# Primary Care Approach to Genetic Cancer Syndromes

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Jason M. Goldman, MD, MACP
President
American College of Physicians

Affiliate Professor of General Internal Medicine,
Charles E. Schmidt College of Medicine,
Florida Atlantic University

Clinical Assistant Professor of Medicine,
Nova Southeastern College of Medicine

ACP Liaison to the ACIP (Advisory Committee on Immunization Practices) for the CDC

# Financial Disclosure

Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

# Syndromes

- Hereditary Breast and Ovarian Cancer (HBOC)
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC) i.e. Lynch Syndrome
- Familial Adenomatous Polyposis (FAP)
- Melanoma
- Li-Fraumeni Syndrome (LFS)

# Objectives

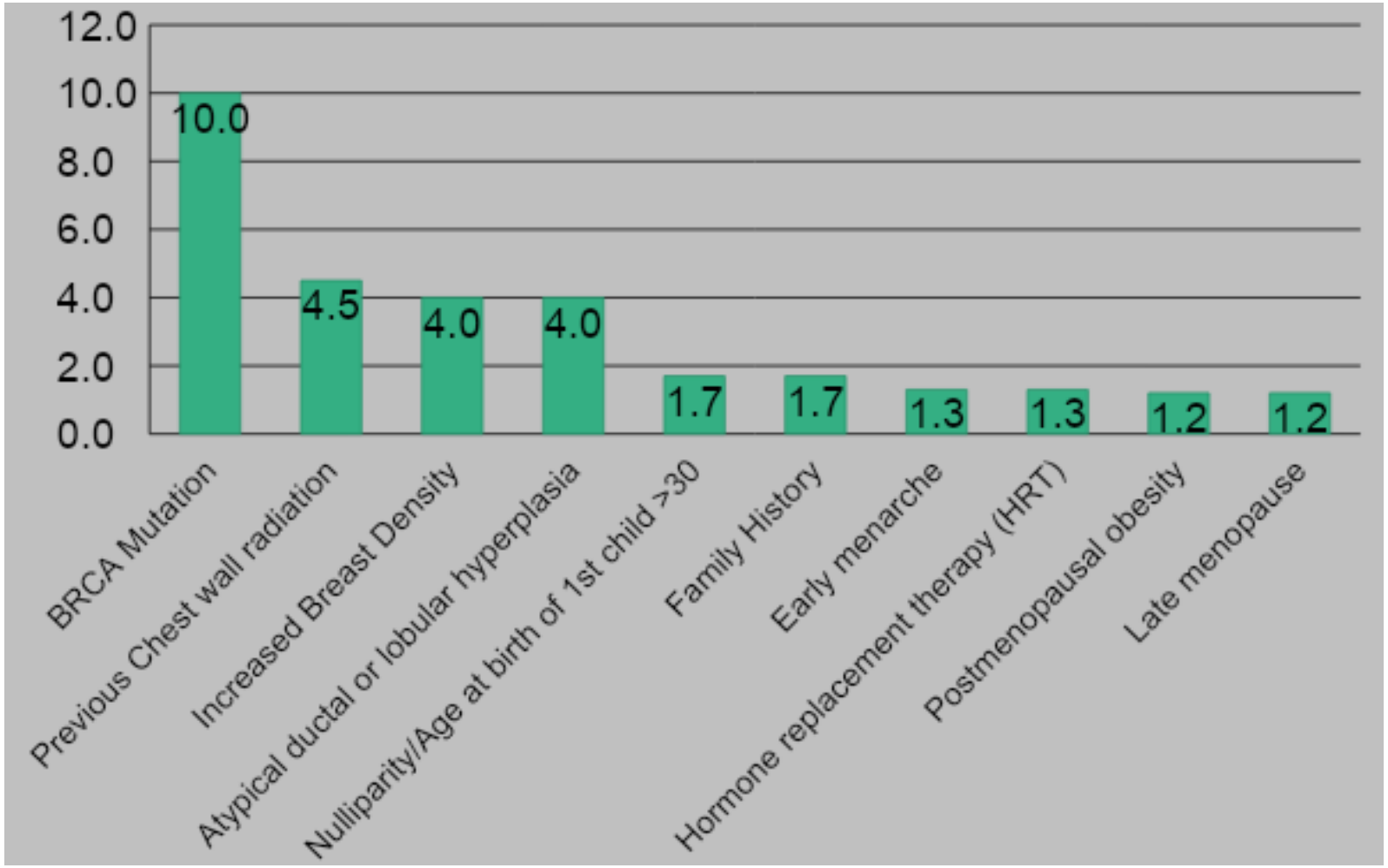
- Identify Risk Factors for BRCA gene mutations
- Identify patients at risk for Hereditary Breast and Ovarian Cancer Syndrome (HBOC)
- Clinical features of HBOC
- Management of HBOC
- Interpretation of BRCA test results
- Utilize BRCA testing in the clinical setting

# Overview

- Relative Risk
- Why test
- Who to test
- Results
- Management

# Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

# Relative Risk




NEJM 2000;342:564-571
Annals of surgery 2003;237(4):474-482
JNCI 2009;101(6):384-398

# HBOC Risk

Patients with a personal history of cancer

- About 22% of breast cancer patients at risk for HBOC
- 100% of ovarian cancer patients at risk for HBOC

Patients with only a Family History of Cancer

- 6% of all patients are considered high risk and need evaluation
- 9% of a primary care practice have family history of breast or ovarian cancer

- 1 in 400 people in general population have BRCA mutation
- 1 in 40 Ashkenazi Jewish ancestry have BRCA mutation

Journal of General Internal Medicine 2009;24(7):822-28
Breast J 2003 Jan-Feb;9(1)19-25
Genet in Med 2009;11:783-789

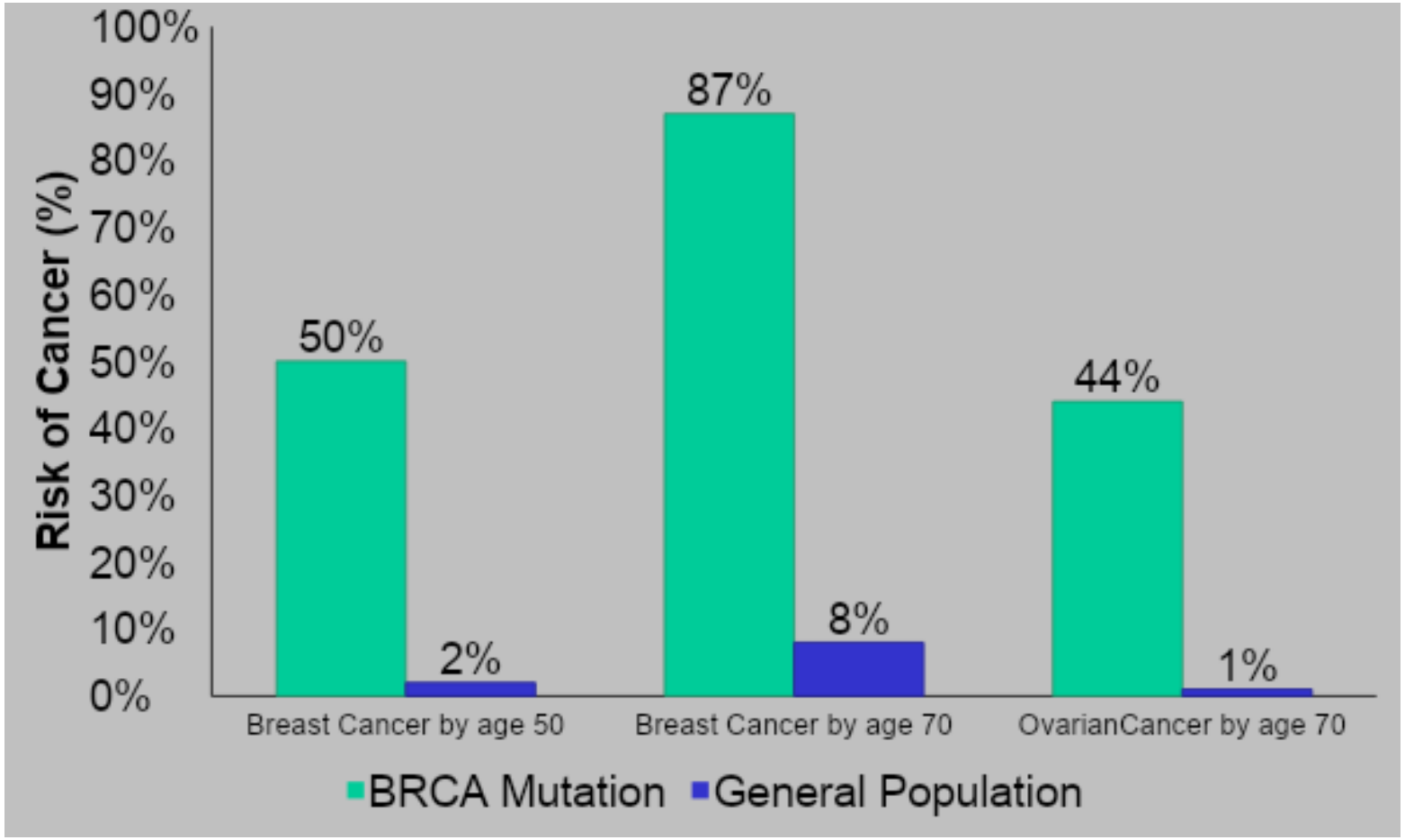
Gynecology Oncol 2011;121(2):352-7
Cancer 2005;104(12):2807-16
Nat Rev Cancer 2004;4(9):665-76
Cancer 2005;104(9):1849-53

