, 22 controls	5.6% ACF change; P=0.3	No effect
Vinogradova et al. [54]	2011	Case-control	11,749 CRC, 48,624 controls	OR 1.23 (95% CI 1.10-1.38); P n/a	Increased
Mamtani et al. [42]	2016	Case-control	22,163 CRC, 86,538 controls	OR 0.92, (95% CI 0.85-0.99) for use shorter than 1 year; P n/a	Reduced
Sehdev et al. [55]	2014	Case-control	357,702 patients	aOR 0.74 (95% CI 0.72-0.77); P<0.001	Reduced
Ananthkrishnan et al.[58]	2016	Cohort	11,001 patients, 1,376 using statins	OR 0.42 (95% CI 0.28-0.62)	Reduced
Renman et al. [53]	2017	Case-control	260 CRC, 73 controls	OR 1.6; P=0.050	No effect
Lash et al. [67]	2017	Cohort	21,152 patients	aHR 1.01 (95% CI 0.93-1.09)	No effect

ACF – aberrant crypt foci; aHR – adjusted hazard ratio; aOR – adjusted odds ratio; CI – confidence interval; CRC – colorectal cancer; HR – hazard ratio; n/a – not available; OR – odds ratio.

Dobrzycka Exp Clin Endocrinol Diabetes 2020 Statins and Colorectal Cancer – A Systematic Review



► **Fig. 2** Possible mechanisms of the anticancer action of statins. CRC: colorectal cancer; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; VEGF: endothelial growth factor.

# Chimio-prévention par statine dans les MICI: résultats discordants

Analysis of Statin and NSAID or Aspirin use and Odds of Colorectal Cancer Stratified by IBD

Variable	Case	Control	Unadjusted OR	Adjusted OR <sup>*#</sup>
<b>No IBD</b>				
Statin use:			<b>0.49 (0.39, 0.62)</b>	<b>0.56 (0.44, 0.72)</b>
Yes	115 (6.1)	224 (11.8)	<b>P&lt;0.001</b>	<b>P&lt;0.001</b>
No	1767 (93.9)	1676 (88.2)		
NSAID/ASA use:			<b>0.60 (0.51, 0.71)</b>	<b>0.62 (0.53, 0.73)</b>
Yes	310 (16.5)	474 (24.9)	<b>P&lt;0.001</b>	<b>P&lt;0.001</b>
No	1572(83.5)	1426 (75.1)		
<b>IBD</b>				
Statin use:			<b>0.07 (0.01, 0.78)</b>	0.10 (0.01, 1.31)
Yes	1 (2.6)	5 (23.8)	<b>P=0.029</b>	P=0.080
No	38 (97.4)	16 (76.2)		
NSAID/ASA use:			0.47 (0.12, 1.86)	0.49 (0.07, 3.32)
Yes	5 (12.8)	5 (23.8)	P=0.283	P=0.461
No	34 (87.2)	16 (76.2)		

\* Unmatched analysis.

# Analyses adjusted for age, sex, ethnic group, presence or absence of sports participation, level of vegetable consumption, smoking status and history of colorectal cancer in a first degree relative.

Cohorte Monocentrique Etats Unis  
Patients MICI surveillance endo (si CSP ou >8y): 57  
sous statines/585 non exposés aux statines

