Risk and Prevention of Colon Cancer in Inflammatory Bowel Disease

- by Allan Peck M.D.
- Gastroenterology Consultants of Greater Cincinnati

Objectives

- Risk factors for colorectal cancer
- Colitis-associated colon cancer vs sporadic colon cancer
- Preventive strategies
  - Surveillance
  - Surgery
  - Pharmacologic agents
    - Folic acid
    - Ursodeoxycholic acid
    - 5-ASA

Background

- Inflammatory Bowel Disease (IBD) accounts for 1-2% of all cases of Colorectal Cancer (CRC) in the general population
- CRC accounts for one in six of all deaths in IBD patients.
- Irrespective of actual incidence, CRC has a profound impact on patients' psychological well-being[3,4]

1 Choi PM, et al. *Gut* 1994;35:950-954.
2 Gyde S, et al. *Gastroenterology* 1982;83:36-43
3 Sharan R, Schoen RE.Gastroenterol Clin North Am. 2002 Mar;31(1):237-54.
4 Kurina LM, Goldacre MJ, Yeates D, Gill LE J Epidemiol Community Health. 2001 Oct;55(10):716-20.

Goals of Therapy in IBD

- Induce Remission of Active Disease
- Maintenance of Remission
- Maintain/Restore Nutrition
- Avoid Surgery
- Avoid Complications
  - Therapy-related
  - Disease-related
- Quality of Life

Risk Factors

Risk Factors in the Development of CRC in UC

Risk Factor	Importance
Extent of disease[1,2]	++++
Duration of disease[1,2]	++++
Presence of PSC[3]	+++
Young age at onset[1,2]	++
Colonic stricture	++
Positive family history[1,2]	+
Severity of inflammation[4]	+/-
Backwash ileitis[5,6]	+/-

1 Choi PM, et al. Gastroenterol Clin North Am 1995;24:671-87

2. Eaden J. Am J Gastroenterol 2000;95:2710-2719.

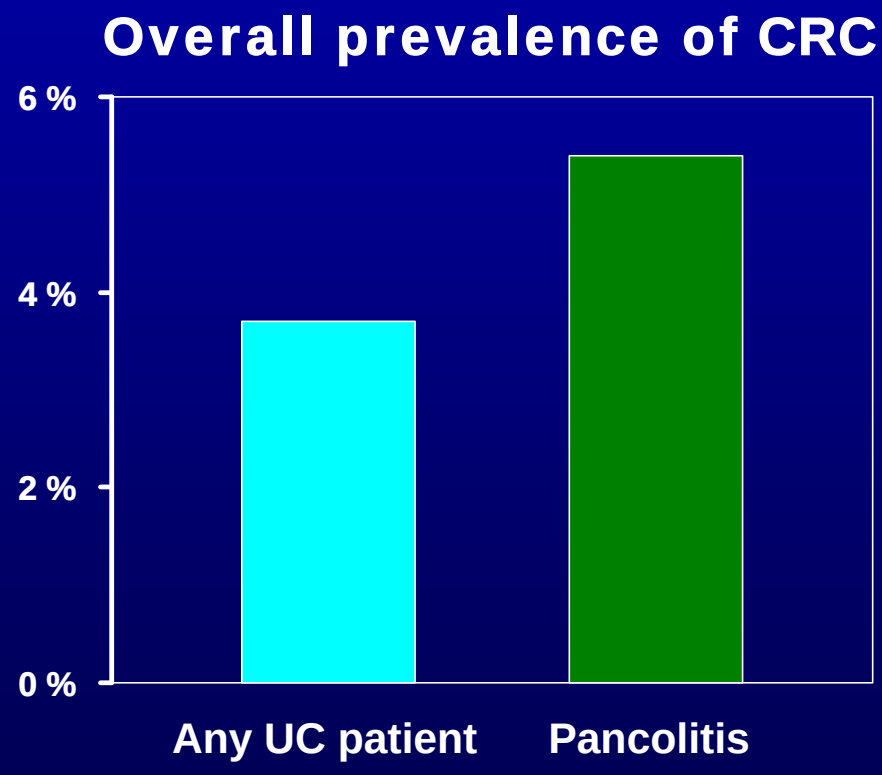
3 Lagergren J et al Gastroenterology. 2001 Sep;121(3):542-7

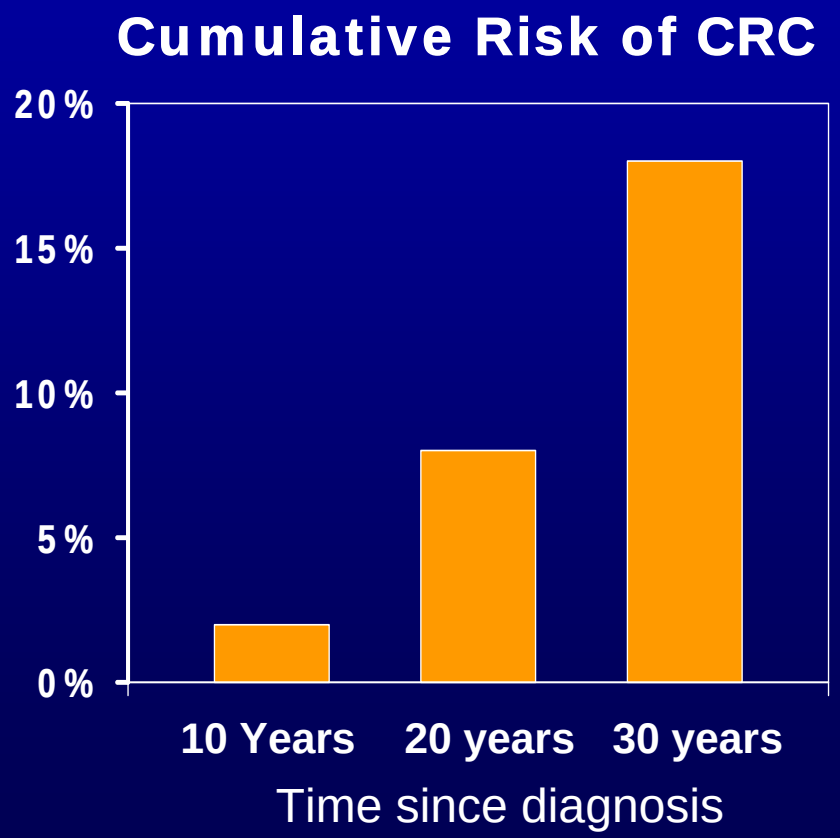
4 Rutter M et al Gastroenterology 2004; 126:451-459

