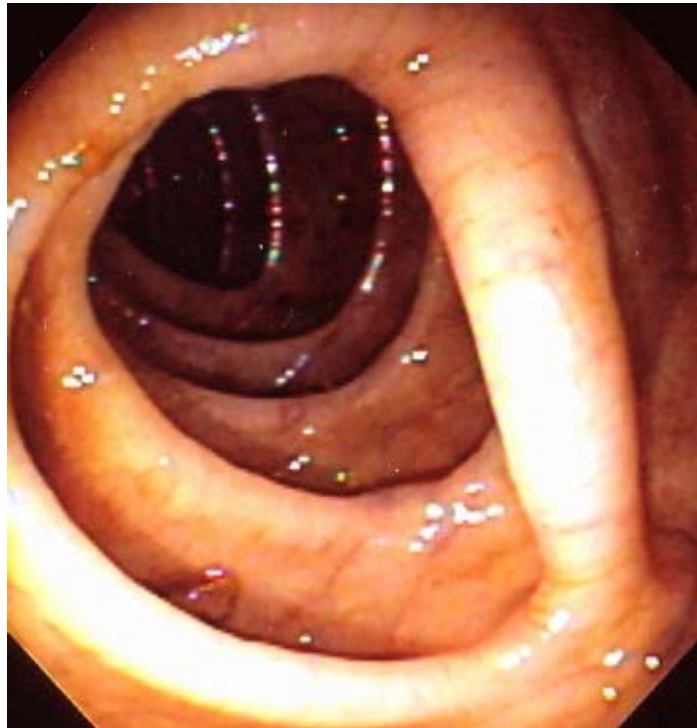


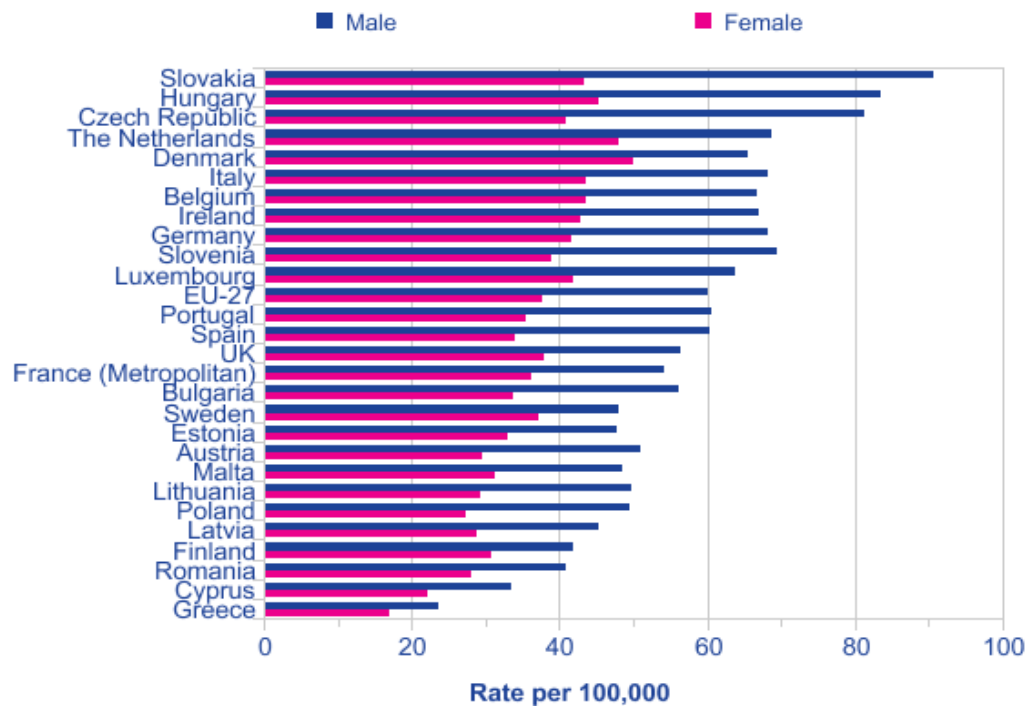
Colorectal Cancer



DR. F.M. BHOLAH OSK FRCP LONDON

Bowel including Anal Cancer (C18-C21): 2008 Estimates

European Age-Standardised Incidence Rates per 100,000, EU-27 Countries



Please include the citation provided in our Frequently Asked Questions when reproducing this chart: <http://info.cancerresearchuk.org/cancerstats/faqs/#How>

Prepared by Cancer Research UK

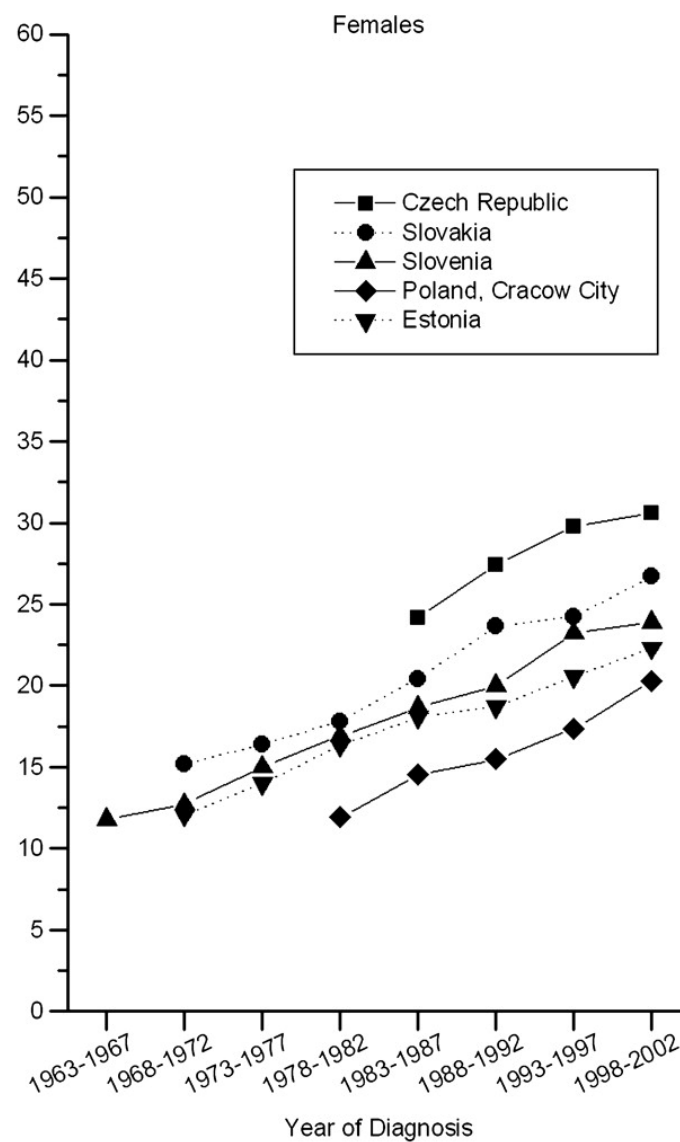
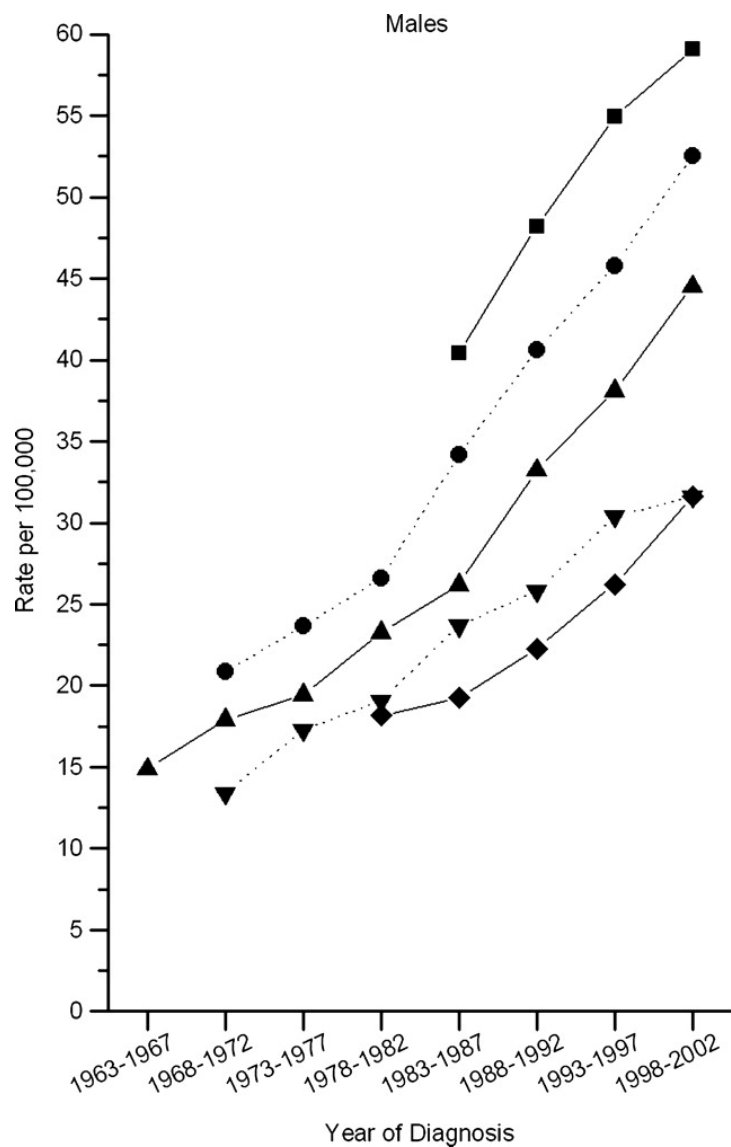
Original data sources:

European age-standardised rates were calculated by the Statistical Information Team at Cancer Research UK, 2011 using data from GLOBOCAN, IARC, 2010, version 1.2. Available from: <http://globocan.iarc.fr>. Accessed May 2011.



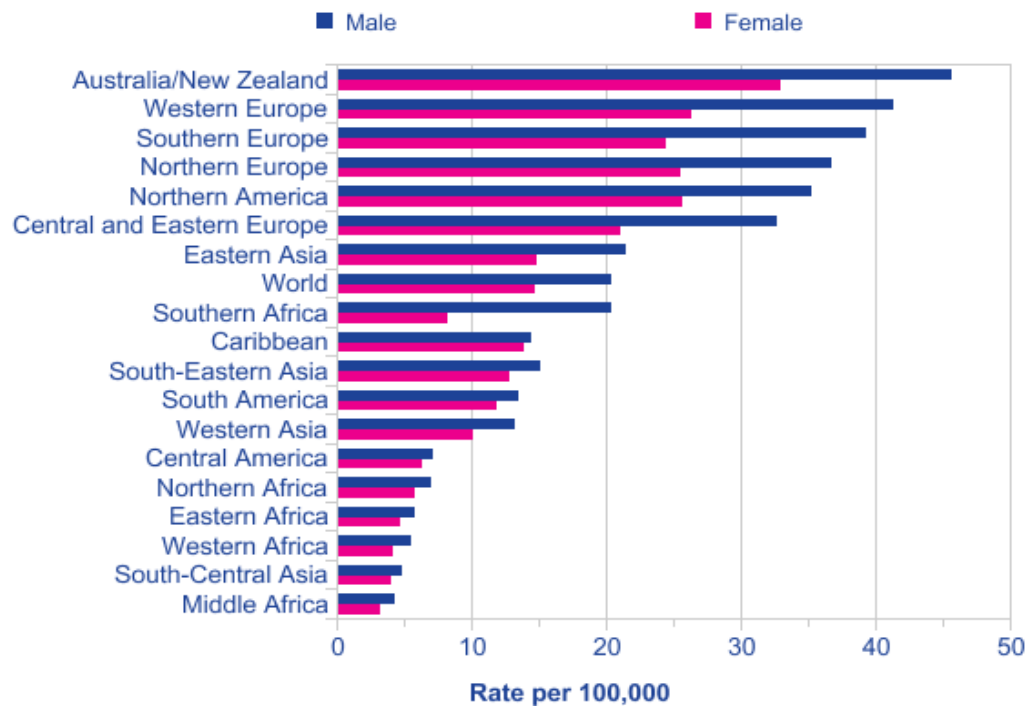


Trends in colorectal cancer incidence rates in select countries of Eastern Europe by sex (Cancer Incidence in Five Continents, 1963-2002).



Bowel including Anal Cancer (C18-C21): 2008 Estimates

World Age-Standardised Incidence Rates per 100,000 Population, World Regions



Please include the citation provided in our Frequently Asked Questions when reproducing this chart: <http://info.cancerresearchuk.org/cancerstats/faqs/#How>

Prepared by Cancer Research UK

Original data sources:

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010. Available from: <http://globocan.iarc.fr>. Accessed May 2011.



