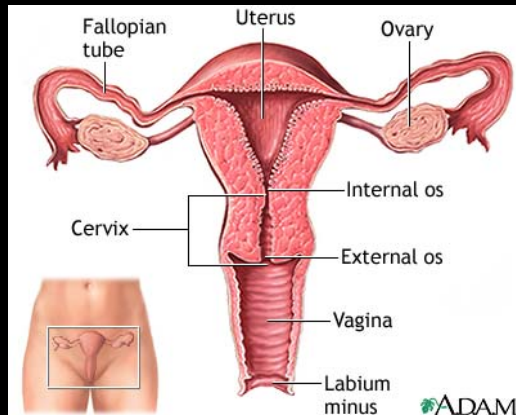
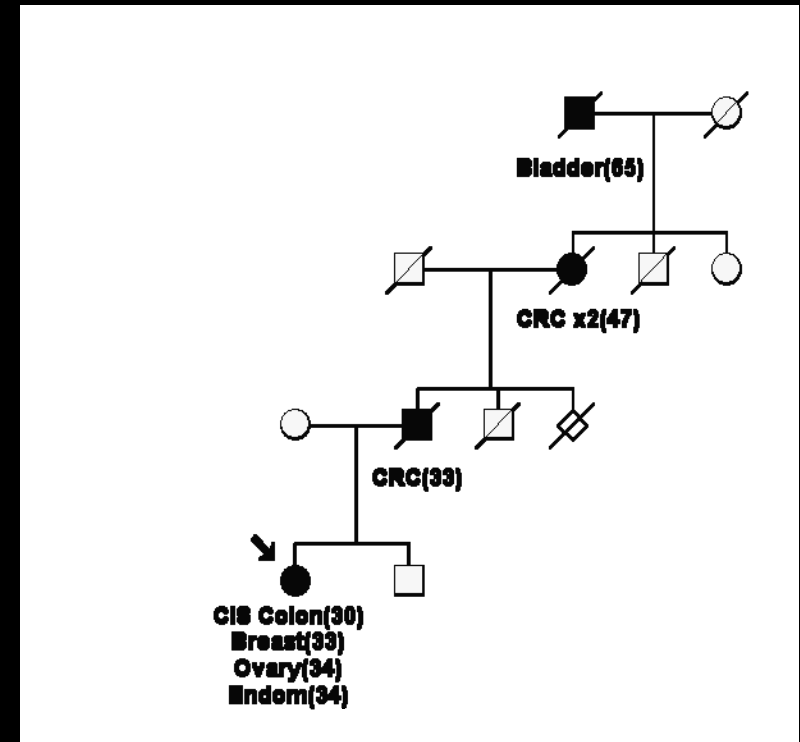


Management of Familial Cancer Syndromes for the Gynecologist



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Objectives

- Review profile of BRCA and Lynch syndromes
- Outline gynecologic cancers associated with these mutations
- Discuss prevention strategies for at-risk women
 - Screening
 - Surgery
- Real life cases

HNPPCC History

- Warthin 1913 Cancer Family "G"
- Lynch 1966
- 1971 autosomal dominant
- 1984 Lynch Syndrome
 - Lynch I : colon cancer only
 - Lynch II: uterine and other cancers
- 1985 "Hereditary non-polyposis colon cancer"
- 1993 chromosome 2p, 3p : DNA mismatch repair genes



DNA Mismatch Repair

- The main function of DNA mismatch repair (MMR) is to maintain genomic stability by correcting mismatches occurring during DNA replication



HNPPCC/Lynch Clinical Syndrome

- Colon
30-85%
- Endometrium
30-50%
- All others
10%
- 18% two
cancers

Site	N	Age
stomach	26	48.9 (23-82)
Small bowel	23	48.7 (23-69)
Brain	19	43 (2-79)
Ovaries	28	45.7 (19-75)
Urinary Tract	28	57.6 (40-73)

Aarnio et al. 1999

Standardized incidence ratios

Colorectal 68
(CI, 56 to 81)

Endometrial 62 *
(CI, 44 to 86)

Ovarian 13
(CI, 5.3 to 25),

Gastric 6.9
(CI, 3.6 to 12),

Biliary tract 9.1
(CI 1.1 to 33),

Uro-epithelial 7.6
(CI, 2.5 to 18)

Kidney 4.7
(CI, 1 to 14)

CNS 4.5
(CI 1.2 to 12)

The cumulative cancer incidences was 60 % for endometrial and 12% for ovarian cancer.

