Primary sclerosing cholangitis, colitis and cancer

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Objectives

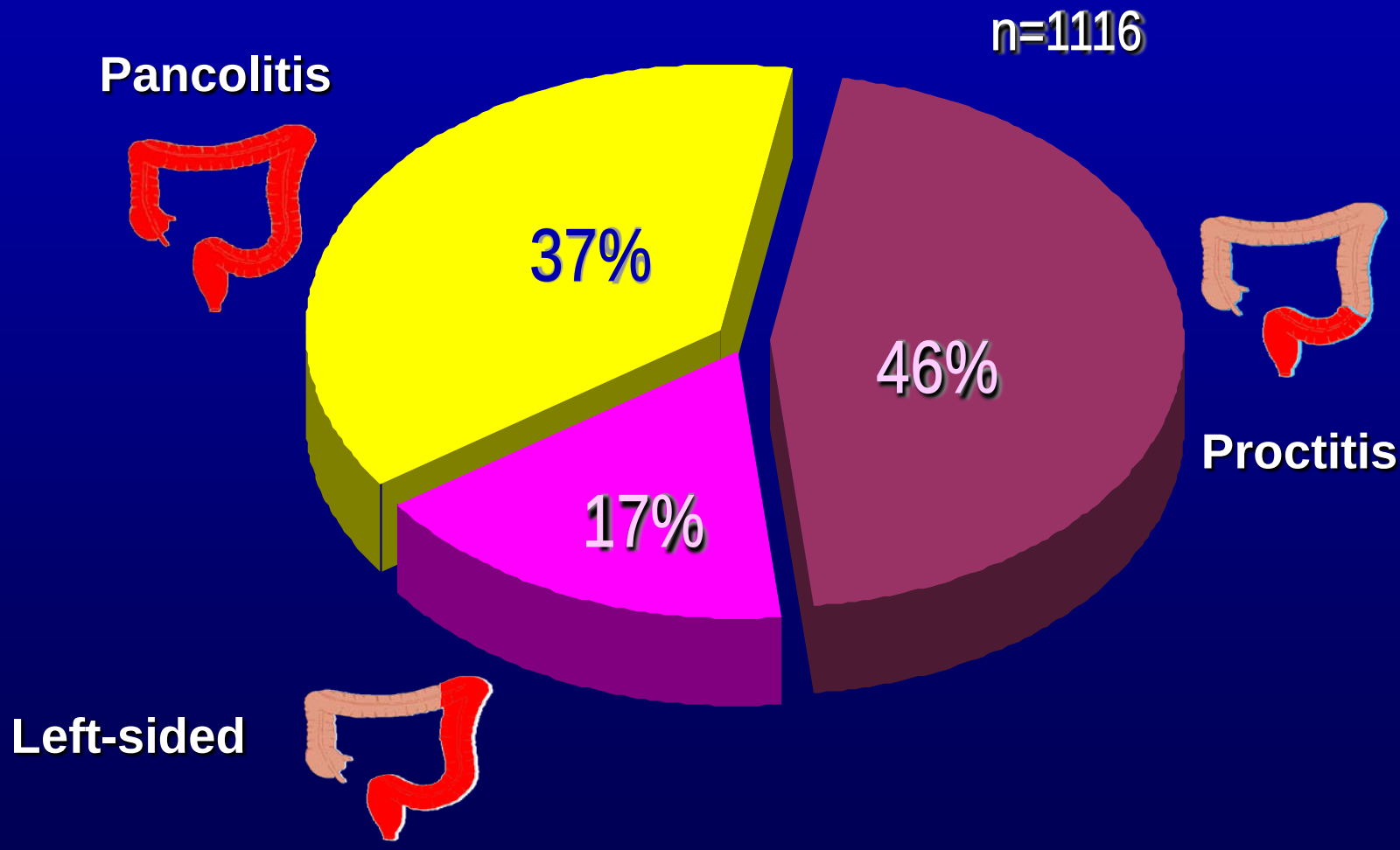
- Risk factors for colorectal cancer
- Colitis-associated colon cancer vs sporadic colon cancer
- Preventive strategies
  - Surveillance
  - Surgery
  - Pharmacologic agents
    - Folic acid
    - Ursodeoxycholic acid
    - 5-ASA

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.