Incidence of Colorectal Ca in KSA Versus USA

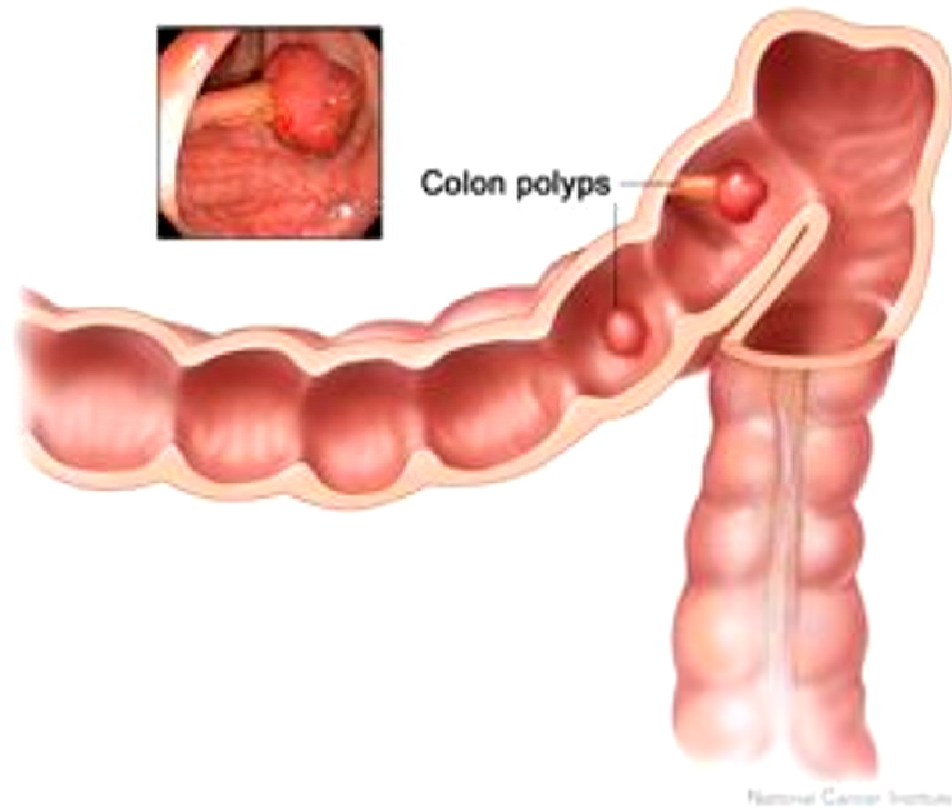
ASR for colorectal cancer (1994-2003) in the Kingdom of Saudi Arabia and the United States of America

| Year | ASR for Incidence (KSA) | | | ASR for Incidence (USA) | | |
|------|-------------------------|---------|------|-------------------------|---------|-------|
| | Males | Females | ALL | Males | Females | ALL |
| 1994 | 3.36 | 3.45 | 3.38 | 40.80 | 28.90 | 33.41 |
| 1995 | 3.25 | 4.02 | 3.56 | 39.20 | 28.80 | 32.63 |
| 1996 | 2.93 | 3.73 | 3.25 | 40.70 | 28.20 | 33.01 |
| 1997 | 3.05 | 3.51 | 3.22 | 41.90 | 29.30 | 34.06 |
| 1998 | 3.45 | 3.52 | 3.48 | 41.00 | 30.20 | 34.14 |
| 1999 | 3.98 | 4.63 | 4.26 | 40.60 | 29.40 | 33.59 |
| 2000 | 3.70 | 4.28 | 3.95 | 39.70 | 28.50 | 32.82 |
| 2001 | 4.15 | 4.92 | 4.48 | 39.10 | 28.00 | 32.24 |
| 2002 | 5.09 | 5.07 | 5.07 | 38.20 | 28.40 | 32.11 |
| 2003 | 6.06 | 5.60 | 5.84 | 36.90 | 26.50 | 30.49 |

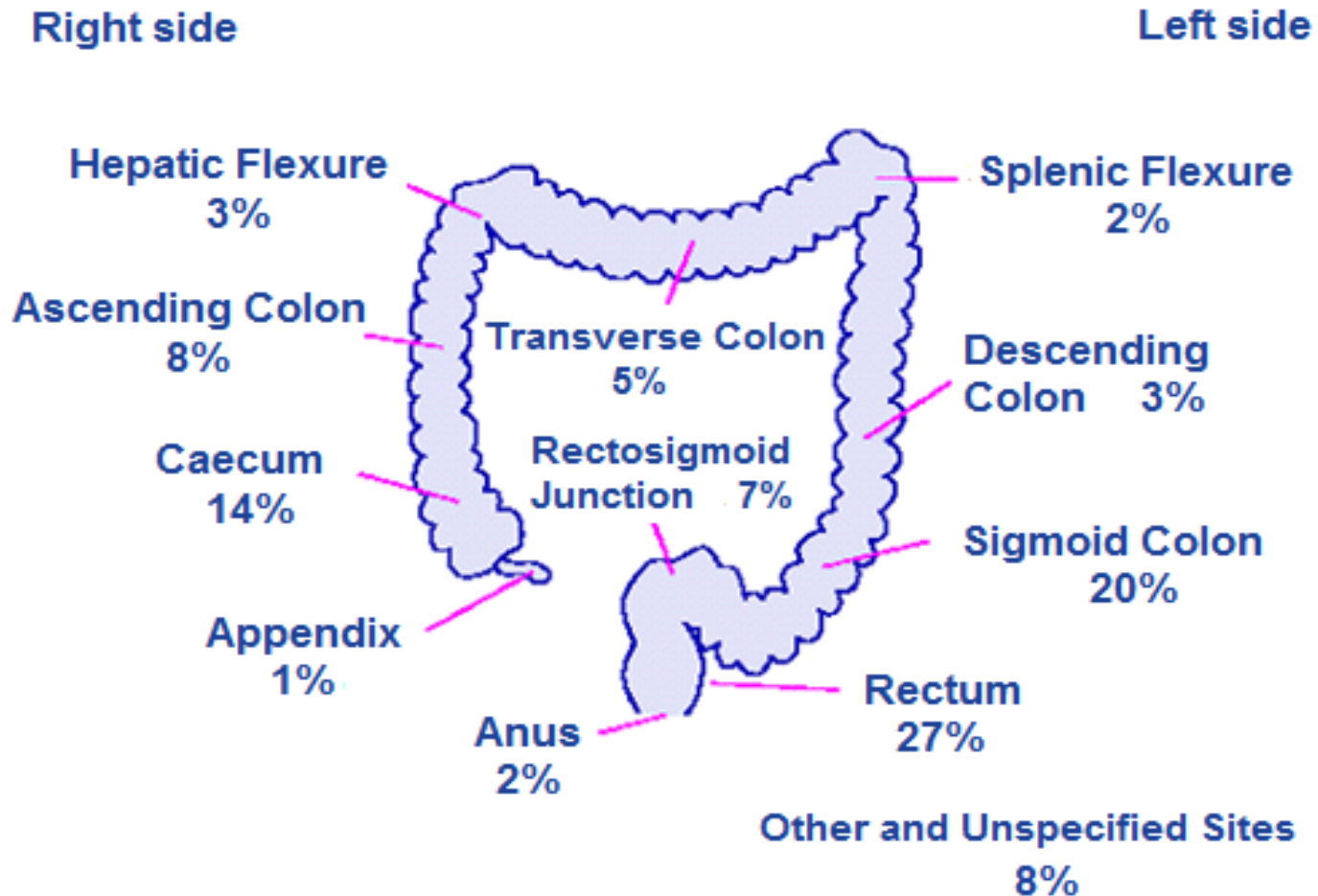
Source: Ibrahim, E. *et al.* (2008). Past, Present and Future of Colorectal Cancer in the Kingdom of Saudi Arabia. *The Saudi Journal of Gastroenterology*. 14(4): 178–182.

Colorectal Cancer

- Over 95% of colon and rectal cancers are adenocarcinomas (cancers that begin in cells that make and release mucous and other fluids). These cells line the inside of the colon and rectum.



Number of New Cases and Percentage Distribution of Cases within the Large Bowel, Great Britain





Flat Lesions

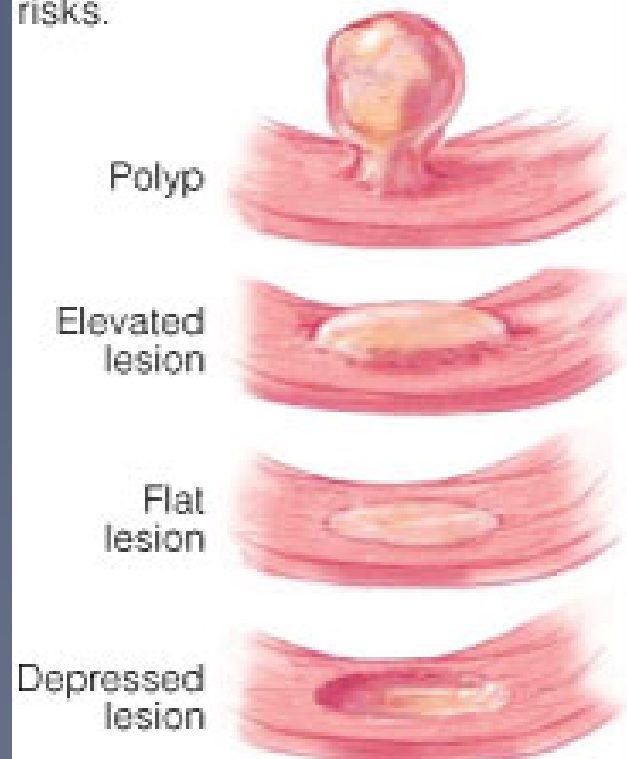
Caveats

- Most lesions not truly flat

Soetikno, JAMA 2008

New Sources of Risk

Colorectal cancer prevention largely focuses on finding polyps, but flatter, less visible lesions that are not polyps are also cancer risks.



THE NEW YORK TIMES. ILLUSTRATIONS BY JAMA



Human colon carcinogenesis

Normal



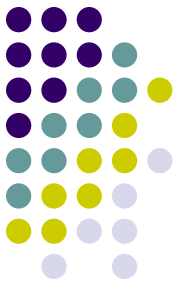
Polyp



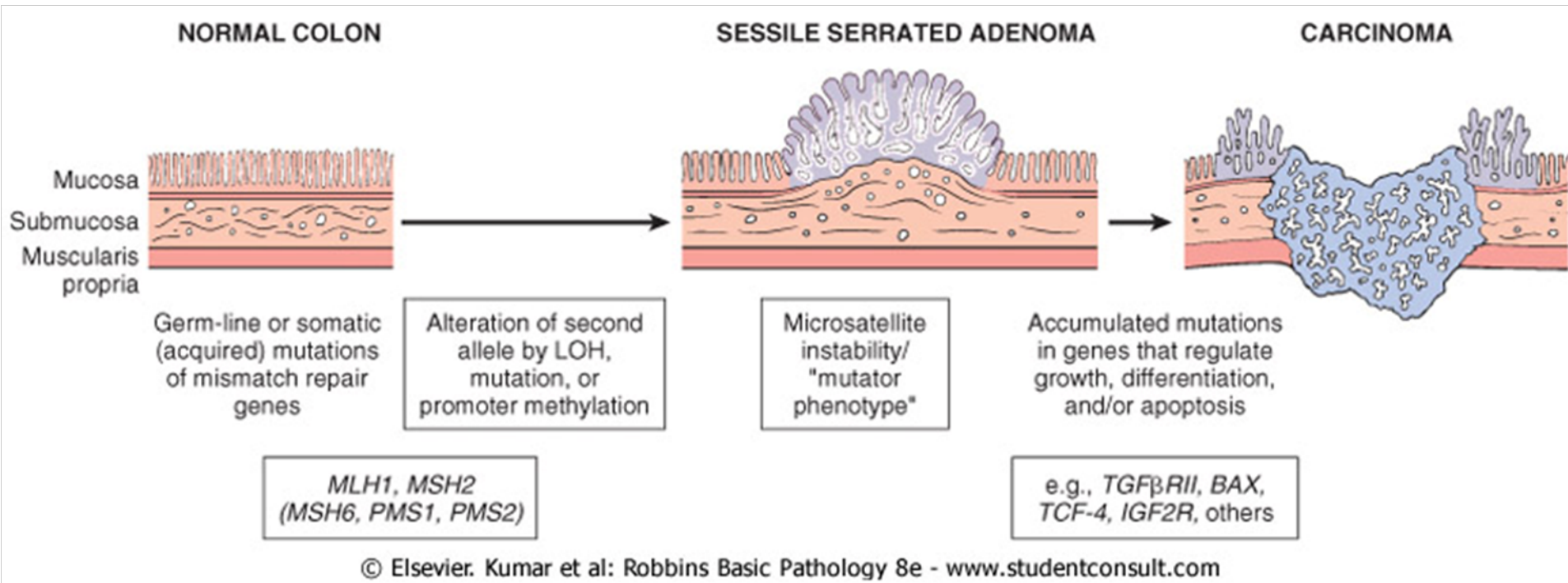
Cancer



Carcinogenesis

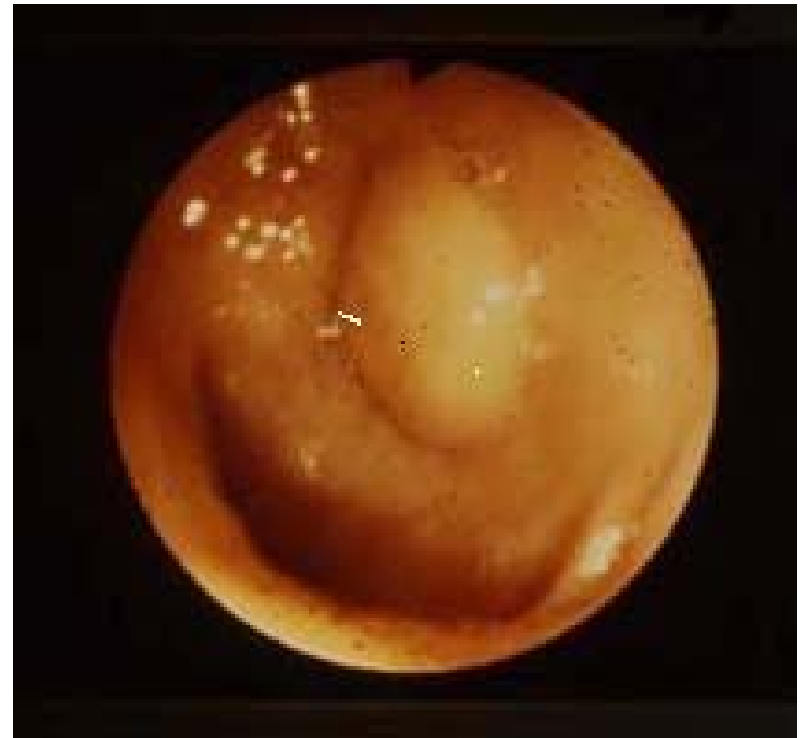


- mismatch repair (microsatellite instability) pathway



Symptoms of Colorectal Cancer

- Early colon cancer usually presents with no symptoms. Symptoms appear with more advanced disease.
- Symptoms include:
 - a change in bowel habits (diarrhea, constipation, or narrowing of the stool for more than a few days)
 - a constant urgency of needing to have a bowel movement
 - bleeding from the rectum or blood in the stool (the stool often looks normal)
 - cramping or steady stomach pain
 - weakness and fatigue or anemia
 - unexplained weight loss



A polyp as seen during colonoscopy

What Are the Risk Factors for Colorectal Cancer?