5. Schlippert W et al Am J Med. 1979 May;66(5):879-82

6. Heuschen UA et al Gastroenterology. 2001 Mar;120(4):841-7

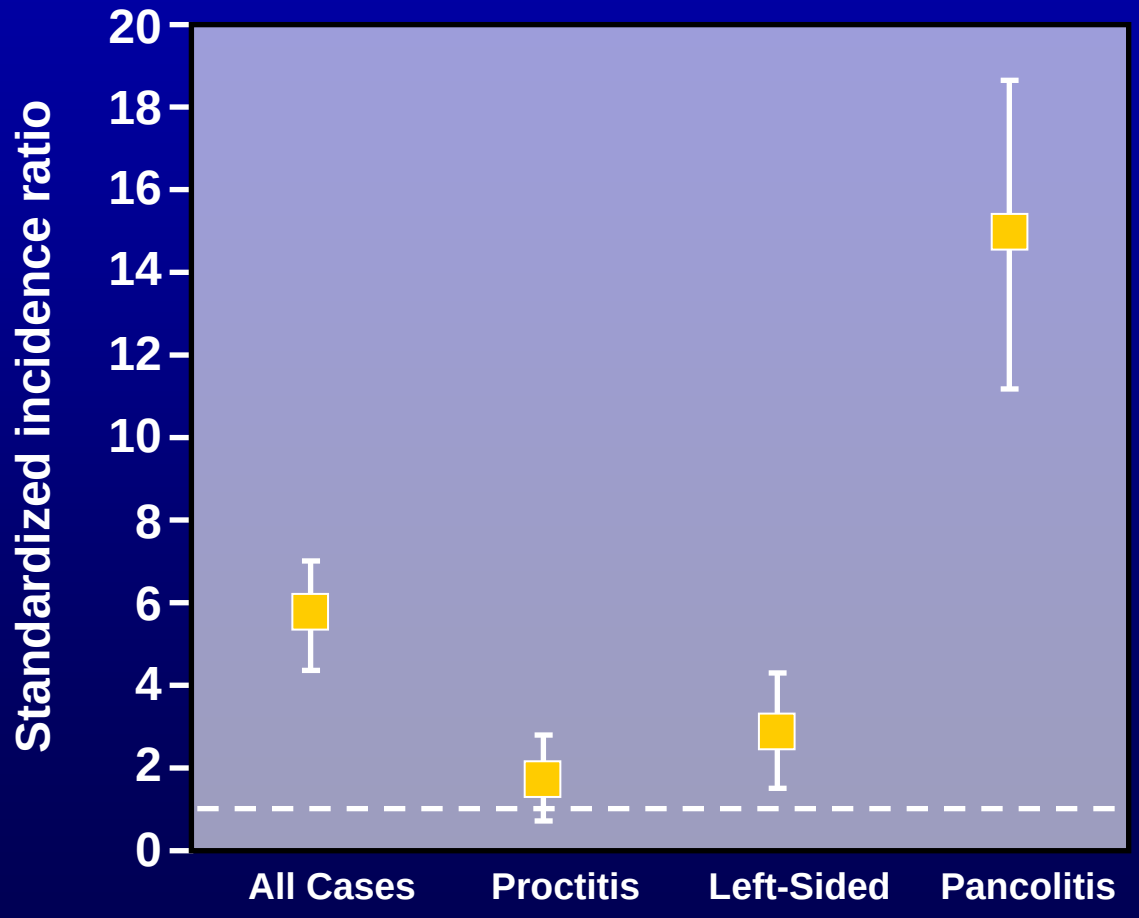
Prevalence and Cumulative Risk of Developing CRC in UC





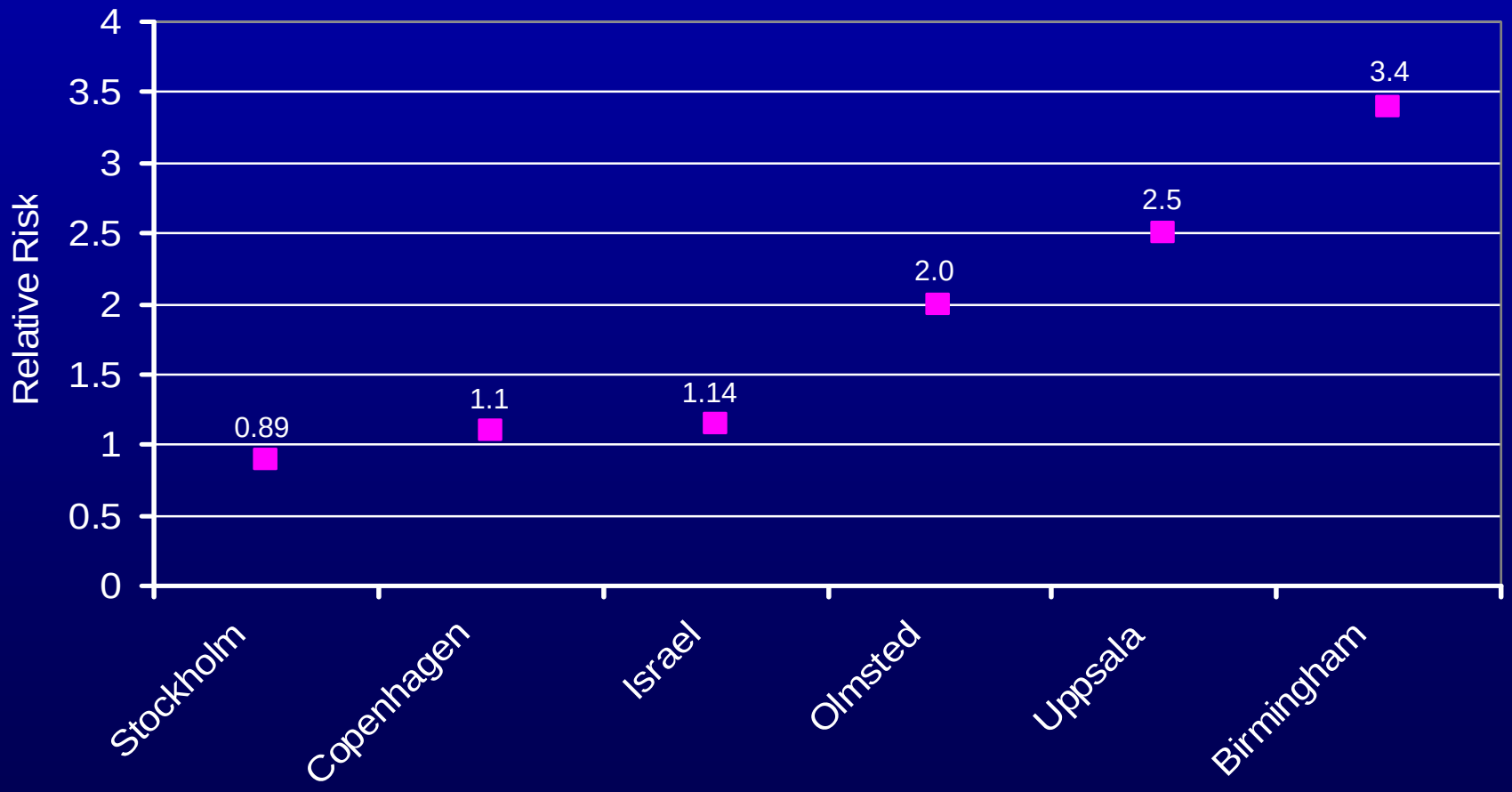
Eaden JA, et al. *Gut* 2001;48:526-35.

