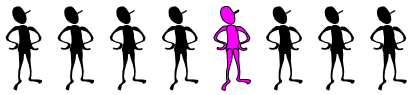
Risk Predictors for Breast Cancer

Heather Hampel, MS, CGC
Doreen Agnese, MD

Breast cancer is common

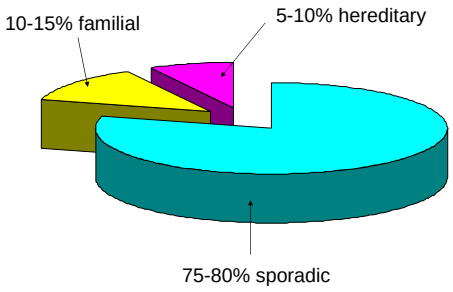
1 in every 8 American women will be diagnosed with breast cancer in their lifetimes



Risk Factors for Breast Cancer

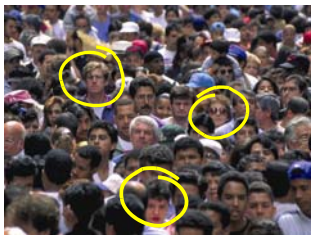
- Gender
- Increasing age
- Family history
- Early menarche/ late menopause
- Nulliparity
- Personal history
- LCIS
- Atypical hyperplasia
- Hormone replacement therapy

Most cancers are not inherited



Who Is at High Risk for Cancer?

History is the key….



Accurate risk assessment

Appropriate medical follow-up

Risk Assessment Tools

- Models that predict the lifetime risk for developing breast cancer
  - Gail Model
  - Claus Model
- Models that predict the likelihood that someone has a BRCA gene mutation
  - BRCApro
  - UPenn model
  - Myriad Prevalence tables

Gail Model

Incorporates

- Current age
- Reproductive history
- Number of breast biopsies (and presence of atypical hyperplasia)
- Family history of breast cancer in first-degree relatives only (up to a maximum of two)

Does not incorporate

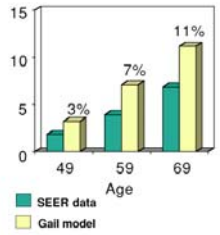
- Family history of
  - other cancers (e.g., ovarian)
  - breast cancer in second-degree relatives
  - breast cancer in paternal relatives
- Age at breast cancer diagnosis in relatives

Gail MH et al. *J Natl Cancer Inst.* 1989;81:1879-1886.

ASCO

Risk Analysis Using Gail Model

Age at menarche: 15
Previous breast biopsies: 0
Atypical hyperplasia: none
Age at birth of 1st child: none
Mother/sisters with breast cancer: 1

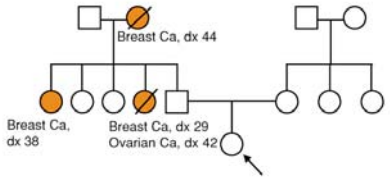


Gail MH et al. *J Natl Cancer Inst.* 1989;81:1879-1886.

ASCO

http://www.cancer.gov/bcrisktool/

Gail Model Can Underestimate Hereditary Risk of Breast Cancer



This woman's breast cancer risk would be greatly underestimated

ASCO

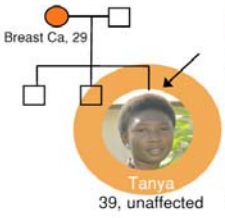
Claus Tables

- Statistical model to calculate cumulative breast cancer risk based on family history
- Risk estimates derived from the family history of 5,000 breast cancer cases (age range, 20–54 years) and age-matched controls in the United States
- Family history of breast cancer is the only risk factor considered

Claus EB, et al. *Cancer.* 1994;73:643-651.

