Colorectal Cancer Prevention and Early Detection

April 29, 2010

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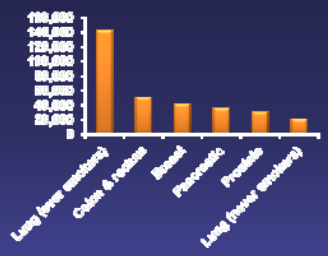
Common Causes of Cancer Death

Clin Cancer Res 15: 5622-5655 (2009)



Other Cancers

- Non-Hodgkins lymphoma
- Liver & intrahepatic biliary
- Ovarian
- Gastric
- Bladder
- Brain
- Kidney
- Myeloma
- Acute myeloid leukemia
- Melanoma

Cancer Deaths from Smoking

Nat Rev Cancer 9: 655-664 (2009)

- Est. 450 million deaths globally, 2000 to 2050
- Cessation before middle age avoids >90% of lung cancer mortality
- Aggressive tax policy is effective (France)
- Steep increases in smoking in low- and middle-income countries
- Effective treatments for tobacco dependence ARE available

Cancer Statistics, 2009

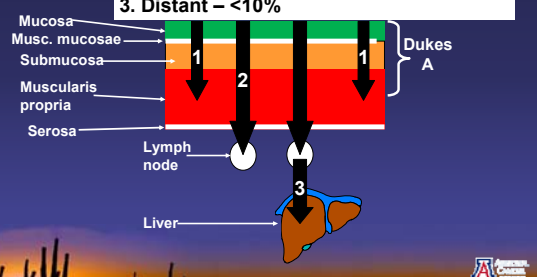
Jemal. CA Cancer J Clin 59:225-249 (2009)

Cancer Site	Estimated New Cases	Estimated Deaths
Lung	219,440	159,390
Colorectal	146,970	49,920
Breast	194,280	40,610
Prostate	192,280	27,360

COLORECTAL CANCER STAGING AND TIME TRENDS

5-Year Survival (%) According to Stage

1. Localized – ≥80%
2. Regional – ~30 to ~70% (no. of nodes)
3. Distant – <10%

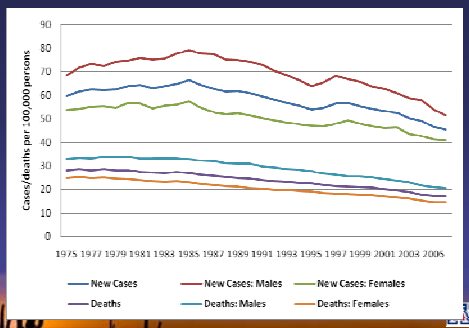


Colorectal Cancer Staging

Clinical		TNM
Localized	I: Primary tumor within bowel wall	T1-2, N0, M0
Regional	II: Primary tumor penetrates bowel wall (IIA), & invades other organs (IIB) without nodes	T1-4, N0 (II) or N1 (III), MO
	III: Within bowel wall + nodes (IIIA), penetrates bowel + nodes (IIIB or C)	T1-4, N1-2, M0
Distant	IV: Distant metastases	T (any), N (any), M1

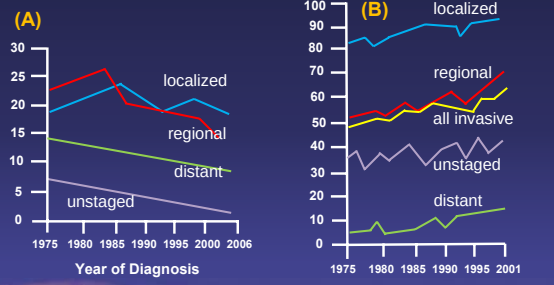
Colorectal Cancer Incidence and Mortality 1975-2006

www.interscience.wiley.com/cancer/report2009



CRC Trends: Incidence (A) & 5-y Survival (B)

www.interscience.wiley.com/cancer/report2009



Age-Standardized Colorectal Cancer Incidence and Mortality

Incidence

	White	Af. Am.	As./PI	AI/AN	Hisp.
M	64.1	72.4	57.2	37.5	49.8
F	46.2	56.2	38.8	32.6	32.9

Mortality

M	25.3	34.6	15.8	18.5	18.4
F	17.5	24.6	11.0	12.1	11.4

Ward et al. CA Cancer J Clin 54, 78-93 (2004)