Relative Risk of CRC Based on Extent of UC



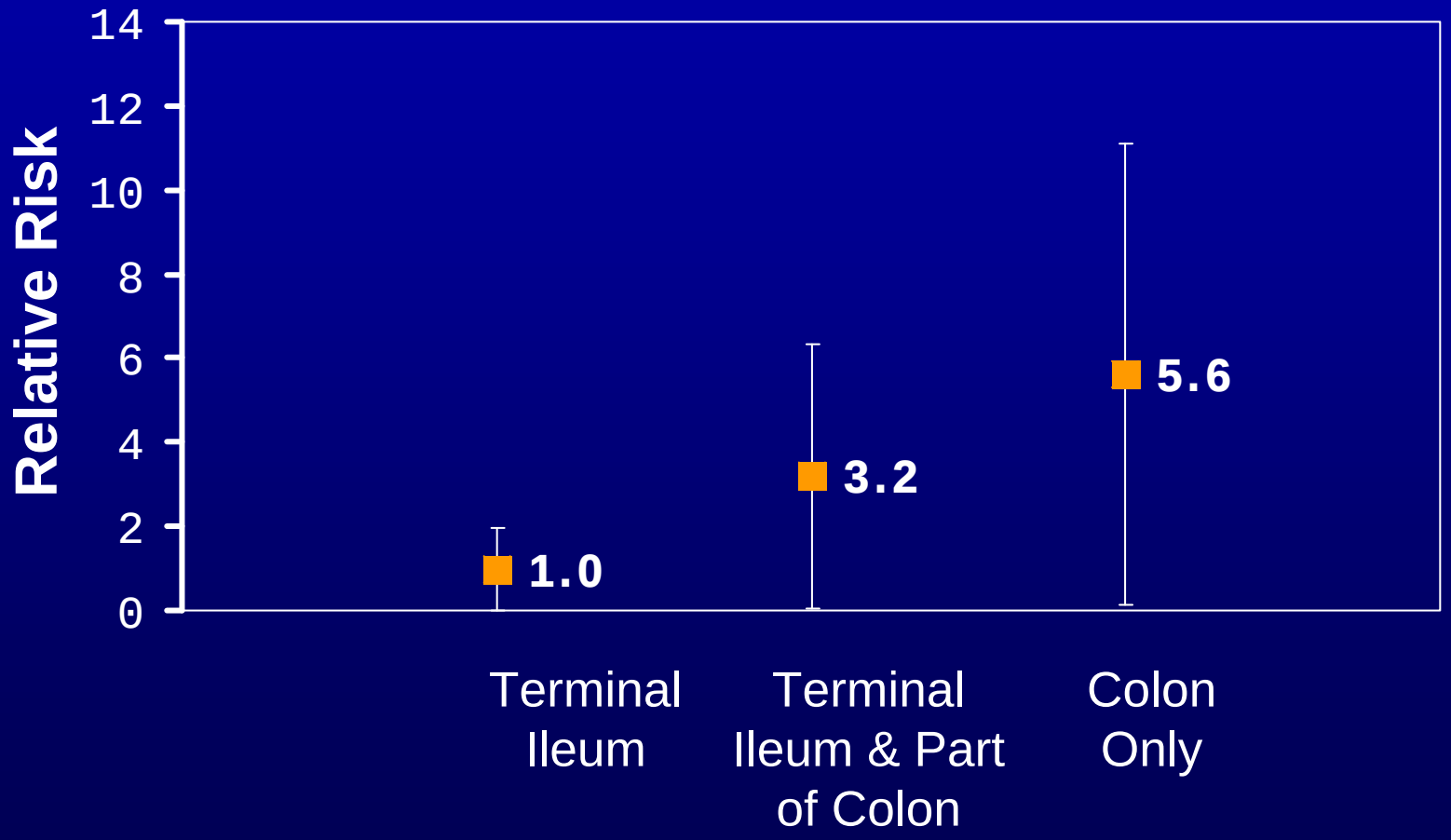
Ekbom A, et al. *N Engl J Med*. 1990;323:1228-1233.

Risk of Developing CRC in CD



Munkholm P. *Aliment Pharmacol Ther* 2003; 18(Suppl. 2): 1 - 5

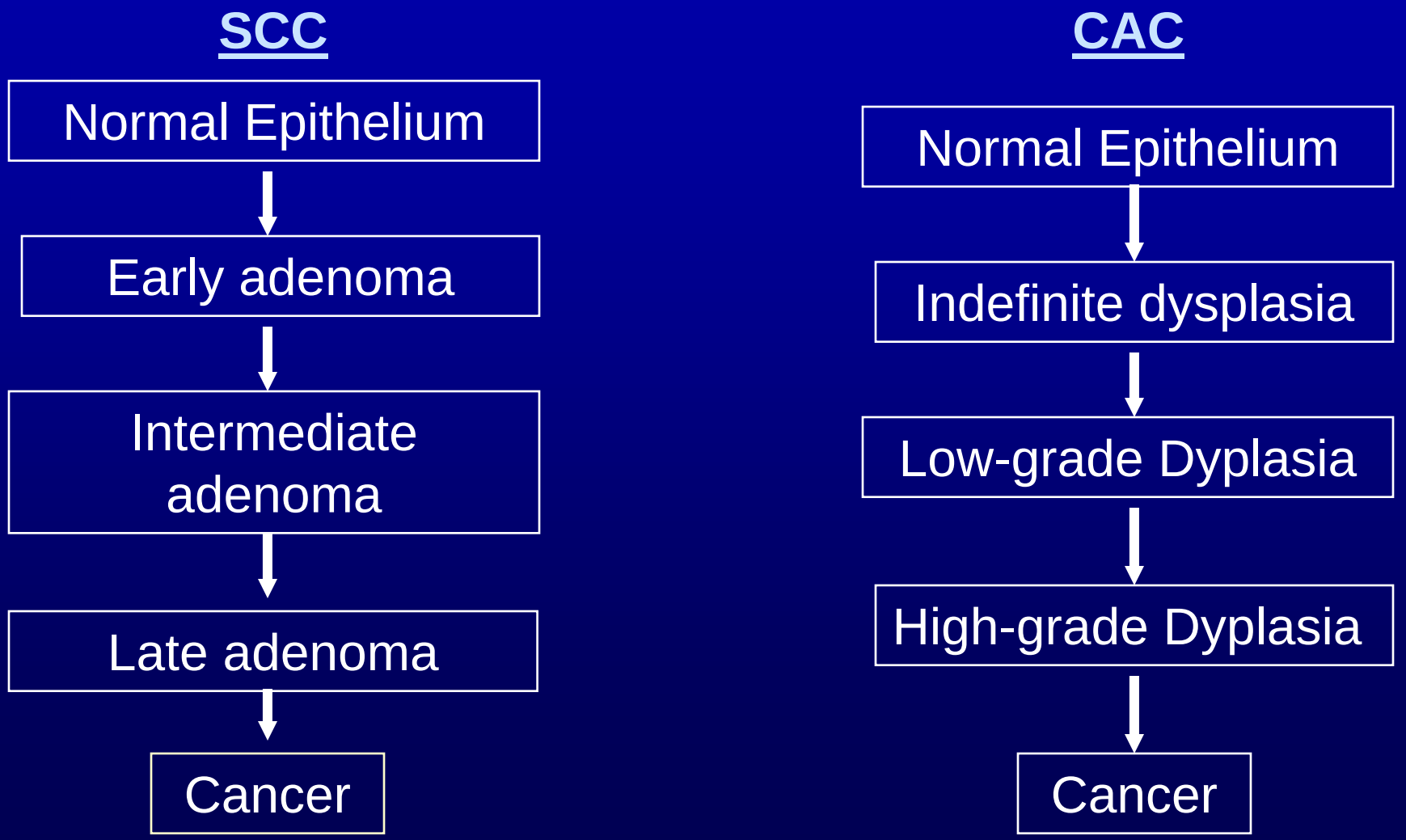
Relative Risk of CRC Based on Extent of CD



