

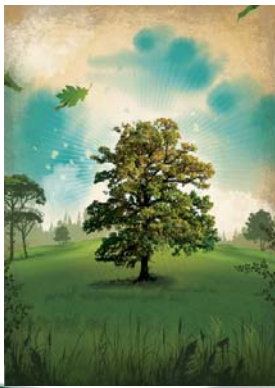
## Breast Cancer Risk Evaluation & Management

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Northwest Cancer Specialists



## Disclosures

- Speaker's Bureau
  - Myriad Genetic Laboratories



## Case #1

- 63 year old woman presents for routine screening mammogram
- History of 'cyst' removed from breast 'many years ago'



## Audience Participation

- What additional information is needed to assess this patient's risk of breast cancer?
  - A. Nothing more, her age is sufficient.
  - B. Whether there is breast cancer in the family.
  - C. What her ethnic background is
  - D. Information about her menstrual and reproductive history
  - E. All except A



## Audience Participation

- Answer : E



## Definition of High Risk

- NSABP-P1: Breast Cancer Prevention Trial
  - Tamoxifen vs. Placebo
  - Women age 60 and older
  - Women age 35-59 with an increased risk of breast cancer equivalent to that of a 60-year old (1.7% 5-year risk)



## Gail Model

- Current Age
- Age at Menarche
- Ethnicity
- Number of first-degree relatives with breast cancer
- Number of prior breast biopsies
- Atypia on breast biopsy
- Age at first live birth
- 5-year and lifetime estimates of breast cancer risk
- Relative risk of cancer:

Age at first live birth	# of affected relatives		
	0	1	2 or more
20 or younger	1	2.6	6.8
20-24	1.2	2.7	5.8
25-29 or no child	1.5	2.8	4.9
30 or older	1.9	2.8	4.2



## Case #1, continued

- 4 sisters, one with breast cancer in 40's
- 4 brothers, one with prostate cancer at 65
- Mother lived until age 76 without cancer
- Mother's twin had breast cancer in 40's
- Menarche at age 13
- First child at 26



## Audience Participation

- What is this woman's lifetime risk of breast cancer?
  - A. 10%
  - B. 20%
  - C. 30%
  - D. 40%

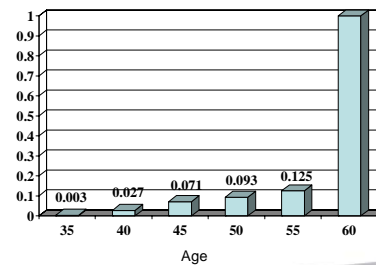


## Answer:

- Gail Model:
  - 5-year risk = 8.8%
  - Lifetime risk = 32.5%



## 'High-Risk' by Age



## Limitations of the Gail Model

- Only considers first-degree relatives
- Only includes relatives with breast cancer
- Personal history of other malignancy is not considered
- Does not help to define the possible presence of a genetic mutation
- Other plausible risk factors are not included, such as breast density, use of hormone replacement therapy, etc.



## The 'Other' Model: Claus

- Primarily family history based
- Includes first- and second-degree relatives
- No other criteria except age considered
- Breast cancer, with or without ovarian cancer



## Claus Table example

Age	Age of onset First Degree Relative					
	20-29	30-39	40-49	50-59	60-69	70-79
29 0.0004	0.007	0.005	0.003	0.002	0.002	0.001
39 0.005	0.025	0.017	0.012	0.008	0.006	0.005
49 0.02	0.062	0.044	0.032	0.023	0.018	0.015
59 0.04	0.116	0.086	0.064	0.049	0.040	0.035
69 0.07	0.171	0.130	0.101	0.082	0.070	0.062
79 0.10	0.211	0.165	0.132	0.110	0.096	0.088

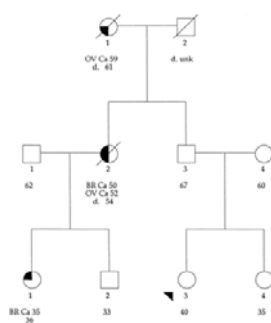


## Tyrer-Cuzick Model

- Estimates prior probability of harboring a BRCA1/2 mutation
- Then takes personal risk factors and modifies that risk
  - Age at menarche
  - Age at menopause
  - Parity, age at first child
  - BMI, height
  - LCIS
  - Atypia on biopsy



Ethnicity: French



- Claus : 9.4%, approximately the same as the general population.
- Gail: 9%-11%
- Modeling estimates reach 89% for BRCA1.
- By mendelian calculations, the chance that she has a mutation is one quarter of the family probability, which is still more than 20%.
  - $20\% \times 85\% = 17\%$



## Alternate Risk Calculators

- Siteman Cancer Center Breast Cancer Quiz
- Dr. Hall's Breast Cancer Risk Calculator
- NCI Risk Calculator (modified Gail)
- Breast Cancer Prevention .com



## Case #1

- 63 yo woman for routine screening mamm
- Changing calcifications noted
- Breast biopsy yields LCIS
- High risk by Gail Model...now what?