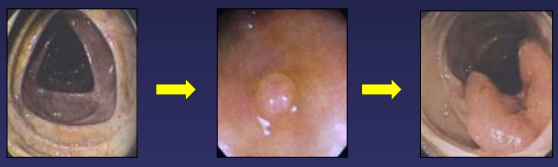
Take Home Message #1

Disparities in access to colorectal cancer prevention and screening measures must be eliminated

- African Americans
- Native Americans
- Hispanics

COLORECTAL NEOPLASIA PATHOBIOLOGY

Adenoma-Carcinoma Sequence

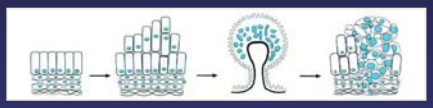


Normal Adenoma Carcinoma

- ~50% of US population have adenoma(s) by 70 yo
- ≤ 10% of adenomas are at risk of progression to CRC

Adenoma-Carcinoma Sequence

Normal epithelium | Hyper-proliferative | Adenoma | Adeno-carcinoma



>50% of population by age 70 years

•Tubular
•Diminutive

<10% of adenomas

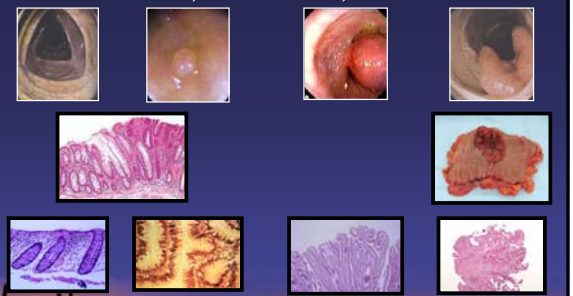
•Multiple
•Villous
•Large

Progression to adenocarcinoma rare before age 50 y in average-risk population

Advanced adenomas

Colorectal Carcinogenesis

Normal | Non-Adv. Ad. Tubular, 5 mm | Advanced Ad. Villous, 20 mm | Invasive Adenoca.



Advanced Colorectal Neoplasia

Screen detectable, i.e., asymptomatic

Advanced Adenoma

- ≥ 10 mm
- Villous
- High-grade dysplasia

Muscularis mucosa

Localized cancer

Advanced Neoplasm

Advanced Colorectal Neoplasia: Prevalence in Screened Populations

	Population	Prevalence %
Lieberman NEJM, 2000	Male veterans	10.5
Schoenfeld NEJM, 2005	Females, military	4.9
Regula NEJM, 2006	Age 50-66 y Age 40-49 y	5.9 3.4
Kim NEJM, 2007	Healthy screening cohort	3.3

Metachronous Colorectal Adenomas

Martinez ME. Gastroenterology 136, 832-841 (2009)

- Following removal of all adenomas, metachronous (i.e., new or recurrent) adenomas are found in 20-50% of individuals at surveillance colonoscopy performed 3-5 years later
- Individuals at greatest risk for metachronous adenomas and progression to colorectal cancer can be identified from incident/baseline adenoma characteristics:
  - An advanced adenoma (or prior colorectal cancer)
  - More than 2 non-advanced adenomas

Flat adenomas & right-sided adenomas??

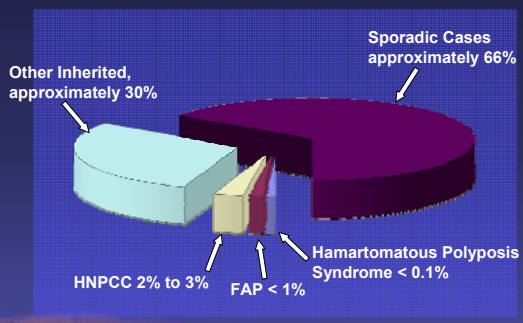
Take Home Message #2

Not all colorectal adenomas are equal

- Prior colorectal cancer
- Advanced adenomas
- Multiple adenomas
- *?Flat adenomas and right-sided lesions*

COLORECTAL CANCER RISK STRATIFICATION

Colorectal Cancer and Inheritance



Take Home Message #3

Every first-degree relative of a patient with colorectal cancer should be aware of this risk factor

- Number of cases
- First degree (parent, sibling or child) or not
- Age(s) at first diagnosis

Gastrointestinal Diseases Predisposing to CRC

Gastroenterology 138, 746-774 (2010)

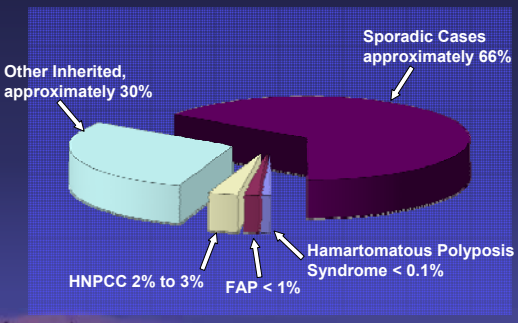
- Ulcerative colitis
- Crohn's colitis

Take Home Message #4

Every patient with a condition that puts them at increased risk for colorectal cancer should be aware of this

