Mortality and cancer in paediatric inflammatory bowel disease: A population-based study
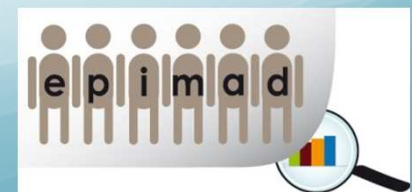
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and the EPIMAD Group

Background

- In adult patients with IBD:
  - An inconsistent increased risk of mortality has been shown[1-2-3]
  - There is an increased risk of colonic and extra-intestinal cancers [4-5-6]

- In paediatric onset patients with IBD the risks of mortality and cancers remain poorly characterized

- Incidence of paediatric IBD continues to increase worldwide [7]
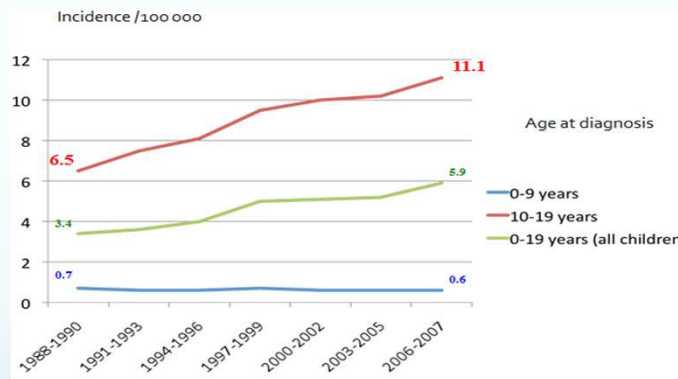
- There is an increasing use of immunosuppressors and biologics in IBD paediatric patients [8]

[1] Romberg-Camps et al. Inflamm Bowel Dis 2010
[2] Jess et al. Gut 2006
[3] Duricova et al. Inflamm Bowel Dis 2010
[4] Hemminki et al. Ann Oncol 2009

[5] Pedersen et al. Am J Gastroenterol 2010
[6] Jess et al. Am J Gastroenterol 2010
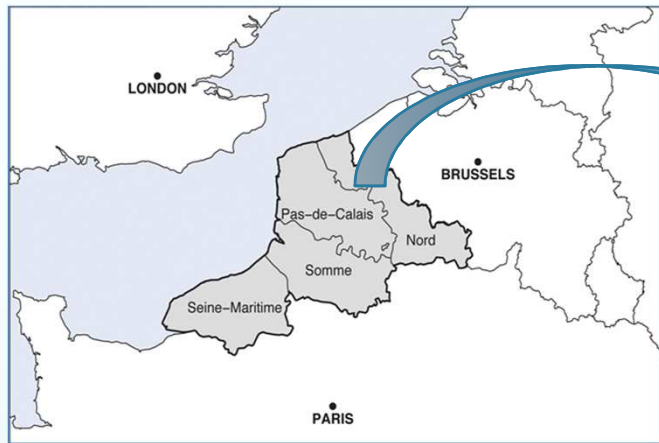[7] Chouraki V et al. Aliment Pharmacol Ther 2011
[8] Vernier-Massouille et al. Gastroenterology 2008

AIMS of the study

- The primary objective was to estimate the risks of mortality and cancers in a paediatric onset population-based IBD cohort.

- The secondary objective was to assess in cancer risk the role of immunosuppressors (IS) and biologics.
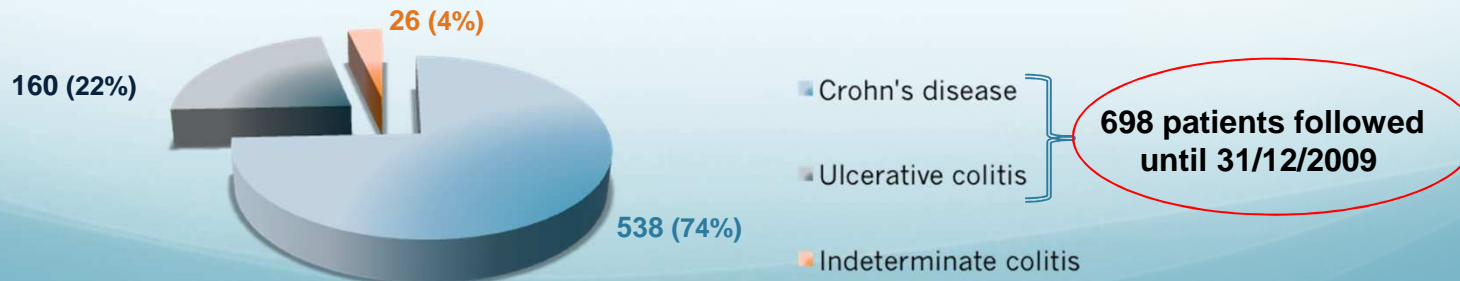
Patients & Methods (1)