- Polyps (a noncancerous or precancerous growth associated with aging)
- Age
- Inflammatory bowel disease (IBD)
- Diet high in saturated fats, such as red meat
- Personal or family history of cancer
- Obesity
- Smoking
- Other

Risk Factors

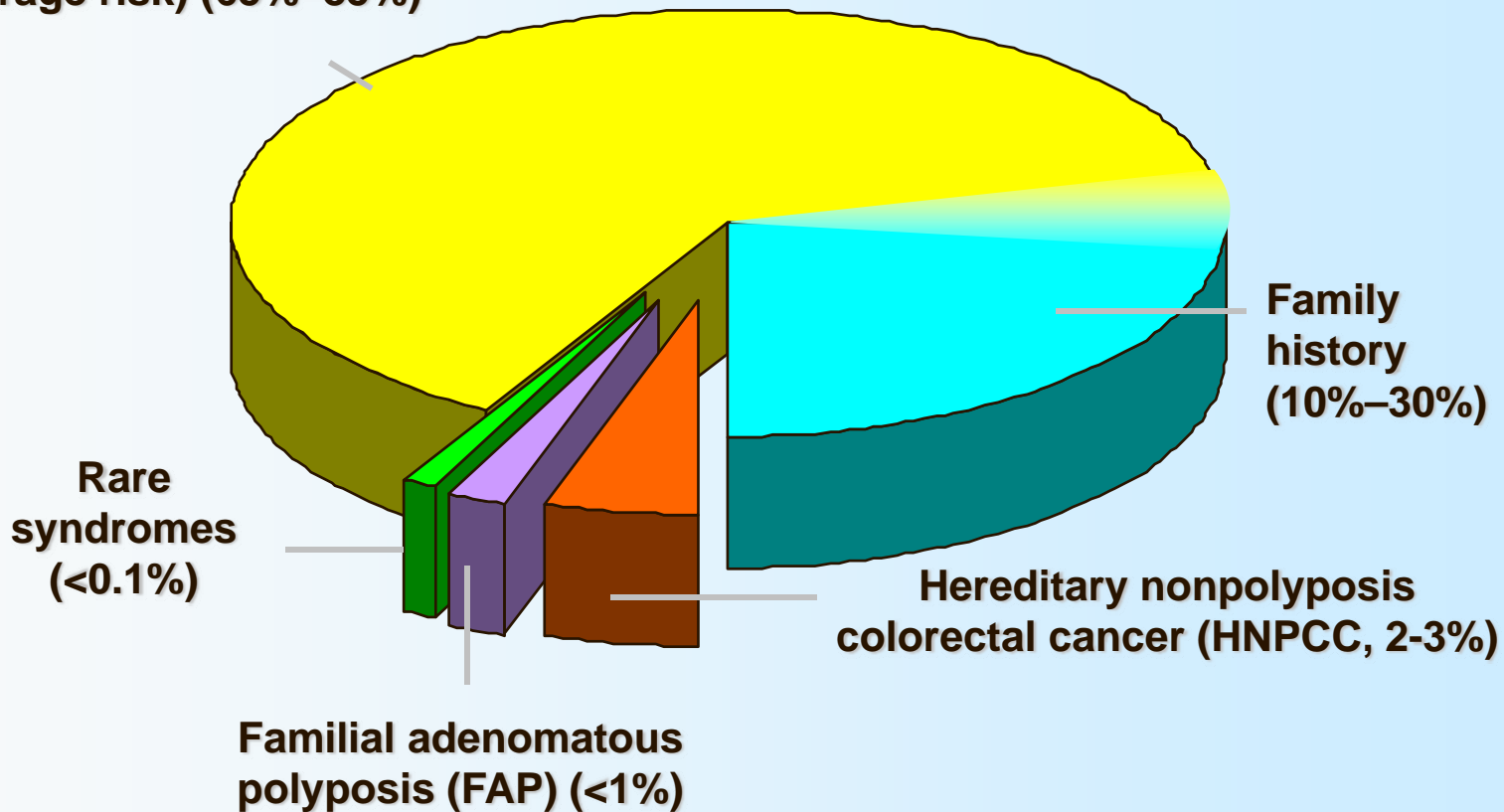
| Risk Factor | Description |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Age | 9 out of 10 cases are over 50 years old |
| History of polyps | ↑ risk if large size, high frequency, or specific types |
| History of bowel disease | Ulcerative colitis and Crohn's disease (IBDs) ↑ risk |
| Certain hereditary family syndromes | Having a family history of familial adenomatous polyposis or hereditary nonpolyposis colon cancer (Lynch Syndrome) ↑ risk |
| Family history (excluding syndromes) | Close relatives with colon cancer ↑ risk esp. if before 60 years (degree of relatedness and # of affected relatives is important) |
| Other cancers and their treatments | Testicular cancer survivors ↑ risk |
| Race | African Americans are at ↑ risk |
| Ethnic background | Ashkenazi Jew descent ↑ risk due to specific genetic factors |

Risk Factors (cont'd)

| Risk Factor | Description |
|-------------------------|-----------------------------------------------------------------------------------|
| Diet | High in fat, especially animal fat, red meats and processed meats ↑ risk |
| Lack of exercise | ↑ risk |
| Overweight | ↑ risk of incidence and death |
| Smoking | -↑ risk of incidence and death -30-40% more likely to die of colorectal cancer |
| Alcohol | Heavy use of alcohol ↑ risk |
| Diabetes | 30% ↑ risk of incidence and ↑ death rate |
| Night shift work | More research is needed but over time may ↑ risk |

Colorectal Cancer Cases by Risk History

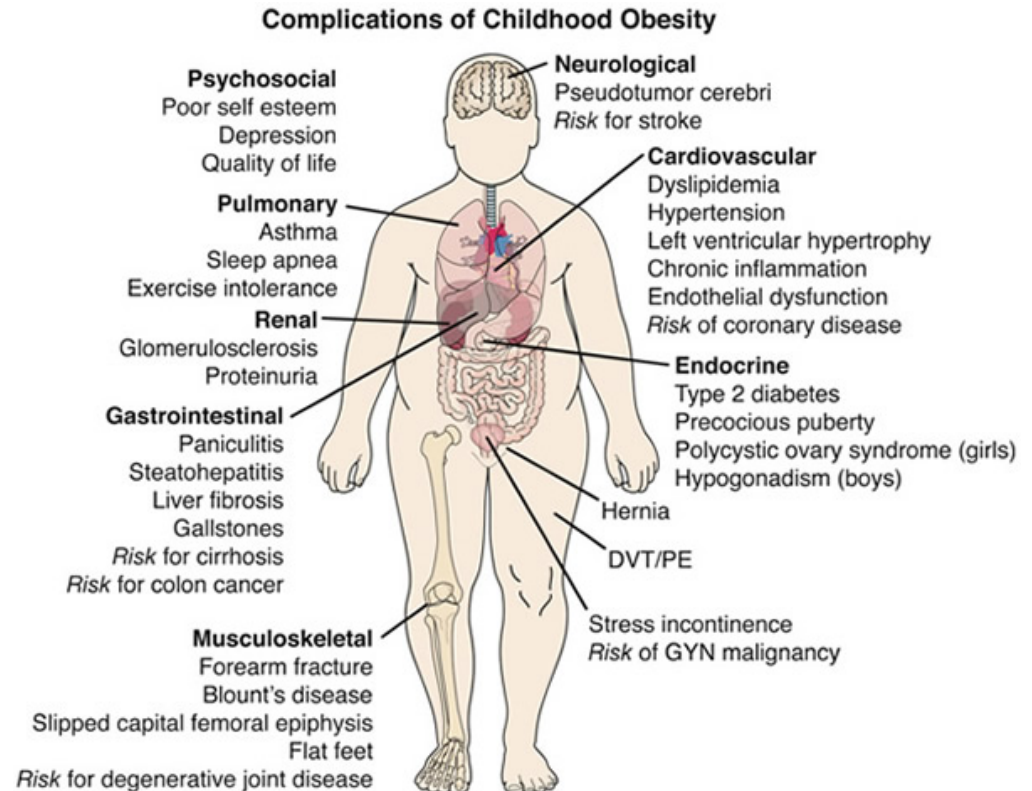
**Sporadic
(average risk) (65%–85%)**



Risk Factors-Inactivity and Obesity

- **Physical activity and obesity:**

- Obese women have a 1.5-fold ↑ risk
- ↑ trend in risk with ↑ hip-to-waist ratio
- Physical Inactivity leads to obesity and an ↑ risk of colorectal cancer
- Physical activity is also believed to benefit bowel transit time, immune system, serum cholesterol, and bile acid metabolism
- Individuals with higher, more efficient metabolism may be at a ↓ risk



Risk Factors-Smoking

<http://www.chinadaily.com.cn/world/images/attachement/jpg/site1/20080403/0013729e4abe095e606c22.jpg>

- **Smoking:**

- 12% colorectal cases are attributed to smoking
- Long term heavy smokers have a 2-3 fold ↑ in colorectal adenomas
- There is a greater frequency of adenomatous polyps in former smokers even after 10 years of smoking cessation
- Incidence of colorectal cancer occurs at a younger age

- Potential biological mechanisms:**

- Carcinogens ↑ cancer growth in colon and rectum. Could reach colorectal mucosa through alimentary tract or circulatory system and then damage or alter expression of cancer-related genes
- no p53 over expression in heavy cigarette smokers (p53 is a tumor suppressor gene that plays a central role in the DNA damage response)



an adenomatous polyp

http://www2.medford.k12.wi.us:8400/guidance/Flu%20Vaccine%20and%20Children_files/levi-1214.gif

Risk Factors-Alcohol

- Alcohol:**

-regular drinking \Rightarrow 2 fold \uparrow risk in colorectal cancer

-Diagnosis at younger age

-Evidence to suggest increase in risk may be attributed to p53:

-heavy beer consumption associated with p53 over expression in early colorectal neoplasia

-p53 over expression correlated with p53 gene mutations

-p53 over expression \uparrow from adenomatous polyps \Rightarrow carcinoma in situ \Rightarrow intramucosal carcinoma

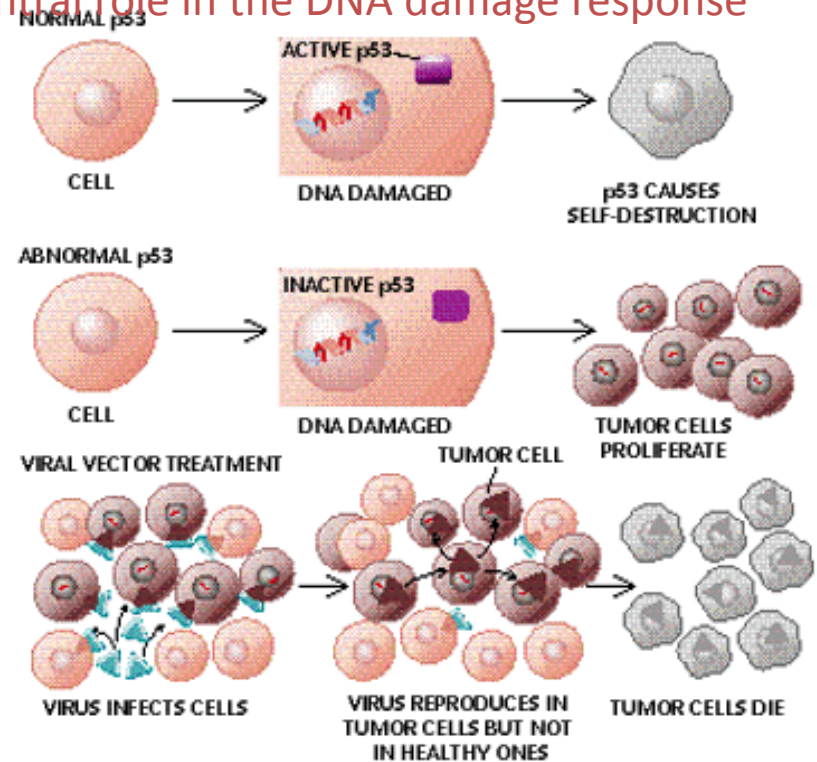
-p53 over expression associated with worse overall survival after diagnosis, more likely found in polyps in distal colon and rectum

p53 is a tumor suppressor gene that plays a central role in the DNA damage response



an example of a standard drink

<http://d.yimg.com/origin1.lifestyles.yahoo.com/ls/he/healthwise/alcohol.jpg>

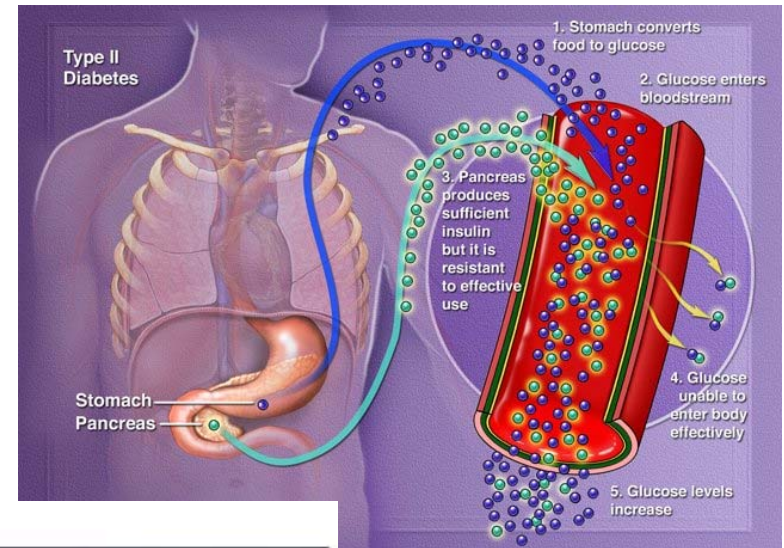


<http://www.wellesley.edu/Chemistry/chem227/nucleicfunction/cancer/adeno-p53.gif>