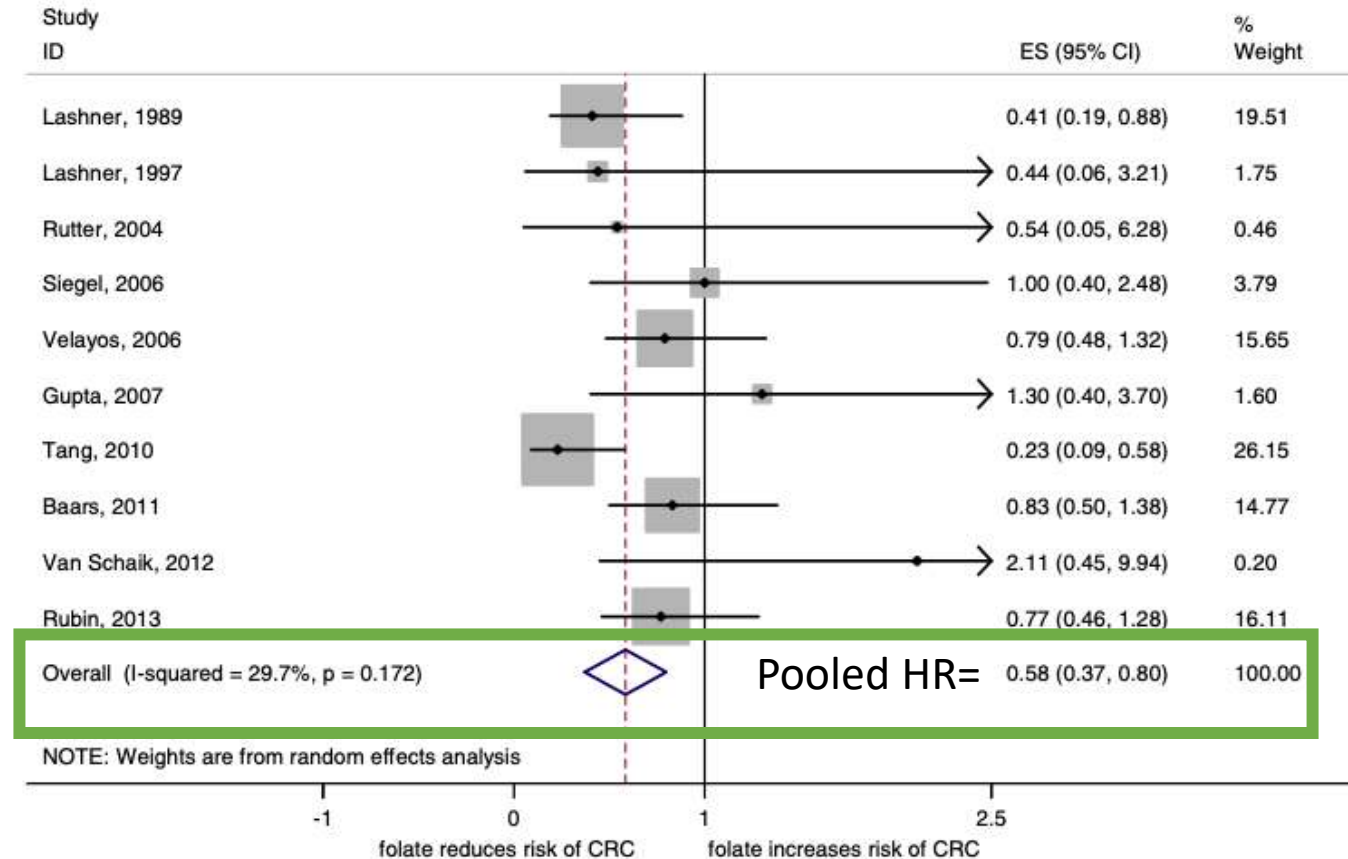
Table 2. Clinical Outcomes in Statin-Exposed versus Nonexposed Patients