Ekbom A, et al. *Lancet* 1990;336:357-359.

Sporadic Colon Cancer
vs.
Colitis-associated Colon Cancer

Pathogenesis of Sporadic Colon Cancer (SCC) vs. Colitis-associated Colon Cancer (CAC)



Itzkowitz SH. *Gastro Clin of NA* 1997;26:129-139.

Sporadic Colon Cancer (SCC) vs. Colitis-associated Colon Cancer (CAC)[1]

SCC

- Only 3-5% experience multiple synchronous colon cancers
- Mean age-60's
- Left sided predominance

CAC

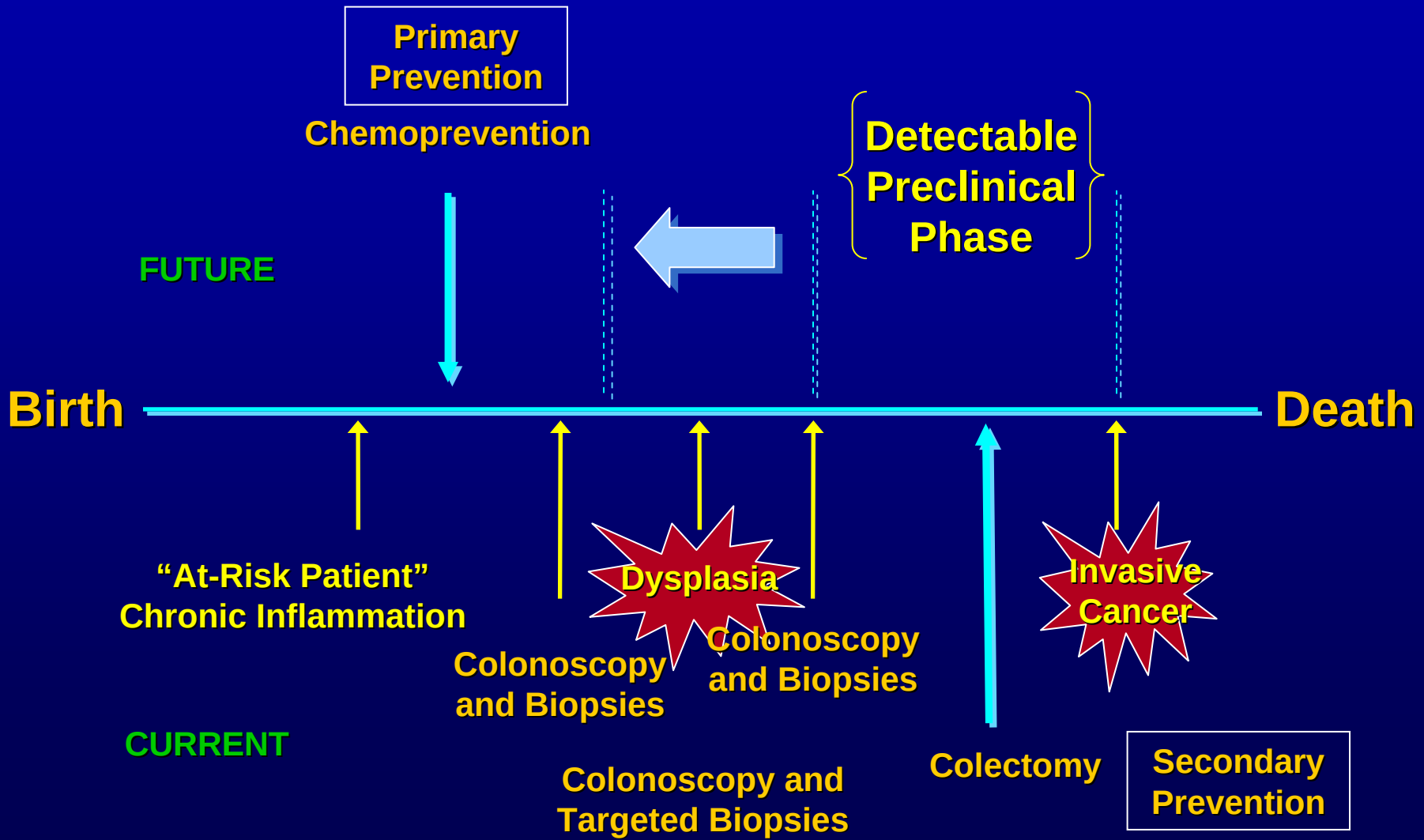
- Approximately 12% experience multiple synchronous colon cancers
- Mean age-30 to 40's
- More uniformly throughout the colon
- More right-sided in IBD pts. with PSC[2]

1 Itzkowitz SH. *Gastro Clin of NA* 1997;26:129-139

2 Marchesa P et al Am J Gastroenterol. 1997 Aug;92(8):1285-8

Prevention of CRC

Cancer in IBD: Natural History and Prevention Opportunities



Prevention of CRC

- **Secondary Prevention**
  - **Surveillance**
  - **Surgery**
    - **Polypectomy**
    - **Colectomy**
- **Primary Prevention**
  - **Prophylactic colectomy (rarely used)**
  - **Pharmacologic agents (chemoprevention)**

Surveillance

Surveillance Recommendations

- **Colonoscopy:**
  - **After 8-10 years of colitis, annually or biannually with multiple biopsies at regular intervals**
  - **Evidence is not sufficiently strong to justify different guidelines for left-sided colitis vs pancolitis**

Kornbluth A et al Am J Gastroenterol. 2004 Jul;99(7):1371-85..