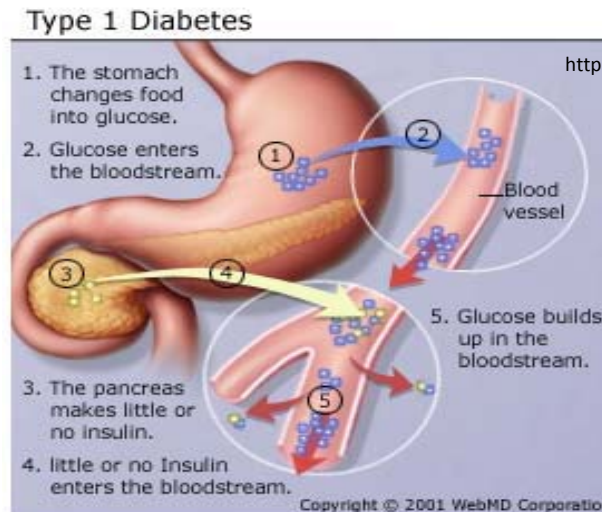
Risk Factors-Diabetes, Insulin, Insulin-like growth factor (IGF-1)

- **Diabetes, Insulin, and Insulin-like growth factor:**

- Links to \uparrow risk of colorectal cancer:
 - Elevated circulating IGF-1 (Insulin-like growth factor)
 - Insulin resistance and associated complications: elevated fasting plasma insulin, glucose, and free fatty acids, glucose intolerance, \uparrow BMI, visceral adiposity
 - Elevated plasma glucose and diabetes
- Insulin and IGFs stimulate proliferation of colorectal cells
- Elevated insulin and glucose associated with \uparrow adenoma risk and \downarrow apoptosis (cell death) in normal rectal mucosa



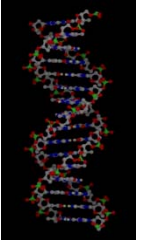
http://www.soylabs.com/img/diabetes_type2.jpg



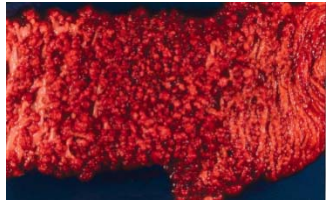
<http://www.scubasewj.com/wp-content/uploads/2006/12/Type%201%20Diabetes.jpg>

Risk factors – Hereditary Family Syndromes

- The development of colorectal cancer is a multi-step process involving genetic mutations in the mucosal cells, activation of tumor promoting genes, and the loss of genes that suppress tumor formation
 - *Tumor suppressor genes* constitute the most important class of genes responsible for hereditary cancer syndromes
 - Familial Adenomatous Polyposis (FAP): A syndrome attributed to a tumor suppressor gene called Adenomatous Polyposis Coli (APC)
 - Increased risk of colon and intestinal cancers
 - *Tumor suppressor genes* are normal genes that slow down cell division, repair DNA mistakes, and promote apoptosis (programmed cell death). Defects in tumor suppressor genes cause cells to grow out of control which can then lead to cancer



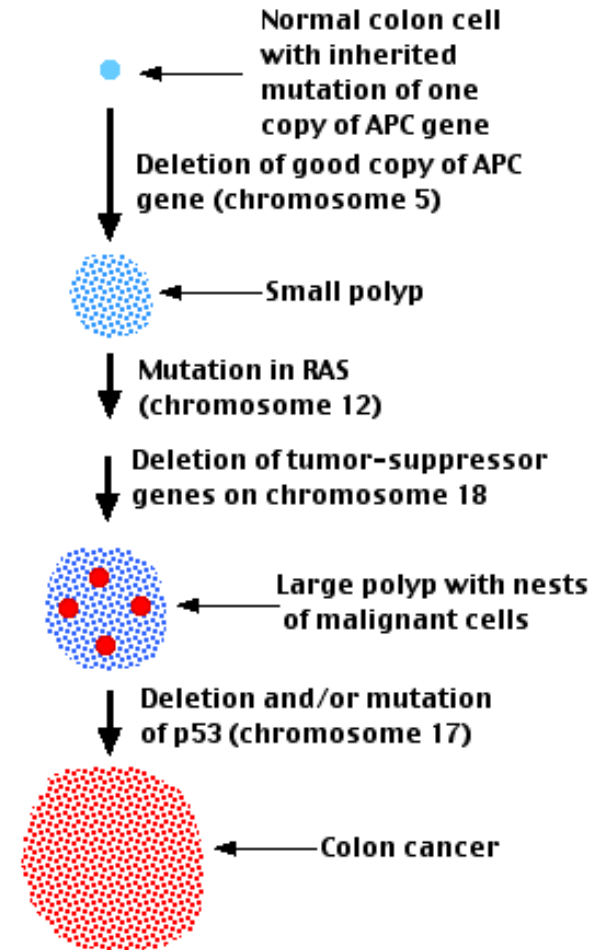
Familial Adenomatous Polyposis (FAP)



<http://www.nature.com/modpathol/journal/v16/n4/images/3880773f1.jpg>

■ FAP:

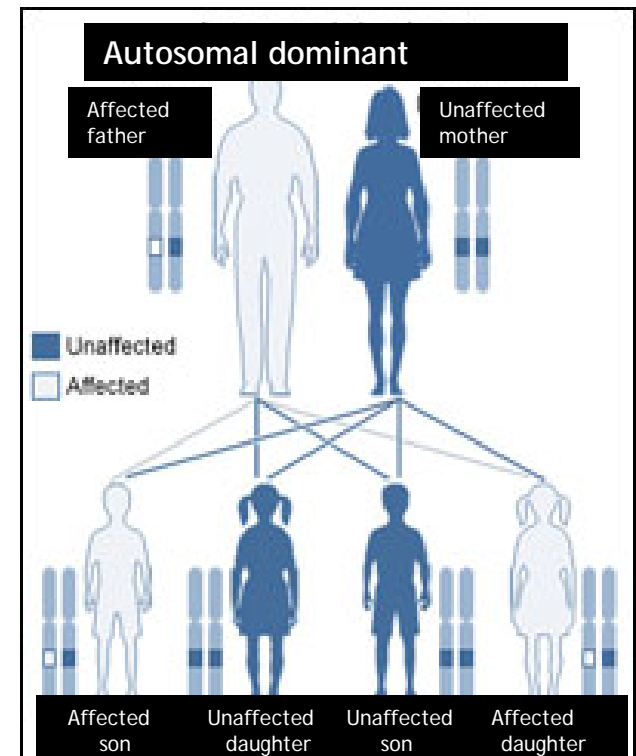
- Multiple colonic polyps
- Patients with an APC mutation have a 100% lifetime risk of colorectal cancer if patient fails to undergo total colectomy
- Adenomas (>100) occur in: colon, small bowel & stomach
- Cancer onset ~39 years
- Screening recommendations:
 - DNA testing for APC gene mutation
 - Annual colonoscopy starting 10-12 yrs old until 15-20 yrs
 - Upper endoscopy (scope through mouth to examine the esophagus, stomach and the first part of the small intestine, the duodenum). Frequency of 1-3/year when colonic polyps are detected
 - Older than 20 years annual upper endoscopy and colonoscopy needed



<http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/ColonCancer.png>

Lynch Syndrome (also known as HNPCC)

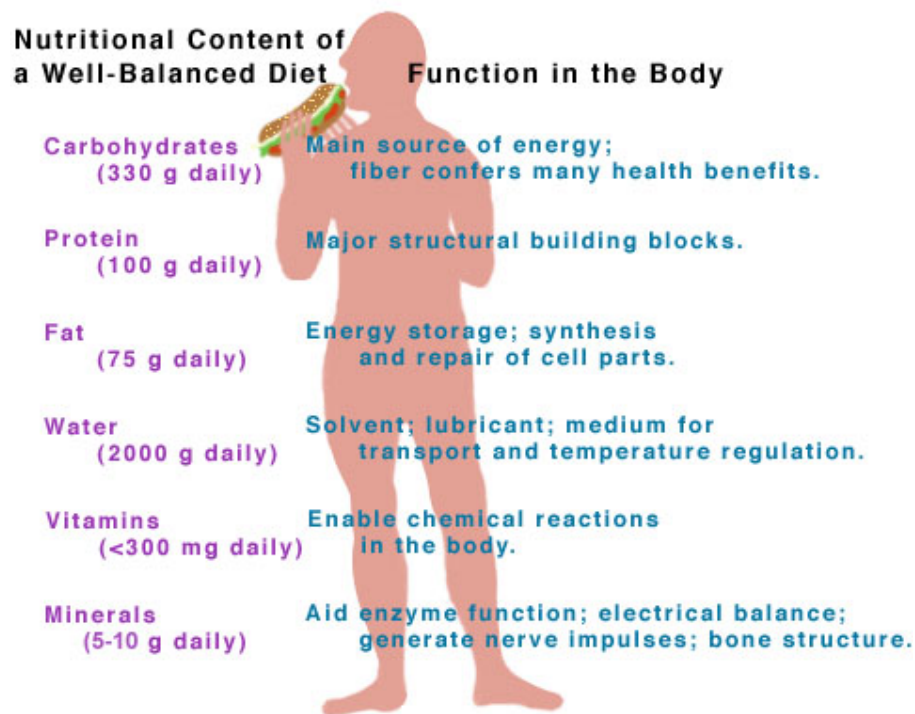
- **Lynch syndrome:**
- Also known as hereditary nonpolyposis colorectal cancer (HNPCC)
- A rare inherited condition that increases risk of colon cancer and other cancers
- 2-3% colon cancers attributed to Lynch Syndrome
- Increase risk for malignancy of: endometrial carcinoma (60%), ovary (15%), stomach, small bowel, hepatobiliary tract, pancreas, upper uro-epithelial tract, and brain
- Caused by autosomal dominant inheritance pattern (if one parent carries a gene mutation for Lynch syndrome, then 50% chance mutation passed to child)
- Cancer occurs at younger age <45 years
- Accelerated carcinogenesis: a small adenoma may develop into a carcinoma with in 2-3 yrs as opposed to ~10 yrs in general population
- Screening:
 - Colonoscopy every other year starting in 20s, and every year once reach 30s
- Education and genetic counseling recommended at 21 years



<http://media.npr.org/programs/atc/features/2006/dec/pgd/dom200.jpg>

Summary: Risk Reduction Factors

- Risk Reduction Factors
 - General
 - Diet
 - Vitamins and minerals
 - NSAIDS



Factors that may reduce risk

| Method | Description |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Screening | Regular screening can prevent colon cancer completely (it usually takes 10-15 years from the time of the first abnormal cells until cancer develops). Screening can detect polyps and remove before cancerous, or early detection with a better prognosis. |
| Diet and Exercise | Fruits, vegetables, whole grains, minimal high-fat foods and 30-60 minutes of exercise 5 times per week help ↓ risk |
| Vitamins, calcium w/D, magnesium | Aid in ↓ risk |
| NSAIDs (Non-steroidal anti-inflammatory drugs) | 20-50% ↓ risk of colorectal cancer and adenomatous polyps; however, NSAIDs can cause serious or life threatening implications on the GI tract and other organs |
| Female Hormones | HRT (hormone replacement therapy) may ↓ risk esp. amongst long term users, but if cancer develops, it may be more aggressive. HRT ↓ risk of osteoporosis, but may ↑ risk heart disease, blood clots, breast and uterine cancers |

Risk reduction - Diet

Fiber:

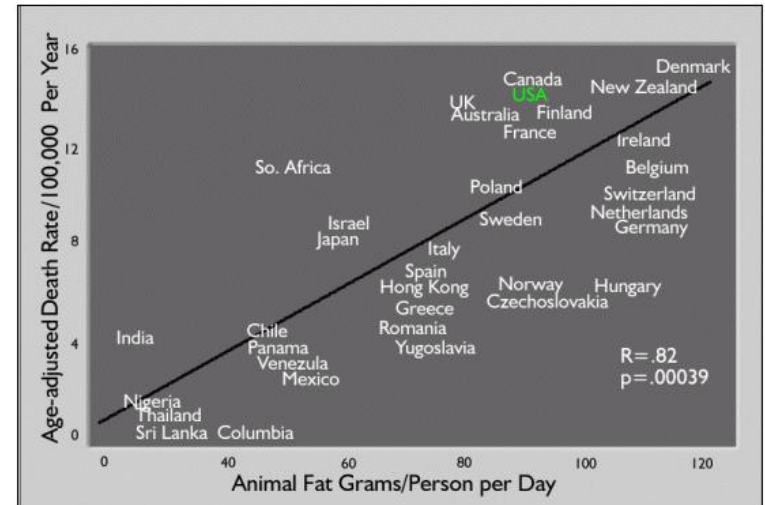
- Need ~20-35 g/day
- ↑ daily intake ⇒ ↑ fecal bulk and ↓ transit time
- Insoluble fiber-non-degradable constituents (cereal)
- Studies show no protection against colorectal cancer from cereal fibers
- Soluble fiber-degradable constituents (fruits and vegetables)
- Studies found protective effect from fibers from fruits and vegetables

Fat:

- ↓ fat (30% or less of total daily calories)

Meat:

- Substitute meats with ↑ fat for chicken and fish
- ↑ risk w/daily ↑ of 100g of all meat or red meat
- ↑ risk w/daily ↑ of 25g processed meat
- ↑ intake of carcinogenic compounds produced when meat is well cooked at high temperatures ⇒ ↑ risk of adenomas



<http://www.diseaseproof.com/Animal%20Fat%20vs%20Intestinal%20Cancer.jpg>

Cruciferous vegetables:

- Broccoli, cauliflower, cabbage, brussel sprouts, bok choy and kale
- Inverse association with colorectal cancer risk

Risk reduction– Vitamins & Minerals

There is evidence to suggest that the following are potentially beneficial at reducing risk:

Calcium

Vitamin E

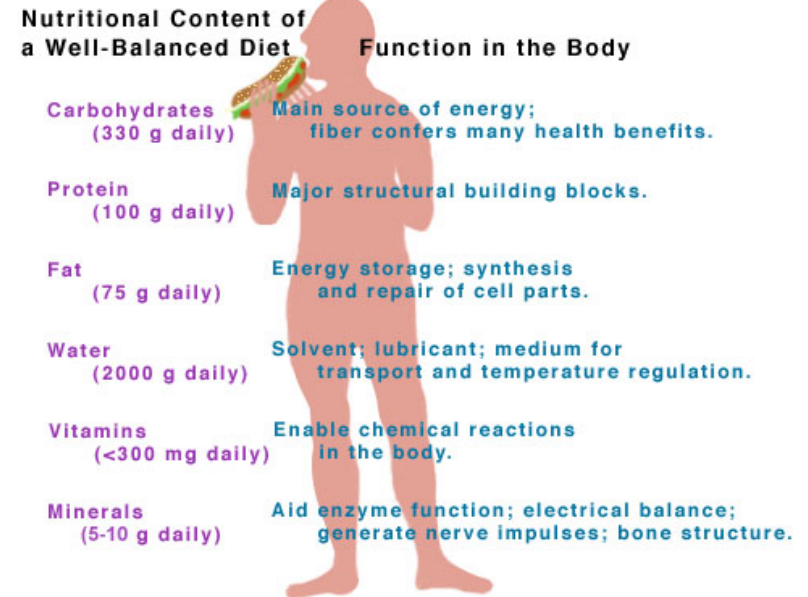
Selenium

β-carotene

Lactobacilli

Folate

- Folate is an essential cofactor needed in DNA synthesis, stability, integrity, and repair
- Folate helps ↓ risk colon cancer (not rectal)
- Smokers may benefit from a higher daily intake of folate (smoking interferes with folate utilization and/or metabolism)
- Folate deficiency is implicated in carcinogenesis, particularly in rapidly proliferative tissues, such as the colorectal mucosa



Risk reduction-NSAIDs

- Prospects for chemoprevention (a reduced risk of developing colorectal cancer and/or preventing polyp occurrence): Vitamins A, C, D, E, β -carotene, calcium, folate, anti-inflammatories (NSAIDs, non-steroidal anti-inflammatory drugs), and H2 antagonists (COX-2 inhibitors).