# WHY TEST?

# Increased Cancer Risk

- Positive female patients have up to 87% chance of getting breast cancer
- Positive female patients have up to 44% chance of ovarian cancer
- 10 fold ovarian cancer risk after breast cancer
- Positive male patients have up to 10% chance of male breast cancer
- Positive male patients have up to 20% chance of prostate cancer
- Significant increase in other cancers including Pancreatic and Melanoma
- Appropriate Intervention Improves outcome

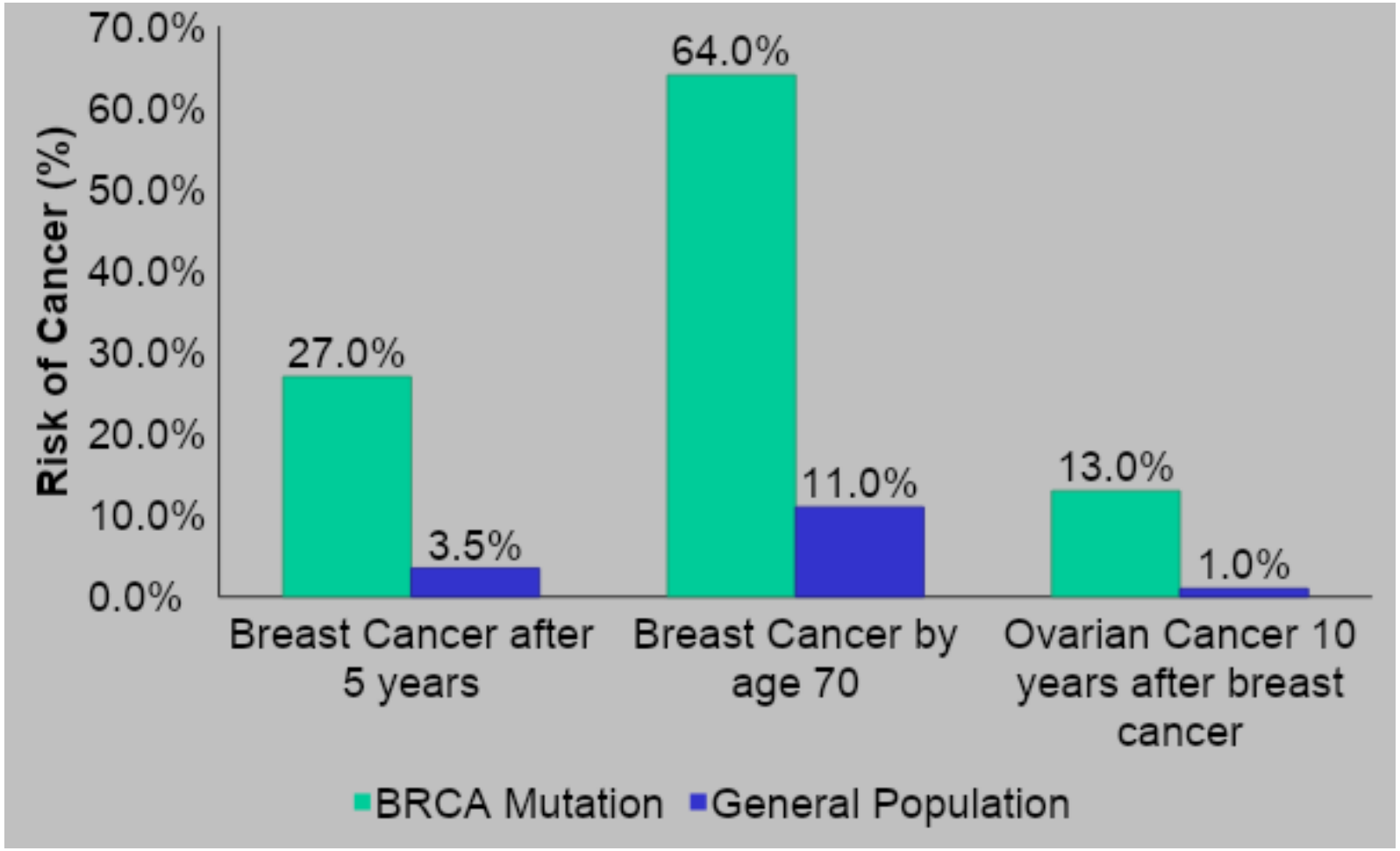
# Increase risk of Breast and Ovarian Cancer with BRCA mutation





Lancet 1994;343:692-5
NEJM 1997;336:1401-8
AJHG 2003;72:1117-30
JNCI 1999;15:1310-6
JCO 2007;25(11):1329-33
AJHG 1995:56:265-71
Science 2003;643-6
JCO 2005;23(8):1656-63
NCI (SEER) 2011

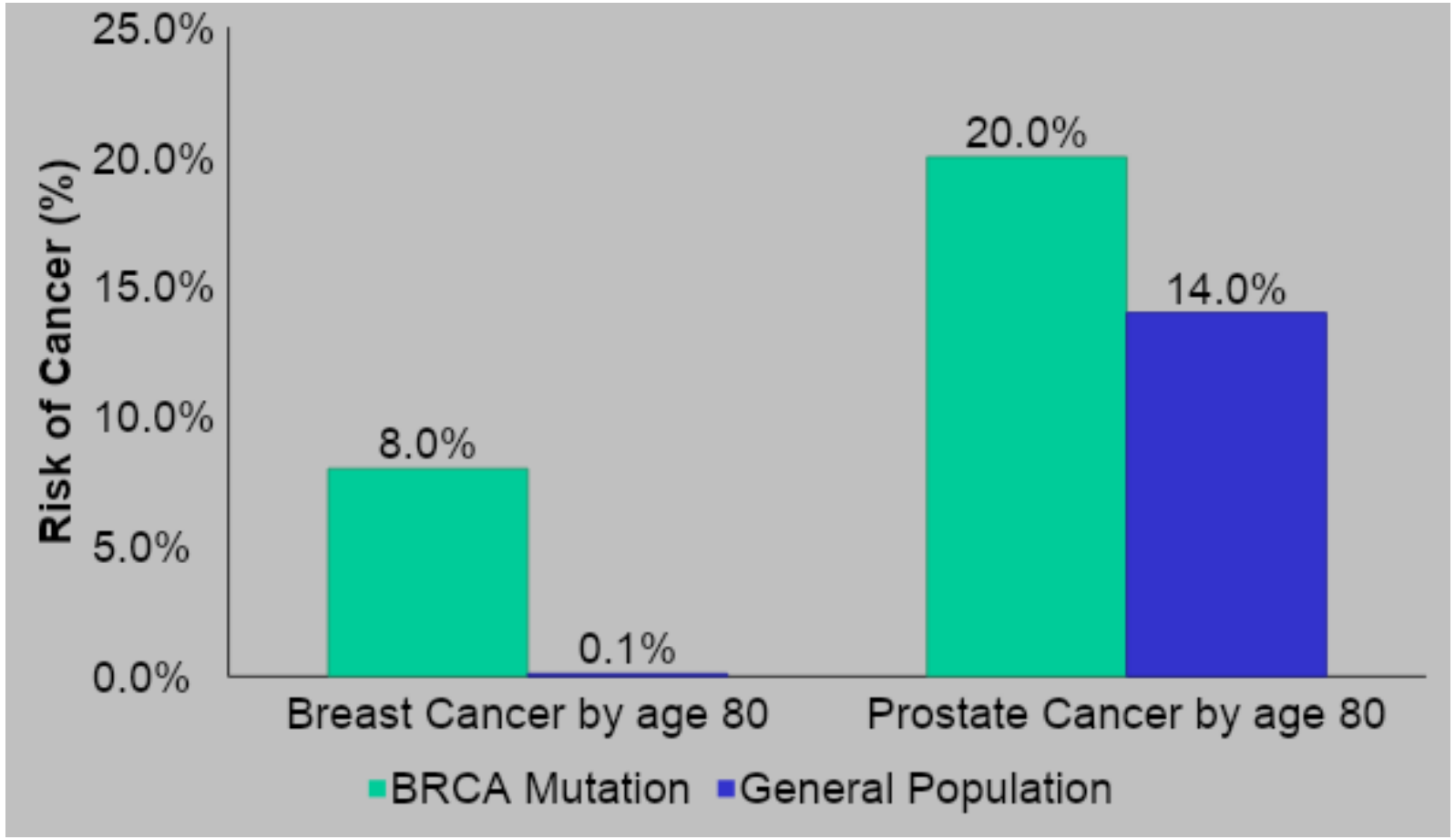
# Risk of Second Cancer with BRCA mutation