Amsterdam Criteria 1990/1999

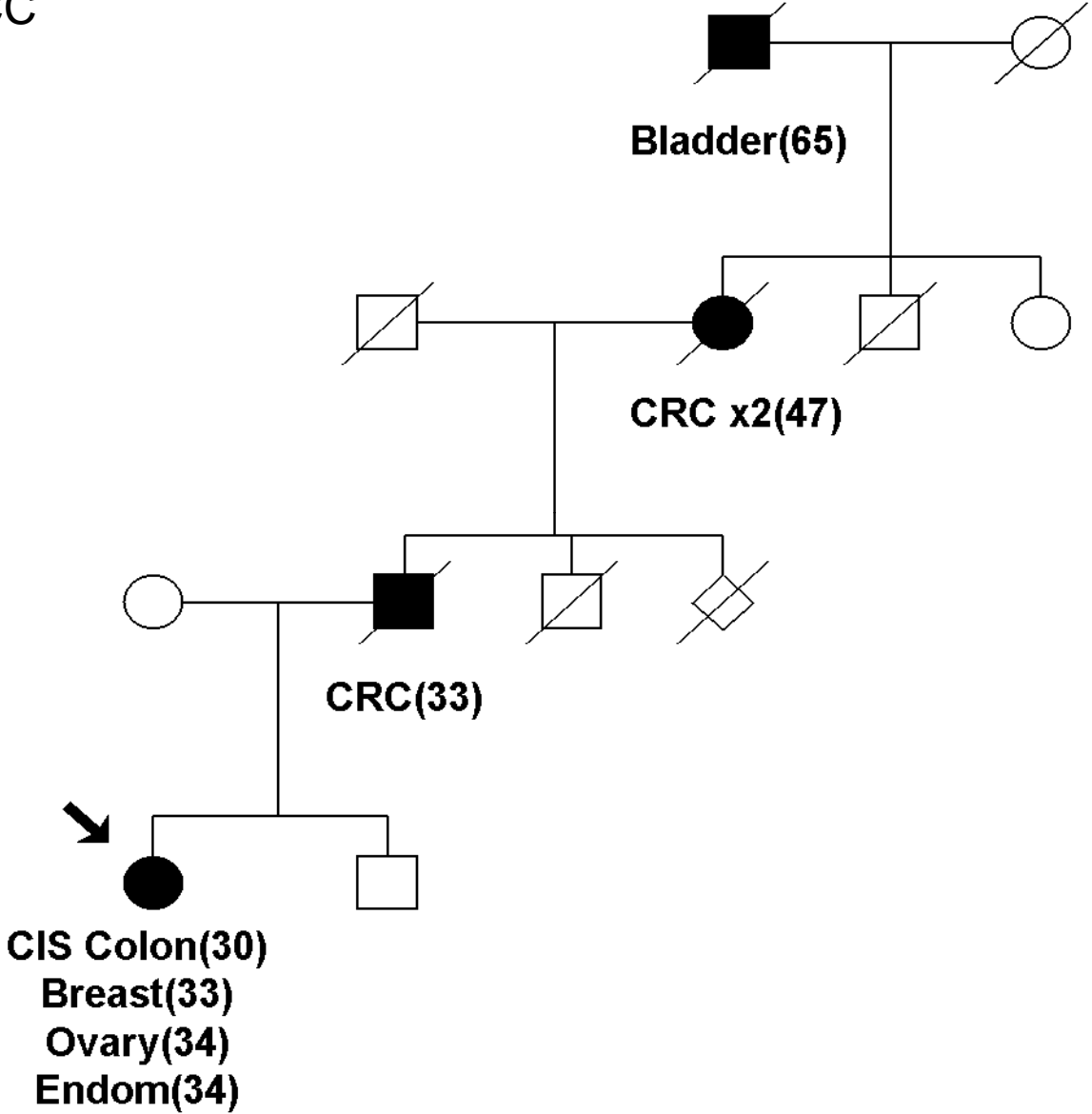
- Three affected family members with any HNPCC cancer
 - One is first degree relative of the other two
 - Two successive generations
 - One before 50y
 - Exclusion of familial adenomatous polyposis



1999 revision:

endometrial, ovarian,
stomach, ureter/renal pelvis,
brain, small bowel,
hepatobiliary tract,
sebaceous skin

LYNCH/HNPCC
Family



Summary Lynch Colon Ca

- Cancer onset 20-25 years earlier than sporadic counterpart
- Predominance of cancer of the proximal colon(70% proximal to splenic flexure)
- Excess incidence of two CRC
- Accelerated carcinogenesis CRC



Apparent better survival.