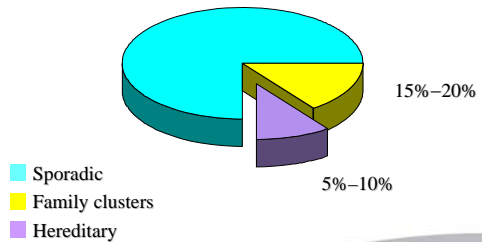


## Audience Participation

- What would you recommend?
  - A. Continue routine surveillance
  - B. Increase breast surveillance only
  - C. Increase breast surveillance and consider chemoprevention with tamoxifen
  - D. Go directly to prophylactic mastectomies because the risk of cancer is so high



## How Much Breast Cancer Is Hereditary?



## Features Suggestive of a Hereditary Risk of Breast Cancer

- Female breast cancer < 45-50
- 2+ on the same side of the family, diagnosed with breast cancer < 50
- Multiple primary tumors
  - (e.g., breast/ovary, breast/thyroid, breast/sarcoma, breast/breast)
- Ovarian cancer
- Ashkenazi Jewish ancestry
- Male breast cancer
- Early-onset breast cancer and ovarian cancer in the same bloodline
- Pancreatic cancer and a family history of breast cancer
- Early-onset prostate cancer (before age 60) and a family history of breast cancer
- Breast or ovarian cancer and melanin spots on the lips or buccal mucosa
- Breast cancer and oral papillomatosis and/or facial trichilemmomas
- Several generations of people with the same or related cancer (autosomal dominant pattern)



## Hereditary Breast Cancer Syndromes

- HBOC (BRCA)
  - up to 85%
- LiFraumeni (TP53)
  - Leukemia, soft tissue sarcoma, adrenocortical carcinomas
  - Risk of cancer 50% by age 30
- Cowden (PTEN)
  - Benign breast disease, benign thyroid tumors
  - Pathognomonic skin lesions
- Others:
  - Peutz-Jeghers
  - Ataxia Telangiectasia
  - CHK2\*1100delC
  - Lynch Syndrome (HNPCC) ??





## Case #2

- 39 yo woman diagnosed with invasive ductal carcinoma, ER/PR+, HER2 neg
- Unknown family history (adopted)
- Neoadjuvant chemotherapy

## Prevalence of BRCA Mutations

- General U.S. Population:
  - **1 in 500**
- Eastern European Jews (Ashkenazi)
  - **1 in 40**
  - Most due to three “founder” mutations commonly found in this population
- Founder mutations have been identified in Northern European groups and individuals of Hispanic descent as well.

## Prevalence of BRCA Mutations

Patient's History	Family History		
	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	2.8%	4.5%	5.6%
Breast cancer <50	6.8%	15.8%	16.9%
Ovarian cancer, no breast cancer	8.8%	23.1%	21.1%

[www.brcacalculator.com](http://www.brcacalculator.com)

JCO. 2002.20.1485-1490

## Prevalence of Mutations in Ashkenazi Jewish Individuals

Patient's History	Family History		
	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	6.9%	13.7%	15.6%
Breast cancer <50	12.0%	24.2%	38.8%
Ovarian cancer, no breast cancer	22.2%	37.0%	42.0%

[www.brcacalculator.com](http://www.brcacalculator.com)

JCO. 2002.20.1485-1490

## Watch out for the “Negative” Family History

- Adoption, Small family, or male-dominated family
- Early death from other causes
- Misunderstood diagnoses – “stomach cancer” that was actually widespread ovarian ca
- Family estrangement
- Surgical removal of the ovaries in premenopausal females lowers the risk of both ovarian and breast cancer