Surveillance Guidelines
(Secondary Prevention)

- **Who: all patients with left-sided or pan-UC more than 8-10 years (exception: PSC and UC- start immediately)**
- **Technique: 4-quadrant biopsies every 10 cm of mucosa; at least 33 biopsies; extra focus on nodules, masses, strictures**
- **How often: based on duration, extent, age, PSC and family history of colorectal cancer (q 6 months-2 years)**
- **Outcome (reviewed by second pathologist):**
  - **High-grade dysplasia: colectomy**
  - **Low-grade dysplasia: "prompt consideration of colectomy"**
  - **Indefinite dysplasia: increase surveillance?**
  - **Atypia or indeterminate: treatment of active disease, repeat colonoscopy and biopsies**

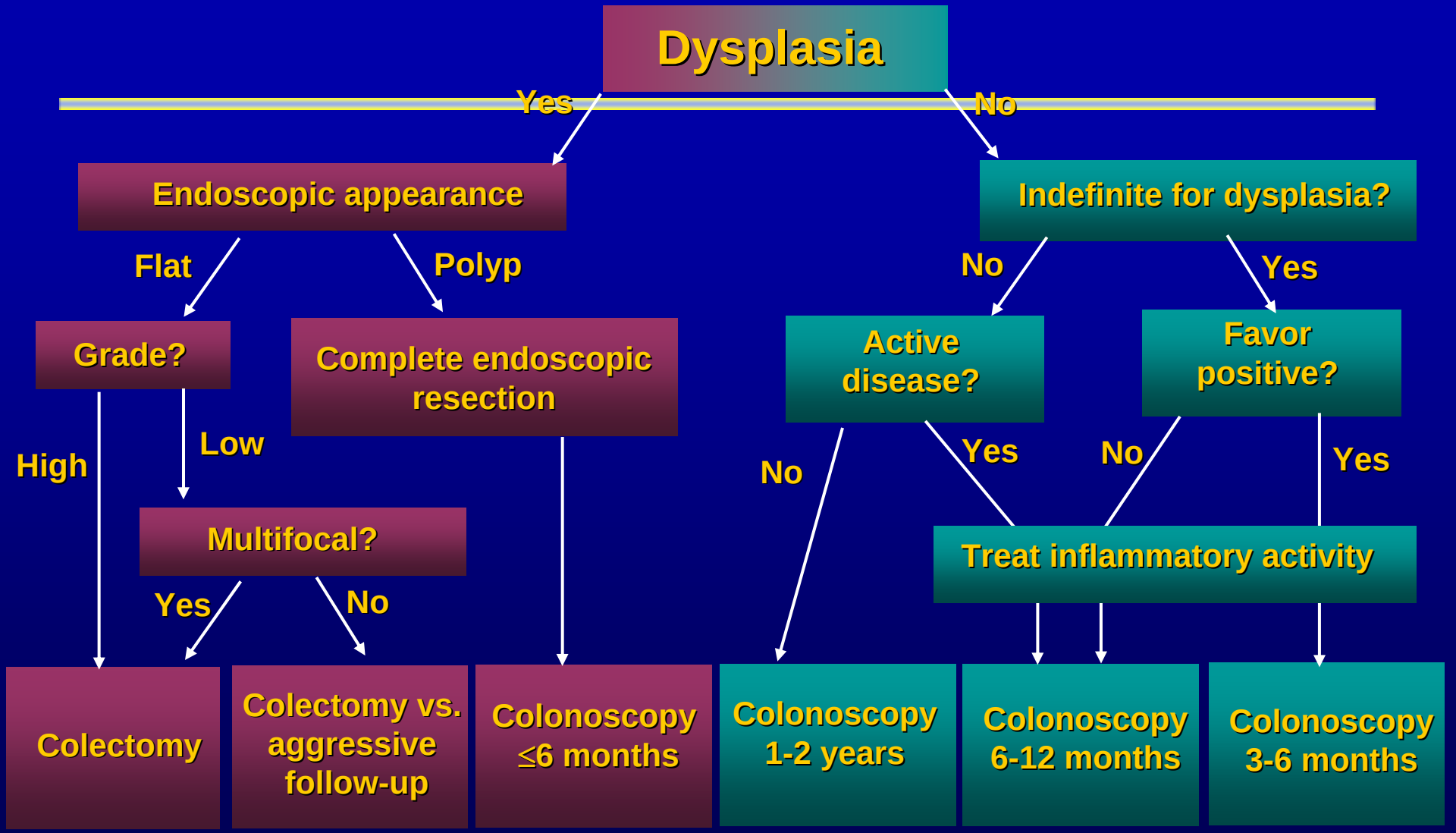
Kornbluth and Sachar, Ulcerative colitis practice guidelines (update). Am J Gastro, 2004.

Surveillance Recommendations

- **Biopsies:**
  - **Four every 10 cms from cecum to rectum**
  - **Additional samples of the rectosigmoid area may be advocated**
  - **Polyps should be assessed and removed separately**
    - **with sampling of surrounding flat mucosa.**

Riddell RH. *Scand J Gastroenterol* Suppl 1990; 175: 177-84.
Eaden JA, et al. *Gut* 2002;51:v10-V12.

