Breast Cancer Screening and

No longer a One Size Fits All

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Risk assessment

- *Assessment* of an **individual's** risk for breast cancer is a **Key Step** in cancer prevention
- Current **lifetime risk** of breast cancer in the US is **12.7%**

Or, **One in Eight women**

Risk assessment

Most women wrongly estimate their risk for breast cancer (survey of 10,000 women on LI)

- Only **1 in 10** women has a good idea of her **lifetime risk** for breast cancer

Risk assessment

- Of the **90%** of women who **wrongly** estimated their risk of developing breast cancer, **Half underestimated** their risk and **Half overestimated** it

Risk assessment

- 40% of women had never discussed their **personal risk** for the disease with their doctor
- Without a formal estimation, a woman will be essentially **guessing** her risk

Risk assessment

- Women should be aware of their **Breast Cancer Risk Number** just as they know their *blood pressure*, *cholesterol*, and their *BMI*

Risk assessment

- The fact that **45%** of women surveyed **underestimated** their risk for breast cancer means that these women are likely missing out on **additional surveillance** with **MRI** and **risk reduction** with **tamoxifen** and **raloxifene**

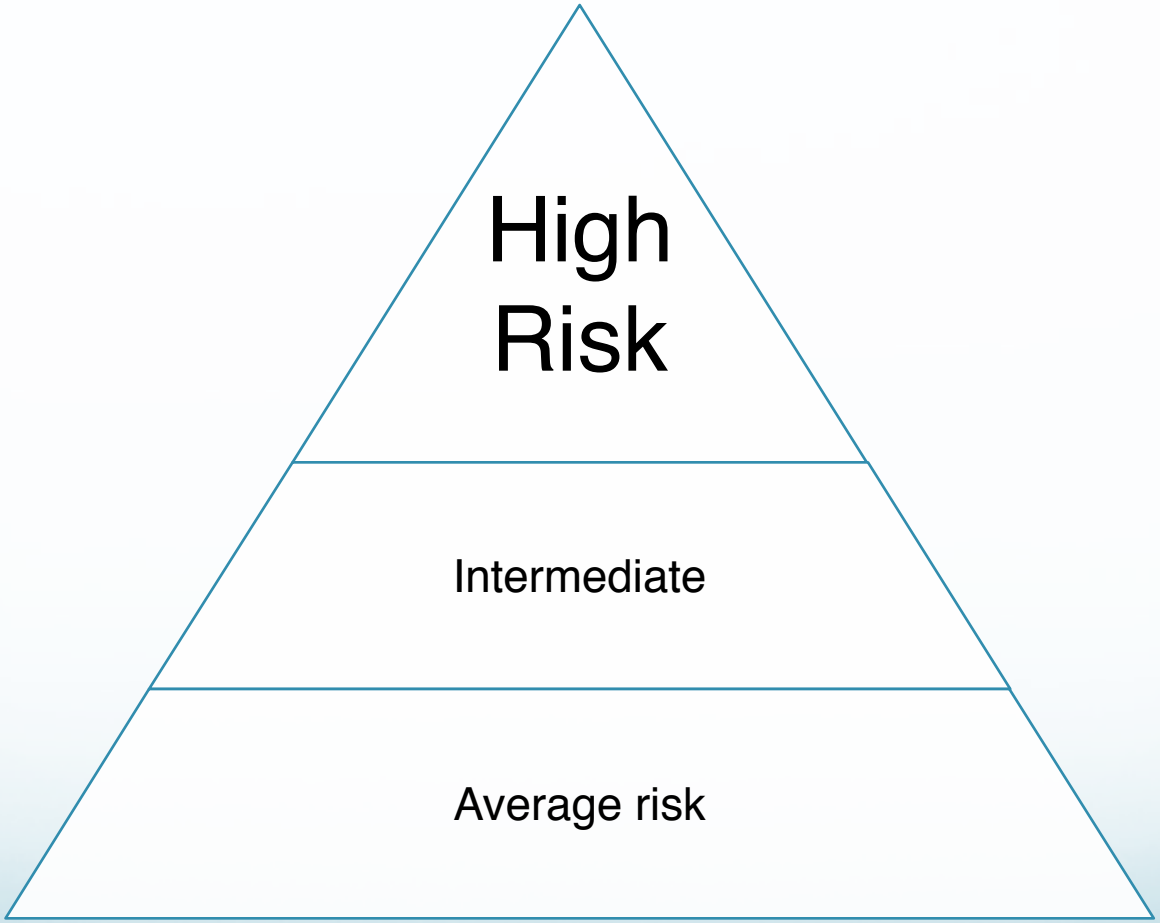
Risk assessment

- *Conversely*, the **45%** who **overestimate** their risk for breast cancer are “worrying more than they really have too”
- The risks of **over treatment**:

  too much screening

  psychological harm from anxiety

Individualized risk stratification



- The women at **increased** risk stand to benefit the most from this knowledge with **extra surveillance** and/or **risk reduction strategies**

Risk Factors	Estimated Relative Risk
Advanced Age	>4
Family History	
FH of **ovarian** cancer at any age	>5
One first degree relative	>2x
Two or more first degree relatives	>5x
Askenazi Jewish descent	>2x
*Further impact with family members diagnosed at **50 yrs or younger**	

Risk Factors

Risk Factors	Estimated Relative Risk
Breast density	5x
Personal history of breast cancer	3-4

Risk Factors

Risk Factors	Estimated Relative Risk
Previous Breast Biopsy	
Atypia	4-5
LCIS or DCIS	8-10
Hyperplasia	1.5
Complex fibroadenoma	2-4
Radial scar	2
papillomatosis	3
Sclerosing adenosis	1.5-2

Risk Factors

Risk Factors	Estimated Relative Risk
Reproductive History	
Early age of **menarche <12**	2
Late age of first term pregnancy **>30 or nulliparity**	2
Late age of **menopause >50**	1.5-2
Use of combined estrogen/ progesterone **HRT**	1.5-2
Current use of **BCPs**	1.25

- The **later the age** at first full term pregnancy, the more likely that DNA mistakes have occurred that will be propagated with the proliferation of mammary cells during pregnancy.

- The susceptibility of mammary tissue to carcinogens decreases after the first pregnancy, reflecting the differentiation of the mammary gland.

Reproductive risk factors

- **HRT**-no significant increase in breast cancer risk for women who had **quit** using HRT **5 years** or more, regardless of their duration of use
- The *Million Woman Study*-observed **no** significant difference in RR of breast cancer comparing transdermal patch to oral therapy

Risk Factor	Estimated relative risk
Lifestyle Factors	
ETOH consumption	1.5-2
Sedentary lifestyle	1.3-1.5
Adult weight gain	1.5

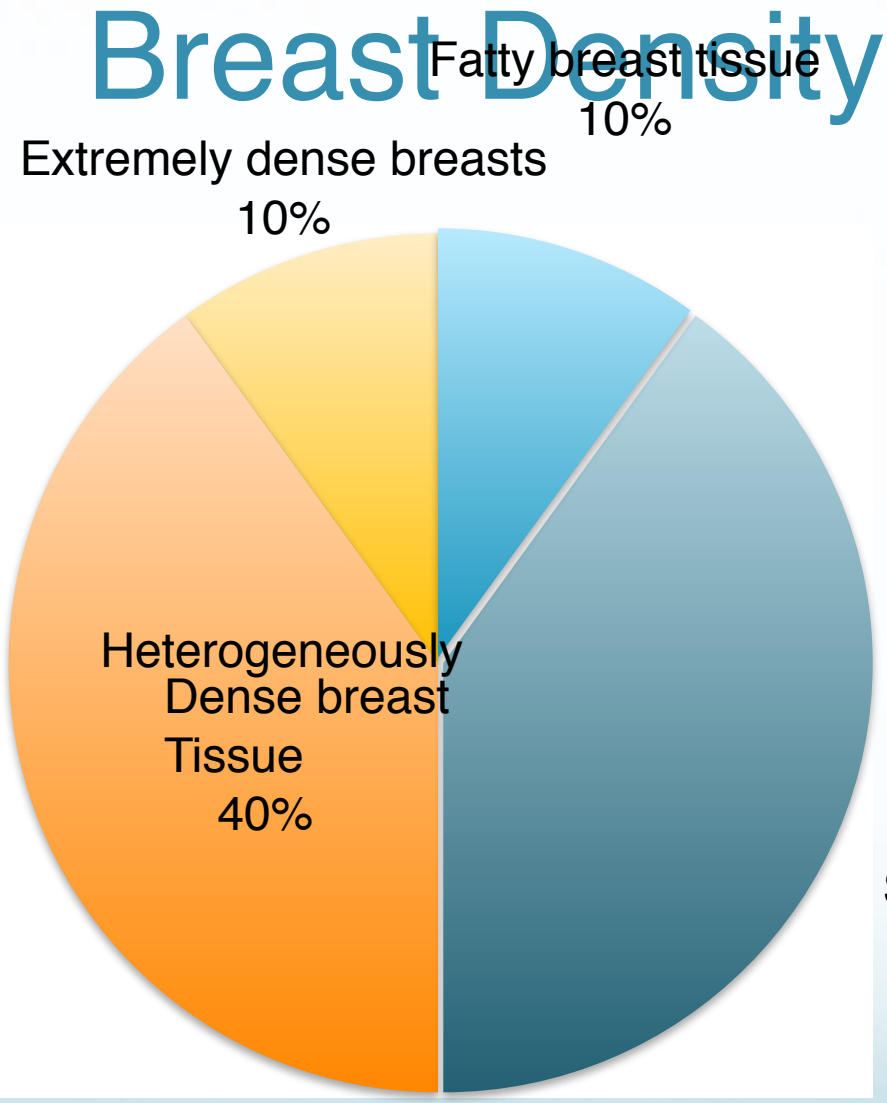
- Consumption of 2 alcoholic drinks/day increases estrogen levels
- Beer, wine and liquor all contribute to the positive association