## Case #2

- Tested for HBOC
  - Found to have a mutation in BRCA2



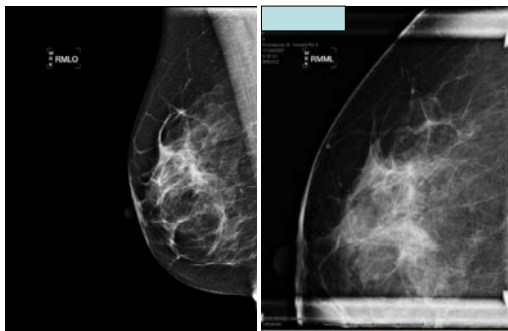
## Case #3

- 34 yo woman with T2N1M0 invasive ductal carcinoma, ER/PR+, HER2 neg
- NO family history
  - (9 siblings, 11 aunts/uncles)
- Lumpectomy followed by single mastectomy
  - Adjuvant chemotherapy
  - Adjuvant hormonal therapy refused



## Case #3, 4 years later

- 38 yo, new contralateral breast mass
- invasive ductal carcinoma, ER+/PRneg, HER2 neg
- Staging workup reveals mets to liver, lung, and bones



## Case #3, BRCA testing

- Tested for HBOC
  - BRCA2 mutation



## BRCA1 vs BRCA2

- Mutations in BRCA1 are roughly twice as common as those in BRCA2
- While mutations in either can cause cancer to develop at any age, or with a variety of clinical characteristics, there are some general tendencies that distinguish the two

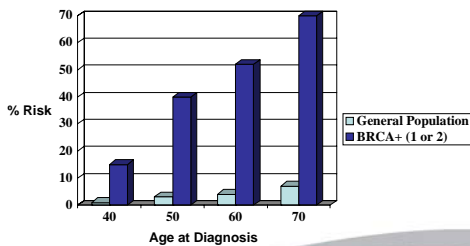


## Breast Cancer Features BRCA1 vs BRCA2

- Tend to be younger
- 70% ER negative
- Often triple negative
- Medullary histology
- More aggressive
- Ovary ca risk 40%
- Male breast ca 1-2%
- Closer to average age
- 70% ER positive
- Rarely triple negative
- Medullary is rare
- Average behavior
- Ovary ca risk 15-20%
- Male breast ca 7%



## Breast Cancer Risk by Age



## What about DCIS/LCIS/ADH?

- Current consensus is that DCIS carries the same weight as invasive breast cancer in determining an individual's risk for carrying a BRCA mutation (JAMA 2005)
- LCIS and ADH have not yet been shown to have an association with BRCA mutations



## Audience Participation

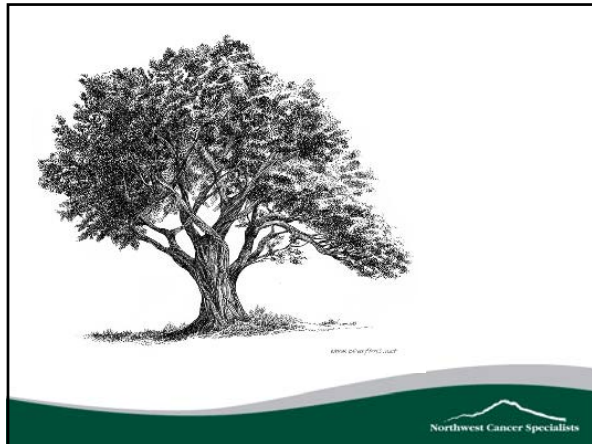
- Which heritable breast cancer syndrome is also associated with increased incidence of melanoma, pancreatic cancer, and prostate cancer?
  - A. LiFraumeni
  - B. Cowden
  - C. CHK2
  - D. BRCA1/2



## Answer

- D





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## Genetic Discrimination

- Over 200,000 pts have now been tested, and there are no documented cases of health care discrimination
- HIPAA, state laws
- GINA: Genetic Information Nondiscrimination Act

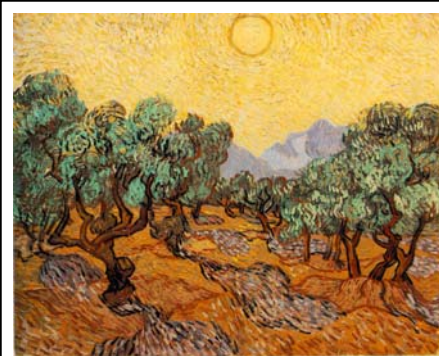


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State	Restricts Discrimination Based on Genetic Information in Life Insurance	Restricts... Disability Insurance	Restricts... Long-term Care Insurance	Requires Actuarial Justification to Use Genetic Information in Life Insurance	Requires Informed Consent to Use Genetic Information
OR	X	X	X		X
WA					