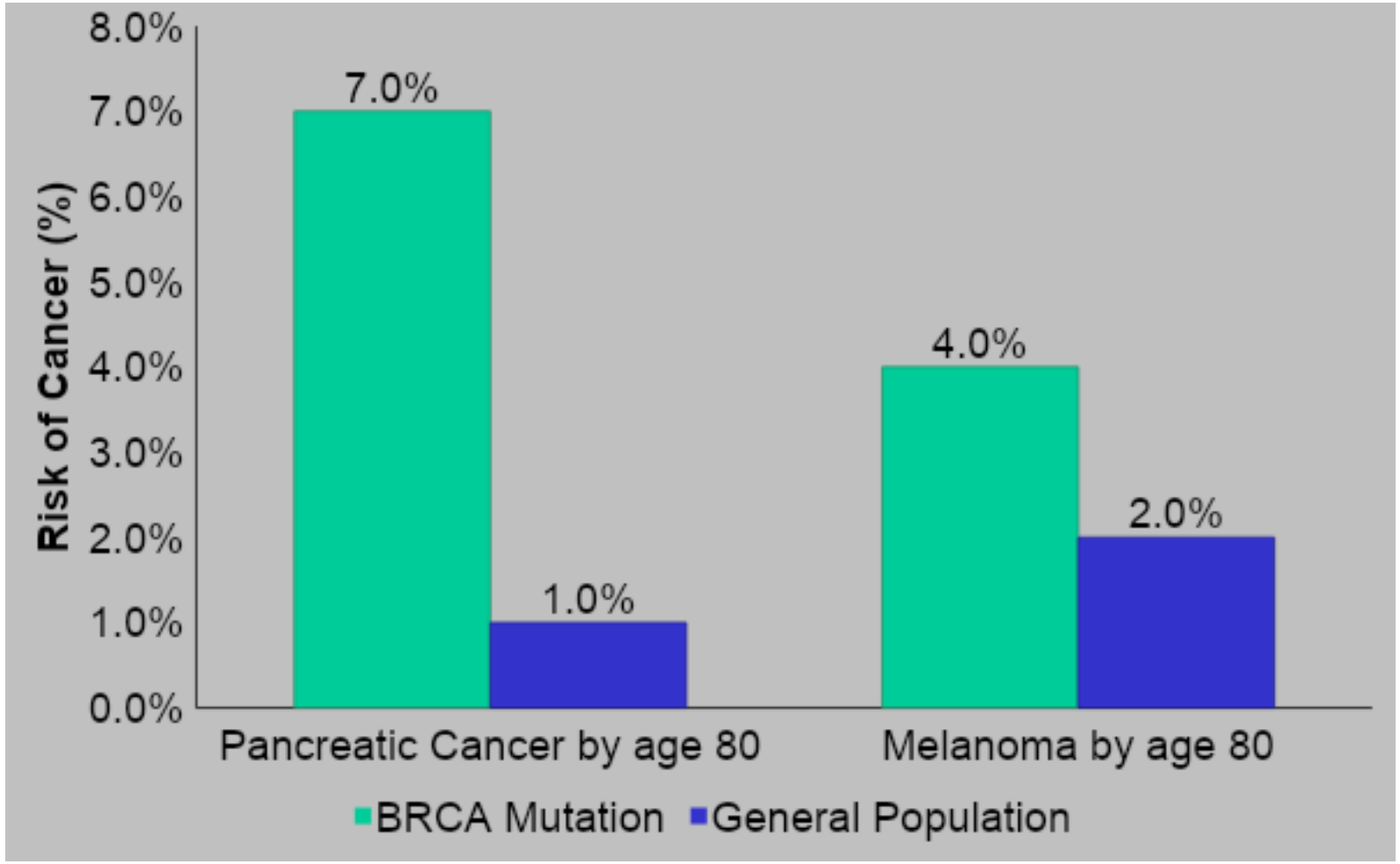
Ca Epi Biomarkers Prev. 1999;8(10):855-61
JNCI 1999;15:1310-6
JCO 1998;16:2417-25
Lancet 1998;351:1316-21
JCO 2004;22:2328-35
Lancet 1994;3343:692-5
Gynecol Oncol 2005 Jan;96(1):222-6
JCO 2010;28(14):2404-10

# Male Cancer Risk with BRCA mutation




JCO 2004;22:735-42
NCI (SEER) 2011
JNCI 2007 5;99(23):1811-4
JNCI 1999;15:1310-16

# Other Cancer risk with BRCA mutation




JNCI 1999;15:1310-6
JNCI 2002;94:1365-72
J Med Genet. 2005;42(9):711-9
NCI (SEER) 2011

# Who To Test

# Risk Factors Based on Family History

- Family history include up to third degree relative
- Any ovarian cancer
- Any breast cancer diagnosed before age 50
- 2 breast cancers on the same side of the family or in one individual
- Any male breast cancer
- Any BRCA mutation in the family
- Pancreatic cancer and additional Breast or ovarian cancer
- Ashkenazi Jewish ancestry with any HBOC cancer (Breast, Ovarian, Pancreatic)
- Triple Negative (Estrogen, Progesterone, Her2Neu)

# Key Points

- Mutation is Autosomal Dominant
- One gene from mother and one from father
- Each offspring has 50% risk of inheritance from affected parent
- Men and Women should be screened for risk and tested appropriately
- Men have **equal** chance of carrying the genetic mutation
- Family history should include third degree relatives

# Ductal Carcinoma in Situ (DCIS)

- 3.2 % of women with DCIS had BRCA1 or BRCA2
- 5.9% of women with Carcinoma in Situ have BRCA1 or BRCA2 mutation
- DCIS must be considered as a risk factor for HBOC

JAMA 2005 Feb 23;293(8):964-9
Cancer Prev Res 2010;3:1579-1585
Clin Cancer Res 2007 Jul 15;13(14):4306-1(
www.nccn.org

# Results

# Possible Results

- Positive for pathogenic mutation
  - BRCA 1 or BRCA 2 mutation present
- Negative for pathogenic mutation
  - No mutation present
- Polymorphism
  - Mutation present but not associated with increased cancer risk
- Genetic Variant of Unknown Significance
  - Mutation present but not enough data to determine if cancer risk is increased

# Histology and Prognosis

- Breast Cancer
  - BRCA1
    - Prognosis needs further study
    - Majority triple negative
    - More likely basal phenotype
  - BRCA2
    - Similar to non-BRCA tumors
- Ovarian Cancer
  - Majority papillary serous
  - May improve survival compared to non BRCA ovarian cancer

Am J Hum Genet 2001;68:700-710
Cancer 2005;104(12):2807-2816
Gynecol Oncol 2011 ;121(2):352-7
J Clin Oncol 2008;26(34):5530-36
Gynecol Oncol 2011;121(2):358-63
JCO 2000;18:119s-24s
J Natl Cancer Inst. 2003 Oct 1;95(19):1482-5
Clinical Cancer Research 2011;17(5):1082-89
JCO2008;26(26):4282-8
NEJM 2007;357(2):115-23
Breast Cancer Research 2010;12(Suppl 2):S3-62

# Management options

- Increased Surveillance
- Surgery
- Chemoprevention

# Surveillance Options

- Self-Breast Exam
- Clinical Breast Exam
- Mammogram
- Ultrasound
- MRI
- Pelvic Exam
- CA-125

# Female BRCA carriers

| | Procedure | Age to start | Frequency |
|---|---|---|---|
| Breast Cancer | Breast awareness | 18 | |
| | Clinical Exam | 25 | Every 6-12 months |
| | Mammogram | 30 | Yearly |
| | MRI | 25 | Yearly |
| Ovarian Cancer * | Pelvic exam | 35 | Every 6 months |
| | Ultrasound and CA-125* | 35 | Every 6 months |