Disease Distribution at Presentation



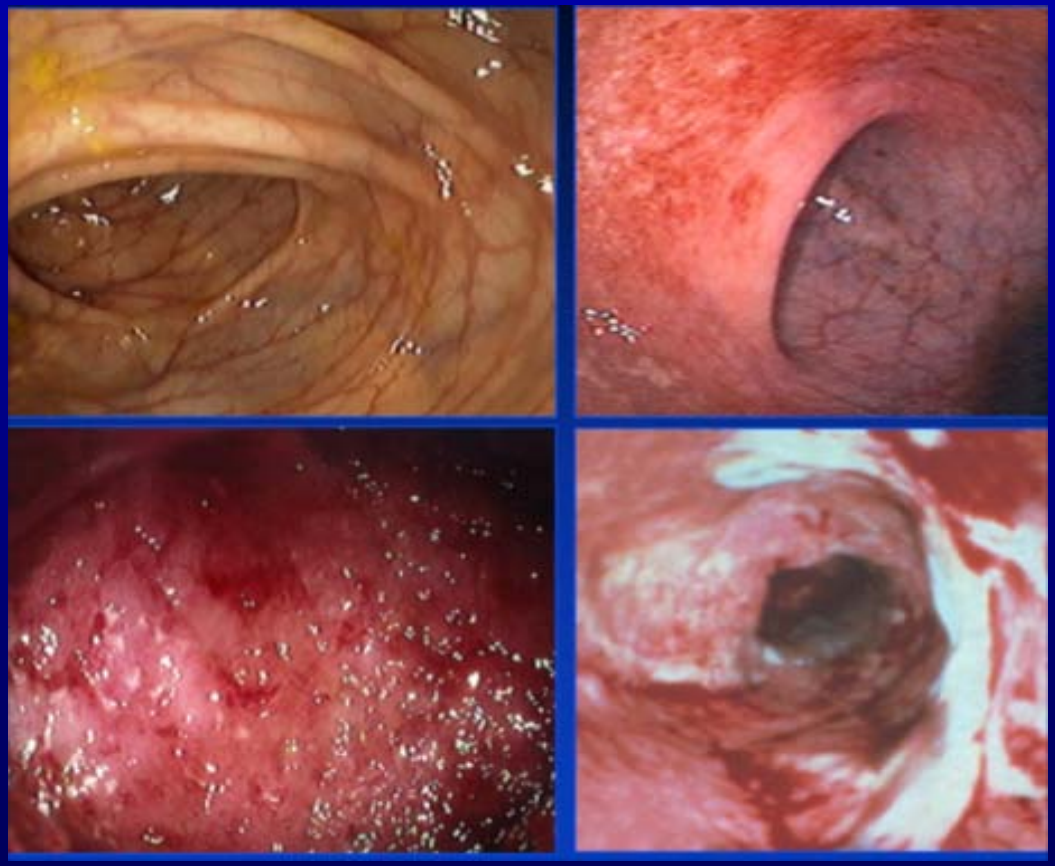
Farmer RG, Easley KA, Rankin GB. Dig Dis Sci 1993;38(6):1137-1146

Endoscopic Spectrum of Severity

UC – Spectrum of Disease

Normal

Mild



Moderate

Severe

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]	+
Psuedopolyps	+/-
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.

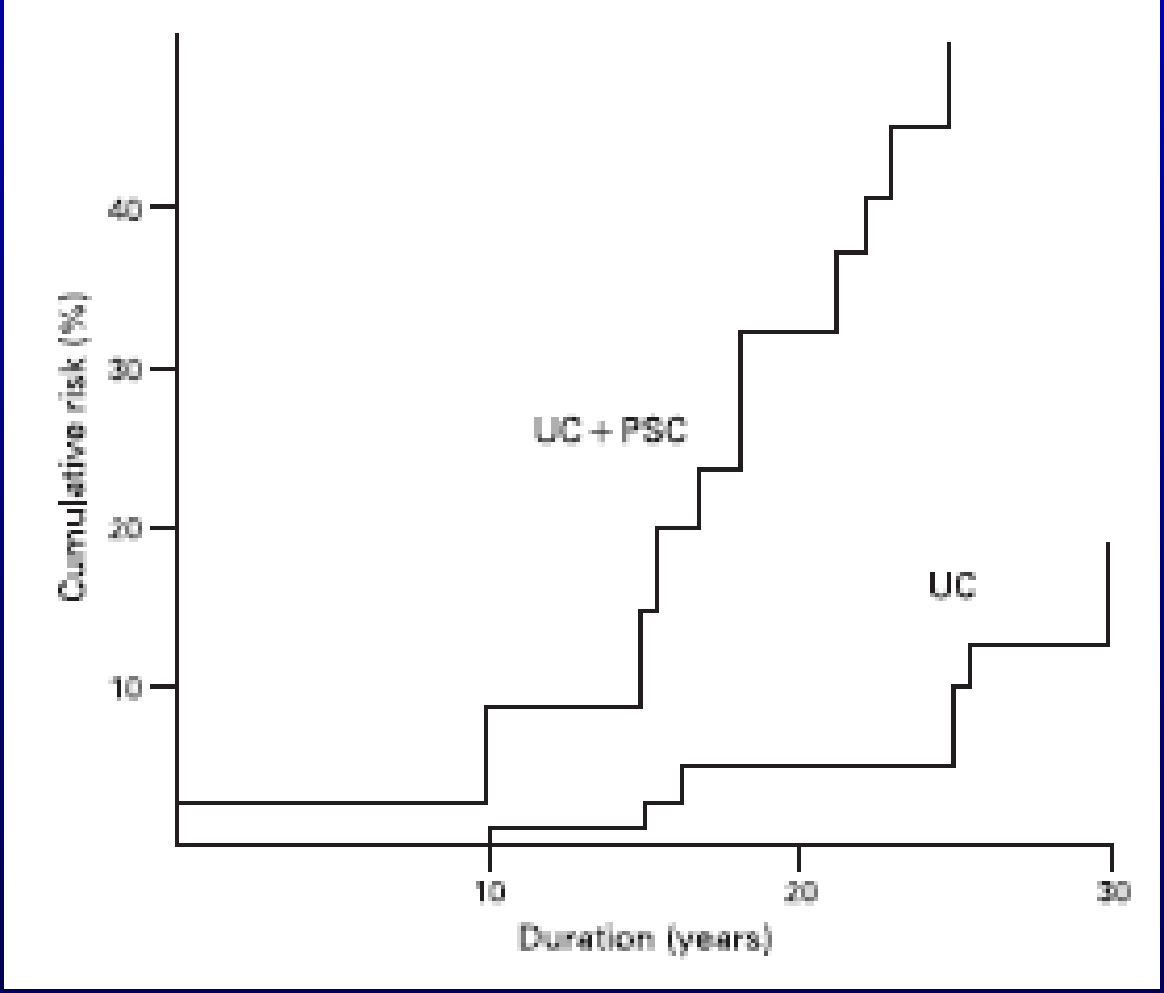
3 Lagergren J et al Gastroenterology. 2001 Sep;121(3):542-7