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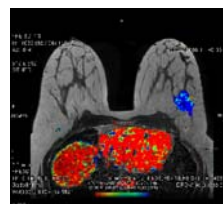
## Managing Patients Across the Risk Spectrum: The tools

- Surveillance
- Chemoprevention
- Prophylactic Surgery



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## Surveillance



- Imaging
- Breast Self-Exam
- Clinical Breast Exam

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Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer  
Kuhl CK, et al. JCO 2005

	Mammography		Ultrasound		Mamm + U/S		MRI		Mamm + MRI	
	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
All women	32.6	96.8	39.5	90.5	48.8	89	90.7	97.2	93.0	96.1
Without a personal history of cancer	33.3	95.5	41.7	88.3	41.7	87.1	66.6	96.2	75	95.1
Personal history of cancer	32.3	97.1	38.7	91	51.6	89.4	100	97.5	100	96.3
Risk 20%	50	96.5	67.7	90.4	83.3	88.2	100	97.4	100	95.5
Risk 21-40%	25	97.4	30	91.2	45	89.9	100	97.7	100	97.0
Mutation Carriers	25	96.9	25	91.2	37.5	88.7	100	97.5	100	94.1

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USPSTF Screening Mammography for Women Aged 40-50  
2002 vs 2009

- 2002: recommends the service  
*“the precise age at which the benefits justify the potential harms is a subjective judgment and should take into account patient preferences”*
- 2009: recommends against routine screening  
-based on systematic review<sup>1</sup> and modeling data<sup>2</sup>

<sup>1</sup>Nelson et al, Ann Intern Med 2009  
<sup>2</sup>Mandelblatt et al, Ann Intern Med 2009

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Screening for Breast Cancer: an update for the USPSTF  
Nelson et al, Ann Intern Med 2009

*“the number needed to invite for screening to prevent one breast cancer death is **1904** for women aged 40-49 years and **1339** for women aged 50-59 years”*

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Cancer Intervention and Surveillance Modeling Network  
Mendelblatt et al, Ann Intern Med 2009

*“the frontier curves for the mortality outcome show only **small gains** yet larger numbers of mammograms required when screening is started at age 40 years vs 50 years”*

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Screening Mammography Reduces Mortality

	relative risk reduction in the odds of death (%)
age 39-49	15
age 50-59	14
age 60-69	32
age 65-74	28
age 70-74	0

Biennial screening between ages 50-69 produces a projected 17% reduction in mortality, yet by initiating biennial screening to start at age 40, extending to age 79, there are only minor improvements in mortality, a further reduction of 3% and 7%, respectively.

Nelson et al, Ann Intern Med, 2009  
Henderson et al, Ann Intern Med, 2002  
Mandelblatt et al, Ann Intern Med, 2009

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USPSTF Assessment Harms of Detection/Early Intervention

- psychological stress
- unnecessary follow-up imaging tests and biopsies
  - false (+) results are more common in women aged 40-49
- overdiagnosis/overtreatment
  - detecting/treating a lesion that may never manifest clinically
- radiation exposure

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## USPSTF, 2009 Summary of Recommendations

- recommends biennial screening mammography for women aged 50-74  
*“there is moderate certainty that the net benefit is moderate”*
- current evidence is insufficient to offer a recommendation for screening mammography in women 75+ yrs

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## USPSTF, 2009 Summary of Recommendations

- recommends against routine mammographic screening in women aged 40-49  
*“there is moderate certainty that the net benefit is small and that moderate harms from screening remain at any age”*
- the decision to start regular, biennial screening mammography before age 50 should be individualized, taking into account the patient’s values with respect to benefits/harms

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## Other Recommendations

- ACS, AMA, NCCN
  - annual mammography beginning at age 40
- ACOG
  - mammography every 1-2 yrs ages 40-49, then annually after age 50
- ACP
  - screening mammography decisions in women aged 40-49 should be individualized
- AAFP
  - has endorsed USPSTF recommendations in the past

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### Perspective

On Screening Mammography in Women aged 40-49

*“The benefit is that the likelihood of dying of breast cancer is decreased and I don’t see how any of the risks that they (USPSTF) state outweighs that benefit”*

David Dershaw, M.D.  
Director of Breast Imaging  
Memorial Sloan-Kettering Cancer Center

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### Perspective

On Screening Mammography in Women aged 40-49

*“Women need a clear message: early detection offers a woman the best chance for a cure, and mammography is essential for early detection of breast cancer. Failing to identify those women in their 40’s with cancer and having them wait until they are screened at age 50 is a disservice. By then breast cancer can be advanced and more difficult to treat.”*

Constance Lehman, M.D.  
Director of Breast Imaging  
Seattle Cancer Care Alliance

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## Audience Participation

- After learning about the new USPSTF recommendations, how would you describe your current practice patterns (assuming average risk women)?
  - A. I continue to recommend annual mammography to all women starting at age 40.
  - B. I am now recommending age 50 to start.
  - C. I am much more tuned in to individual risk now and I tailor my recommendations for each woman.
  - D. I am really confused!