- The EPIMAD Registry
  - French population-based study *(9.3 % of the whole French population)*
  - Records all new incident IBD cases since 1988 [1]

9,114 IBD patients recorded (1988-2004)

724 (7.9%) paediatric onset IBD (<17 yrs)

Pediatric IBD diagnosis

26 (4%)

160 (22%)

538 (74%)
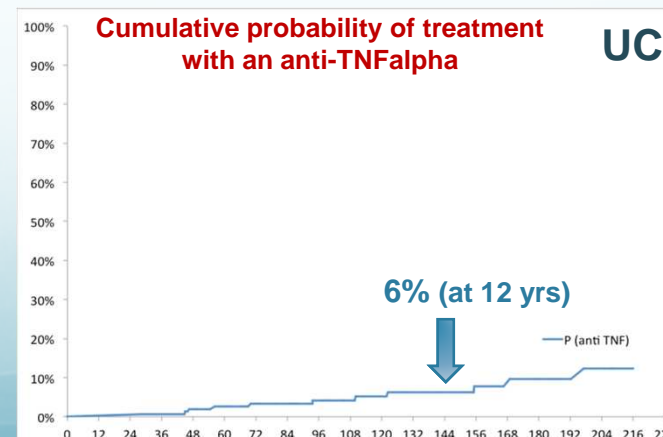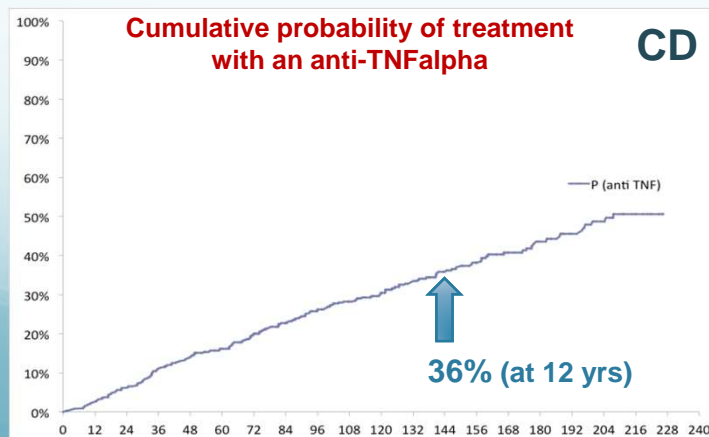
- Crohn's disease
- Ulcerative colitis
- Indeterminate colitis

698 patients followed until 31/12/2009

[1] *Gower-Rousseau et al. Gut 1994*

Patients

	CD (n=538)	UC (n=160)
Median age at diagnosis [Q1-Q3]	**14.6** [12.2-16.1]	**14.5** [11.5-16.1]
Gender (male / female)	**293 / 245**	**67 / 93**
Median follow-up [Q1-Q3]	**11.2** [7.4-15.1]	**11.6** [8.2-15.8]
Location at diagnosis*	L1: **14%**	E1: **14%**
	L2: **16%**	E2: **26%**
	L3: **70%**	E3: **60%**
	L4: **37%**	-
	APL: **8.6%**	-
Behaviour at diagnosis*	B1: **73%**	-
	B2: **23%**	-
	B3: **4%**	-
EIMs at diagnosis	**22%**	**20%**

according to Montreal classification

Patients

	CD (n=538)	UC (n=160)
5 ASA (in the 1st month after diagnosis)	93%	95%
Steroids (in the 1st month after diagnosis)	36%	27%
Cumulative probability of surgery (at 5yrs)	0.30	0.17

Cumulative probability of treatment with immunosuppressors CD

69% (at 12 yrs)

Cumulative probability of treatment with immunosuppressors UC

36% (at 12 yrs)

Cumulative probability of treatment with an anti-TNFalpha CD

36% (at 12 yrs)