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

PSC increases cancer risk in colitis



PSC increases cancer risk in colitis

PSC and colonoscopy

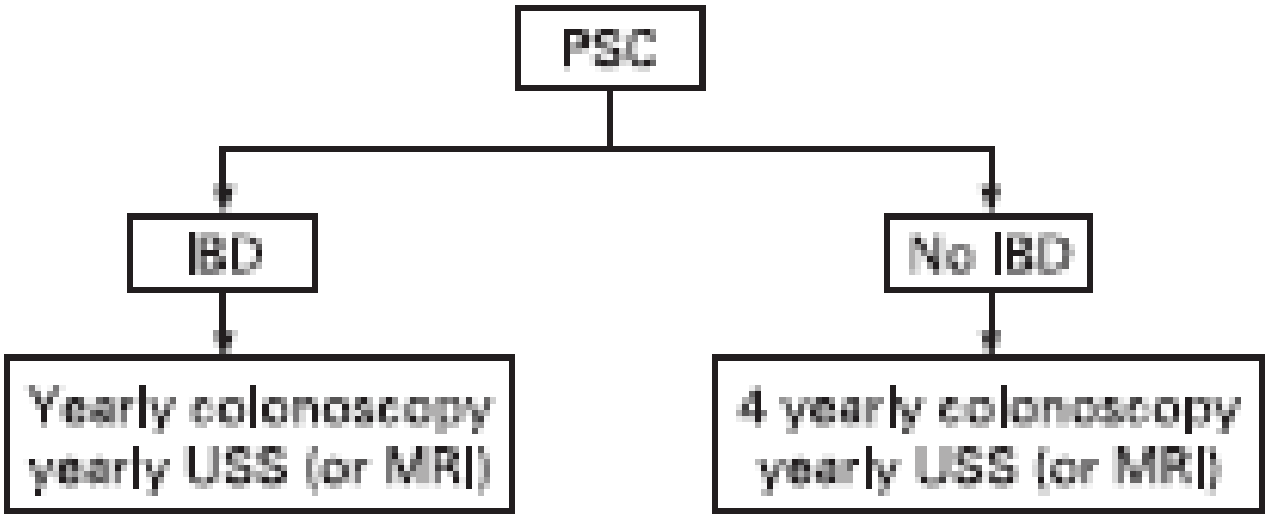
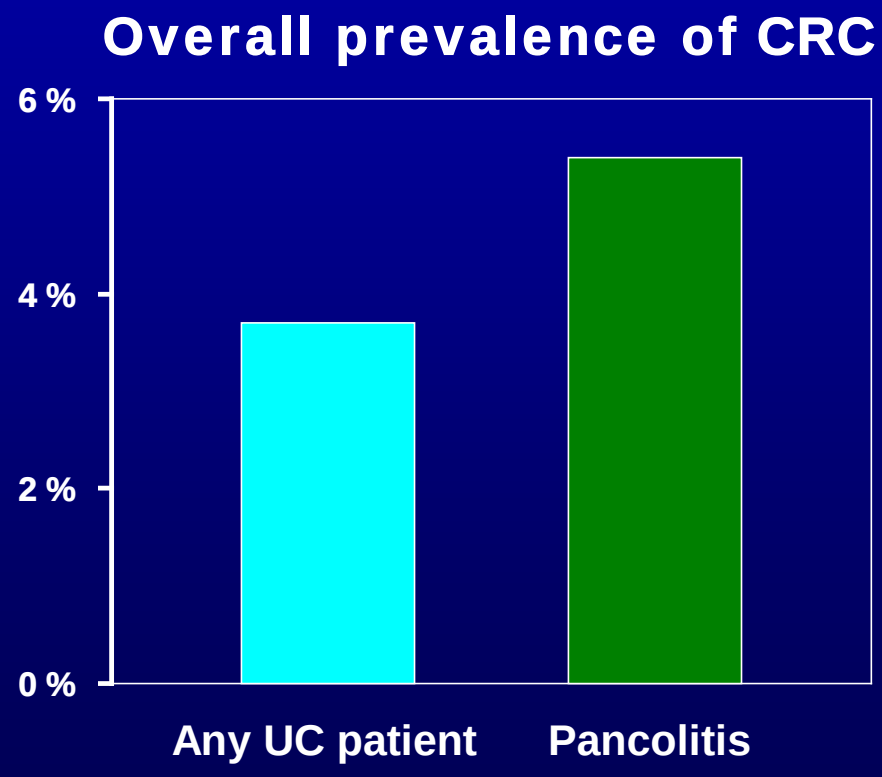