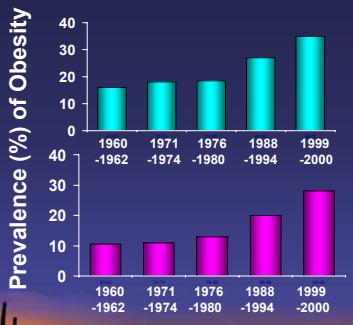
- Ulcerative colitis
- Crohn's colitis

Sporadic Colorectal Cancer



Obesity Trends

www.cdc.gov/obesity/data/trends.html



Physical Activity, BMI and Colorectal Cancer

- Up to 50% ↓ in risk for colon cancer with physical activity
- Recent evidence suggests similar effect on rectal cancer risk
- At low levels of physical activity, obesity may ↑ risk for colon cancer
- Less evidence that obesity influences rectal cancer risk

BMI, Metabolic Syndrome & CRA Recurrence

Jacobs E. Clin Gastroenterol Hepatol 5, 982-990 (2007);
Jacobs E. Am J Epidemiol, in press; Ashbeck E, submitted

Increased Risk for CRA Recurrence

	Obesity Alone	Inc. of [gluc] & waist circumference
Male	Yes	Yes
Female	No	Yes

- Proximal neoplasia
- Compounded by family history
- Insulin resistance

Take Home Message #5

Lifestyle factors are major risk factors for colorectal cancer and should be addressed aggressively as early as possible

- Physical activity
- BMI
- Smoking

COLORECTAL CANCER EARLY DETECTION/ SCREENING

Colorectal Cancer Screening Tests

Structural

- Flexible sigmoidoscopy (FSIG)
- Optical colonoscopy (OC)
- Computed tomographic colonography (CTC)

Fecal

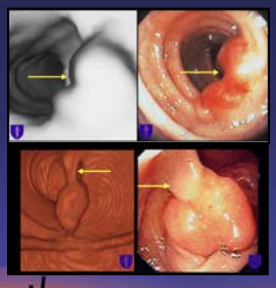
- Fecal blood test (FBT)
  - Guaiac-based occult (gFOBT); Hemoccult II
  - High-sensitivity gFOBT; Hemoccult SENSA
  - Fecal immunochemical tests (FIT; FlexSure, HemeSelect
- Stool DNA (sDNA)

Optical Colonoscopy – The Benchmark

Cotton JAMA, 2004	OC vs. VC (CTC)	100% sens. (≥ 10 mm)
van Rijn AJG, 2006	Tandem OC	2.1% miss rate (≥ 10 mm)
Barclay NEJM, 2006	Withdrawal time < 6 vs. ≥ 6 min n = 7,882	Advanced neopl. 2.6% vs. 6.4%
Dominitz Gastrointest. Endosc., 2003	Complications of OC	Perforation rates 1-3 per 1,000

Optical Colonoscopy & Computed Tomographic Colonography

Advanced Colorectal Neoplasia



Adenocarcinoma

Advanced Adenoma
(Diameter ≥ 10 mm)

Performance of Non-Invasive Screening Tests – Advanced Neoplasia

	Sensitivity %	Specificity %	Source
gFOBT	13	93	Morikawa 2005
FIT	20	95	Morikawa 2005
Fecal DNA	18	94	Imperiale 2004
CTC	90	86	Johnson 2008

Performance of Newer Fecal Blood Tests

Allison JE. J Natl Acad Sci 99, 1462-1470 (2007)

		Sensitivity %	Specificity %
FIT	CRC	81.8	96.9
	AA	29.5	97.3
Sensitive GT	CRC	64.3	90.1
	AA	41.3	90.6
FIT + Sensitive GT	CRC	64.3	98.1
	AA	22.8	98.4

FIT: Fecal immunochemical test; FlexSure OBT/Hemoccult ICT
Sensitive GT: Guaiac fecal occult blood test; Hemoccult Sensa

Current Screening Recommendations

Levin B. CA Cancer J Clin 58, 130-160 (2008)