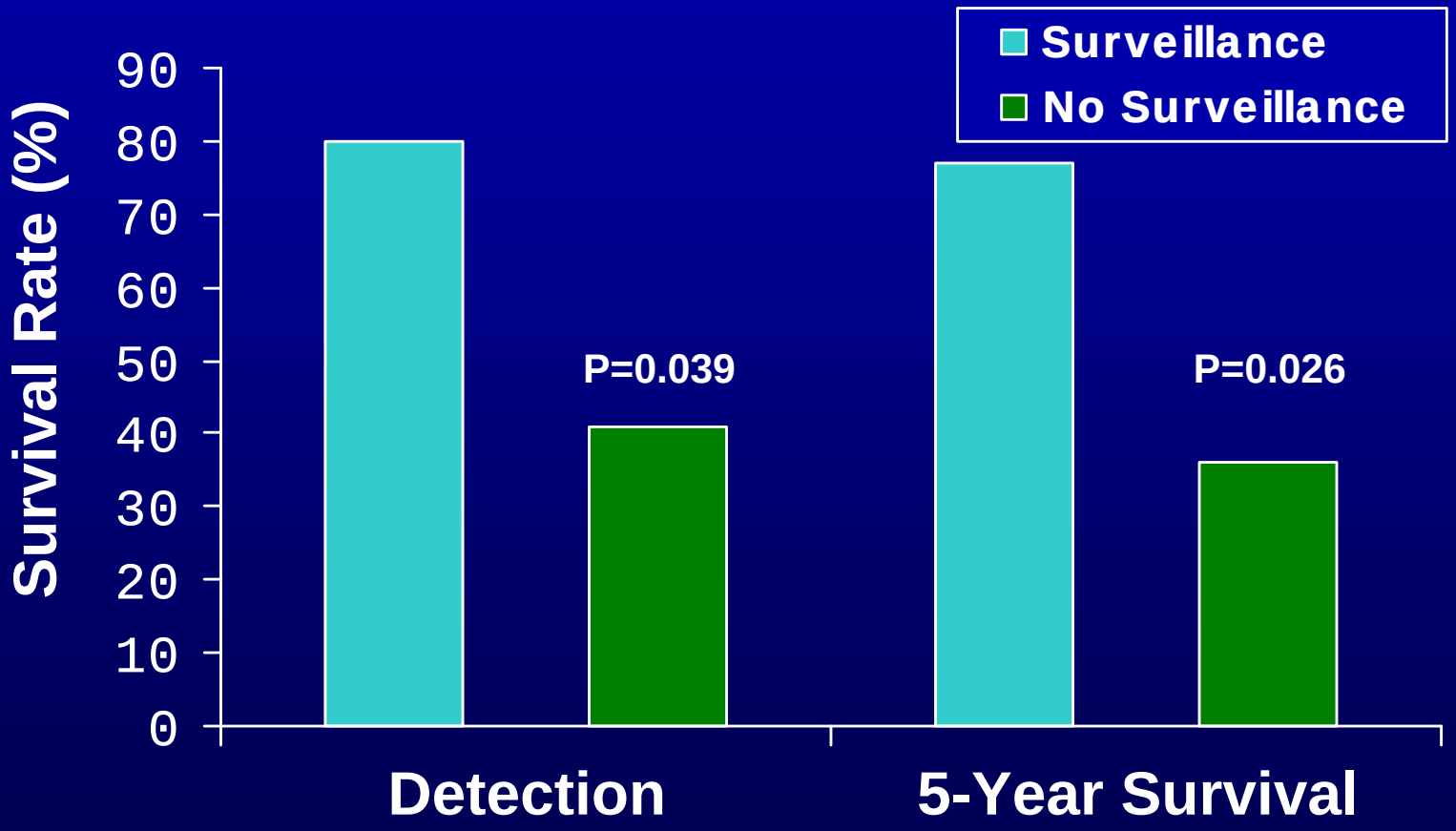
Suggested Approach to Dysplasia



Rubin DT, Turner JH. *Clin Gastroenterol Hepatol*. 2006.

Surveillance May Decrease the Risk or Mortality of Colon Cancer

Results from an 18 year surveillance program in the US



Choi PM, et al.. *Gastroenterology* 1993;105:418-24.

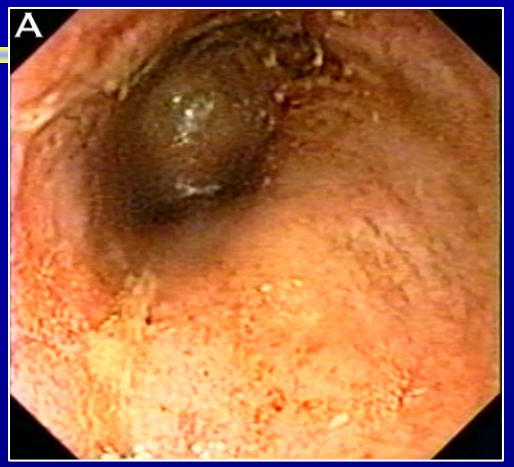
Limitations of Surveillance

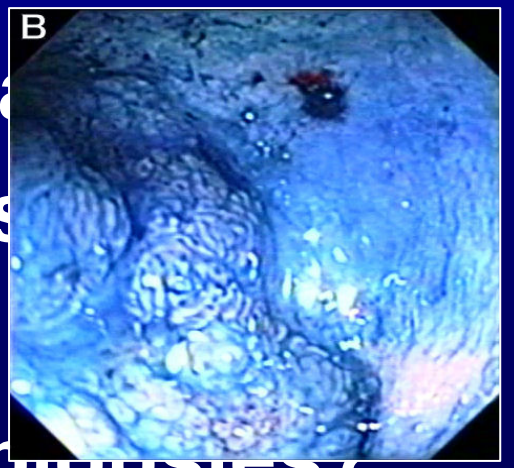
- Dysplasia may be missed when obtaining biopsies
- Intra- and inter-observer variation in interpretation of dysplasia
- Patient Compliance
- High Cost to Benefit Ratio

Eaden JA, et al. *Am J Gastroenterol* 2000; 95(10): 2710-19.

Will New Technology Increase Visibility of Neoplasia in IBD?

- Chromoendoscopy
- Magnifying endoscopy
- Narrow band imaging
- Fluorescence endoscopy
- Optical coherence tomogra
- Confocal laser endomicros
- Fecal DNA?
- Molecular assessment of biopsies?





Surgery

Surgery

- Colectomy
  - Recommended for patients with low-grade dysplasia, high-grade dysplasia, DALMs, or cancer
- Polypectomy
  - Adenoma-like DALM ?

Kornbluth A et al Am J Gastroenterol. 2004 Jul;99(7):1371-85..
Lichtenstein GR. *Rev Gastroenterol Disord* 2002;2(suppl):S16-24.
Friedman S, et al. *Inflamm Bowel Dis* 2003;9:260-266.

Pharmacologic Agents

Prevention of Colorectal Cancer

- **Pharmacologic agents (chemoprevention)**

Sporadic Colon Cancer	Colitis-associated Colon Cancer
Aspirin	Folic Acid
NSAIDs	Ursodeoxycholic acid
Calcium / Vitamin D	5-ASA
Folic Acid	
CEE + MPA (Prempro®)	