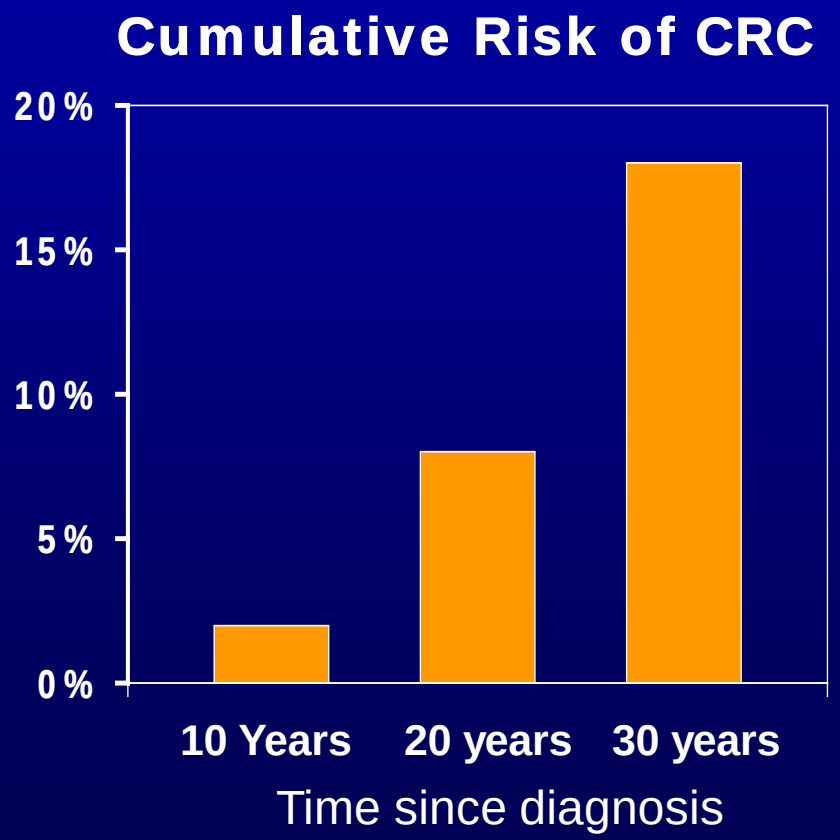
Figure 5 Routine screening/surveillance investigations in asymptomatic patients with primary sclerosing cholangitis (PSC). IBD, irritable bowel disease; USS, ultrasonography.

Why is risk higher in PSC?

- Milder disease (paradoxical)
- Subclinical disease – less treatment
- Fewer early colectomies
- Immuno-supression (transplant)
- Mutations that cause cancer in PSC also cause cancer in colitis
- Carcinogenic bile acids (more right sided disease)

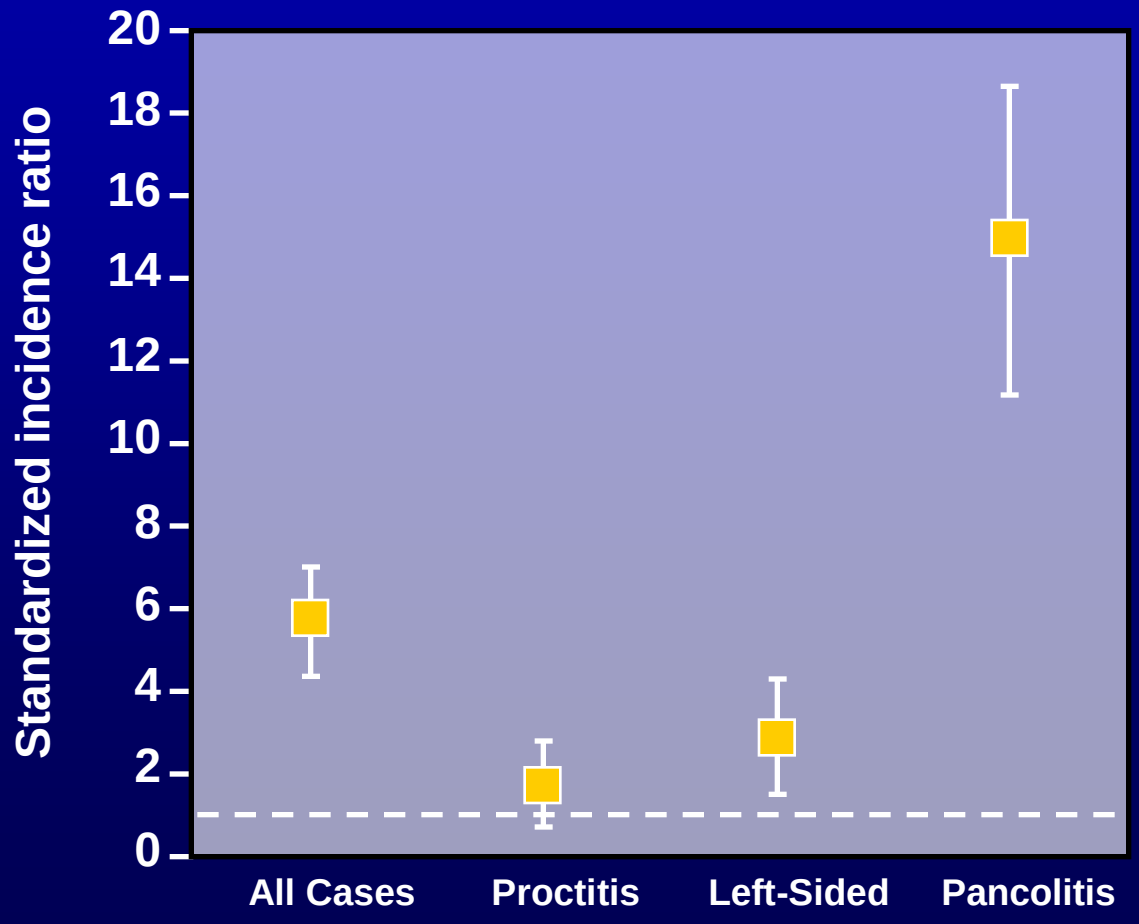
Prevalence and Cumulative Risk of Developing CRC in UC