	Statin exposed (n=57)		Statin non-exposed (n=585)		Adjusted HR (95% CI)	p-value*
	5-yr KM estimate	100 patient-yr rate	5-yr KM estimate	100 patient-yr rate		
CRC or HGD	2 (3.6)	2 (0.9)	15 (4.4)	15 (0.8)	0.63 (0.14–2.90) <sup>†</sup>	0.55
CRC	1 (1.8)	1 (0.5)	5 (1.5)	5 (0.3)	0.56 (0.06–4.92) <sup>†</sup>	0.60
HGD	1 (1.8)	1 (0.5)	10 (2.9)	10 (0.5)	0.72 (0.08–6.29) <sup>†</sup>	0.76
IND or LGD	9 (18.0)	9 (4.1)	64 (17.2)	64 (3.5)	1.04 (0.45–2.41)	0.92
IND	4 (7.4)	4 (1.8)	35 (9.6)	35 (1.9)	0.93 (0.31–2.79) <sup>‡</sup>	0.90
LGD	8 (16.5)	8 (3.6)	50 (14.0)	50 (2.7)	0.95 (0.38–2.34)	0.91
CRC, HGD, IND or LGD	9 (18.0)	9 (4.1)	66 (17.7)	66 (3.6)	0.98 (0.43–2.25)	0.96

Sammader NJ Cancer 2011 Risk of Colorectal Cancer in Self-Reported Inflammatory Bowel Disease and Modification of Risk by Statin and NSAID Use

Statin Exposure Is Not Associated with Reduced Prevalence of Colorectal Neoplasia in Patients with Inflammatory Bowel Disease