- Among postmenopausal women physical activity may lower breast cancer risk by reducing fat stores which convert androgens to estrogen.
- Physical activity may also increase levels of SHBG which would reduce bioavailable estrogens.
- Nurses' Health Study-those who gained $\geq$25 kg after age 18 had double the risk of breast cancer c/w women who maintained their weight.

Breast density

- **Breast density** is a radiologic phenomenon. It is not discernable by palpation, but rather it reflects the way x-rays permeate various types of breast tissue differently.
- Fat-radiolucent, connective tissue and epithelial cells appear dense

Breast Density



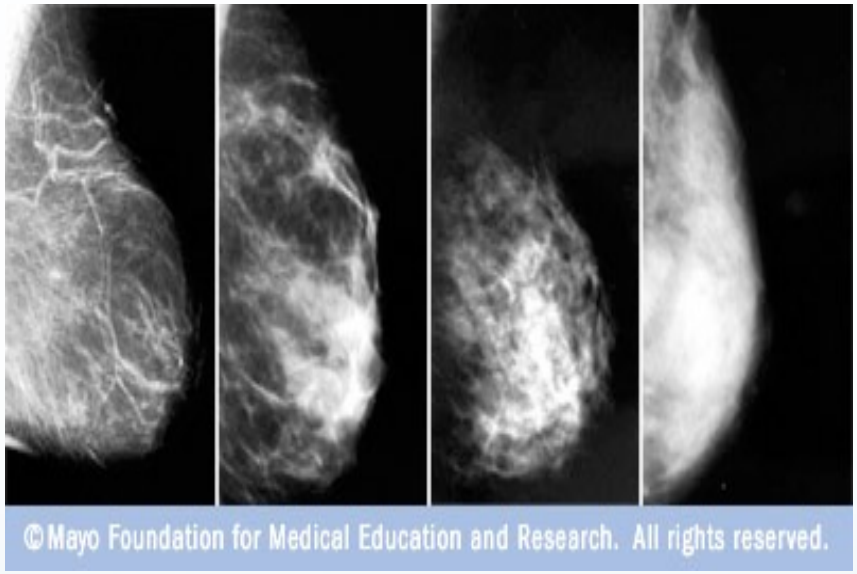
Breast density

- Sensitivity of mammography decreases to **50%** with **high** Breast density
- These women benefit from supplemental imaging such as

✓ **U/S** or **MBI**

✓ **MRI** (high risk)

Breast density



Breast density

- **Inverse** relationship between patient **age** and **breast density**, however, some woman maintain **high** *breast density* even at an **advanced ages**
- Approximately **30%** of *postmenopausal* woman have **dense breasts**

Breast density

- Mammographic breast density is highly influenced by **genetic factors** (60-75%)
  At least *3 genetic variants* have been found to be associated with breast density
- **Environmental factors** account for 20-30%