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

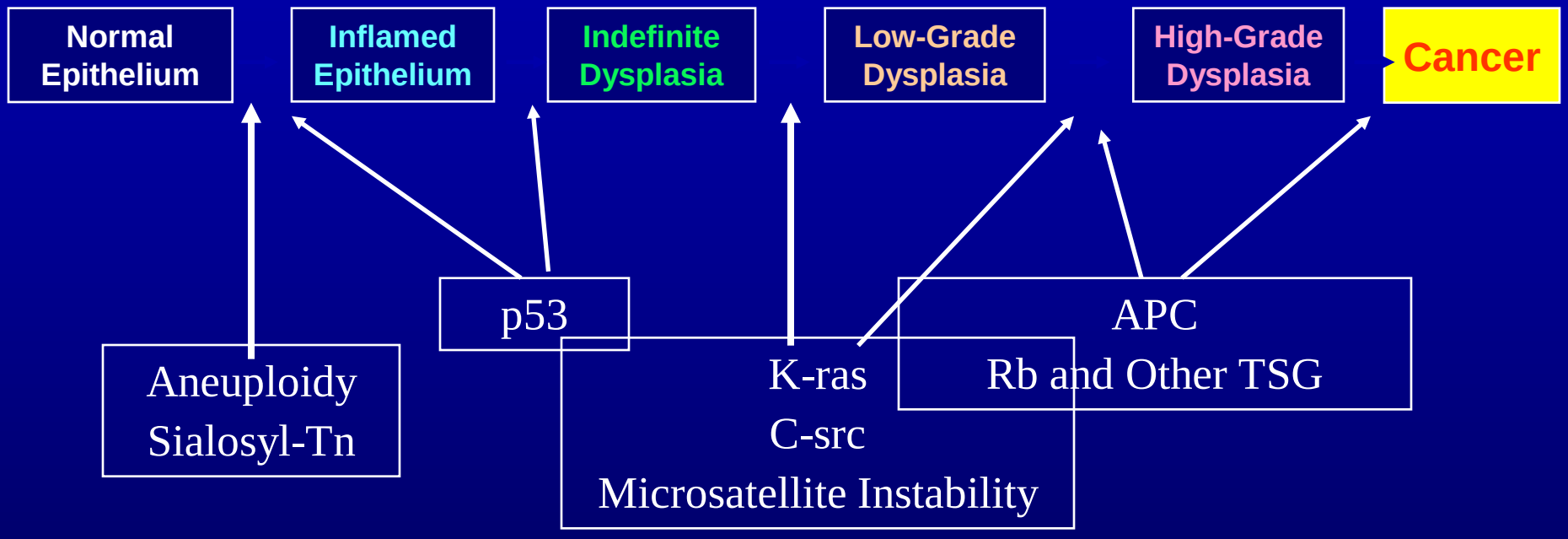
Relative Risk of CRC Based on Extent of UC

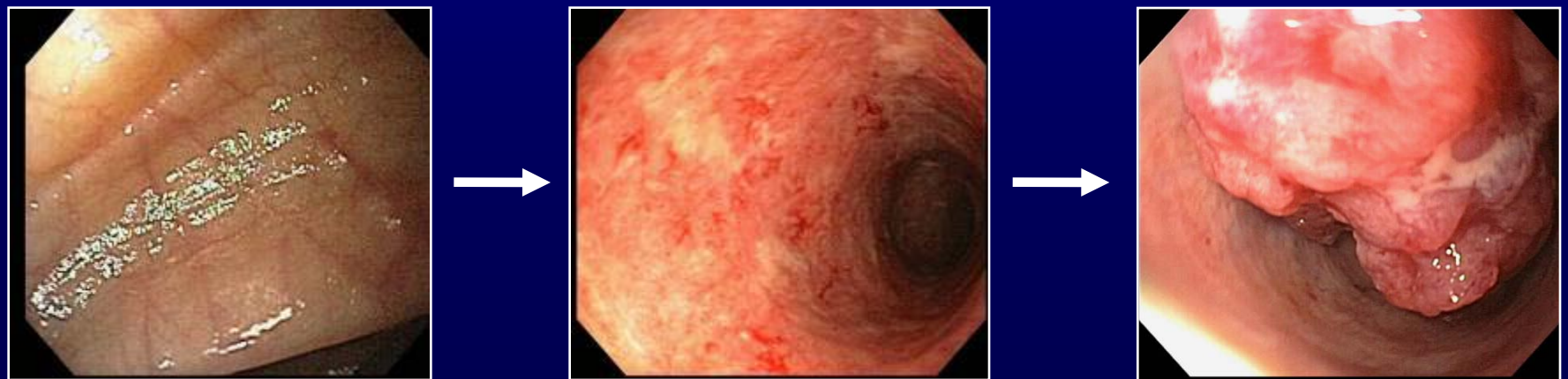


Ekbom A, et al. *N Engl J Med*. 1990;323:1228-1233.