* CA-125 and transvaginal ultrasound of limited efficacy and data
* Ovarian cancer surveillance is not primary treatment

www.nccn.org
CA Cancer J Clin 2007;57(2):75-89

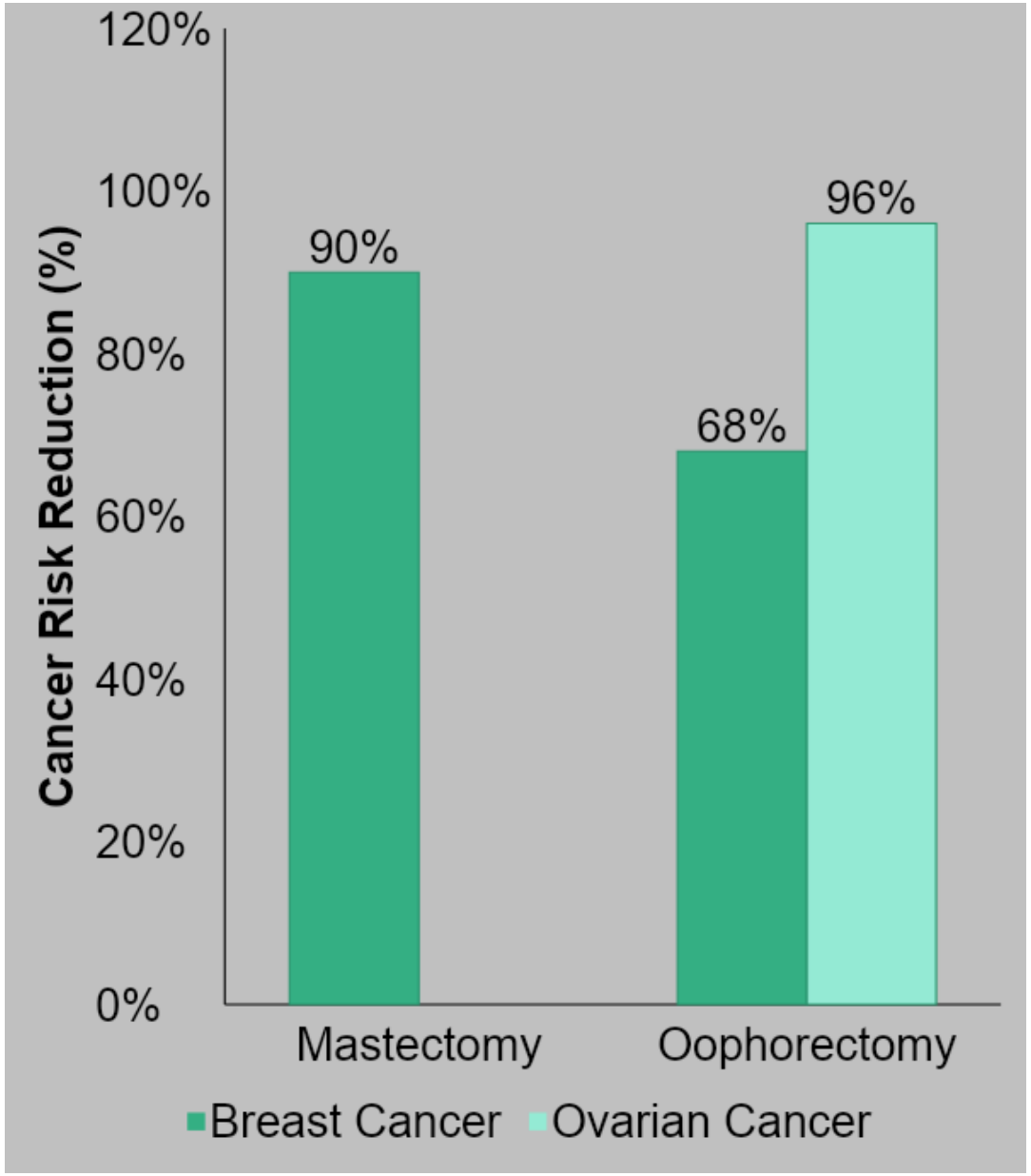
# Male BRCA carriers

| | Procedure | Age to start | Frequency |
|---|---|---|---|
| Breast Cancer | Self-exam | 35 | |
| | Clinical Exam | 35 | Yearly |
| | Mammogram *(consider)* | 40 | Yearly |
| Prostate Cancer *(recommend for BRCA2, consider for BRCA1)* | PSA | 45 | Yearly |
| | Digital Rectal Exam | 45 | Yearly |

Br J Cancer 2010;103(6):918-924
JCO 2004;22:735-42
Breast 2008 Oct;17(5):441-50
www.nccn.org

# Surgical Management

- Bilateral Mastectomy has 90% cancer risk reduction
- Bilateral Salpingo-oophorectomy (BSO) has 96% cancer risk reduction
- BSO advised after childbearing years but by age
- Risk reducing BSO considerations
  - Ovaries and fallopian tubes to level of cornu
  - Ligation of ovarian vessels at pelvic brim
  - Thorough pelvic inspection and washing
  - Complete serial sections
- Studies show 2%-26% occult tumors found in surgery




JAMA 2010;304(9):987-975
NEJM 2002;346:1609-1615
JNCI 2001;93:1633-7
JCO 2004;22:1055-62
JAMA 2006;296:185-92
Clin Oncol 2005 Mar 10;23(8):1656-63
NEJM 2002;346:1616-1622
J Natl Cancer Inst. 2009 Jan 21;101(2):80-7
www.nccn.org

# Chemoprevention

Breast Cancer

- Tamoxifen
  - Possible 45% risk reduction for unaffected BRCA positive
  - Possible 62% reduction in BRCA2
  - Affected BRCA carriers possible 53% reduction in opposite breast
- Raloxifene and Aromatase Inhibitors
  - No specific data for BRCA
  - Risk reduction in post menopausal women

Ovarian Cancer

- Oral contraceptive
  - Possible 60% reduction
  - Unclear risk for increase breast cancer

Int J Cancer. 2006;118(9):2281-4
Lancet 2000;356:1876-81
JAMA 2001;286:2251-6
JNCI 1998; 90:1371-88
Cancer Prevention Research 2011;3(6):696-706

NEJM 1998; 339:424-8
JNCI 2002;94:1773-9
JCO. 2007 ;112(S3):700-709
Cancer Epidemiol Biomarkers Prev. 2006;15(10)
Breast Cancer Res Treat 2010 Feb;120(1):175-83
Eur J Cancer 2010;46:2275-84
www.nccn.org

# Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer: HNPCC)

# Objectives

- Identify Risk Factors for HNPCC gene mutations
- Identify patients at risk for HNPCC
- Clinical features of HNPCC
- Management of HNPCC
- Interpretation of HNPCC test results
- Utilize HNPCC testing in the clinical setting