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## Chemoprevention



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## NSABP P-1

### Breast Cancer Prevention Trial

- Tamoxifen use resulted in
  - 49% fewer cases of invasive breast cancer
  - 50% fewer noninvasive breast cancer diagnoses (DCIS, LCIS)
- Tamoxifen did increase the women's chances of:
  - endometrial cancer
    - 36 cases in the tamoxifen group vs. 15 cases in the placebo group
  - pulmonary embolism
    - 18 cases in the tamoxifen group vs. 6 cases in the placebo group
  - deep vein thrombosis
    - 35 cases in the tamoxifen group vs. 22 cases in the placebo group



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## NSABP P-2 STAR Trial

- Both tamoxifen and raloxifene reduced the risk of developing invasive breast cancer by about 50%.
- Raloxifene had no measurable effect on the incidence of LCIS and DCIS, with tamoxifen showing lower rates (57 cases in the tamoxifen arm compared to 81 cases in the raloxifene group)
- Women on raloxifene had 36% fewer uterine cancers and 29% fewer blood clots when compared to the tamoxifen group.



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## Audience Participation

- Recently, there has been coverage in the NY Times about women's reluctance to take a chemopreventive medication. Knowing that tamoxifen reduces the risk of breast cancer by approximately 50%:
  - A. I am more likely to push tamoxifen more strongly for my high risk patients.
  - B. I am still skeptical and think the side effects outweigh the benefits in most cases.
  - C. I am waiting for Raloxifene to be approved because I think my patients would be more likely to accept this.
  - D. I am really confused!

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## Prophylactic Surgery



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## Prophylactic Surgery

- Bilateral Mastectomy
  - Can reduce risk by more than 90% depending on type and extent of surgery
- Prophylactic Oophorectomy
  - Can reduce *breast cancer* risk by up to 68% if performed premenopausally

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## Average Risk

- Surveillance:
  - Annual screening mammogram
    - Starting at age 40
  - Additional imaging as needed
  - Breast self-exam periodically
  - Clinical breast exam annually
- Lifestyle counseling
  - Breast feeding
  - Avoid exogenous estrogens
  - Maintain healthy body weight
  - Physical activity
  - Reduce alcohol intake annually

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## ‘High-Risk’ by Gail Model

5-year risk at or above 1.7%

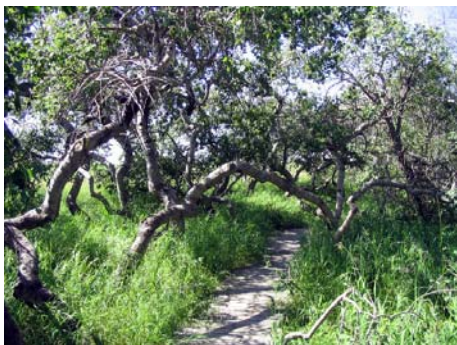
- Surveillance
  - Mammogram and MRI annually
  - Breast self-exam monthly
  - Clinical breast exam 1-2 times yearly
- Chemoprevention
  - Tamoxifen
- Lifestyle counseling
  - Avoid exogenous estrogens
  - Maintain healthy body weight
  - Physical activity
  - Reduce alcohol intake

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## Highest-Risk: Genetic Predisposition

- Surveillance
  - Mammogram and MRI annually
    - Baseline mammogram at 25, annual to start at 30-35
  - Breast self-exam monthly
  - Clinical breast exam twice yearly
- Chemoprevention
  - Tamoxifen
- Preventative Surgery: the ‘gold standard’

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## Audience Participation

- Now that I have heard this talk:
  - A. I feel like I have been practicing very good risk evaluation and now this confirms it.
  - B. I feel like I have some room for improvement and I am going to make some changes to my risk evaluation practices.
  - C. My eyes have really been opened and I am going to completely re-think how I take a family history and assess risk.
  - D. I am really confused!

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