# Acide Folique



Méta analyse de 10 études  
4517 patients inclus  
638 cas de CCR-IBD

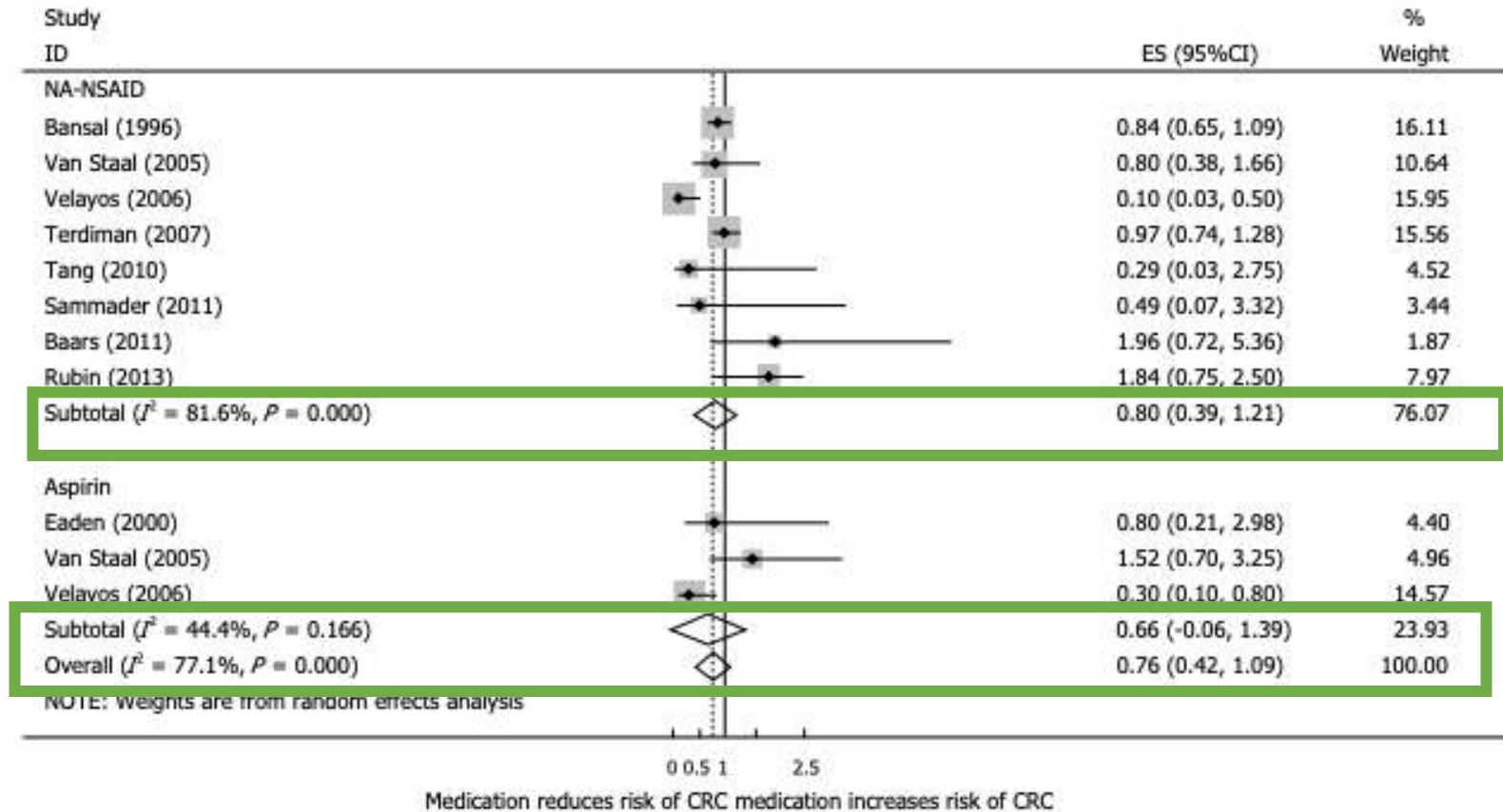
Hétérogénéité faible à modérée

Diminution du risque de CCR

FIGURE 2. Hazard ratios and 95% confidence intervals (CIs) for folic acid as a chemopreventative agent against the development of colorectal cancer in inflammatory bowel disease. Random-effects model. full color available online

# AINS - Aspirine

Eight studies involving 14917 patients and 3 studies involving 1282 patients provided data on the risk of CRC in patients with IBD taking NA-NSAIDs and aspirin respectively



Hétérogénéité élevée

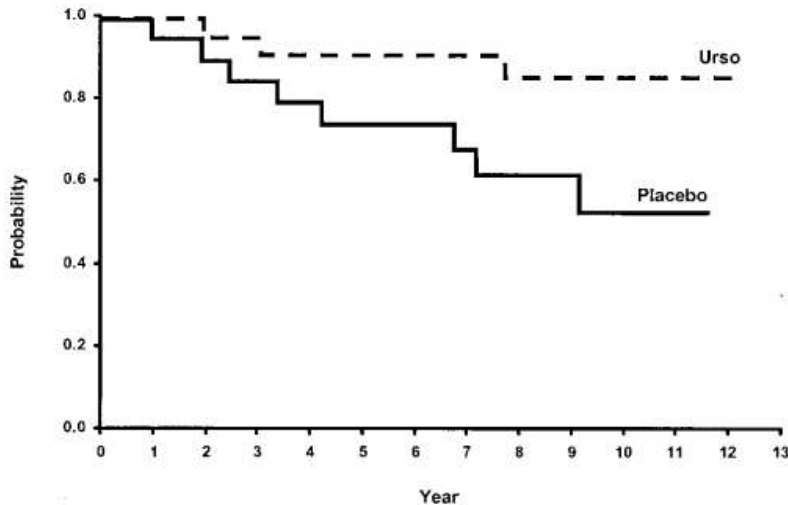
Pas d'effet chimiopréventif des AINS/ aspirine du CCR sur MICI

Figure 2 Forest plot of odds ratios and 95%CI for effect of non-aspirin non-steroids anti-inflammatory drugs or aspirin on colorectal cancer development in patients with inflammatory bowel disease. Random effects model.

Burr World J gastroenterol 2016 Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease?

# Ursodeoxycholic Acid as a Chemopreventive Agent in Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis

MICI + CSP > MICI seule : risque x 5 à 9 de CCR



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

52 patients UC+ CSP  
Randomisés placebo ou AUDC  
Dysplasie chez 3 pts (AUDC) vs 6  
pts (+2CCR) (pbo)


Risque relatif de dysplasie ou  
CCR chez les patients  
initialement sous UDCA en  
comparaison avec le groupe  
placebo: 0.26 (95% CI, 0.06-  
0.92;  $P = 0.034$ )

Meta-analyse de 2013 portant sur 8  
études (5 observationnelles, 3 RCT)  
177 cas de CCR chez 763 patients PSC-IBD

Effet chimioprotecteur significatif **pour le  
risque de CCR et/ou DHG** (OR, 0.35; 95%  
CI, 0.17-0.73).