Cumulative probability of treatment with an anti-TNFalpha UC

6% (at 12 yrs)
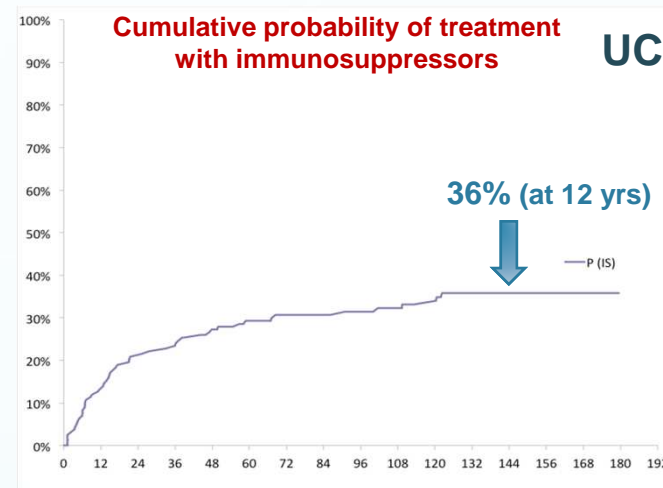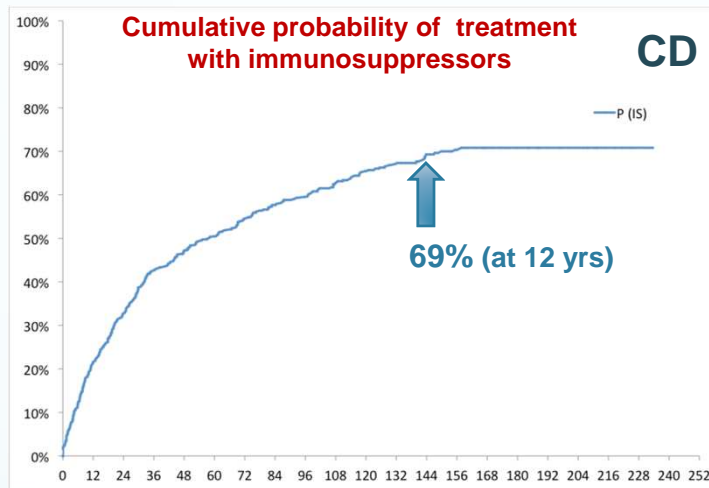
Patients & Methods (4)

- Quantitative variables were expressed as median and interquartile range

- Only death and cancers occurring during follow-up were taken into account

- Calculation of expected cases were gender and age adjusted
  - According to the regional death rate (INSEE)
  - According to the FRANCIM cancer network

- Results were expressed as Standardized Ratio (SMR and SIR and 95% CI calculated by the exact Poisson method of Owen)

- The role of treatments in promoting cancer was evaluated using Standardized Incidence Ratio (SIR)

- Cumulative probabilities were estimated using Kaplan Meier curves

Results (1)

- 6 deaths were observed *(3 males, 3 females)*

- Crude mortality rate : 0.84%

- SMR : 1.3 [0.5 – 2.9] (NS)

- Median age at IBD diagnosis :   12 [7 – 17] years

- Median IBD duration at death : 13 [7 – 16] years

- Median age at death :   25 [19 – 30] years

Results (2)