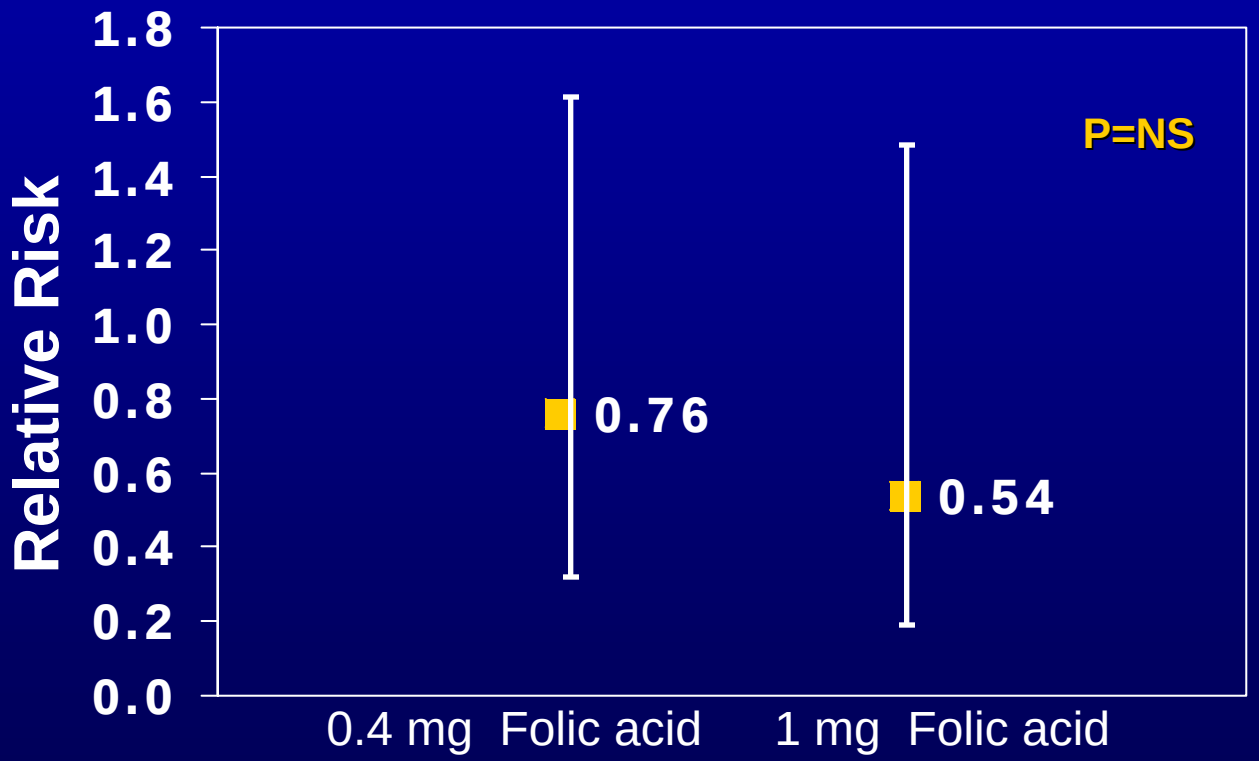
Possible Dysplasia/CRC Chemopreventive Agents in IBD

AGENT	EVIDENCE IN IBD
Folic acid	Rationale, safety good; N.S.[1]
Calcium and vitamin D	Rationale
COX 1/COX 2 inhibitors	May activate colitis
Immunomodulators 6-MP/AZA	Limited Evidence Not Carcinogenic
Ursodeoxycholic acid	In PSC with UC, yes
5-aminosalicylic acid	Of Interest
Statins	Limited Evidence

[1]Lashner BA et al. *Gastroenterology*. 1997;112:29-32.

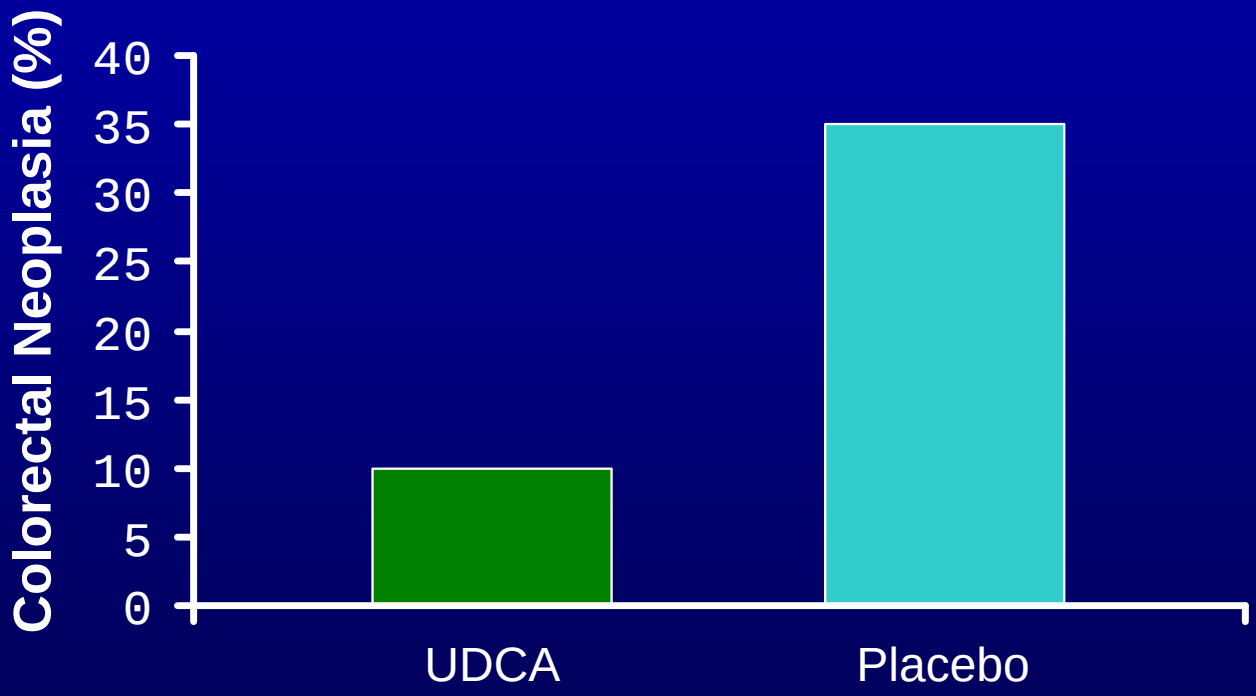
Folic Acid

Retrospective case-control



Lashner BA, et al. *Gastroenterology* 1997;112:29-32.

Ursodeoxycholic acid (UDCA)

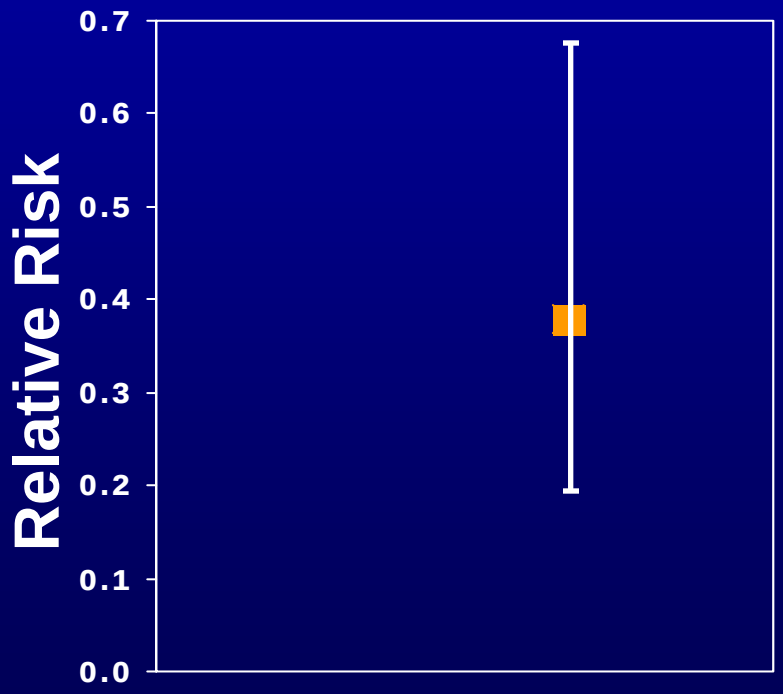


Relative Risk = 0.26 (95% CI, 0.06 - 0.92; p=0.034)

Pardi DS, et al. *Gastroenterology* 2003;124:889-893.