ASCO

Cumulative Risk Using Claus Tables



Woman's current age	Age at diagnosis of first-degree relative with breast cancer			
	20–29	30–39	40–49	70–79
29	.007	.005	.003	.001
39	.025	.017	.012	.005
49	.062	.044	.032	.015
59	.116	.086	.064	.035
69	.171	.130	.101	.062
79	.211	.165	.132	.088

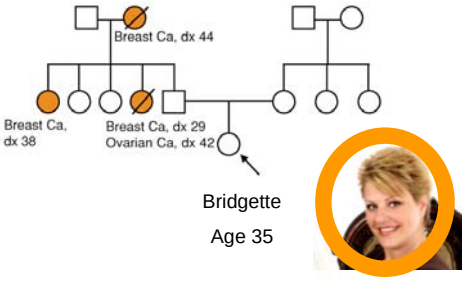
Claus EB, et al. *Cancer.* 1994;73:643-651.

ASCO

Clinical Features that suggest a BRCA mutation may be present

- Multiple cases of early onset breast cancer (<50)
- Ovarian cancer
- Male breast cancer
- BRCAPRO risk >10%
- Ashkenazi Jewish or Icelandic person with breast and/or ovarian cancer
- Any person in family with known *BRCA1* or *BRCA2* mutation

What is the risk that this family has a BRCA mutation?



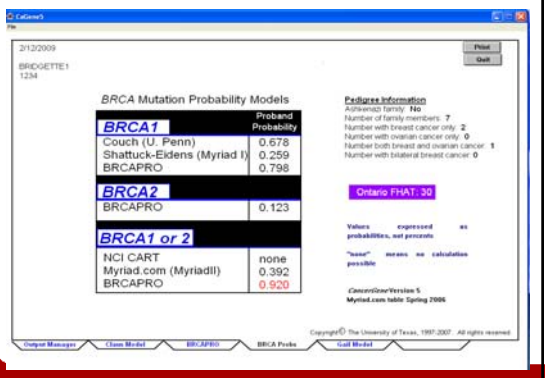
Estimating *BRCA1* and *BRCA2* Carrier Probability: BRCAPRO

- Computerized, statistical Bayesian model that calculates *BRCA1* and *BRCA2* carrier probability based on
  - History of breast or ovarian cancer, and age(s) at diagnosis in the proband and in first and second degree relatives
  - Current age/age at death of unaffected relatives
- Derived from published estimates of gene prevalence and penetrance, which are updated periodically
- Licensing agreement and free access is available through http://astor.som.jhmi.edu/brcapro
- The model is also part of CancerGene, a free comprehensive breast cancer risk assessment package: http://www.swmed.edu/home_pages/cancergene.

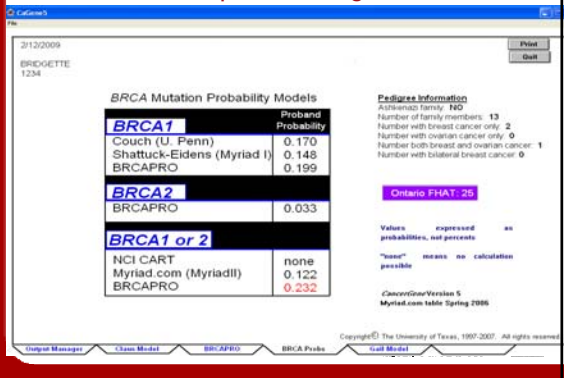
Parmigiani G et al. *Am J Hum Genet*. 1998;62:145-158.