PSC: Primary Sclerosing Cholangitis
IS: Immunosuppressors
DS: Definitive Stoma

6 deaths were observed
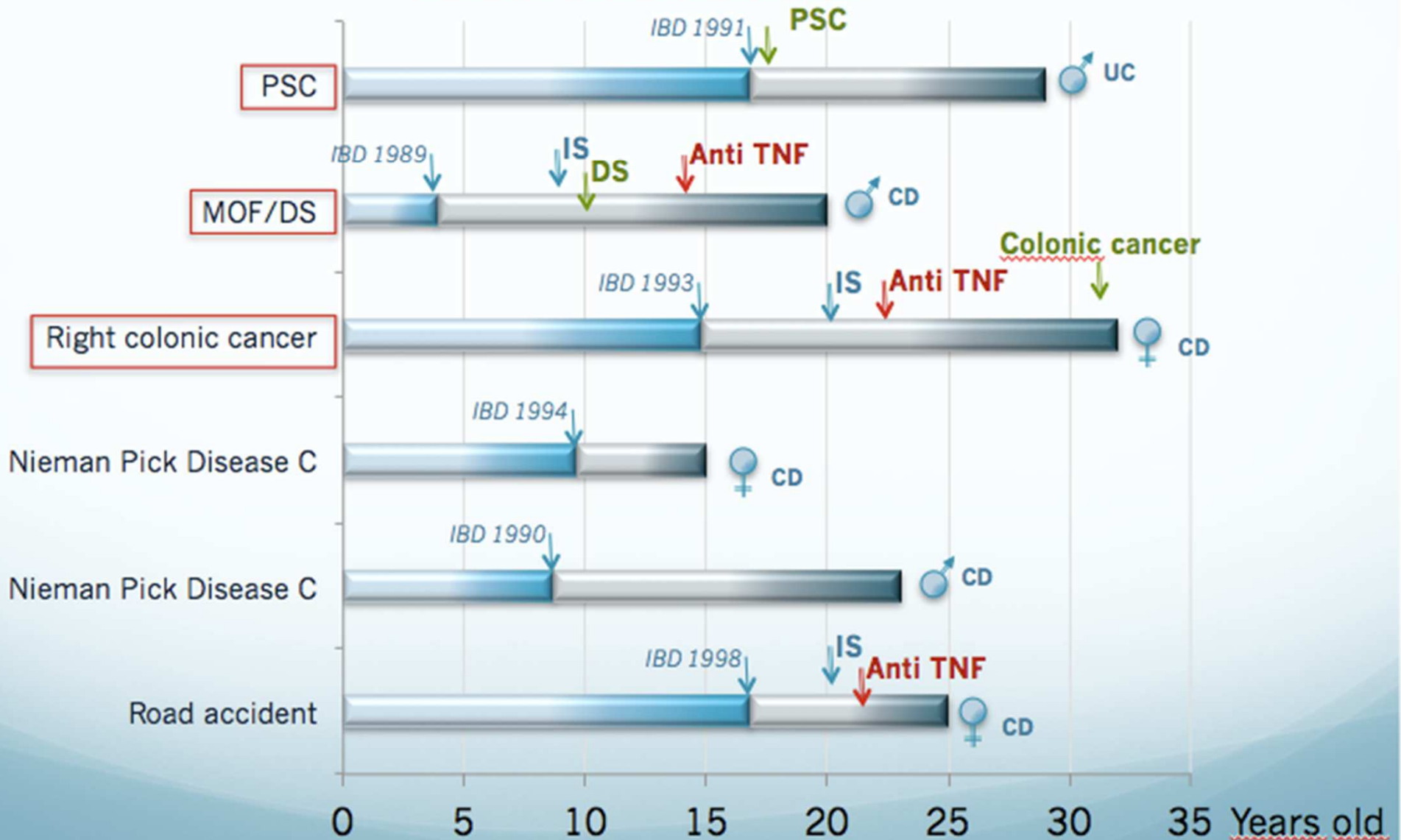
Results (3)