# Overview

- Relative Risk
- Why test
- Who to test
- Results
- Management

# Relative Risk, Prevalence and Facts

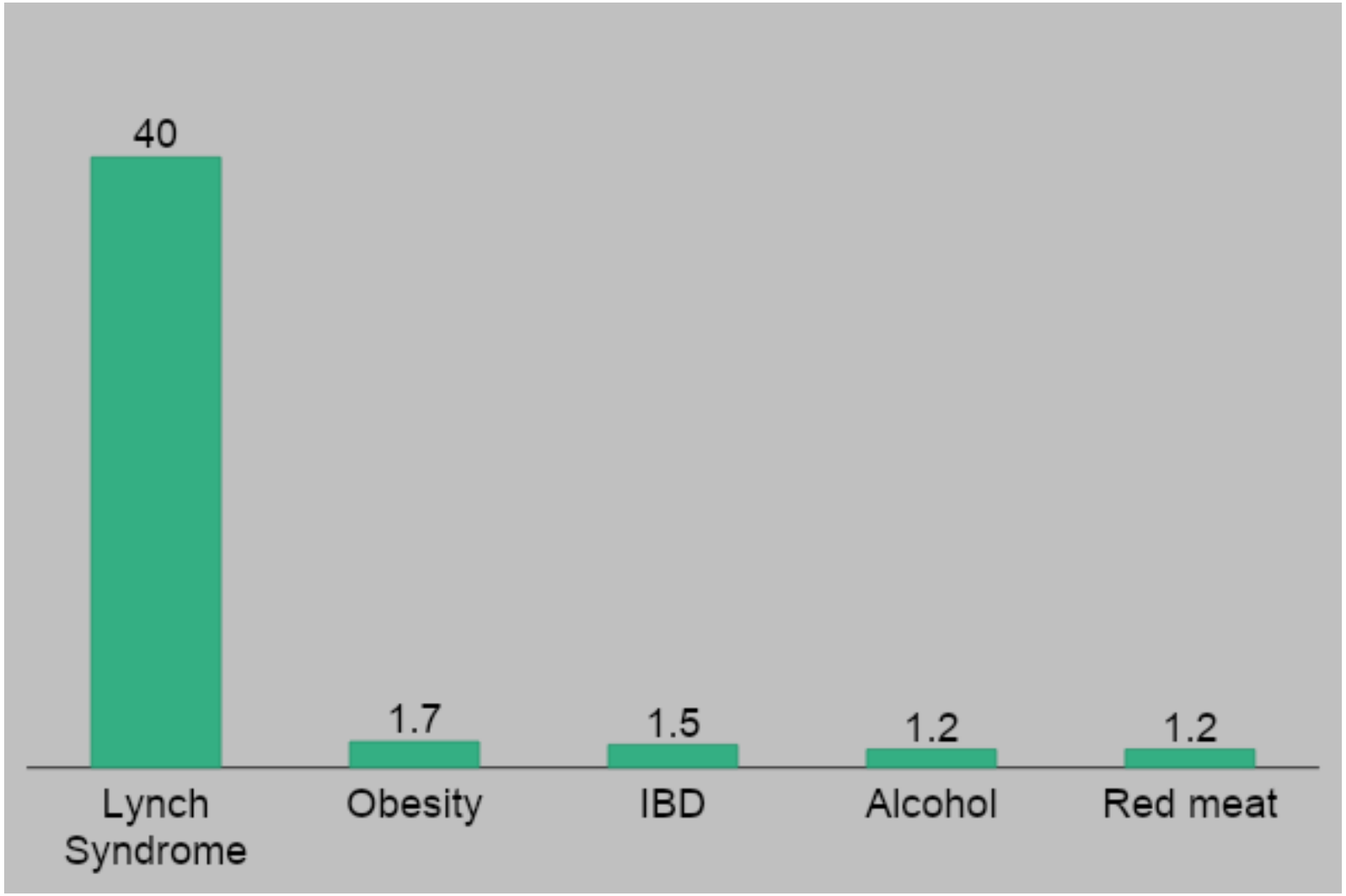
- About 1 in 300 to 1 in 500 people affected
- Increased colon and endometrial cancer risk
- Mutations: MLH1, MSH2, MSH6, PMS2, EPCAM
- Autosomal dominance
- 2-4% of colorectal cancer caused by mutation
- Age of onset usually under age 58
- About 6% of colon cancer under age 50 is lynch related
- 2-4% of endometrial cancer caused by Lynch
- 9% of endometrial cancers under age 50 caused by lynch
- 50% of women with Lynch will present with gynecologic malignancy first


Cancer Control 2009;16:14–22 .
Journal of Clinical Oncology 2007; 25(33):5158-5164.
Obstetrics and Gynecology 2005;105:569-74.

N Engl J Med 2005;352:1851–1860.
J Clin Oncol 2000;18:2193–200.
Familial Cancer 2005;4:239-44.
Gastroenterology 2005 Aug;129(2):415-21.

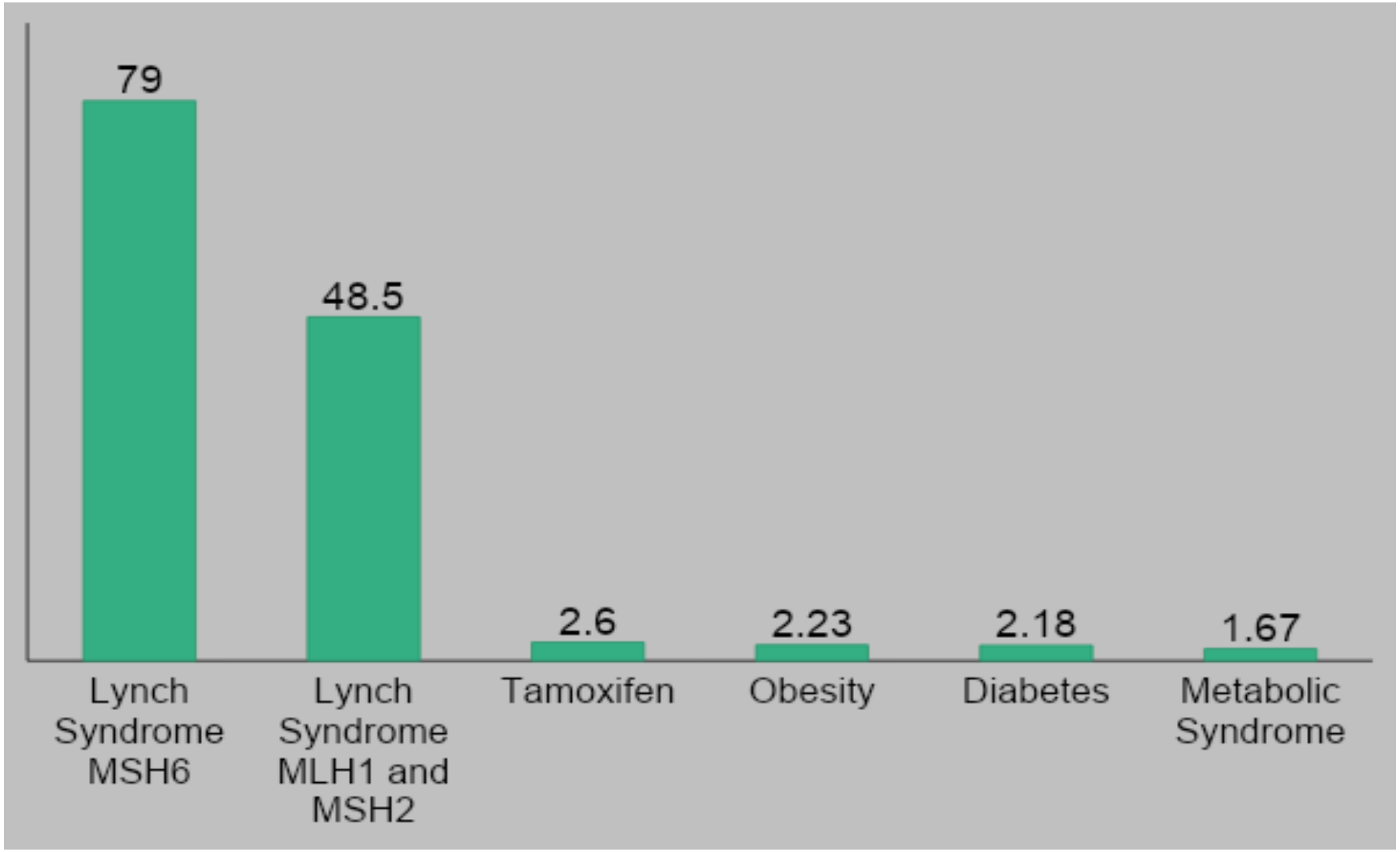
Gastroenterology 2010;138: 2197.
Surg Oncol Clin N Am 2009;18:687-703.
Nature Genetics 2009;41:112-7.

# Relative Risk for Colorectal Cancer




Cancer Causes Control 2000;11: 477-88.
Seer.cancer.gov/statistics/

# Relative Risk for Endometrial Cancer

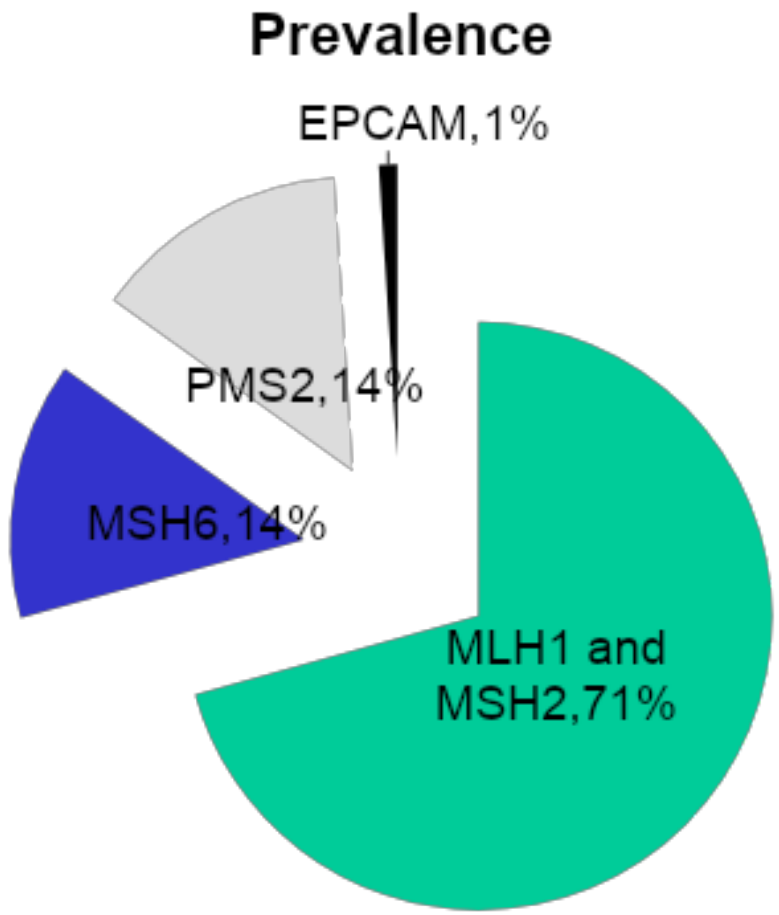



Ann Oncol 2010 EPUB ahead of print.
Lancet Oncol 2009;10:400-408.
Journal of Clinical Oncology 2008;25:4151-4159.