Endometrial Cancer Lynch Syndrome

- 50% of cases endometrial is the first cancer
- Incidence of Lynch Syndrome in endometrial ca pt.
 - 8% cases under 50y
 - 23% if <50y & first degree relative with cancer
 - 18% if synchronous colon and endometrial



" By identifying that an endometrial cancer patient has Lynch syndrome, clinicians may institute screening for colon cancer and prevent the development of a second potentially lethal cancer."

K Lu et al. Gynecologic Cancers in Lynch Syndrome 2005

Newfoundland Lynch Families

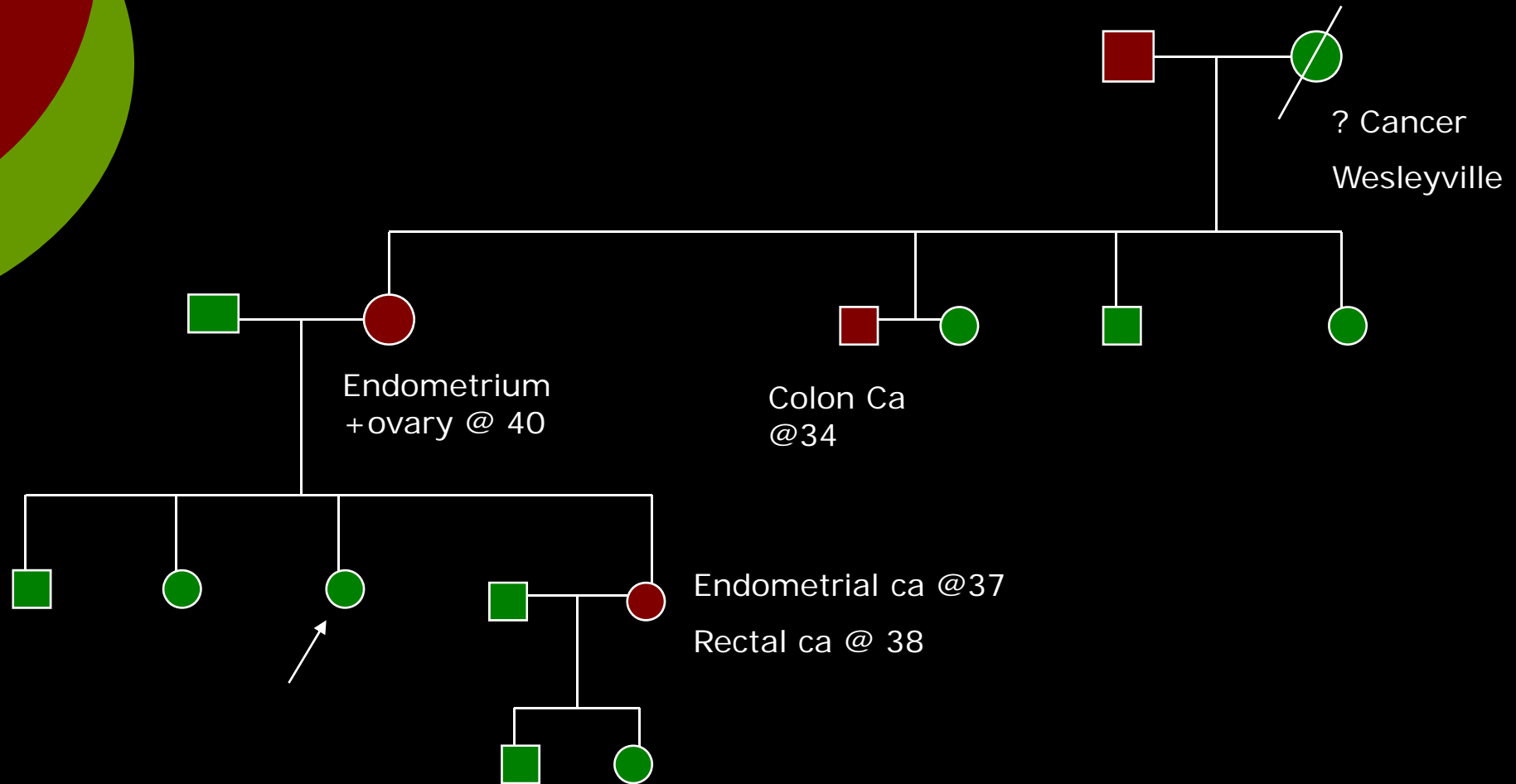


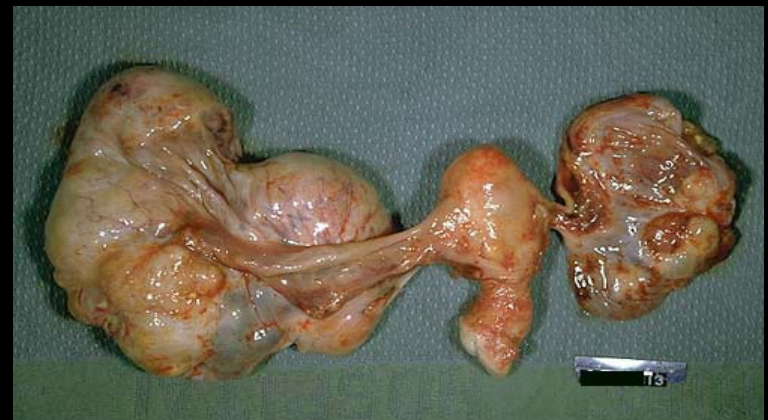
Table 4.