ASCO

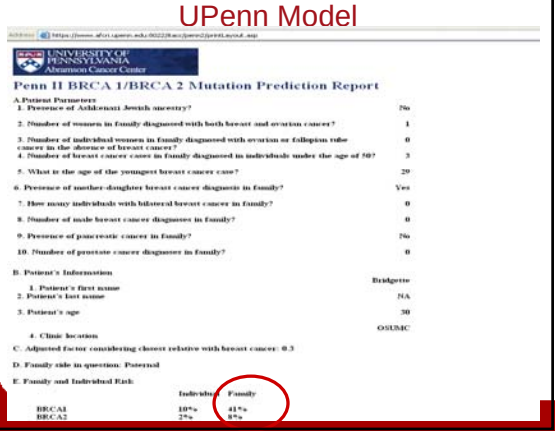
BRCApro for paternal aunt



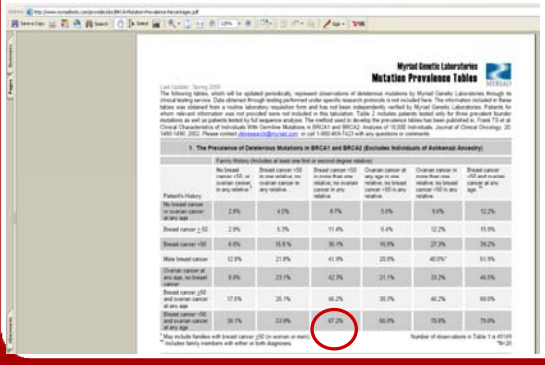
BRCApro for Bridgette



UPenn Model



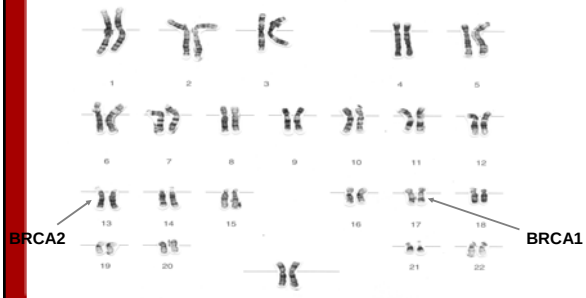
Myriad Prevalence Tables



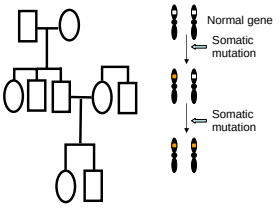
Which of the following models is not appropriate for a women with a strong family history of breast cancer?

1. BRCApro
2. Gail model
3. Myriad prevalence tables
4. UPenn model

Hereditary Breast-Ovarian Cancer (HBOC)

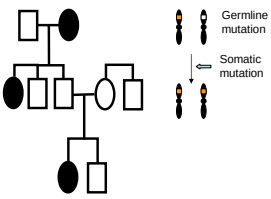


Sporadic



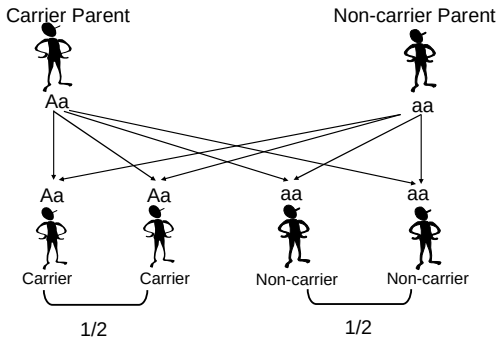
- Later age at onset (60s or 70s)
- Little or no family history of cancer
- Single or unilateral tumors

Inherited

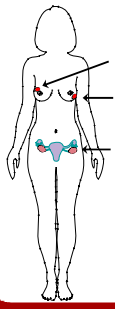


- Early age at onset (<50)
- Multiple generations with cancer
- Clustering of certain cancers (i.e. breast/ovarian)

Autosomal Dominant Inheritance



BRCA1-Associated Cancers: Risk by age 70



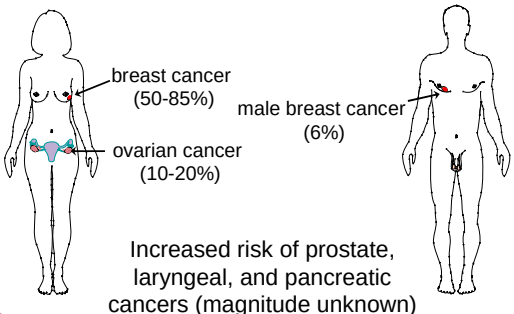
Breast cancer 50-85% (often early age at onset)