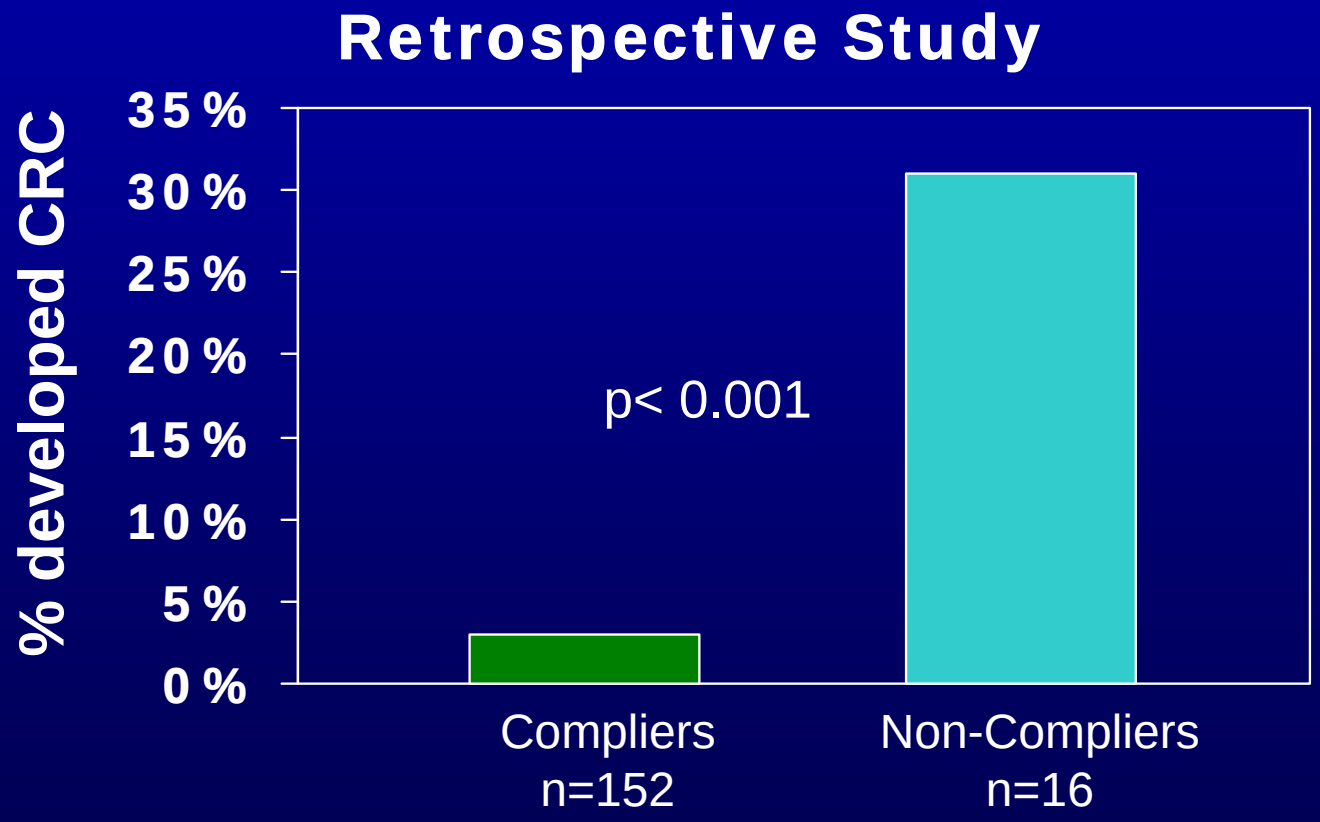
Effect of sulfasalazine on CRC risk in patients with UC

Retrospective case-control



Pinczowski D, et al. *Gastroenterology* 1994;107:117-120.

Impact of long-term sulfasalazine on CRC risk in UC



Moody GA, et al. *Europ J Gastroenterol Hepatol* 1996;8:1179-1183.

Effect of 5-ASA on CRC risk among patients with UC

Retrospective case-control

Drug	Odds Ratio	95% CI	P-value	Risk Reduction (%)
5-ASA (variable doses)	**0.47**	**0.22 – 1.00**	**0.05**	**53%**
Mesalamine < 1.2 g/day	0.18	0.02 – 1.92	0.16	-
Mesalamine ≥ 1.2 g/day	0.19	0.06 – 0.61	0.006	81%
Sulfasalazine < 2 g/day	0.93	0.22 – 3.91	0.92	-
Sulfasalazine ≥ 2 g/day	0.85	0.32 – 2.26	0.75	-
Other (variable doses)	1.21	0.08 – 18.97	0.89	-

Eaden J, et al. *Aliment Pharmacol Ther 2000;14:145-153.*

Effect of 5-ASA use on the development of CRC in IBD patients

Retrospective case-control

	Cases (n)	Controls (n)	Adjusted OR
Irregular users	**54**	**265**	**Reference**
Regular users	**46**	**335**	**0.60***
Sulfasalazine			
6-12 prescriptions	**3**	**12**	**0.95**
13-30 prescriptions	**5**	**53**	**0.41**
30+ prescriptions	**14**	**72**	**0.77**
Mesalamine			
6-12 prescriptions	**10**	**44**	**1.13**
13-30 prescriptions	**5**	**71**	**0.30***
30+ prescriptions	**5**	**71**	**0.31***

*statistically significant

Regular use - received ≥ 6 5ASA prescriptions in the 12 months before

Van Staa TP, et al. ACG Abstract and Oral Presentation, 2003.

5-ASA Summary

Study	Drug	% Risk Reduction
Pinczowski	sulfasalazine	62
Eaden	Various 5-ASAs (various doses)	53
Eaden	Mesalamine (≥ 1.2 g/day)	81
Rubin	Various 5-ASAs (≥ 1.2 g/day)	72
Bernstein	Various 5-ASAs (various doses)	----

Prevention of Cancer in IBD
Advancing Science and Understanding

- **Degree of inflammation as a risk for CRC in IBD**
  - May need to adopt "mucosal healing" as therapeutic target
- **Chemoprevention**
  - **5-ASA: possibly effective**
    - Provides one additional reason to encourage adherence to therapy
  - **6-MP/AZA: mixed chemoprevention results, not carcinogenic**
    - Insufficiently studied
  - **Statins: unclear, possibly not effective in IBD**
    - Limited evidence
- **Better detection of dysplasia**
  - **Is visible in some patients with current optical equipment- keep your eyes open!**
  - **Chromoendoscopy better at detecting dysplasia, but unclear how or when this will matter**