Sporadic Colon Cancer
vs.
Colitis-associated Colon Cancer

Molecular Progression of UC to CRC





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

Prevention of CRC

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

Surveillance

Surveillance Recommendations

- **Colonoscopy:**
  - **UC - After 8-10 years of colitis, annually or biannually with multiple biopsies at regular intervals**
  - **PSC – begin in patients with colitis at the first year of diagnosis then annually**
  - **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..

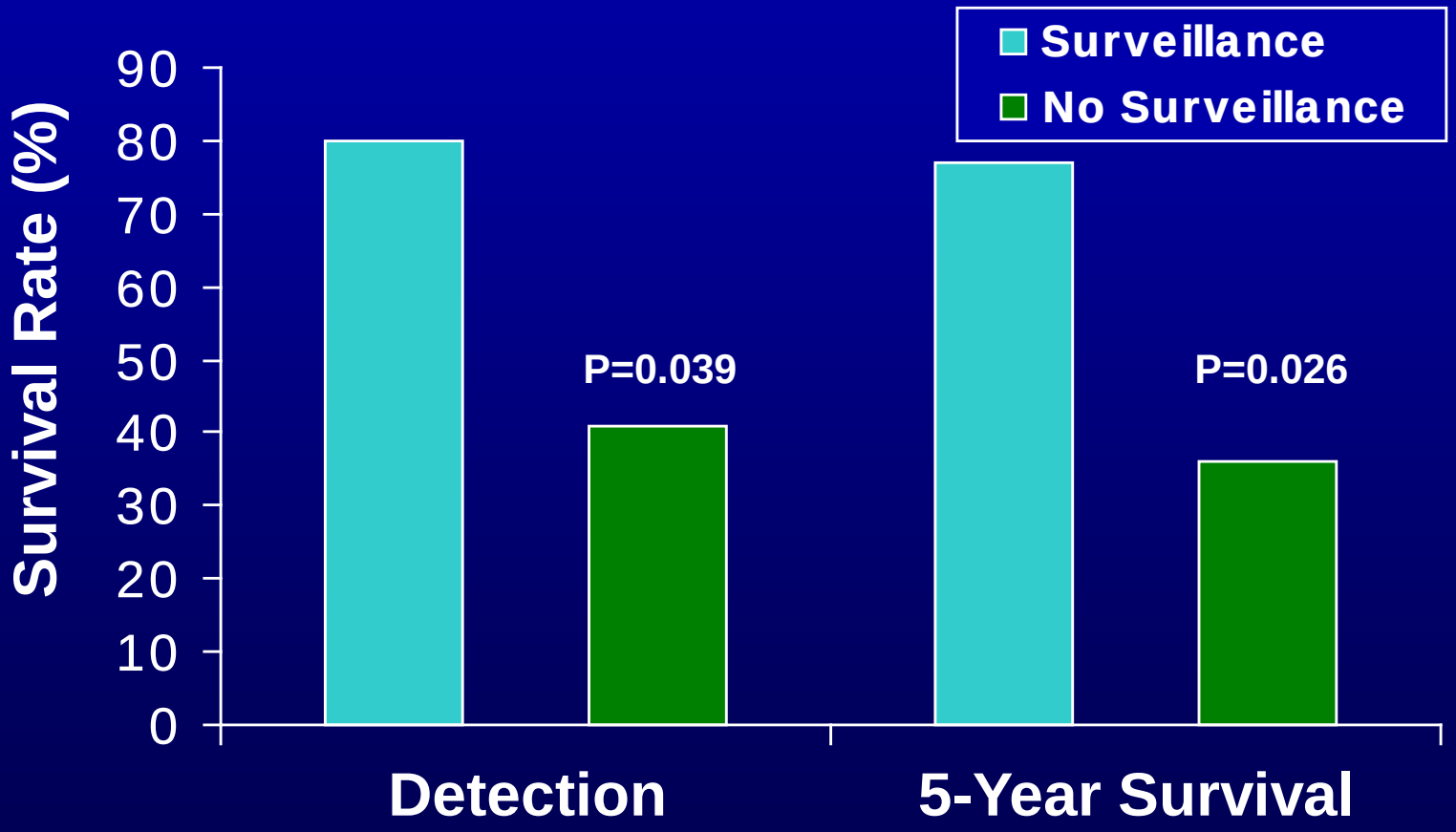
Surveillance Recommendations

- **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.

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.