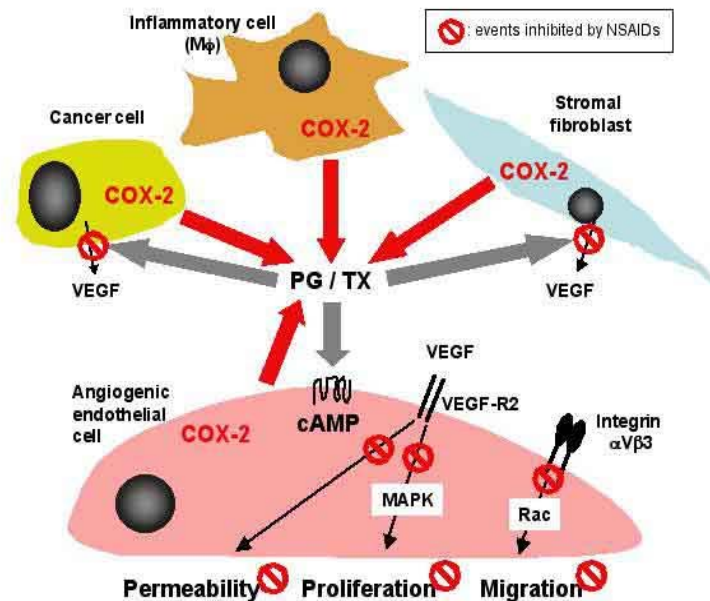
■ Evidence that NSAIDs and COX-2 inhibitors are most useful

■ NSAID use:

- Appears to prevent or reduce frequency of carcinogen-induced animal colonic tumors
- NSAIDs appear to reduce growth rates in colon cancer cell lines
- NSAIDs have adverse effects on: kidney, skin, lung, liver, gastrointestinal bleeding, peptic ulcers
- The dose and duration of treatment is related to its beneficial effects

■ COX-2 Inhibitors:

- Are useful because COX-2 levels are \uparrow in inflamed tissues



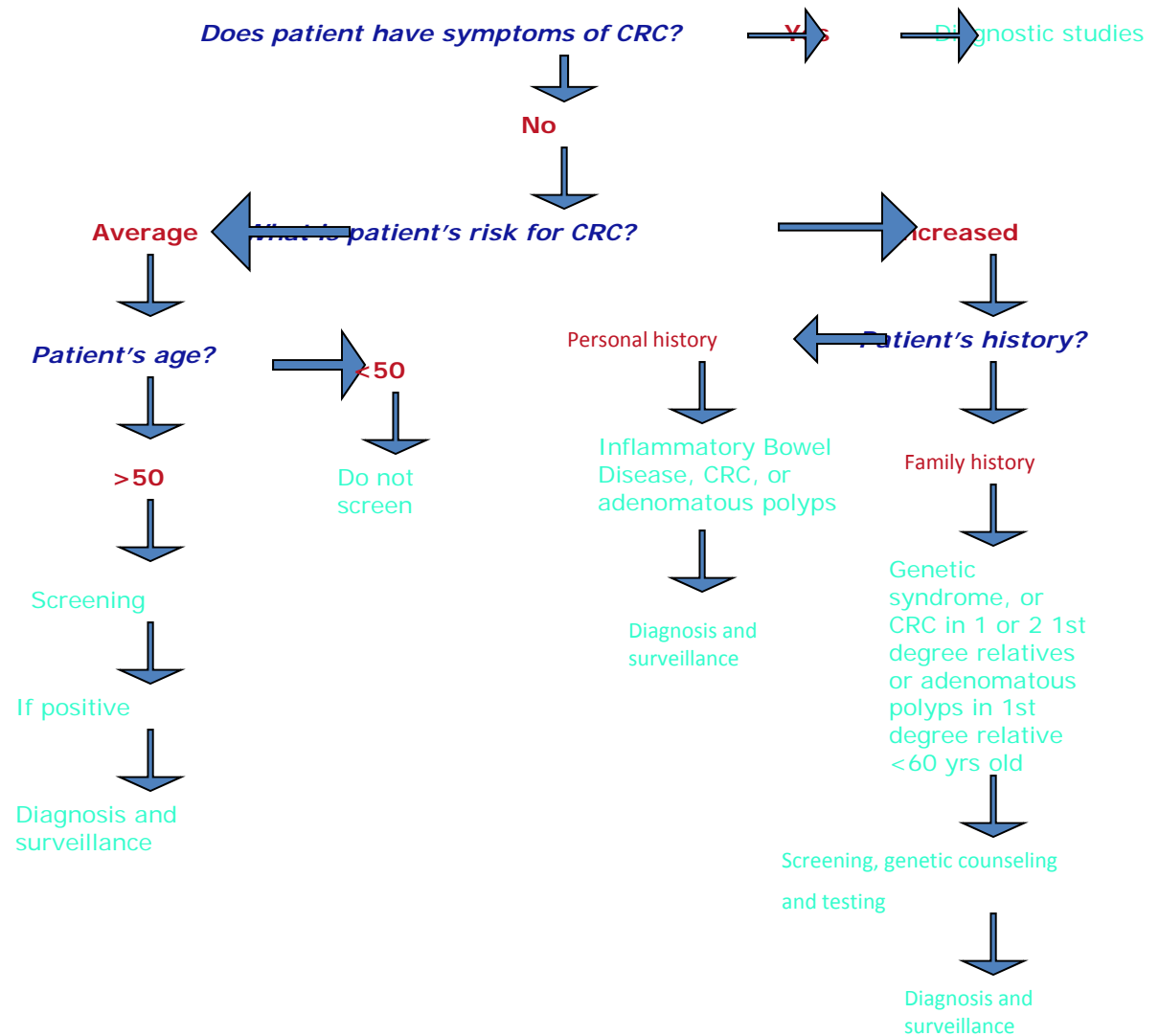
Screening Methods for Colorectal Cancer

- Colonoscopy (currently the best way to prevent and detect colorectal cancer)
- Virtual colonography
- Sigmoidoscopy
- Fecal occult blood test
- Double contrast barium enema
- Digital rectal examination

Screening

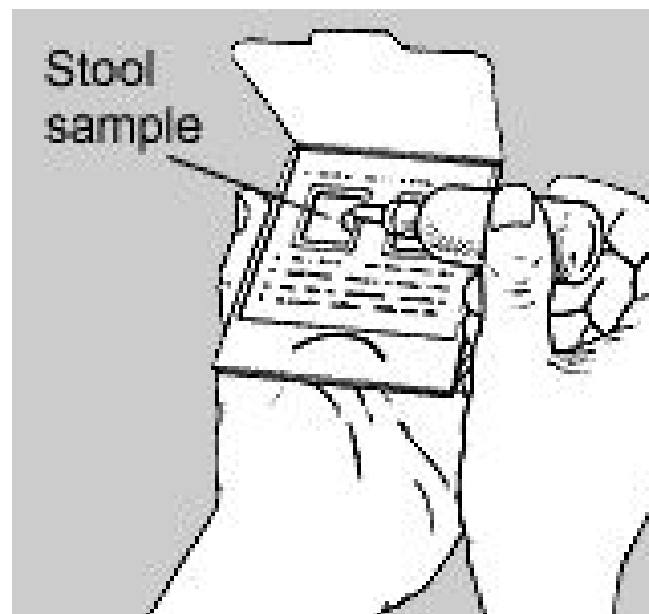
- Medical History and Physical Exam:**

A history (symptoms and risk factors) and DRE (digital rectal exam) is performed for patients thought to have colon cancer. An abdominal exam is performed to feel for masses or enlarged organs.



Screening Options: Fecal Occult Blood Test

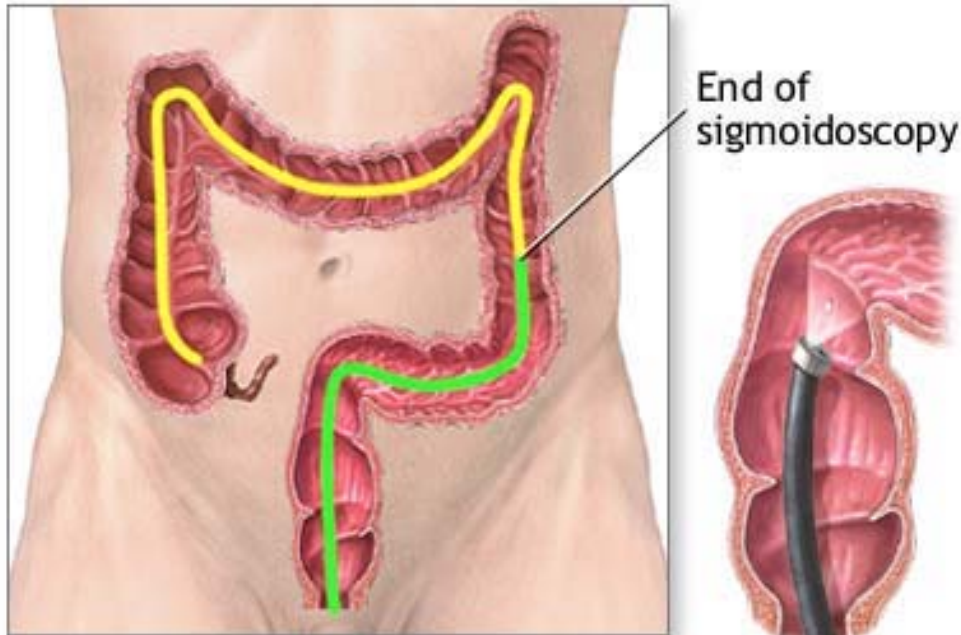
- **Stool Blood Test (FOBT or FIT):** Used to find small amounts of blood in the stool. If found further testing should be done.



<http://digestive.niddk.nih.gov/ddiseases/pubs/dictionary/pages/images/fobt.gif>

<http://www.owenmed.com/hemocult.jpg>

Screening: Flexible Sigmoidoscopy



Colonoscopy examines the entire length of the colon; sigmoidoscopy examines only the lower third

ADAM.

<http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/1083.jpg>

- **Flexible Sigmoidoscopy:** A sigmoidoscope, a slender, lighted tube the thickness of a finger, is placed into lower part of colon through rectum
- It allows physician to look at inside of rectum and lower third of colon for cancer or polyps
- Is uncomfortable but not painful. Preparation consists of an enema to clean out lower colon
- If small polyp found then will be removed. If adenoma polyp or cancer found, then colonoscopy will be done to look at the entire colon

Screening: Barium Enema

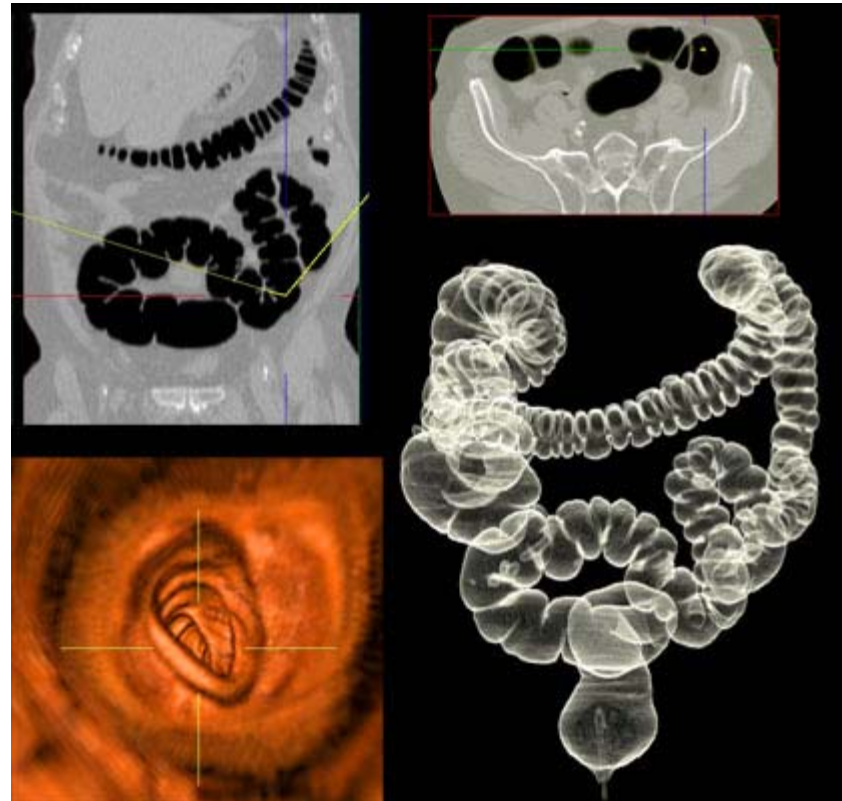


- **Barium enema with air contrast:**
A chalky substance is used to partially fill and open up the colon
- Air is then pumped in which causes the colon to expand and allows clear x-rays to be taken
- If an area looks abnormal then a colonoscopy will be done