ADENOMAS & CANCER

- FSIG – 5 y interval or
- Colonoscopy – 10 y or
- DCBE – 5 y or
- CTC – 5 y

PRIMARILY CANCER

- Annual gFOBT or
- Annual FIT or
- Stool DNA test – interval uncertain

AN ALREADY CONFUSING MESSAGE MADE MORE CONFUSING

Colorectal Cancer Screening
US Preventive Services Task Force

Ann Intern Med 149, 627-637 (2008)

TEST	FREQUENCY
High-sensitivity FBT, Hemocult SENSA or FIT	Annual
High-sensitivity FBT	Every 3 years
+ FSIG	Every 5 years
Colonoscopy	Every 10 years

For reasons not evidence-based, availability of FSIG is now very restricted in US

DEFICIENCIES OF COLONOSCOPY
Fixable and Unfixable

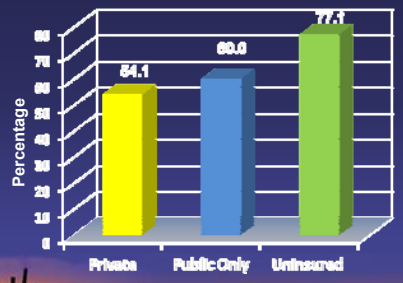
Screening Colonoscopy – Disadvantages, Deficiencies, Misuse

1. Costs
2. Complications – finite mortality
3. Subject reluctance
4. Missed and subtle lesions: post-screening invasive CRC
5. The right-sided conundrum
6. Under- and overuse

Adults Aged 50 to 64 Years

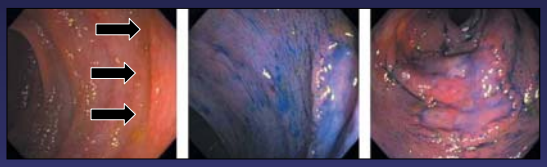
Percentages Who Never Had Colonoscopy

Mitka M. JAMA 299, 622 (2008)



Non-Polypoid Colorectal Neoplasms (NP-CRN)

Soetikno et al. JAMA 299, 1027-1035 (2008)



Prevalence of NP-CRN in screenees = 5.84%

NON-POLYPOID MORPHOLOGY ↑ CARCINOMA RISK

	OR	CI
Overall	9.78	3.93-24.4
Size-adjusted	2.01	0.27-15.3

Colonoscopy and Death From Colorectal Cancer

Baxter E. Ann Intern Med 150, 1-8 (2009)

- 10,292 deaths from CRC and 5 matched controls/case
- 7.0% of case patients and 9.8% of controls had colonoscopy

Odds Ratio (95% CI)

All Cancer	Right-Sided Cancer	Left-Sided Cancer
0.69 (0.63-0.74)	0.99 (0.86-1.14)	0.33 (0.28-0.39)

Colonoscopy Follow-Up/Surveillance

Gastroenterology 130, 1872-1875 (2006)

No Adenoma	10 years
Non-Advanced Adenoma	5 years
*Advanced Adenoma or >2 Adenomas	3 years

*Diameter ≥ 10 mm, or villous histology or high-grade dysplasia

Surveillance Colonoscopy – Utilization

Schoen R. Gastroenterology 138, 73-81 (2010)

Surveillance colonoscopy within 5 years:

Advanced adenoma	58.4%
> 2 Non-advanced adenomas	57.5%
1 or 2 Non-advanced adenomas	46.7%
No adenomas	26.5%

Substantial overuse of colonoscopy in low-risk subjects and underuse in subjects with advanced adenomas or >2 adenomas

RECOMMENDATION

Descending order of preference

Colonoscopy

⬇

CTC

⬇

FIT or Hemoccult SENSA

- FBT *only* as recommended by manufacturer i.e., never smear from DRE for screening
- Abandon use of traditional guaiac tests (Hemoccult II)

Take Home Message #6

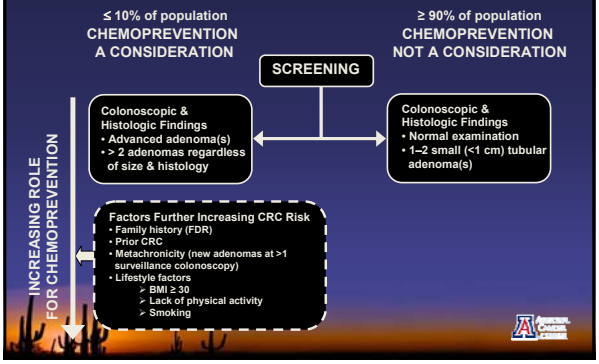
Everyone should undergo periodic screening for colorectal cancer between the ages of 50 and 75 years