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

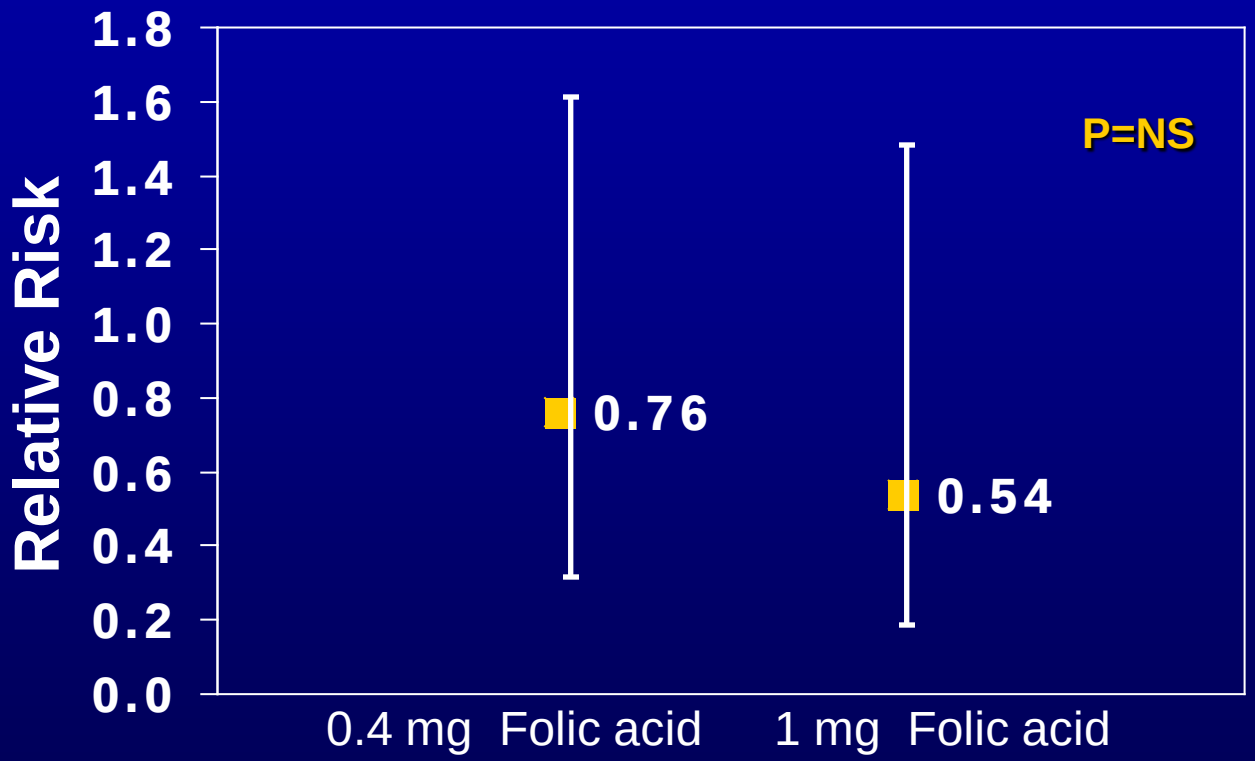
Prevention of Colorectal Cancer

- **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®)	

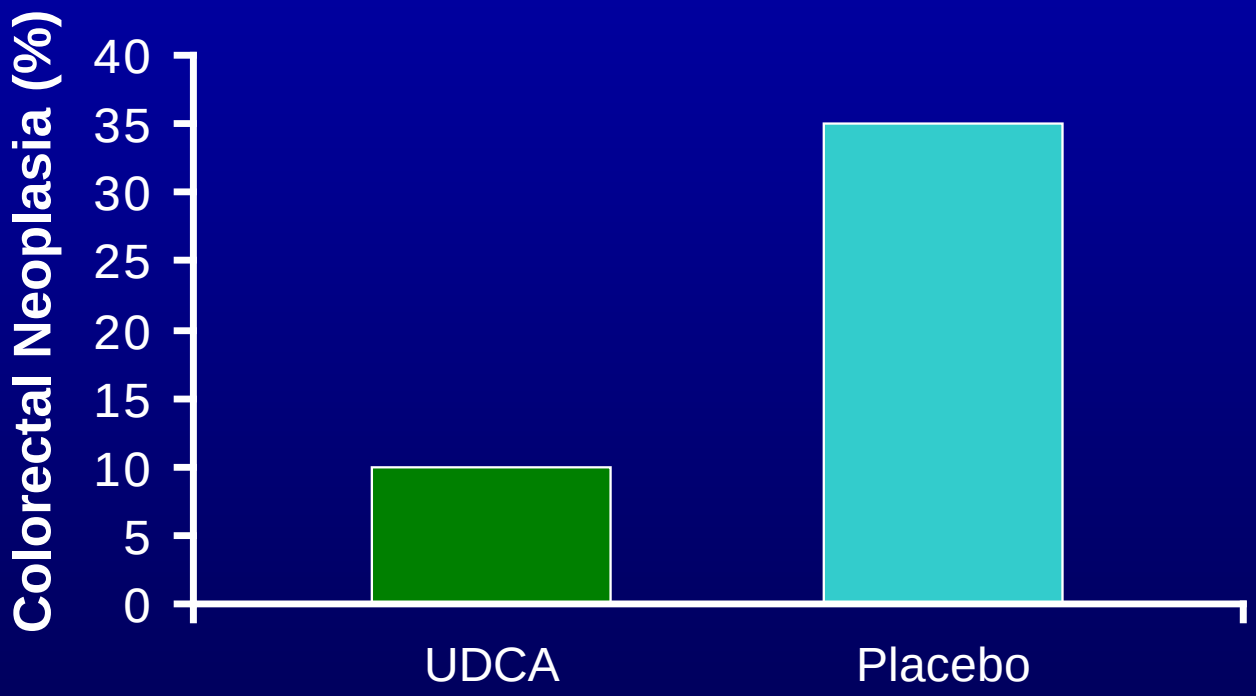
Folic Acid

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.