Cumulative Risk of Developing Any Cancer; of Developing Colorectal, Endometrial, Ovarian, and Other Cancers; and of Death Resulting From Cancer in 75 Male and 77 Female HNPCC Mutation Carriers

Clinical Event	Carriers (n)	Events (n)	Cumulative Risk by Age (yr)						Relative Risk	P Value
			≤30	≤40	≤50	≤60	≤70	≤80		
First cancer										
Males	75	44	0.1	0.41	0.72	0.86	1	1	NS	
Females	77	47	0.04	0.25	0.72	0.9	0.9	1		
CRC										
Males	75	36	0.09	0.32	0.62	0.77	0.92	0.92	2.8	0.001
Females	77	22	0.01	0.08	0.36	0.39	0.64	0.82		
Endometrial (Females)	77	22	—	0.09	0.37	0.59	0.79	0.79	—	
Ovarian (females)	77	12	—	0.06	0.22	0.22	0.36	0.36	—	
Other cancers										
Males	75	19	0.01	0.11	0.33	0.45	0.82	0.82	NS	
Females	77	21	0.03	0.11	0.21	0.34	0.57	0.79		
Cancer deaths										
Males	75	29	0.07	0.23	0.40	0.56	0.80	0.9	2.1	0.01
Females	77	22	0.01	0.06	0.18	0.43	0.59	0.69		

HNPCC = hereditary nonpolyposis colorectal cancer; NS = not significant; CRC = colorectal cancer.

Ovarian Cancer



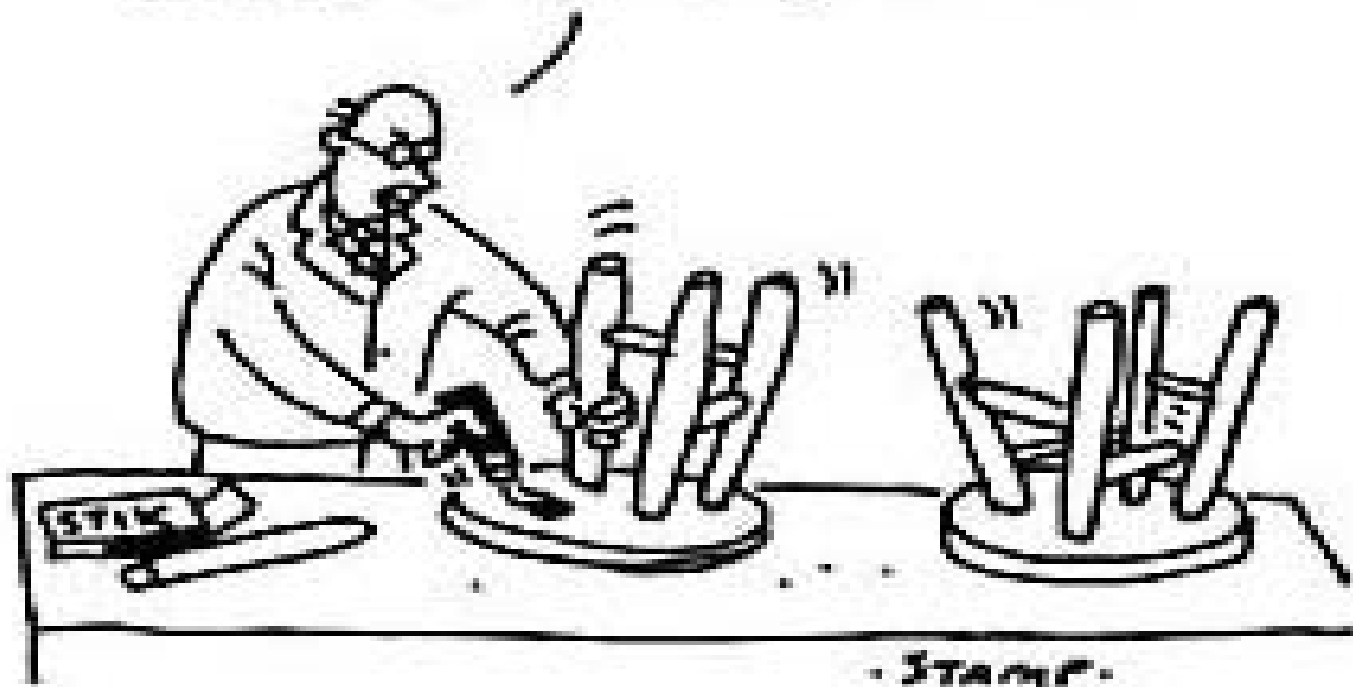
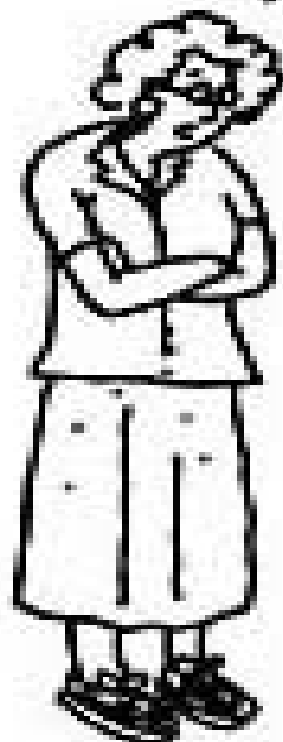