- 9 cancers were observed *(5 males, 4 females)*
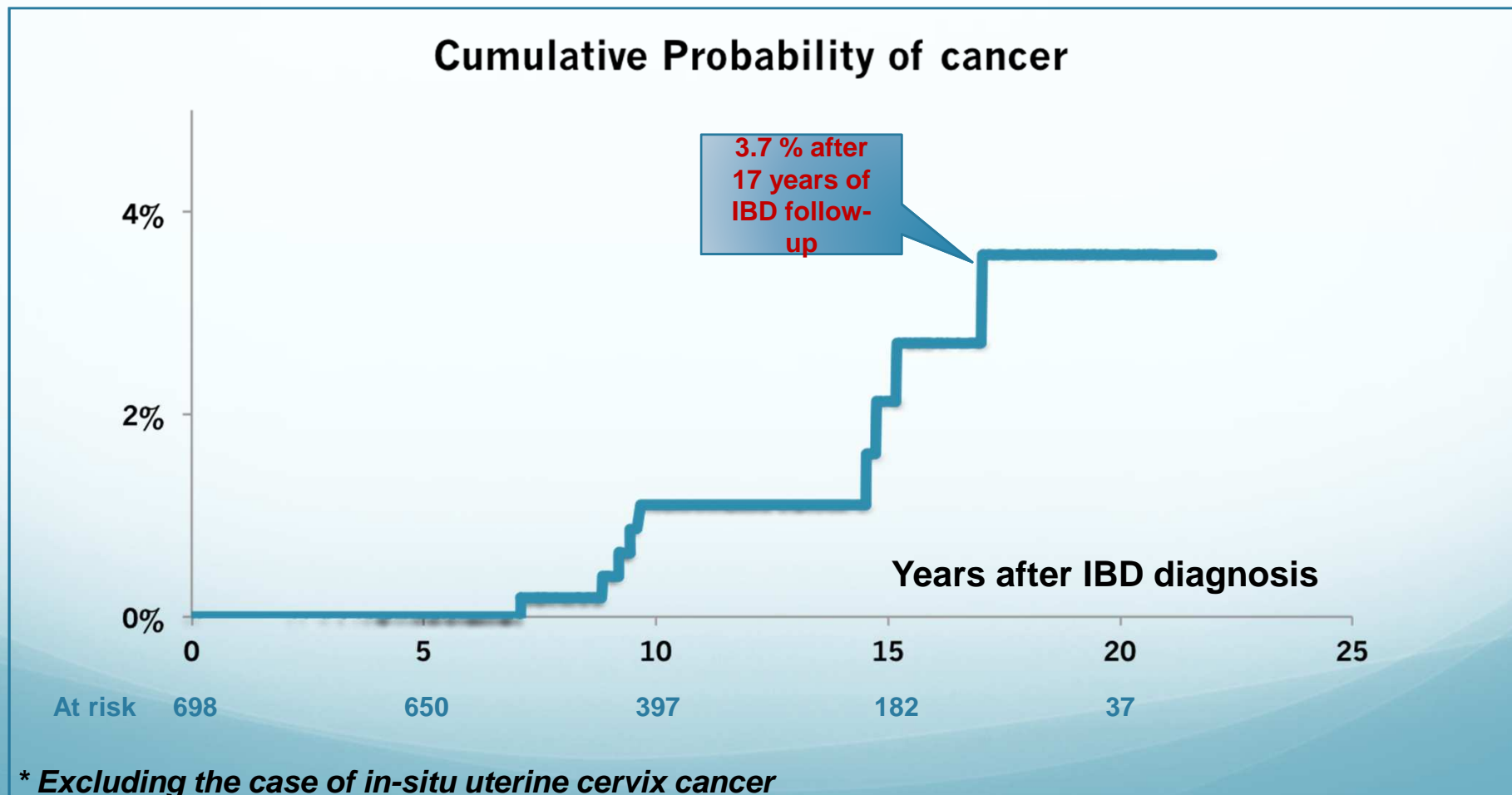
- Crude cancer rate : 1.3 %

	Median (years)	Interquartile range
age at IBD diagnosis	**15**	[10 – 17]
Time between IBD and cancer diagnosis	**15**	[10 – 17]
age at maximal follow-up	**29**	[27 – 36]

Results (4)

Global cancer Standardized Incidence Ratio
(age and gender adjusted)