# Conclusion

Lynch syndrome is the single most common explanation for hereditary colon and gynecologic malignancies

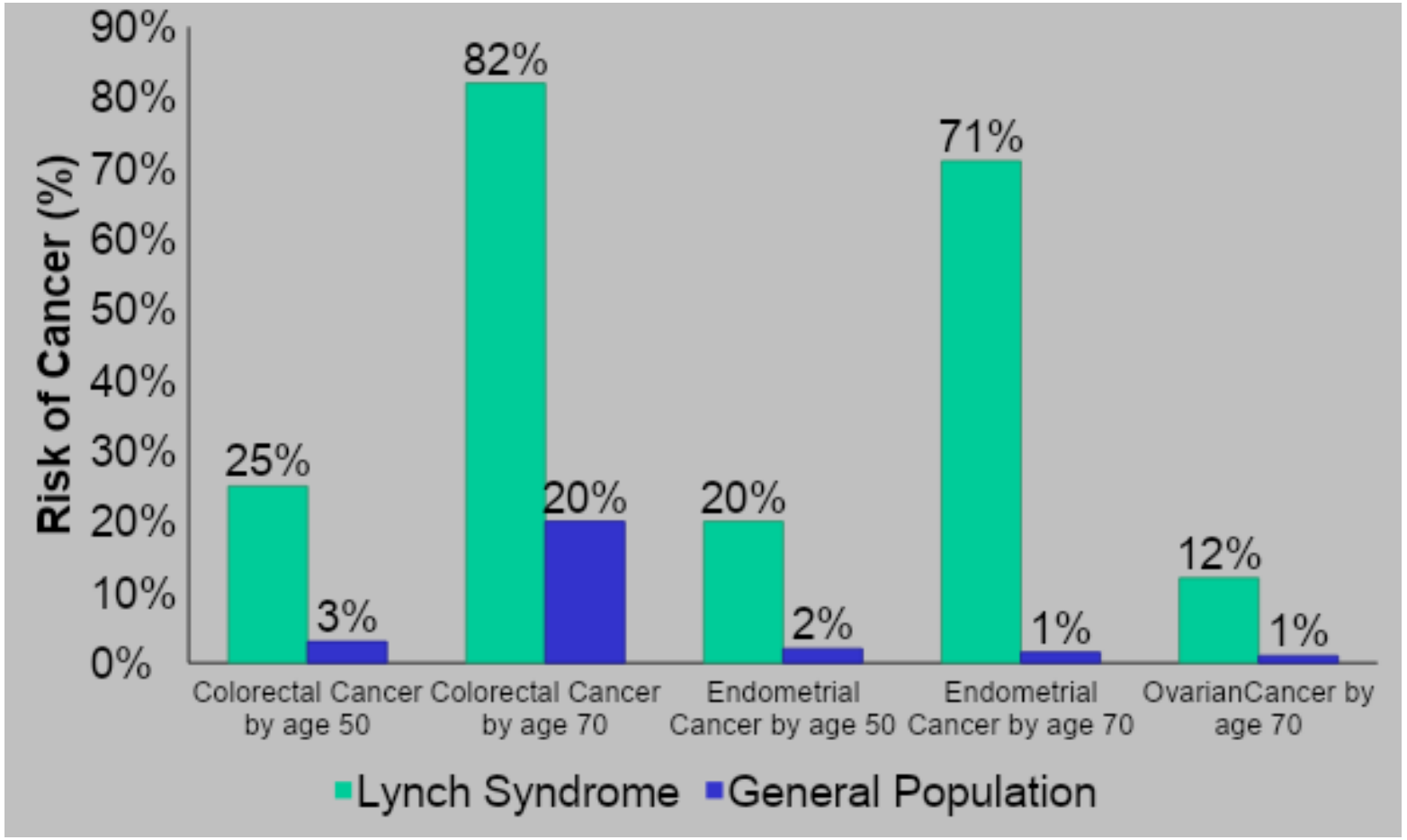
# Gene Mutation Prevalence




Genet Med 2009;11:42-65.
Gastroenterology 2008;135: 419-28.
Human Mutation 2011;32:407-414.

# WHY TEST?

# Increase risk of Colorectal and Gynecologic Cancer with Lynch



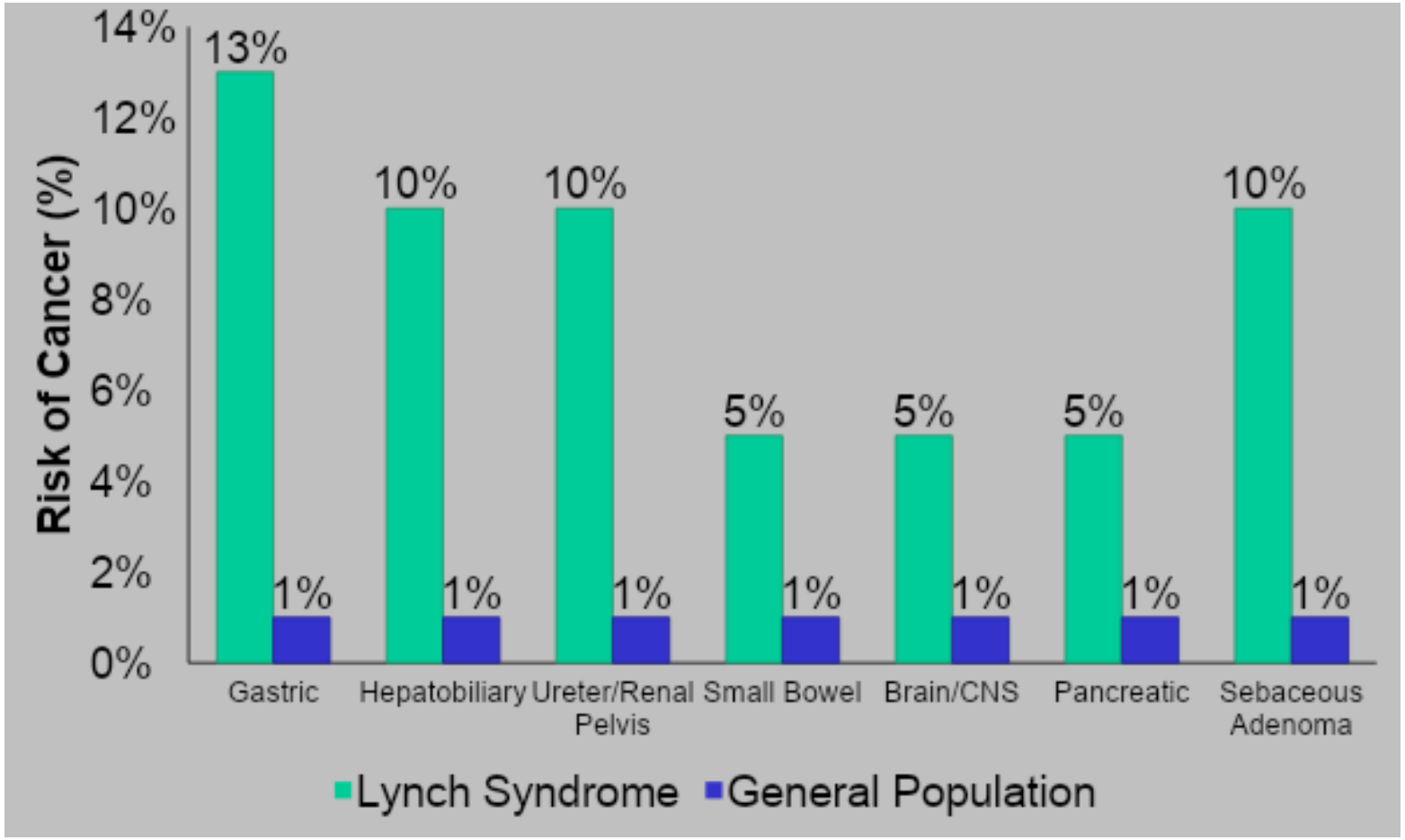

Gastroenterology 1996;110:1020-7.
Int J Cancer 1999;81:214-8.
Gastroenterology 2004;127:17-25.

Lancet Oncol 2011;12:49-55.
Gastroenterology 2009;137(5):1621–1627.
Gastroenterology 2008;135(2):419-28.