Ovarian Cancer in Lynch Syndrome

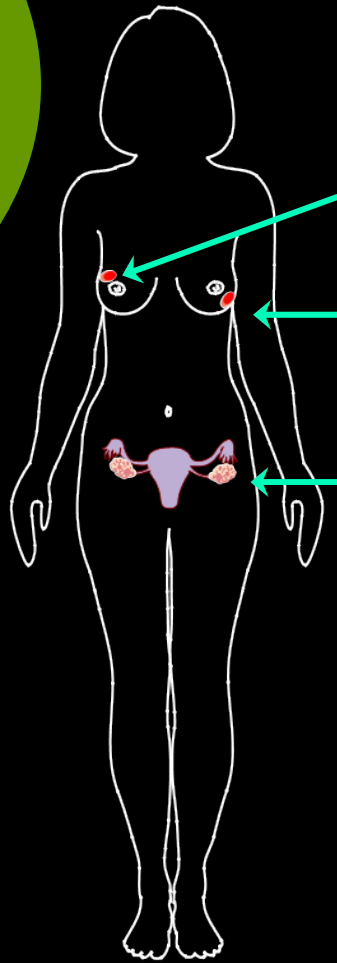
- Less well understood
- Age at onset younger 42.7 years
- 94% epithelial
- Preliminary research one big difference:
 - Earlier stage at diagnosis 84% Stage I or II
 - Overall survival 69%

Loose
Stools?

Irritable dowel syndrome



BRCA-Associated Cancers: Lifetime Risk



Breast cancer 56%–84% (often early age)

Second primary breast cancer 40%–60%

Ovarian cancer BRCA 1 35%–60%
BRCA 2 10-27%

Two different mutations

BRCA 1 mutation : Chromosome 17 1990

BRCA 2 mutation : Chromosome 13 1994

BRCA1/BRCA2

- Tumor suppressor genes located on 17q and 13q
- 1/800 north american women carry BRCA1
- 1/100 eastern european jewish ancestry
- Autosomal dominant with variable penetrance

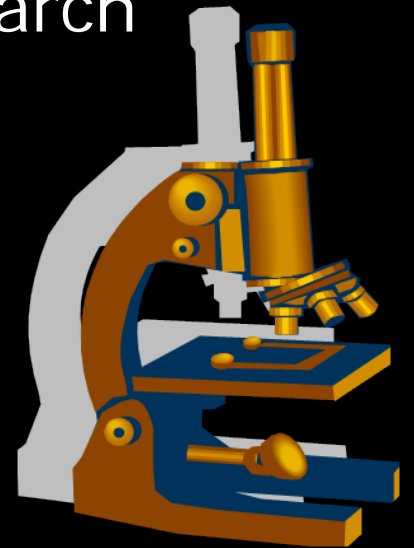


BRCA Syndromes

- Ovarian cancer survival is the same as sporadic cancers *NEJM 2007 Jul*
- Age of onset 49years
- BRCA 1 less likely to be estrogen sensitive
- Prevention complicated by
 - Fear of estrogen
 - TRAM flaps
 - Tamoxifen