Second primary breast cancer 40%-60%

Ovarian cancer 15-45%

Possible increased risk of other cancers (eg, prostate)

BRCA2-Associated Cancers: Risk by age 70



Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)

Benefits, Risks, and Limitations of BRCA Testing

Benefits	Risks and Limitations
• Identifies high-risk individuals	• Does not detect *all* mutations
• Identifies noncarriers in families with a known mutation	• Continued risk of sporadic cancer – those who test neg may have false sense of assurance
• Allows early detection and prevention strategies	• Efficacy of interventions unproven
• May relieve anxiety	• May result in psychosocial or economic harm

Cost of Testing

- Comprehensive analysis
  - $3120
- Follow-up testing for large gene rearrangements
  - $650
- Single-site analysis
  - $440
- Multi-site 3
  - $535

Possible Results

- Positive
- Negative
  - True negative
  - Negative in affected individual
- Variant of uncertain significance
  - Additional information needed

BRCA Variant Study

- OSU is a contributing site to this NCI-funded Mayo-based study
- The goal is to functionally, genetically, statistically and phylogenetically decipher the pathogenicity of missense mutations (mutations of uncertain significance) within the *BRCA1/2* genes

Genetic Counseling Is Integral to the Testing Process

Genetic Counseling: typical session

- Collection of personal and family history
  - 3 generation pedigree
  - Validation with medical records
- Education and risk assessment
- Options for genetic testing and medical management
  - Discussion of risks, benefits and limitations
  - Screening/Chemoprevention/Prophylaxis
- Follow-up
  - Provide support
  - Family members

http://www.cancer.gov/search/genetics_services/

Probability of a *BRCA1* or *BRCA2* Mutation in a Woman w/Breast Ca <50

Any relative with Br Ca < 50?	Any relative with Ov Ca?	Proband with Bilateral Br or Ov Ca?	Probability (%)
✓			25
	✓		35
		✓	51
	✓	✓	71

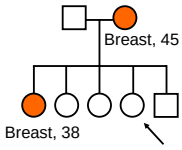
Frank TS et al. *J Clin Oncol* 16:2417, 1998

What is the relevance of Ashkenazi Jewish background?

- 1 in 40 Ashkenazi Jews (males and females) carries a BRCA1 or BRCA2 mutation
- 2-3% of the Jewish community may have a susceptibility for hereditary breast and ovarian cancer
- 1/400 carrier rate in non-Jewish populations

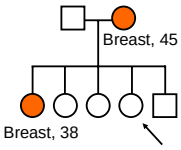
Risk of *BRCA* Gene Alteration

Non-Jewish



~20% chance

Ashkenazi Jewish



~32% chance

Which person has the highest likelihood of having a BRCA mutation?

- Non-Jewish women with breast cancer at 30
- Jewish women with breast cancer at 30
- Non-Jewish women with ovarian cancer at 45
- Jewish women with ovarian cancer at 45

Our Cases

- Jennifer has an 11% lifetime risk for breast cancer
- Tanya has a 21.1% lifetime risk for breast cancer
- Bridgette has tested positive for a BRCA mutation found in her aunt

Management of Women at Elevated Risk

- Surveillance
- Chemoprevention
- Prophylactic Surgery

Breast Cancer: Surveillance

- Monthly BSE beginning at age 18
- CBE every 6 months starting at age 25 (or 5-10y before the earliest dx in family)
- Annual mammography
  - For moderate risk, begin 5-10 years before earliest diagnosis
  - For HBOC, begin at age 25 of 5-10 years before earliest diagnosis

Who should have breast MRI?