Statistics in Medicine 2003;22:1837-48.
Int J Cancer 1999;81:214-8.
Gastroenterology 2009;137(5):1621–1627.

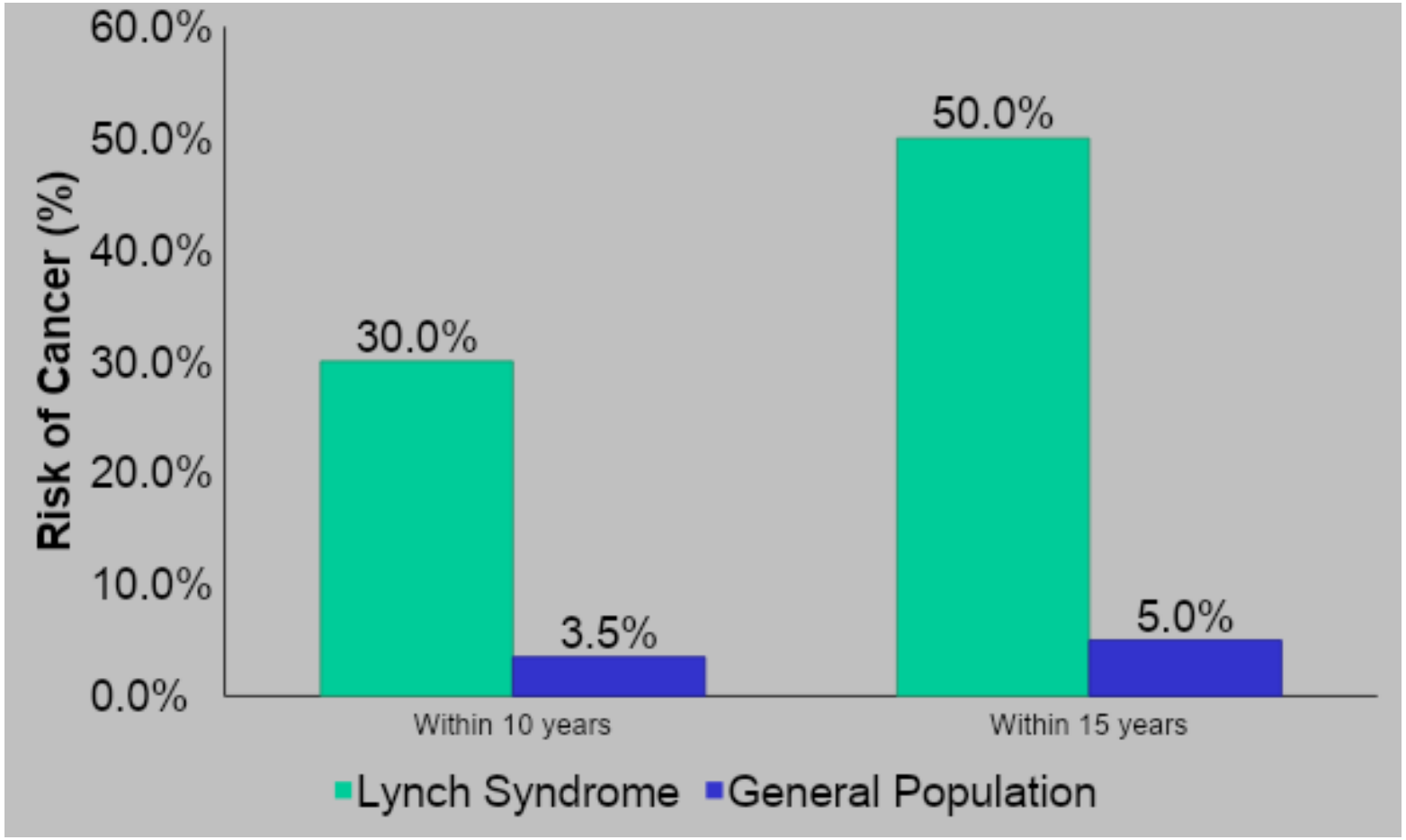
Gastroenterology 1996;110:1020-7.
Lancet Oncol 2011;12:49-55.
Gastroenterology 2008;135(2):419-28.

# Increase risk of other Cancers with Lynch Syndrome




International Journal of Cancer 2008;123:444-449.
Clinical Genetics 2009;75:141-9.

# Increase risk of Second Cancer with Lynch Syndrome




Cancer 1977;40:1849.
Dis Colon Rectum 1986;29:160.
Cancer 1993;36:388-93.

# Who To Test

# Patients With Cancer

- Colorectal or endometrial cancer before age 50
- Two or more lynch syndrome cancers at any age
- Lynch syndrome Cancer and one or more relatives with Lynch syndrome Cancer
- Lynch syndrome mutation in the family
- MSI-High Histology in Colorectal cancer under age 60
  - Medullary growth pattern, Crohn’s like lymphocytic reaction, signet ring, tumor infiltrating lymphocytes, mucinous
- MSI/IHC tumor test results

# Patients without Cancer

- Family history of two or more lynch cancers, one before age 50
- Family history of three or more lynch cancers at any age
- Family history of lynch mutation

# MSI vs. MSI-High histology

- Microsatellite Instability (MSI)
  - PCR based test on tumor tissue
  - Specific order
  - If high, then likely mismatch repair dysfunction which suggests Lynch syndrome
- MSI-High histology
  - Specific histologic features that suggest MSI would show as high
  - Suggestive of lynch syndrome
  - Automatic on pathology report
- Neither are genetic tests for Lynch mutation, only on tumor tissue
- Absence of MSI or MSI-high histology does not exclude genetic mutation

# Management options

- Increased Surveillance
- Surgery

# Colorectal Cancer

- Surveillance
  - Colonoscopy every 1-2 years at age 20-25
  - Lynch cancer usually right sided
  - Cancer risk reduction over 50%
  - General population Adenoma to cancer in 10 years, Lynch syndrome takes **1-3 years**
- Surgical Options
  - Colectomy with ileorectal anastomosis for cancer or more then one advanced adenoma
  - Hemicolectomy with annual colonoscopy


Diseases of the Colon & Rectum 2003;46:1001-12.
www.nccn.org
CA Cancer J Clin 2006 May-Jun;56(3):160-7.
Annals of Surgery 2010;252:507-513.

www.nccn.org
Gastroenterology 2000;118:829-34.
Gastroenterology 2010;138:2300-2306.

Gastroenterology 1993;104:1535-49.
Dis Colon Rectum 2002;45:1588-94.

Am J Med 1999;107:68-77.
Gut 2002 Feb;50(2):228-34.
Clin Gastroenterol Hepatol 2011;9(4):340-43.

# Gynecologic Cancer

- Surveillance
  - Annual endometrial biopsy starting age 30-35
  - Annual Transvaginal ultrasound starting age 30-35*
  - CA-125 testing*
- * Transvaginal u/s and serum CA-125 for ovarian ca have not been shown to be sufficiently sensitive or specific as to support routine recommendation, but may be considered at clinician's discretion

- Surgical Options
  - Hysterectomy and bilateral salpingo-oophorectomy after child bearing years

www.nccn.org
J Clin Oncol 2006 Oct 1;24(28):4642-60.
JAMA 2006 Sep 27;296(12):1507-17.
N Engl J Med 2006 Jan 19;354(3):261-9.

# Other Cancers

- Gastric and small bowel cancer consider EGD and capsule endoscopy yearly starting age 30-35
- Urothelial cancer consider annual urinalysis
- CNS cancer advise annual physical exam
- Pancreatic Cancer no specific recommendations
- Prostate cancer no specific recommendations

# Possible Results

- Positive for deleterious mutation
  - Lynch mutation present
- Negative for deleterious Mutation
  - No mutation present
- Polymorphism
  - Mutation present but not associated with increased cancer risk
- Genetic Variant of Unknown Significance
  - Mutation present but not enough data to determine if cancer risk is increased

# Familial Adenomatous Polyposis

# Important Facts

- About 30% of adults will have adenoma or precancerous polyp
- APC and MYH are associated gene mutations
- Causes about 1% of colon cancer
- About 85% of FAP caused by APC mutation
- About 15% of polyposis syndrome from MYH
- 3 significant syndromes
  - Familial Adenomatous Polyposis (FAP)
  - Attenuated FAP
  - MYH Associated Polyposis (MAP)

# Adenomatous polyposis syndromes

Familial and Attenuated Familial Adenomatous Polyposis Syndrome

- APC gene
- Autosomal dominant
- Hundreds of polyps in FAP
- Less than 100 polyps in AFAP
- Colorectal cancer risk ≥80%by age 70