Genetic Testing

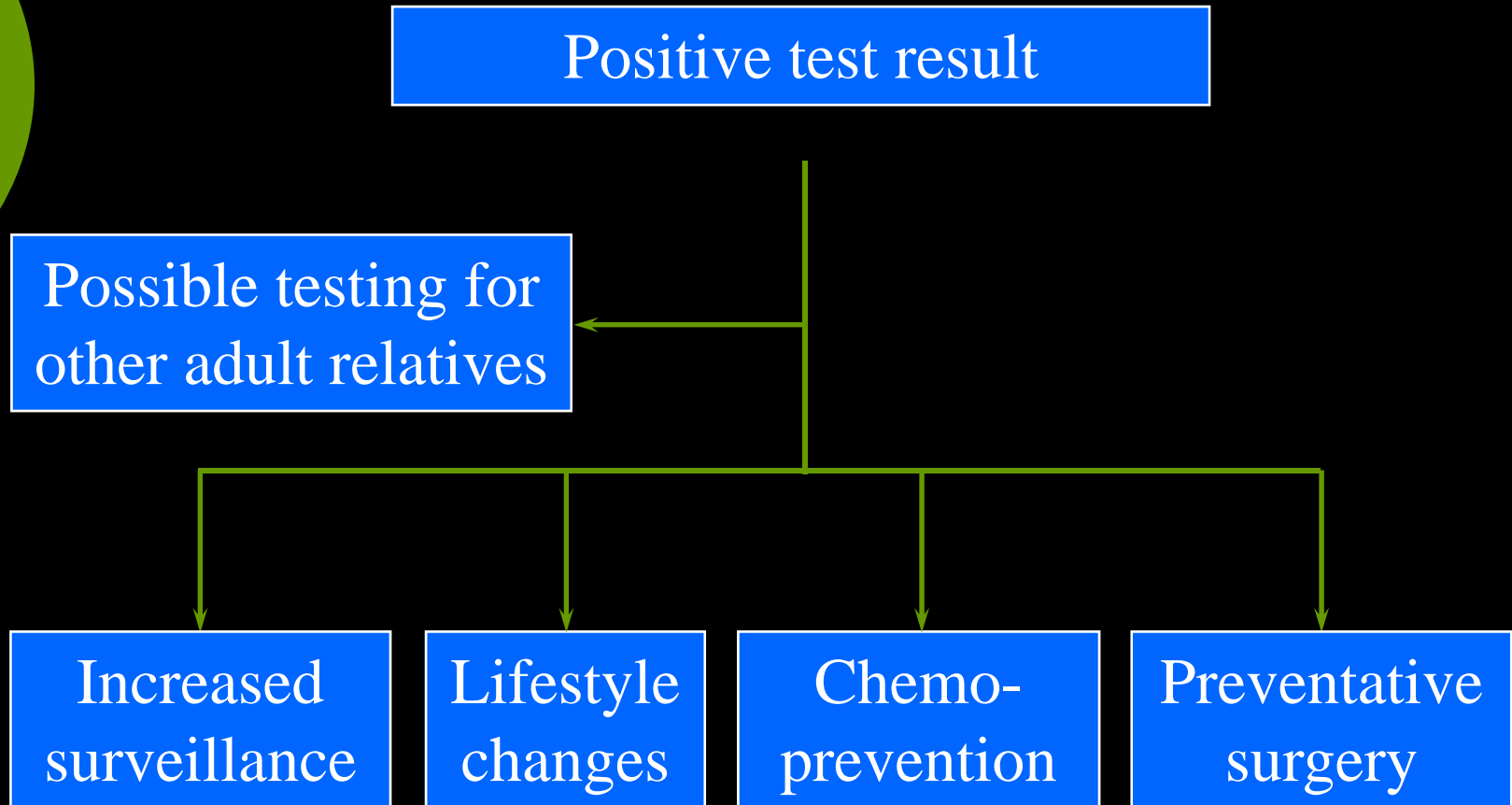
- Never as simple as it seems
- Directed by genetics department
- Must have sample from affected individual
- First look for known mutations
- If these are negative, then a search for other possible mutations is research based.
- Even if the family looks bad, often no mutation is found





*"Are you sure the doctor said
to take ginseng? I think he said
to take gin and sing."*

Clinical Management of a Mutation-Positive Patient



Oral Contraceptive Use for Chemoprevention

Duration OCP Use

RR Ca Ovary

Never

1.0

3-11 months

0.6-0.7

1-4 years

0.6-0.7

5-9 years

0.4

>10 years

0.2

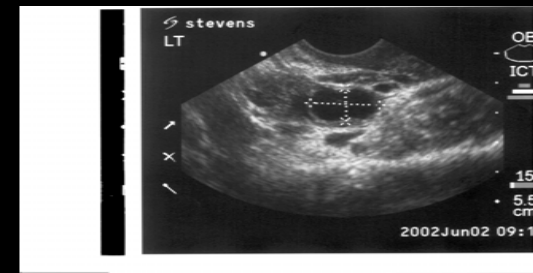


OCP and Ovarian CA

- Narod *et al. NEJM 1998*
 - “Use of OCPs decreases chance of developing ovarian cancer by about 50% in women with BRCA gene mutations”
- Modan *et al NEJM 2001*
 - “Premature to use OCPs for chemoprevention of ovarian cancer in BRCA1/2 pts”