- Women at >20-25 % lifetime risk using models based largely on family history
- Women with a known BRCA1 or BRCA2 mutation

CA Cancer J Clin. 2007;57:75-89.

Breast MRI

- 1909 women with cumulative lifetime risk of breast cancer > 15%
  - 358 carriers of germline mutations
- CBE q 6 mos; Mammo and MRI q 1 year
- Median follow-up 2.9 years
  - 44 invasive cancers
  - 6 DCIS
  - 1 lymphoma
  - 1 LCIS
- Surveillance group compared to 2 groups of age-matched controls

Kriege. *NEJM* 2004; 351(5): 427-437.

Breast MRI

- Sensitivity for detecting invasive ca
  - CBE 17.9%
  - Mammo 33.3%
  - MRI 79.5%
- Specificity
  - CBE 98.1%
  - Mammo 95%
  - MRI 89.8%
- Invasive tumors < 10mm
  - 43.2% vs. 14% (p<0.001)
  - 43.2% vs. 12.5% (p=0.04)
- Incidence of positive axillary nodes and micrometastasis
  - 21.4% vs. 52.4% (p<0.001)
  - 21.4% vs. 56.4% (p=0.001)

Kriege. *NEJM* 2004; 351(5): 427-437.

Breast MRI

- Surveillance study of 236 Canadian women with *BRCA1/2* mutations
- Comparison of CBE, mammo, US and MRI; over 6y, 22 cancers detected (16 invasive, 6 DCIS)
- Sensitivity/specificity
  - MRI 77%/ 95.4%
  - Mammo 36%/99.8%
  - US 33%/96%
  - CBE 9.1%/99.3%
- Sensitivity of all 4 modalities combined vs. mammo + CBE 95% vs. 45%

Warner *JAMA.* 2004; 292(11): 1317.

Breast MRI

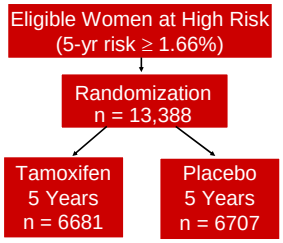
- More specific, but less sensitive than mammogram
- Expensive
- Wind up doing more biopsies of benign lesions to find more cancers
- Can still miss cancers
- Leads to greater number of additional studies (ultrasounds, follow-up MRIs)

Which of our cases should not have breast MRI for screening?

- Jennifer
- Tanya
- Bridgette
- I'm not sure

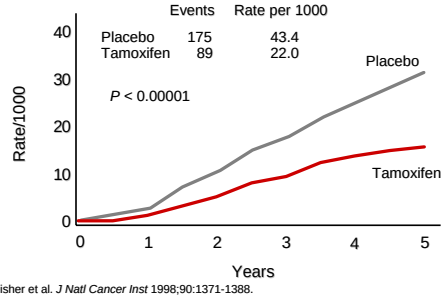
Chemoprevention

Breast Cancer Prevention Trial (P-1) Study Design



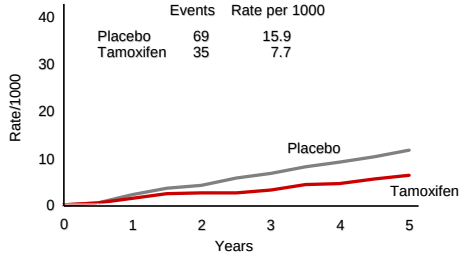
Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Cumulative Rate of Invasive Breast Cancer



Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Cumulative Rate of Noninvasive Breast Cancer*



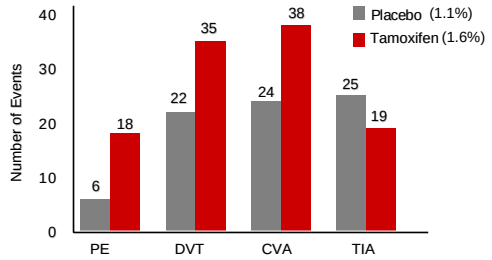
*Analysis included women who had LCIS at baseline.
Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Endometrial Cancer