A cancer of the ascending colon. Tumor appears as oval shadow at left over right pelvic bone

Screening: Virtual Colonoscopy

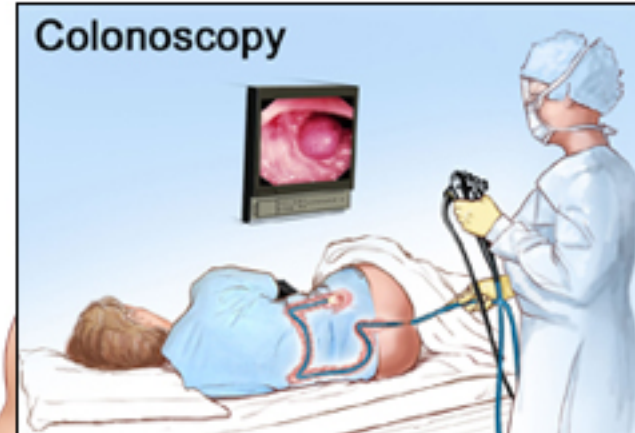
- **Virtual Colonoscopy:** Air is pumped into the colon in order for it to expand followed by a CT scan which takes hundreds of images of the lower abdomen
- Bowel prep is needed but procedure is completely non-invasive and no sedation is needed
- Is not recommended by ACS or other medical organizations for early detection. More studies need to be done to determine its effectiveness in regard to early detection
- Is not recommended if you have a history of colorectal cancer, Chron's disease, or ulcerative colitis
- If abnormalities found then follow-up with colonoscopy



Screening: Colonoscopy



- **Colonoscopy:** A colonoscope, a long, flexible, lighted tube about the thickness of a finger, is inserted through the rectum up into the colon
- Allows physician to see the entire colon
- Bowel prep of strong laxatives to clean out colon, and the day of the procedure an enema will be given
- Procedure lasts ~15-30 minutes and are under mild sedation
- Early cancers can be removed by colonoscope during colonoscopy

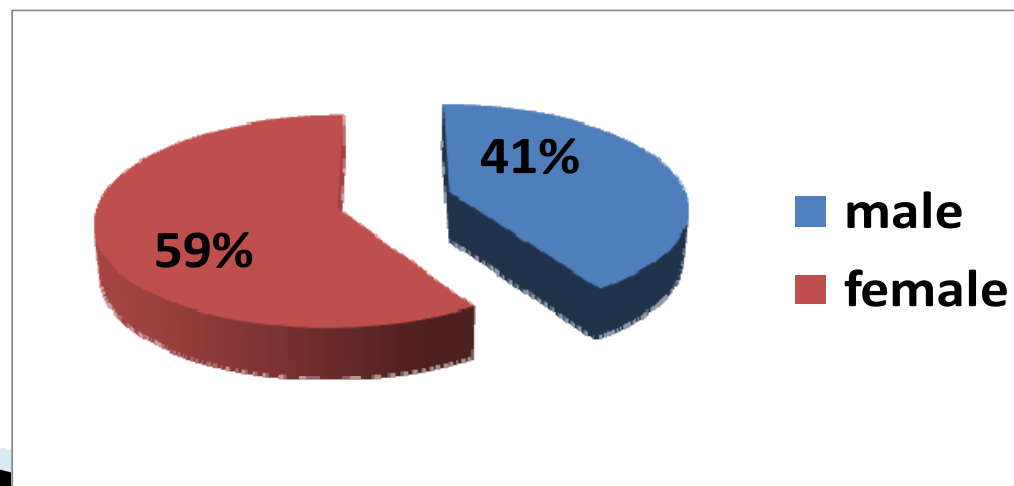


Colorectal cancer in Mauritius

Cancer incidence for 2010-2012

Mauritius

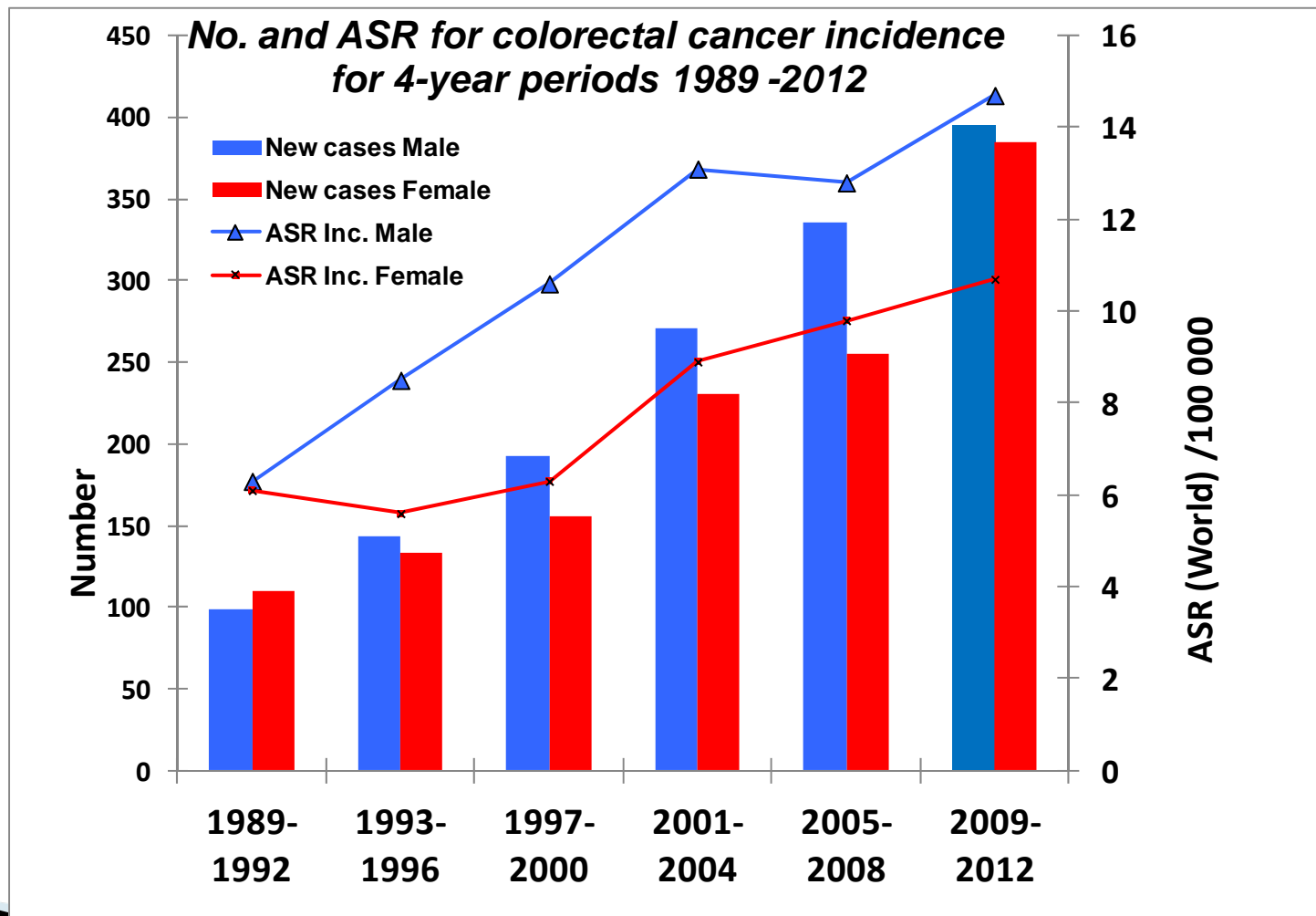
| | Males | Females |
|----------------------|-------|---------|
| Number | 2348 | 3345 |
| Percentage | 41% | 59% |
| Crude incidence rate | 112.8 | 168.2 |
| ASR W | 117.9 | 137.5 |



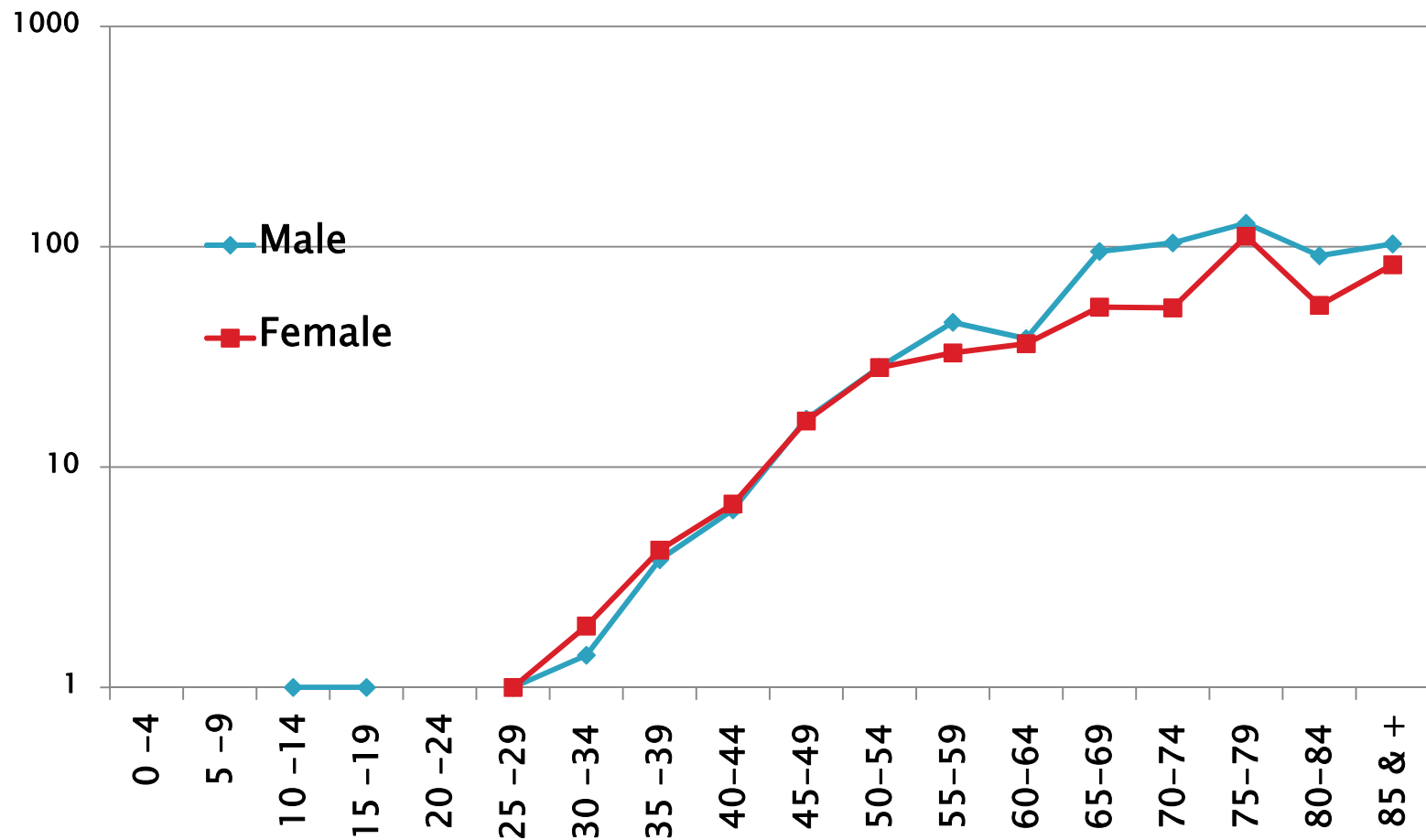
Trends in colorectal cancer incidence, 1989-2012

Colorectal cancer incidence trends

Mauritius 1989-2012

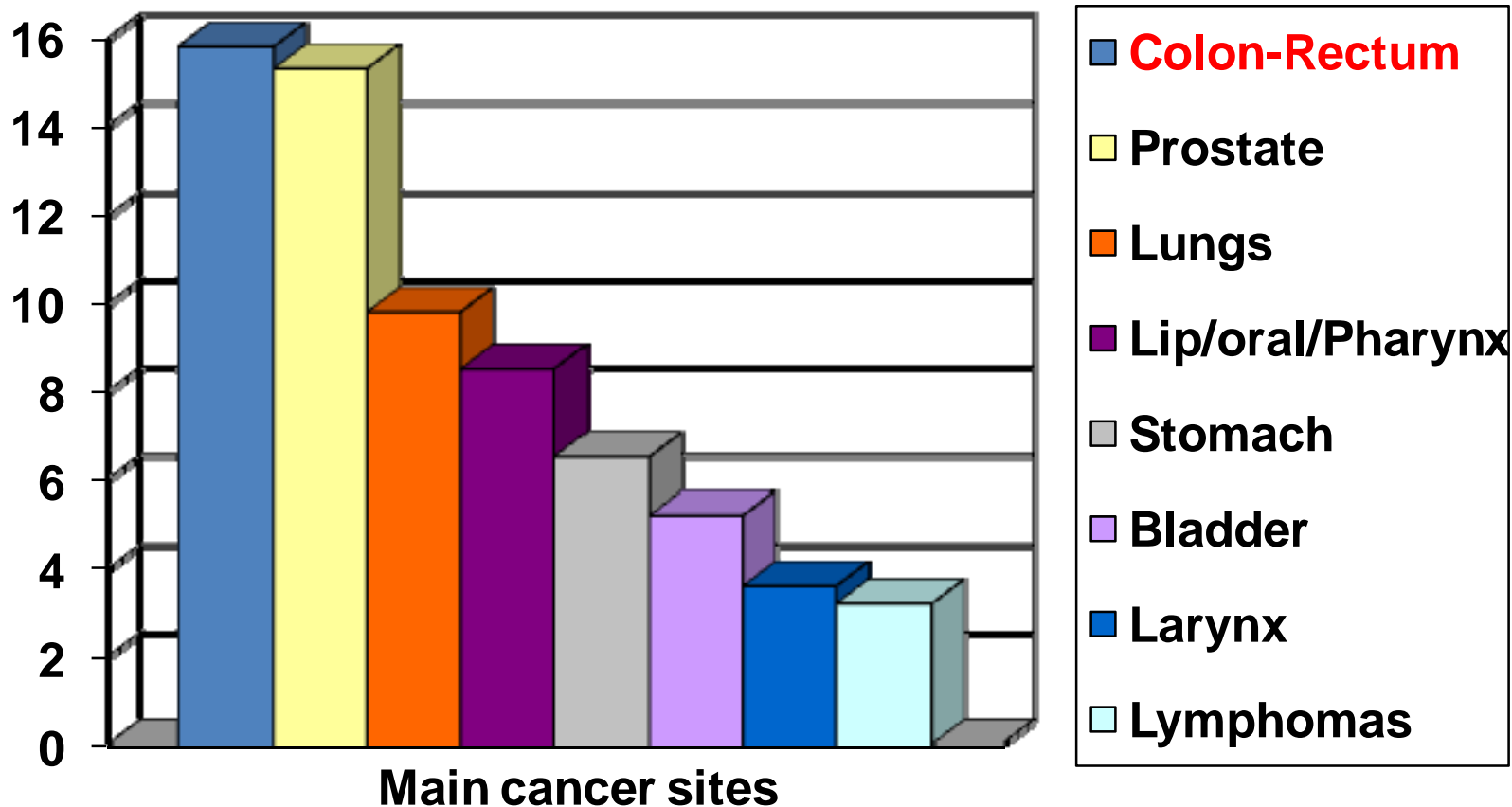


Age-specific incidence rates for colorectal cancer in males & females Mauritius 2009–2012 (source : NCR)