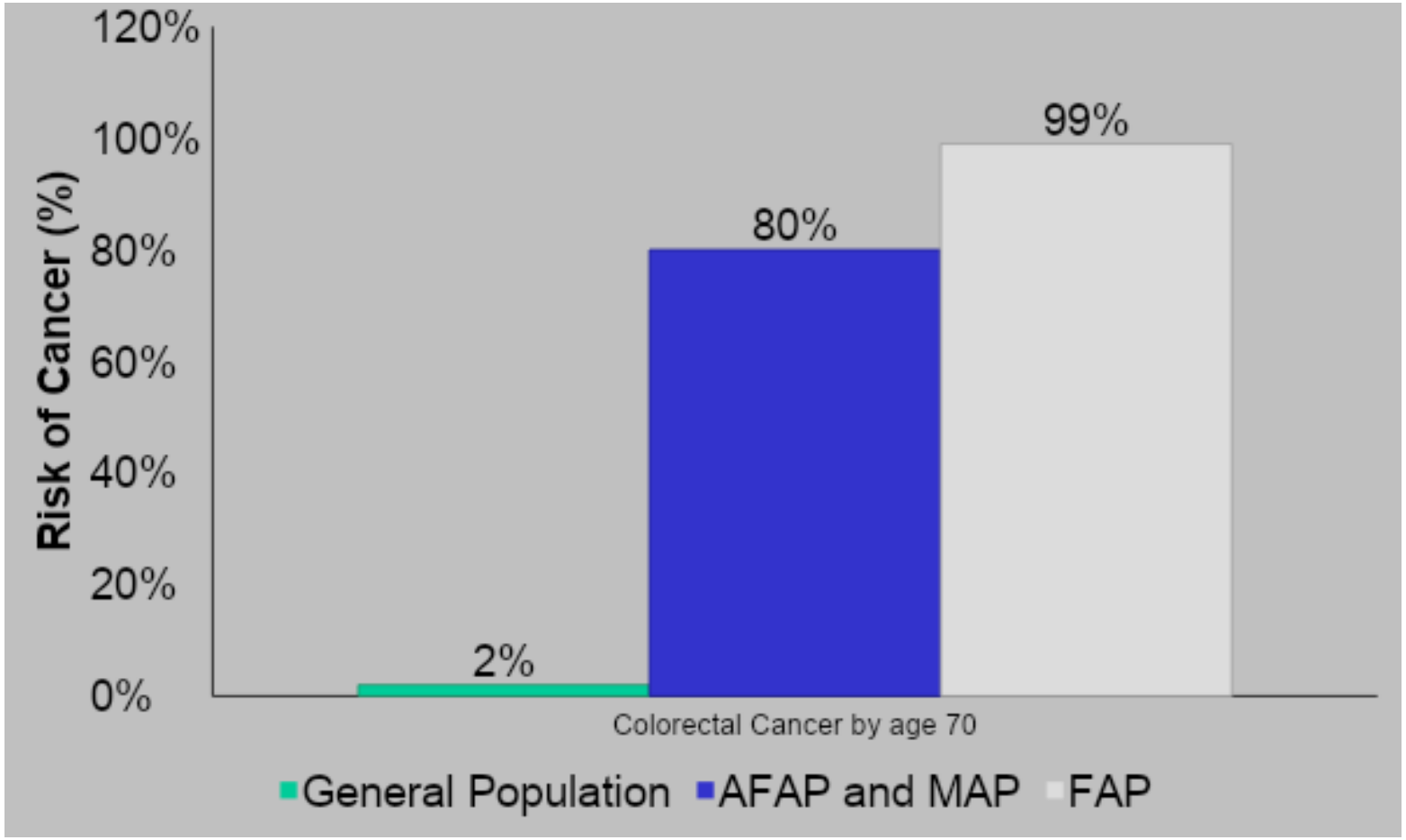
MYH associated polyposis

- MYH gene
- Autosomal recessive
- 0-1000 polyps
- Colorectal cancer risk ≥80% by age 70

Critical Reviews In Oncology Hematology 2010.
Gastroenterology 2004;127:444-451.

FAP causes hundreds of polyps, Attenuated FAP usually less than 100

# Importance of Testing




*Textbook of Gastroenterology. Philadelphia Lippencott Williams and Wilkins 2003:1920.*
*Cancer Epidemiol Biomarkers Prev* 2006 Feb;15(2)
*Am J Gastroenterol*. 2006 Feb;101(2):385-98.

# Risk Factors

- 10 or more adenomatous polyps cumulative, personally or in family
- Colorectal cancer and adenomas
- Positive mutation in family

# Possible Results

- Positive for deleterious mutation
  - Mutation present
- Negative for deleterious Mutation
  - No mutation present
- Polymorphism
  - Mutation present but not associated with increased cancer risk
- Genetic Variant of Unknown Significance
  - Mutation present but not enough data to determine if cancer risk is increased

# Treatment options

- Yearly colonoscopy if FAP
- Possible colectomy for severe polyposis
- Possible chemoprevention with COX-2 inhibitors or Aspirin

# Hereditary Melanoma

# Hereditary Melanoma

- p16 (*CDKN2A*) mutation
- Up to 76% melanoma risk and 17% pancreatic cancer risk
- Risk factors
  - Two or more melanomas in a family
  - Positive p16 mutation in family
  - At least one pancreatic cancer and one melanoma
- If positive needs aggressive and frequent skin exams
- Possible pancreatic screening such as CT, EUS, or research protocols, unclear guidelines

# Li-Fraumeni Syndrome (LFS)

# Li-Fraumeni Syndrome (LFS)

- Autosomal Dominant
- Affects 1/20,000
- TP53 mutation
- 50% risk of LFS cancer by age 30
- 49% breast cancer risk by age 60
- 93% lifetime cancer risk
- Average age of diagnosis 21.9 years
- 5%-8% of women with no family history have TP53 mutation

Breast Cancer Res Treat. 2012 Jun;133(3):1125-30. doi: 10.1007/s10549-012-1993-9. Epub 2012 Mar 4.

# LFS tumors

- Soft tissue sarcoma
- Osteosarcoma
- Brain Tumor
- Premenopausal breast cancer
- Adrenocortical carcinoma
- Leukemia
- Bronchoalveolar lung cancer

# Testing Guidelines

- Woman with Breast Cancer before
- Individual with LFS tumor before age 46 and 1st or 2nd degree relative with LFS tumor before age 56
- Individual with multiple tumors of LFS spectrum with first before age 46
- Individual with adrenocortical carcinoma or choroid plexus tumor
- Individuals with family history of TP53 mutation

# Treatment options

- No definitive data for specific guidelines
- Increased surveillance
  - Annual  MMG alternate with MRI every 6 months
  - Colonoscopy every 2-3 years start age 25
  - Avoid radiation exposure
- Surgical intervention
  - Prophylactic mastectomy
  - Mastectomy advised over lumpectomy

# Case Studies

# Patient H.G.

49 year old unaffected male, Ashkenazi Jewish ancestry

Family history:

Maternal grandmother breast age 50

Maternal grandfather throat cancer age 70

Maternal uncle testicular cancer age 30

Maternal uncle prostate age 60

Mother breast age 50

Father prostate age 30

Testing offered

- BRCA mutation testing

Test Results:

- *BRCA*2 mutation (6174delT one of the three common mutations)

My Recommendations

- Manage with male mammogram follow up with oncology and urologist
- Patient discused results with family members
- Daughter, age 19, tested positive

# Patient A.P.

66 year old male, Ashkenazi Jewish ancestry

Colon cancer diagnosed age 31

Family history

Father colon age 60

Maternal grandmother breast age 75

# Outcome

Recently diagnosed with Stage 1 pancreatic cancer, status post whipple, XRT and undergoing chemo

Daughter tested positive for mutation had subtotal colectomy, hysterectomy and cholecystectomy

# Patient M.H.

59 year old female, Ashkenazi Jewish ancestry

Family history

- Maternal grandmother breast cancer
- Paternal uncle gastric cancer
- Paternal aunt breast cancer age 45
- Paternal cousin breast cancer age 32, *BRCA1*+
- Paternal cousin ovarian cancer age 40
- Paternal uncle prostate cancer

Testing offered

BRCA mutation testing

Lynch mutation

Test Results:

*BRCA*1 187delAG (one of the three common mutations)

My Recommendations

Treatment / Surveillance

M.H. chose bilateral mastectomy, TAH BSO

# Outcome

32 year old daughter tested

*BRCA1 Positive*

- Screening Mammogram done
- Positive for Stage 1 Breast Cancer
- Status post double mastectomy

# Final Comments

# Final Comments

- Genetic testing saves lives
- Genetic testing advised by multiple medical societies
- Testing protected by state and federal Genetic Information Nondiscrimination Act (GINA laws)
- Genetic testing allows for primary prevention of many cancers
- Genetic mutations more common then realized
- Easy to incorporate into practice