Age (yr)	Placebo n	Tamoxifen n	Risk Ratio
≤ 49	8	9	1.21
≥ 50	7	27	4.01
Total	15 (0.2%)	36 (0.5%)	2.53

Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Vascular Events



PE = pulmonary embolism; DVT = deep vein thrombosis; CVA = cerebral vascular accident (stroke); TIA = transient ischemic attack

Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Chemoprevention in HBOC

- Matched case-control study
  - 209 women with bilateral breast ca and *BRCA1* or *BRCA2* mutation
  - 384 women with unilateral breast ca and *BRCA1* or *BRCA2* mutation
- Tamoxifen protected against contralateral breast cancer
  - *BRCA1* odds ratio 0.38 (95% CI 0.19–0.74)
  - *BRCA2* odds ratio 0.63 (95% CI 0.20–1.50)

Narod *Lancet* 2000, 356: 1876

Chemoprevention in HBOC

Analysis of NSABP-P1 data in 320 women who developed cancer (288 with available DNA, 19 with mutations in *BRCA1* or *BRCA2*)

	Placebo	Tamoxifen	Risk Ratio
BRCA1+	3	5	1.67
BRCA2+	8	3	0.38
WT	182	87	0.48
All	211*	109	0.52

*Includes 288 genotyped cases and 32 cases without DNA available

King *JAMA* 2001, 286(18): 2251

Surgical Prophylaxis

Prophylactic Mastectomy

- Total mastectomy is recommended
- Prospective study of 139 women with *BRCA1* or *BRCA2* mutations, mean f/u 3 years
- No breast cancers in 76 women who underwent prophylactic mastectomy
- 8 breast cancers in 63 women undergoing regular surveillance

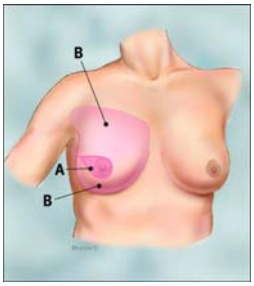
Meijers-Heijboer *NEJM* 2001; 345(3): 159

Prophylactic Mastectomy

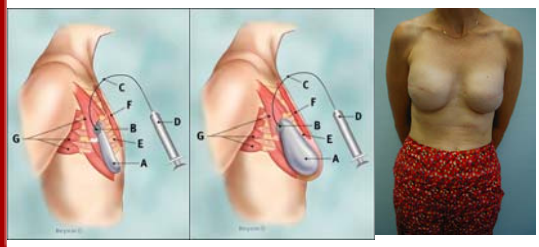
- Study of 483 women with disease-associated mutations in *BRCA1/2*, mean F/U 6.4 years
  - 2/105 (1.9%) women developed breast cancer after bilateral prophylactic mastectomy (subcutaneous)
  - 184/378 (48.7%) matched controls who did not have procedure developed breast cancer
- Significantly reduces breast cancer risk in *BRCA1/2* mutation carriers
  - 90% risk reduction in women with intact ovaries
  - 95% risk reduction in women with prophylactic BSO

Rebbeck *J Clin Oncol* 2004, 22(6): 1055-62

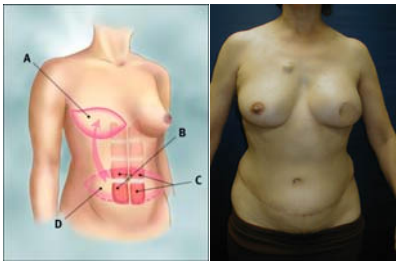
Skin-sparing mastectomy



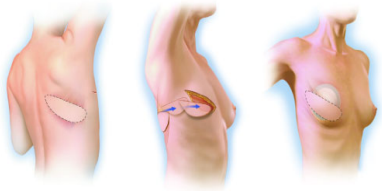
Reconstruction: Tissue expander/implant



Reconstruction: TRAM Flap



Latissimus Dorsi Flap With or Without Breast Implants

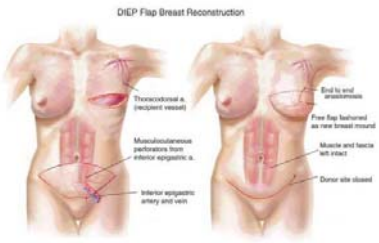


Step 1: A skin flap and muscle are taken from the donor site in the back.