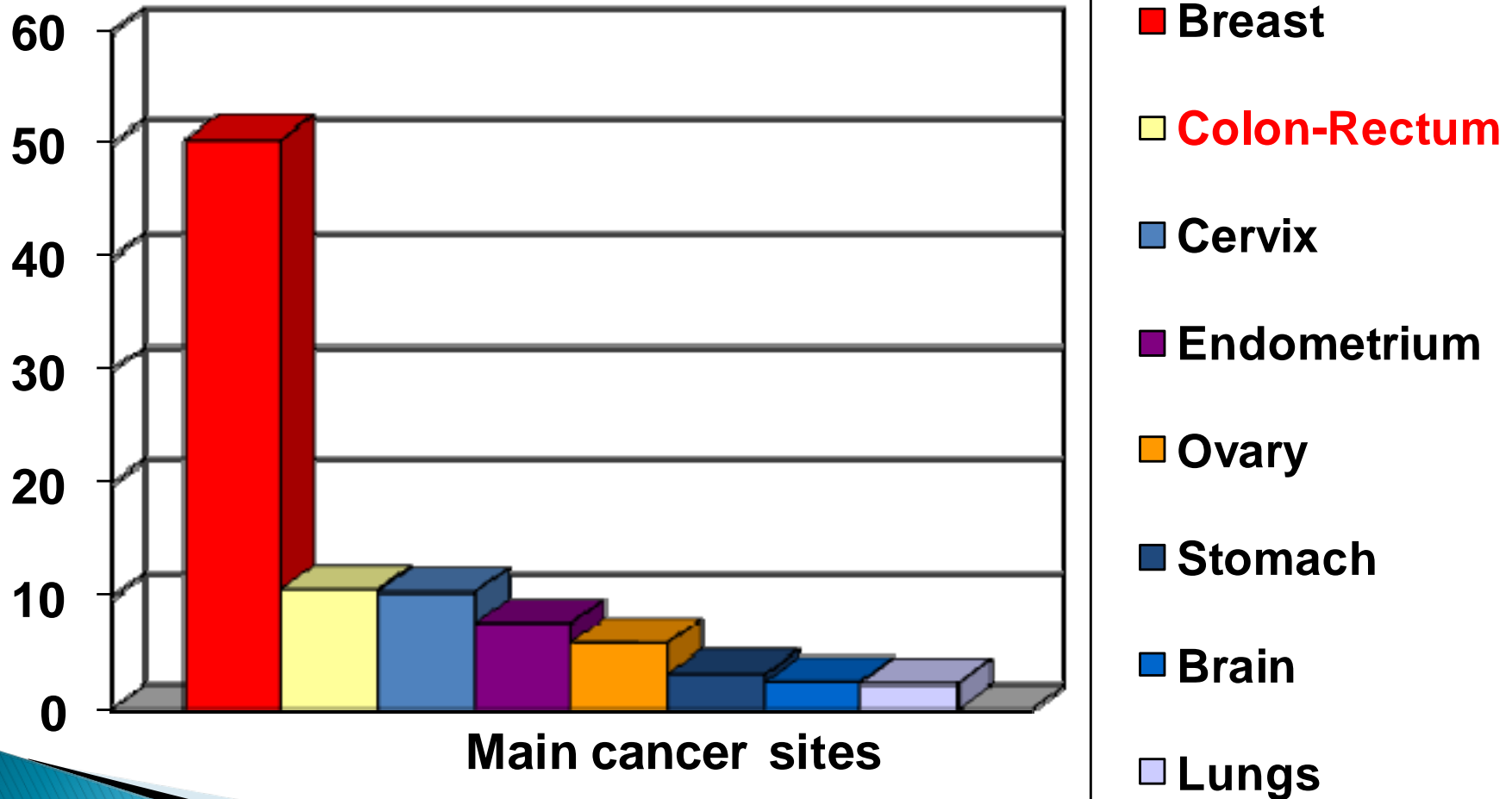
Main sites of cancer in males

ASRW Mauritius 2010 -2012

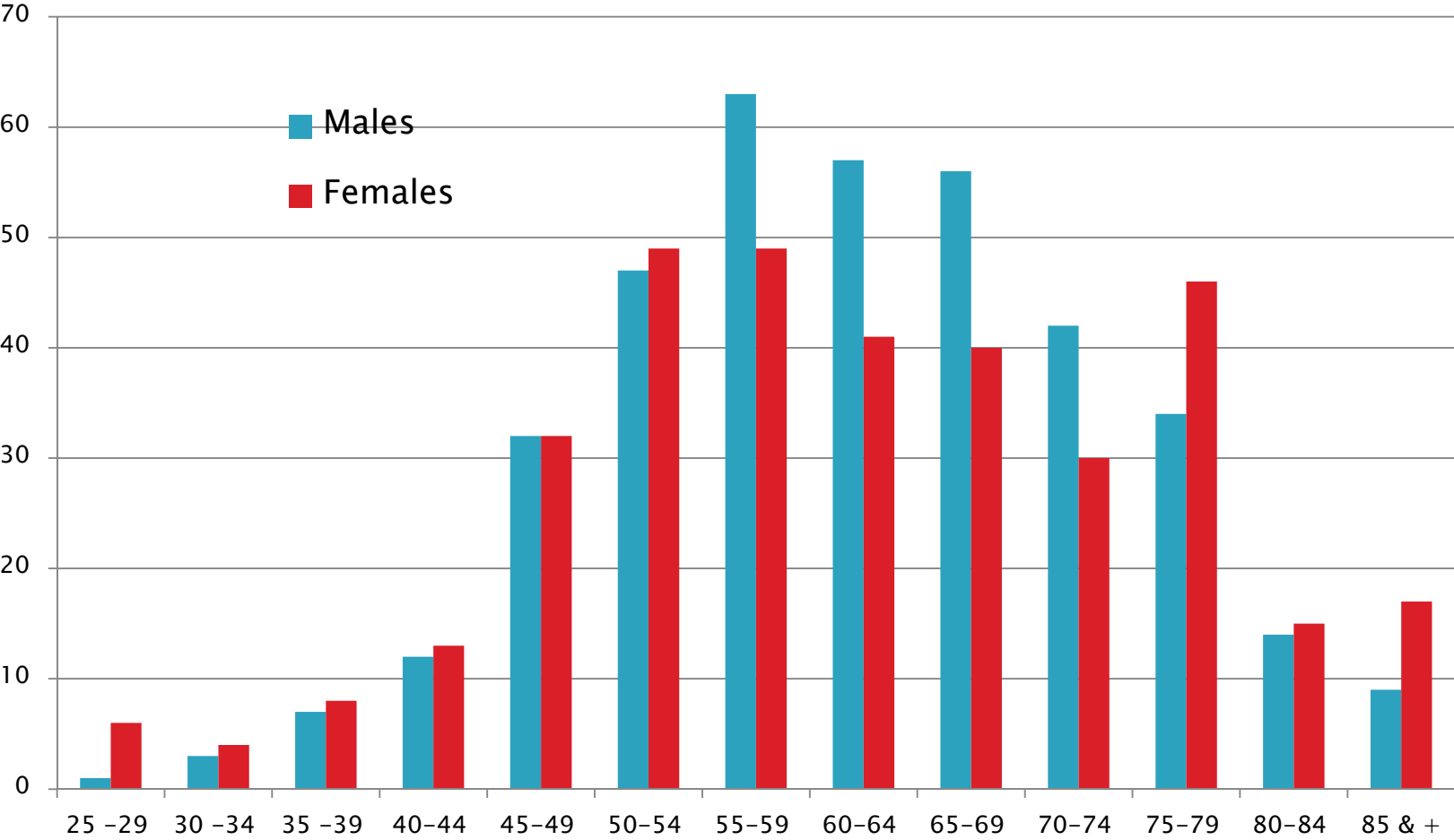


Main sites of cancer in females

ASRW Mauritius 2010 -2012



Distribution of new cases of colorectal cancer by age-groups & by gender; Mauritius 2009-2012 (source : NCR)