Cochrane Review Ovarian Cancer Screening 2007

- 25 prospective screening studies
- N=435-22,000 (U/S and Ca 125)
- High sensitivity
 - ultrasound 100%
 - CA125 85%
- Positive predictive value
 - 3% ultrasound
 - 15% Ca125
- 3-12% women recalled for further testing
- "Lack of evidence on whether screening could reduce mortality"



Ovarian Cancer Screening

Stay Tuned...

High Risk

- RCT not acceptable
- 2 nonrandomized prospective studies in progress
 - CGN (US) n=2200
 - Familial Screening study (UK) n=1500

Population Screening

- 2 large RCTs coming soon
- UKCTOC n=200,000
- PLCO study NIH
 - 74,000

Prophylactic Surgery

- Reduction in ca ovary and breast
- Still can get primary peritoneal cancer 1-2%



- Surgical Risks
- Laparoscopy vs. Laparotomy
- Quality of life :body image
- Management of menopause/HRT afterwards

Prophylactic Oophorectomy in BRCA carriers

- Surgical considerations
 - Rate of occult ca 3-17%
 - Laparoscopy- don't morcellate specimens
 - Pathology ultra-sectioning
- Excellent review: Journal Clinical Oncology July 2007
Kauff N, Barakat R

RRSO in BRCA Patients Study	N= RRSO	Gynecologic Cancer HR (CI)	Breast Cancer HR (CI)
Kauff 2002	98	0.15 (0.02-1.31)	0.32 (0.08-1.20)
Rebbeck 2002	259	0.04 (0.01-0.16)	0.53 (0.33-0.84)
Rutter 2003	251	0.29 (0.12-0.73)	
Eisen 2005	1439		0.46 (0.32-0.65)
Domchek 2006	155	0.11 (0.03-0.47)	0.36 (0.20-0.67)
Finch 2006	1045	0.20 (0.07-0.58)	

No mutation known?

- Breast Cancer Linkage Consortium 1998
 - 237 families 4 breast cancer
 - If one ovarian cancer, linkage to BRCA1/2, even if a mutation could not be identified
- Memorial Sloan Kettering 2005
 - 165 BRCA negative cancer families
 - Risk breast ca 3X
 - Ovary risk not higher

What about the uterus?

- Adds morbidity
- Simplifies HRT
- Distal tube cancer observed in BRCA patients: take out tubes
- ? Serous uterine cancer risk also elevated
- No guideline
 - "certainly reasonable"
 - "informed decision"

Breaking news.....

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prophylactic Surgery to Reduce the Risk of Gynecologic Cancers in the Lynch Syndrome

Kathleen M. Schmeler, M.D., Henry T. Lynch, M.D., Lee-may Chen, M.D., Mark F. Munsell, M.S., Pamela T. Soliman, M.D., Mary Beth Clark, M.S.W., Molly S. Daniels, M.S., Kristin G. White, B.S., Stephanie G. Boyd-Rogers, R.N., Peggy G. Conrad, M.S., Kathleen Y. Yang, M.D., Mary M. Rubin, Ph.D., Charlotte C. Sun, Dr.P.H., Brian M. Slomovitz, M.D., David M. Gershenson, M.D., and Karen H. Lu, M.D.

ABSTRACT

BACKGROUND

Women with the Lynch syndrome (hereditary nonpolyposis colorectal cancer) have a 40 to 60 percent lifetime risk of endometrial cancer and a 10 to 12 percent lifetime risk of ovarian cancer. The benefit of prophylactic gynecologic surgery for women with this syndrome has been uncertain. We designed this study to determine the

N=315

Ovary

Endometrium

12/223 controls

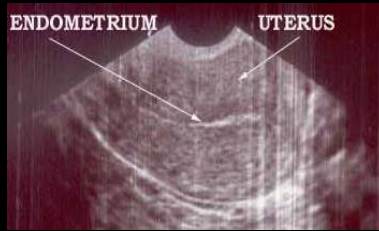
69/210 controls

0/47 cases

0/61 cases

p=0.09

p=0.001



Lynch Syndrome Recommendations

- OCP excellent risk reduction
- Consider hysterectomy at the time of colon surgery
- JAMA 2006 Systematic Review
 - Annual
 - Endometrial pipelle
 - TV Ultrasound
 - Colonoscopy 1-2 years
 - Urine cytology
 - "Evidence supports" prophylactic surgery



"Oh, hi, Steve ... sure I can talk ... I'm just waiting for the doctor to come up with a diagnosis I agree with."