Dans une analyse en sous-groupe: **faible  
dose d’AUDC (8-15 mg/kg/d)** était  
associée à une diminution de risque de  
CCR (OR, 0.19; 95% CI, 0.08-0.49).

# Guideline recommendation for chemoprevention in IBD

Guideline/publication date	Recommendation
Magro et al. [42] ECCO 2017 	<u>"Chemoprevention with mesalamine compounds may reduce the incidence of colorectal cancer in ulcerative colitis. There is insufficient evidence to recommend for or against chemoprevention with thiopurines"</u>
Rubin et al. [44] American College of Gastroenterology 2019	"No medical therapy has demonstrated sufficient prevention of dysplasia or CRC to avoid colonoscopic surveillance in UC." (Key concept statement)
Lamb et al. [43] British Society of Gastroenterology Consensus 2019	<u>"We recommend that patients with ulcerative colitis or IBD-U with left-sided or more extensive disease should be advised to take mesalazine in doses of at least 2 g daily to reduce risk of colorectal cancer."</u> <u>We suggest that thiopurines may reduce the risk of colorectal cancer in patients with ulcerative colitis and IBD-U, but evidence for a chemopreventive role from methotrexate, calcineurin inhibitors, anti-TNF, and anti-integrin agents is lacking at present and they cannot be currently recommended solely for chemoprevention against colorectal cancer (GRADE: weak recommendation, low-quality evidence. Agreement: 93%)</u>
Singh et al. [45] American Gastroenterology Association 2020	"In adult outpatients with moderate to severe UC, who have failed 5-ASAs, and have escalated to therapy with biologic agents, tofacitinib, and/or immunomodulators, <u>there may be no benefit to continuing 5-ASAs over stopping 5-ASAs</u> "

5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease.

Evidence Level 5-ASA	Evidence Level thiopurines, other drugs
Evidence level 2	Insufficient evidence
Insufficient evidence	Insufficient evidence
Strong recommendation but moderate quality evidence	Thiopurines: weak recommendation and low quality evidence Other: Insufficient evidence
Insufficient evidence	Insufficient evidence

# Reco française

## **Recommandation 6.H (85,3 %)**

**Dans quelle situation y a-t-il une indication thérapeutique pour les 5-ASA pour la prévention de la dysplasie et du cancer colorectal au cours de la RCH ?**

Une chimoprévention par 5-ASA permet de réduire l'incidence du cancer colorectal au cours de la RCH chez les patients ayant des facteurs de risque (pancolite et maladie ancienne) [Grade B]. L'effet chimopréventif des thiopurines n'est pas démontré. Il n'existe pas de donnée suffisante pour pouvoir statuer concernant le bénéfice des biothérapies dans cette indication.

# Conclusion

- Absence d'essai randomisé prospectif démontrant l'efficacité des 5-ASA pour réduire l'incidence de la dysplasie et du CCR.
- Toutefois, plusieurs méta-analyses basées sur des études de cohorte et des études cas-témoin ont confirmé le **bénéfice des 5-ASA dans cette indication pour les patients RCH les + à risque (avec pancolite et >10ans)**
- Pas de bénéfice à associer un traitement 5-ASA à une biothérapie pour prévenir le CCR
- L'effet chimopréventif des thiopurines n'est pas démontré.
- Il n'existe pas de donnée suffisante pour pouvoir statuer concernant le bénéfice des biothérapies ou d'autres molécules (statines, aspirine, acide folique) dans cette indication.



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# Chimioprévention de la carcinogénèse colique

Pauline Wils- Lille