SSRNH ENDOSCOPIES

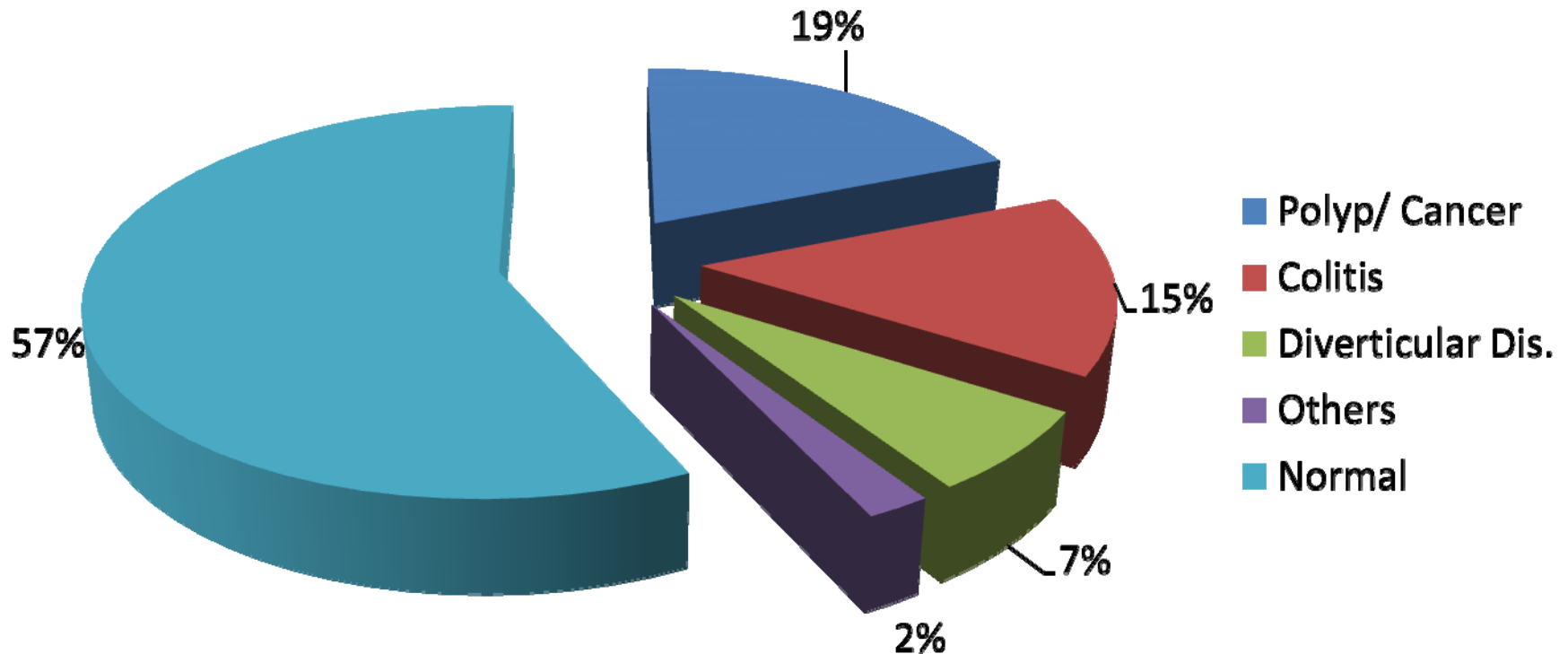
8045 Cases

Gastroscopy
6188

Colonoscopy
1427

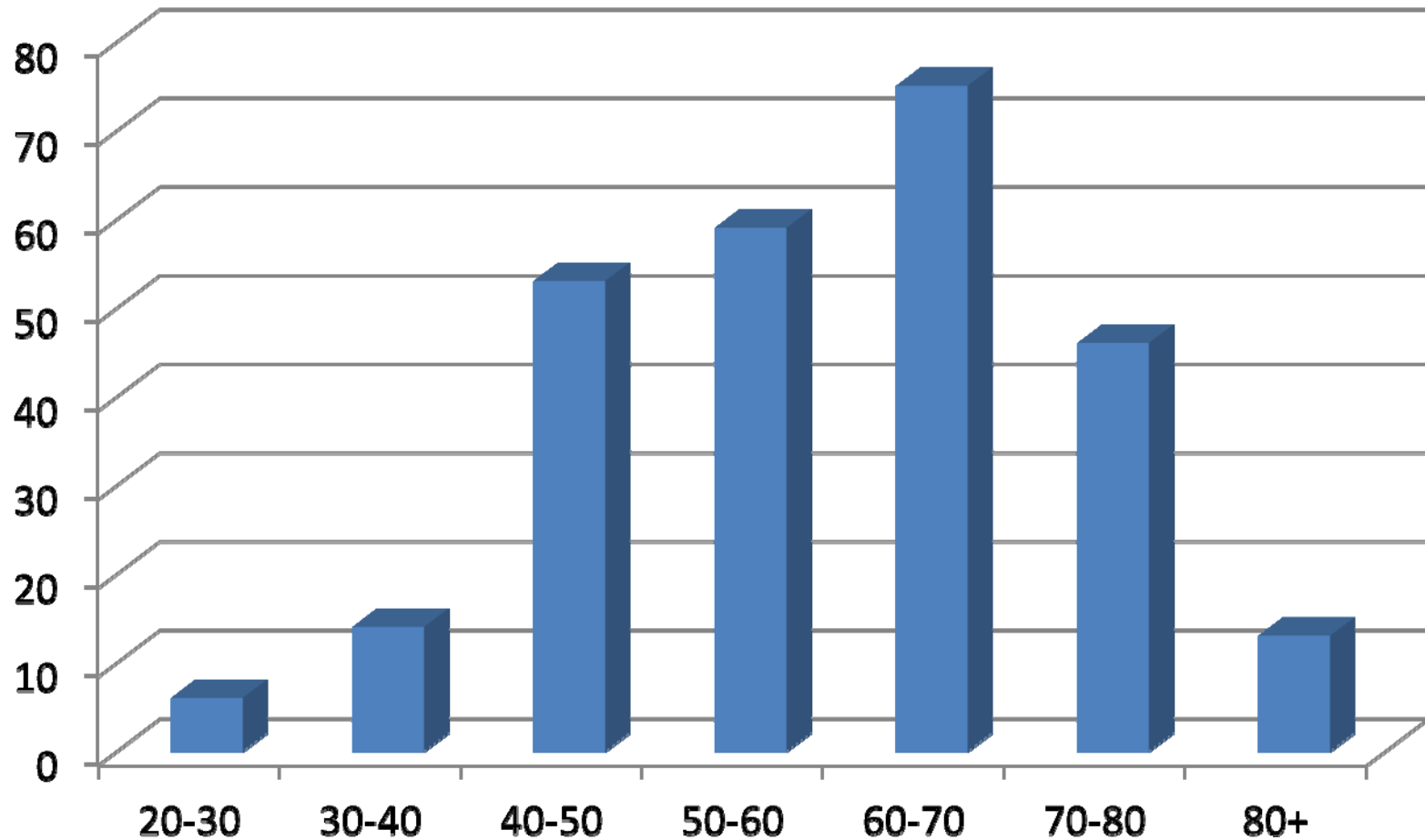
ERCP
430

Colonoscopy 1427





Polyps/Cancer (266)



SSRNH GI Endoscopy Unit



Colon Cancer Screening

No of People

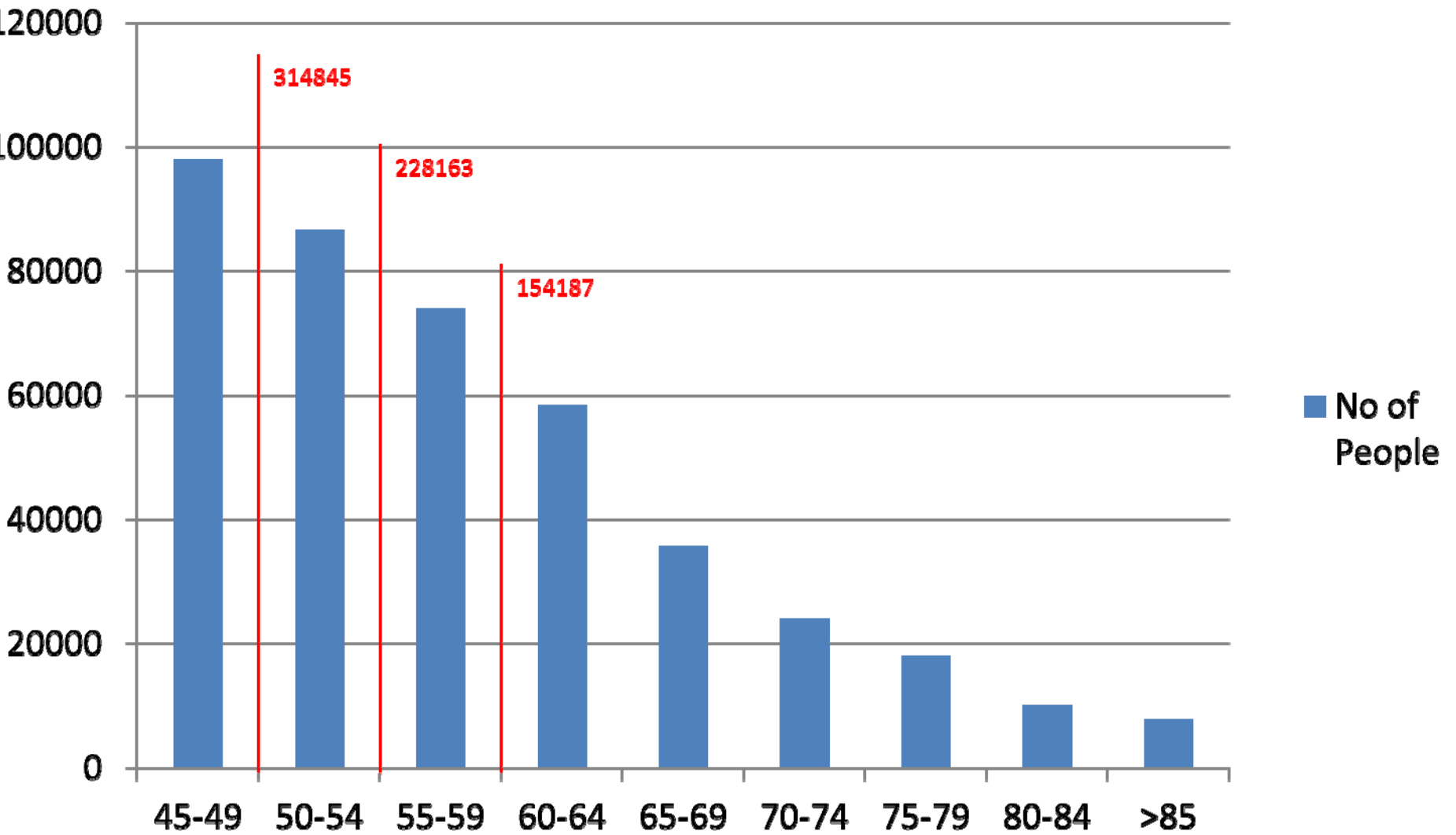


Table 3.4

**Bowel Cancer (C18-C20), Five-Year Relative Survival Rates and Percentage of Cases by
Dukes' Stage at Diagnosis, England, 1996-2002**

| Duke's stage at diagnosis | Percentage of cases | Five-year relative survival |
|----------------------------------|----------------------------|------------------------------------|
| A | 8.7% | 93.2% |
| B | 24.2% | 77.0% |
| C | 23.6% | 47.7% |
| D | 9.2% | 6.6% |
| Unknown | 34.3% | 35.4% |



Risk of CRC

| Group | Approx. lifetime risk of CRC |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| General Population | 5-6% |
| One first degree relative (FDR) with CRC | 2--3-fold increase over general population |
| Two FDRs with CRC | 3--4-fold increase |
| FDR with CRC diagnosed \leq 50 | 3--4-fold increase |
| One second or third degree relative | About 1.5-fold increase |
| Two second degree relatives | About 2--3-fold increase |
| Inflammatory Bowel Disease (ulcerative colitis and Crohn's colitis) | 7-10% have CRC after having ulcerative colitis for 20 years; then ~1%/year |
| Familial adenomatous polyposis (FAP) | ~100% |
| Hereditary non-polyposis colorectal cancer (HNPCC) | ~80+% |

Burt RW. Gastroenterology 2000;119:837-53
 Winawer S, et al. Gastroenterology 2003;124:544-560



Age to Begin Screening by Risk Category

Risk Category

Age to Begin Screening

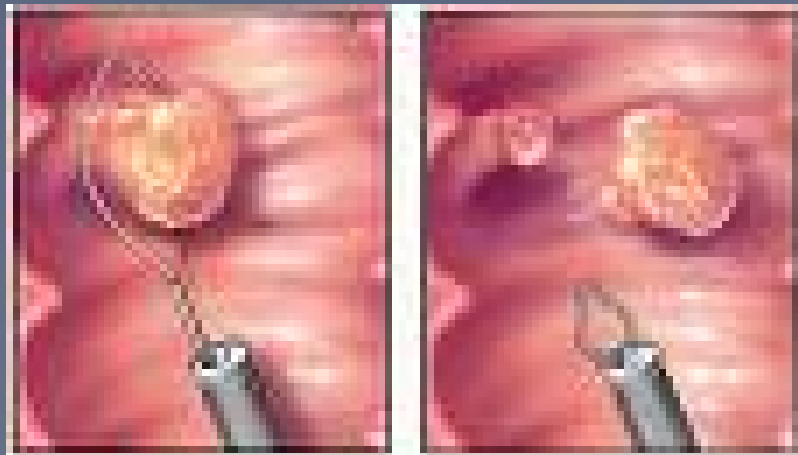
| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Average risk | Age 50 years |
| Increased risk | |
| <p>Family History</p> <p>Colorectal cancer or adenomatous polyp(s)* in an FDR age <60, or in 2 or more FDRs at any age</p> <p>* Especially if advanced adenomas: ≥ 1 cm; villous histology; or high grade dysplasia</p> | Age 40 years, or 10 years before the youngest case in the immediate family, whichever is earlier |
| <p>Genetic syndrome:</p> <p>Familial adenomatous polyposis (FAP)</p> <p>Hereditary non-polyposis colorectal cancer (HNPCC)</p> | <p>Age 10 to 12 years</p> <p>Age 20 to 25 years, or 10 years before the youngest case in the immediate family</p> |
| Inflammatory bowel disease | Cancer risk begins to be significant 8 years after the onset of pancolitis (involvement of entire large intestine), or 12-15 years after the onset of left-sided colitis |



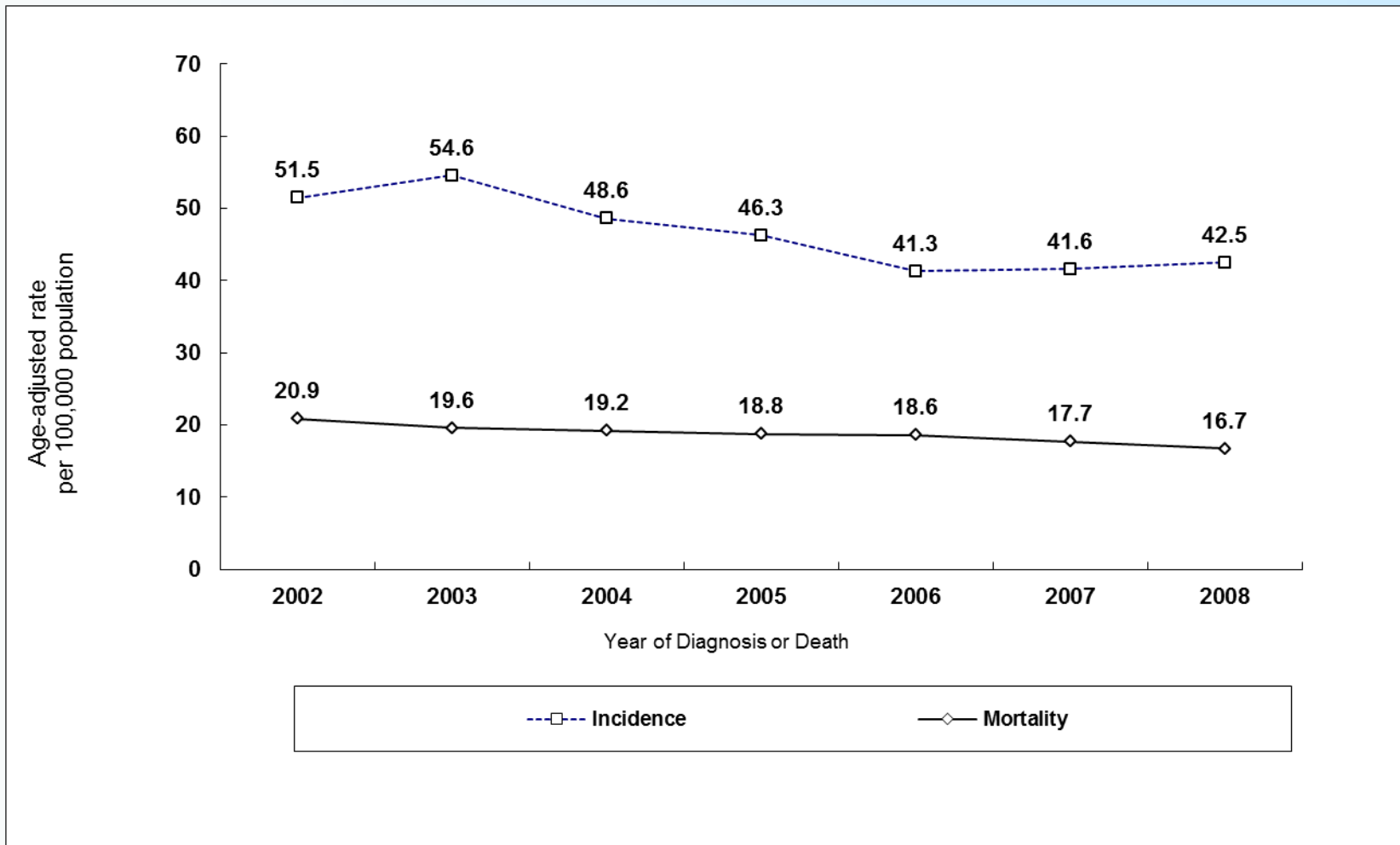
Benefits of CRC Screening

Benefits:

- Cancer Prevention: Removal of pre-cancerous polyps
- Long-term survival: Improved by early detection



Colorectal Cancer Incidence and Mortality Rates by Year of Diagnosis or Death, Maryland, 2002-2008



Maryland Cancer Registry (incidence rates)
NCHS Compressed Mortality File in CDC WONDER (mortality rates)

Prevention and Health Promotion Administration
May 2013



THANK YOU