SIR* : 3.0 [1.3 – 5.9]   p=0.012

Cumulative Probability of cancer

3.7 % after 17 years of IBD follow-up

Years after IBD diagnosis

At risk   698   650   397   182   37

* Excluding the case of in-situ uterine cervix cancer
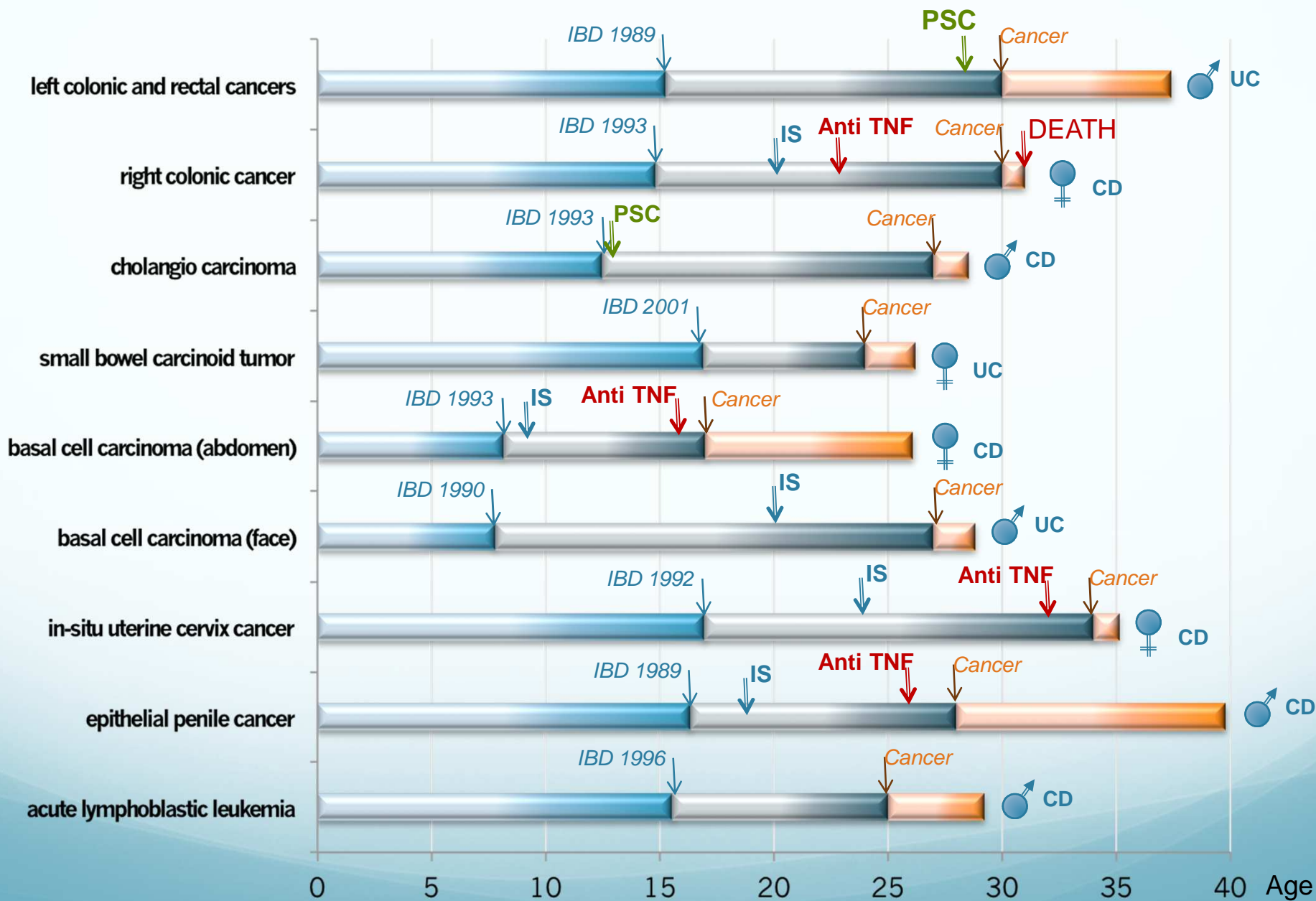
Results (5)

Results (6)

SIR of cancer in paediatric onset IBD

(Univariate analysis)

	Expected number	SIR	95% CI	P value
IBD* (n=8)	2.70	**3.0**	**[1.3 – 5.9]**	**0.012**
UC (n=3)	0.65	4.6	[0.9 – 13.5]	0.06
CD* (n=5)	2.03	2.5	[0.8 – 5.8]	0.11
Cancer location				
Colonic cancer (n=2)	0.05	**45.7**	**[5.5 – 165.3]**	**0.002**
Basal cell carcinoma (n=2)	0.32	6.2	[0.8 – 22.3]	0.08
*Treatment**				
Immunosuppressors (IS) (n=4)	1.14	**4.4**	**[1.4 – 10.1]**	**0.013**
IS + Anti TNF (n=3)	0.38	**8.0**	**[1.6 – 23.0]**	**0.013**

* Excluding the case of in-situ uterine cervix cancer

Discussion

Strength

- Large paediatric onset IBD population based study (n=698)

- Large area covered (9.3% of the French population)

- Median follow-up is 11.5 years (range 3-22 years)

- References are Global French National Data

Weakness

- Small number of recorded events (6 deaths, 9 cancers)

- Multivariate analyses were not performed because of the small number of events

- Putative impact of treatments may be related to illness severity

Conclusions

- **In this large paediatric onset population-based IBD cohort, mortality was not significantly different from that of the general population;**

- **We found:**
  - **a significant 3-fold increased risk of cancer with heterogeneous locations**
  - **mostly colonic cancer that is unfrequent in young patients of general population**
  - **no lymphoma or small bowel adenocarcinoma**

- **IS was associated with a 4-fold increased risk of cancer**

- **Association of IS with anti-TNF displayed a 8-fold increased risk of cancer***
  The impact of anti TNF alone remains questionable as all anti TNF treated patients received IS too

- **The presence of colon, skin and genital cancers pleads for a systematic screening in early onset IBD**

Acknowledgements

- All adult & paediatric gastroenterologists of the EPIMAD area

- The 8 interviewer practitioners of the EPIMAD Registry

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