Ursodeoxycholic acid (UDCA)

- Less severe dysplasia – less mortality

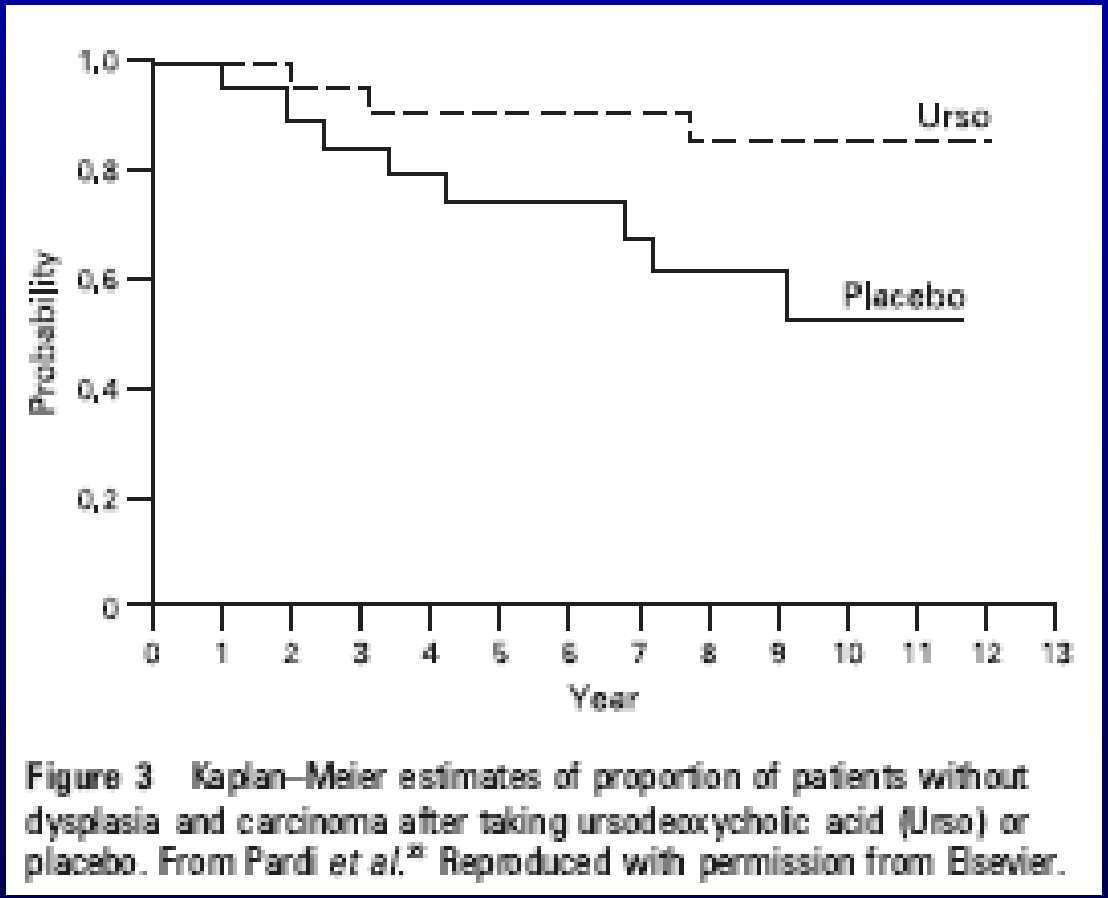


Figure 3 Kaplan–Meier estimates of proportion of patients without dysplasia and carcinoma after taking ursodeoxycholic acid (Urso) or placebo. From Pardi *et al.*[28] Reproduced with permission from Elsevier.

5-ASA

5-ASA Mechanism of Action in CRC Prevention

- **Precise mechanism unknown**
- **Proposed mechanisms**
  - **Oxygen radical scavenger[3]**
  - **Increased apoptosis, decreased proliferation[1,2]**
  - **Inhibition of production of prostaglandins, and leukotrienes[3]**
  - **Improvement in DNA repair[4]**
  - **Block stem cell activation**

1 Choi M, et al. DDW Abstract, 2003.
2 Bus PJ, et al. *Aliment Pharmacol Ther* 1999;13:1397-1402.
3 Allgayer H. *Aliment Pharmacol Ther* 2003;18(Suppl 2):10-14.
4 Gasche B, et al. DDW Abstract, 2001.

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)	----

Summary and future

- The risk for colorectal cancer is higher in patients with PSC and colitis
- Early detection of “subclinical” disease is crucial for detection
- Patients must be monitored early and often
- Treatment with UDCA and 5-ASA likely reduces cancer risk independent of its anti-inflammatory effect
- The higher cancer risk in PSC/UC patients raises the likelyhood that early colectomy will reduce the risk for colitis-induced cancer

Forefront – Detecting activated stem cells in PSC – then preventing their activation!