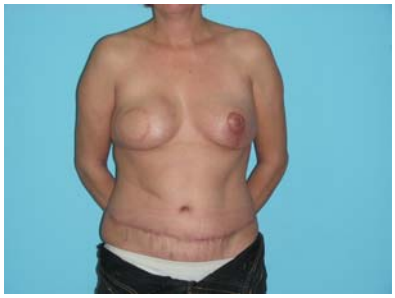
Step 2: The tissue is tunneled to the mastectomy and used to create a breast mound.

Step 3: An implant can also be used to create the breast mound.

DIEP Flap



DIEP Flap



Ovarian Cancer

- Abdominal pressure, bloating, or discomfort
- Nausea, indigestion, or gas
- Constipation, diarrhea, or frequent urination
- Abnormal bleeding
- Unusual fatigue
- Unexplained weight loss or gain
- Shortness of breath

Ovarian Cancer: Surveillance

- Pelvic examination and transvaginal ultrasound with color Doppler imaging every 6 months beginning at age 30-35 (or 5-10 years prior to the earliest dx in the family)
- Concurrent serum CA-125

"There are no data demonstrating that screening these high-risk women reduces their mortality from ovarian cancer. Nonetheless, [these measures] are recommended."*

*NIH Consensus Conference 1995, *JAMA* 273: 491

Ovarian Cancer: Chemoprevention

Oral Contraceptives

40% to 50% risk reduction in general population after 3 years cumulative use

- Limited data available for *BRCA*-mutation carriers; preliminary study showed a 60% risk reduction with ≥6 years use
- May increase breast cancer risk

CASH study *NEJM* 1987, 316:650;
Ursin *Cancer Res* 1997, 57:3678;
Narod *NEJM* 1998, 339:424

Prophylactic Oophorectomy

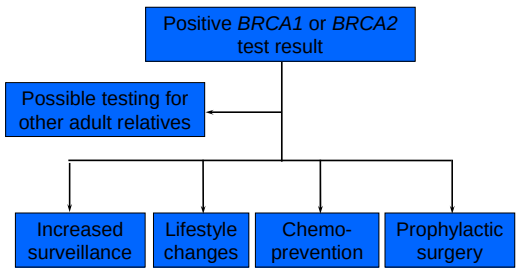
- Decreases risk of ovarian cancer by 95-99% (primary peritoneal carcinoma may still occur)
- Reduces risk of breast cancer by 76% if done prior to age 40 and by 50% if done prior to age 50
- Induces surgical menopause—HRT?
- Laparoscopic procedure reduces postsurgical morbidity

Rebbeck *NEJM* 2002, 346(21):1616;
Kauf *NEJM* 2002, 346(21):1609

Prophylactic oophorectomy

- Can be done laparoscopically
- Washings recommended, pathologic analysis requires serially sectioning rather than bivalving ovaries
- Hysterectomy
- Risk of Fallopian tube cancer
- Short-term HRT permissible

Clinical Management of *BRCA*-Positive Patient



ASCO

Which one of our cases should have prophylactic BSO within the next 5 years?

- Jennifer
- Tanya
- Bridgette
- I'm not sure

Thank you

- Referrals/Questions:
  - 614-293-7240
  - 888-329-1654
- http://www.internalmedicine.osu.edu/genetics/
- Family Health Link
  https://familyhealthlink.osumc.edu/Notice.aspx