Our Approach

- Rely heavily on genetics opinion
- If mutation status known
 - Lynch
 - OCP
 - Endometrial Biopsy/US/Ca 125
 - Discuss surgery
 - Ensure other screening is being done
 - BRCA
 - Oophorectomy favoured if premenopausal breast ca
 - US/Ca125
 - Refer mammogram and breast MRI



Our Approach

- No mutation status is known
 - Evaluate the likelihood of a mutation
 - Usually proceed with screening only
 - Informed patient
 - Significant family history
 - Significant personal history
 - Difficult screening
 - ... surgery

Summary



" You only find what you look for & you only diagnose what you know."

- Ask about family history
- Refer to genetics



Real life case #1

- 38y.o. G0 breast ca @ 34
- Ammenorrhoeic with chemo
- Tamoxifen
- Adopted
- Now pv bleeding

Real life case #1

- 38y.o. Go breast ca @ 34
- Ammenorrhoeic x 2years after chemo
- Tamoxifen
- Now pv bleeding
- Endometrial biopsy proliferative
- FSH normal
- Wants ovaries out

Real Life Case #2

- 59y.o.G2 breast ca 5years ago
- Mother had ovarian cancer @ 50y
- Maternal uncle and grandfather had colon ca @ 45y, 60y.
- TRAM flap with infected mesh last year
- Thickened endometrium



Real Life Case #2

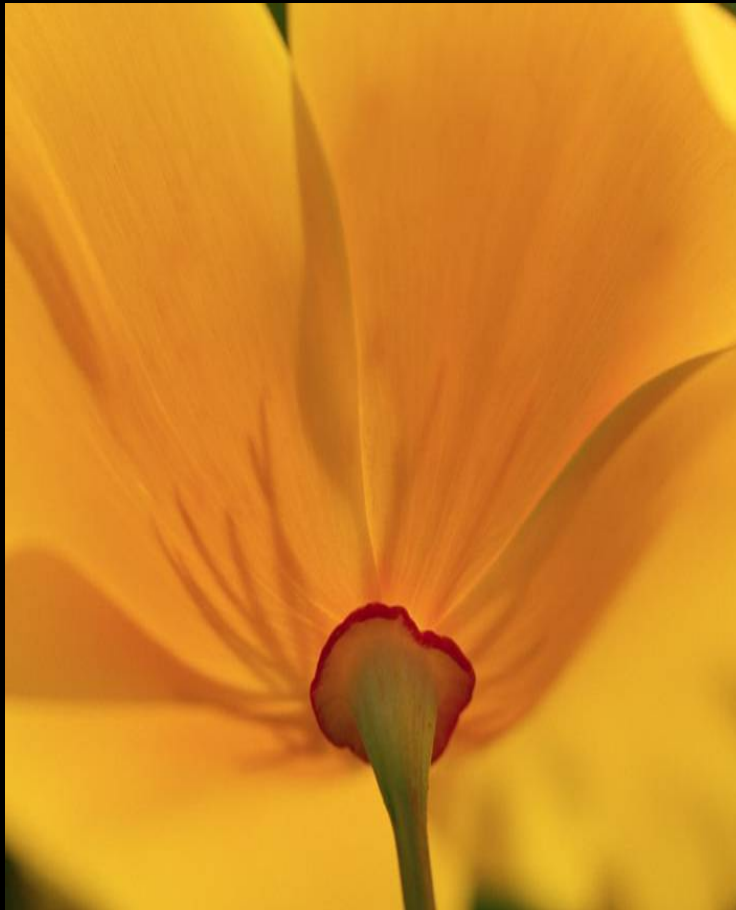
- 59y.o.G2 breast ca 5years ago
- Mother had ovarian cancer @ 50y
- Maternal uncle and grandfather had colon ca @ 45y, 60y.
- TRAM flap with infected mesh last year
- Thickened endometrium
- Blood work for DNA sent to the lab 4 months ago
- Pipelle and D&C normal
- Does not want surgery



Real Life Case #3

- Educated 50y G3
- Ca breast @ 46y
- Both sisters and mother ca breast ~ 50y
- Genetics counseling and testing
 - BRCA1/2 negative
- She wants ovaries removed

Summary



" You only find what you look for & you only diagnose what you know."

- Ask about family history
- Refer to genetics