- Screening should be tailored to individual risk
- Individuals at increased risk should be screened by colonoscopy
- For those at average risk, CT colonography or FBT (FIT or Hemoccult SENSA) are acceptable alternatives, *NOT* Hemoccult II
- When available, FSIG also acceptable

COLORECTAL CANCER PREVENTION
Beyond Lifestyle Changes & Screening

REDUCING CRC MORTALITY
Triaging Risk

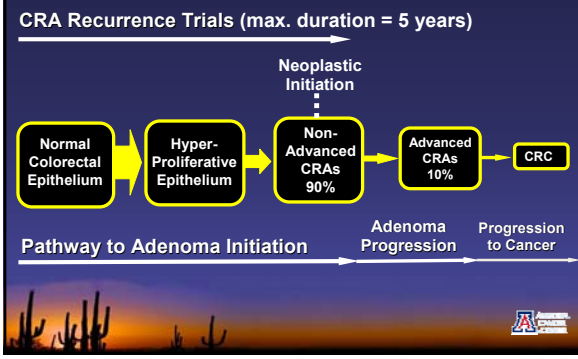
Lance P. Gastroenterology 134, 341-343 (2008)



Chemoprevention – Possible Niches

- Advanced & multiple (>2) adenomas
- Genetically predisposed (family history)
- Predisposing lifestyles, e.g. BMI >30
  + inflammatory markers

Colorectal Adenoma Recurrence
A Surrogate for Colorectal Cancer



Adenoma Recurrence RCTs
Drugs and Micronutrients

	Dose	Result: Positive	Result: Negative
Aspirin	81 mg	×	
	325 mg	×	
Ca^{2+}	1,200 mg	×	
Folic Acid	1 mg		×

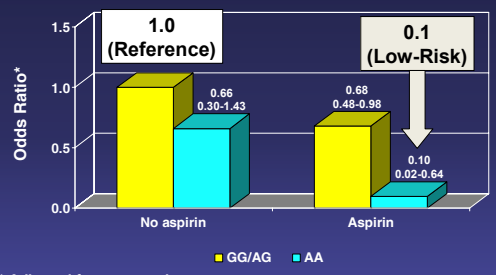
RCT of Difluoromethylornithine (DFMO) + Sulindac

Meyskens FL. Cancer Prev Res 1, 32-38 (2008)

	Recurrence (%)	RR (95% CI)	P
Any Adenoma			
Placebo	41.1	1.0	
DFMO + Sul.	12.3	0.3 (0.18-0.49)	<0.001
Advanced Ad.			
Placebo	8.5	1.0	
DFMO + Sul.	0.7	0.085 (0.011-0.65)	<0.001
Multiple Ad.			
Placebo	13.2	1.0	
DFMO + Sul	0.7	0.055 (0.0074-0.41)	<0.001

DFMO 500 mg daily
Sulindac 150 mg daily

Odds Ratios for Adenoma Recurrence by *ODC* Genotype and Aspirin Use



* Adjusted for age, gender and number of colonoscopies

Martinez ME. Proc Natl Acad Sci USA 100, 7859-7864 (2003)

Take Home Message #7

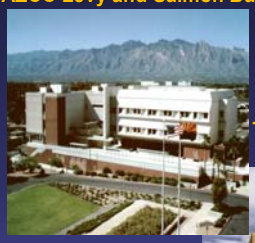
For a minor proportion of the population, chemoprevention may be a consideration, though *not* yet accepted as part of usual care

- Low-dose aspirin and calcium supplements
- DFMO ± NSAID shows considerable promise
- Tailored
- Patient categories for consideration include
  - Prior colorectal cancer
  - Advanced & multiple (>2) adenomas
  - Genetically predisposed (family history)
  - Predisposing lifestyles, e.g. BMI >30 + inflammatory markers (*speculative*)

Preventing Colorectal Cancer

1. Cancer health disparities must be eliminated
2. Prior CRC or advanced/multiple adenomas confer ↑ risk
3. Be informed of family history (FDR) of CRC
4. Patients with ulcerative or Crohn's colitis at ↑ risk
5. Lifestyle factors (obesity/BMI, lack of physical activity) are major risk factors for CRC
6. Everyone between ages of 50 and 75 years should undergo periodic screening
   - Colonoscopy for those at increased risk
   - CTC or FBT (FIT or Hemoccult SENSA) acceptable for those at average risk. If available, FSIG acceptable
7. Chemoprevention a viable consideration for a minority of the population at increased risk for CRC

AZCC Levy and Salmon Building



The AZCC Peter and Paula Fasseas Cancer Clinic