Breast density

- **Environmental factors** that influence breast density include:
  - **Menopausal status**
  - **Weight**- elevated BMI is associated with low breast density
  - **Parity**-*increased* age at first birth is associated with *high* breast density

Breast density

- Exogenous and endogenous levels of hormones
  - Breast density *increases* in 25-30% of women who begin **HRT**
  - **HRT** is associated with **high** breast density that *decreases* after **discontinuation** of therapy

Breast density

- Conversely, breast density **decreases** in some women who are placed on **tamoxifen** or **raloxifene**
  - Absolute mean decrease at of 5% at 18 months and 7% at 52 months

Risk factors are independent but have an additive effect

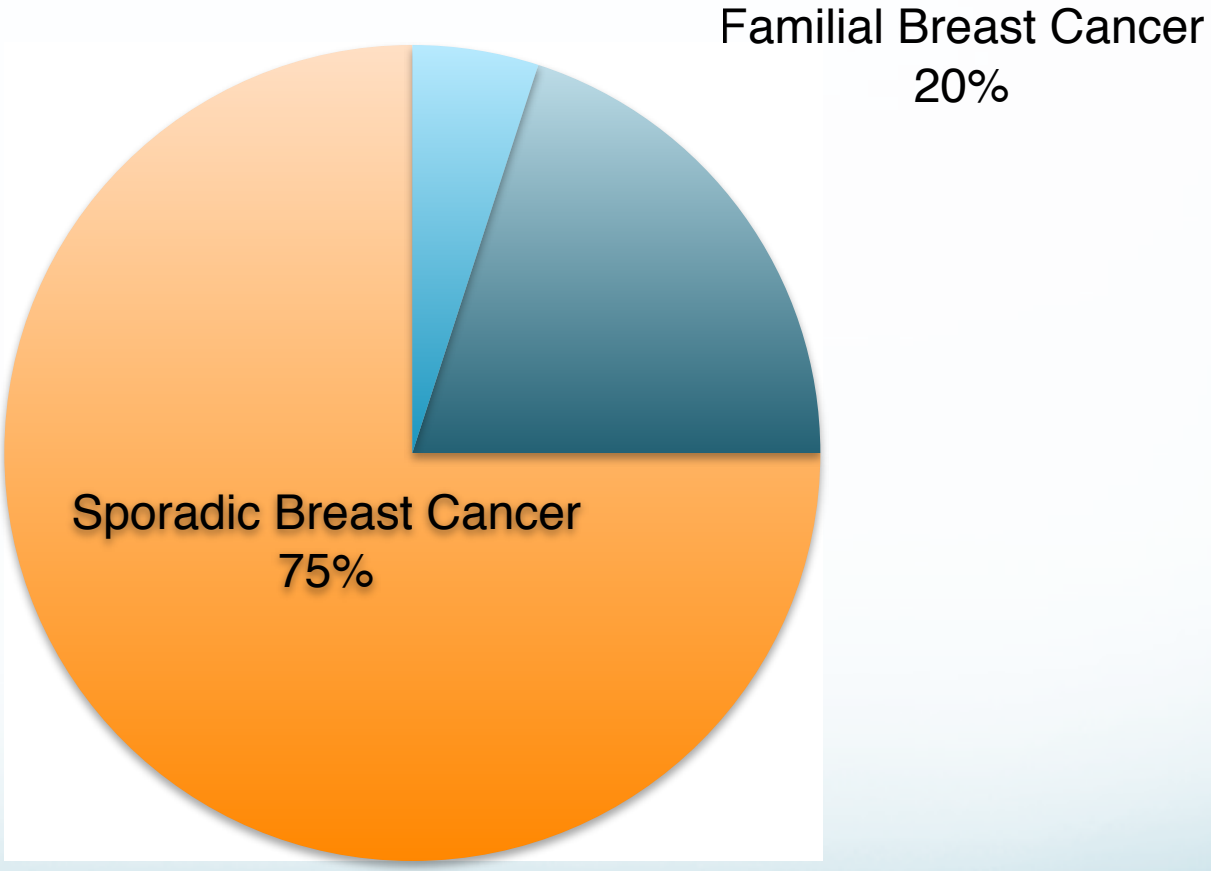
- Women with **high breast density** and a **first degree relative** with breast cancer are at **higher risk** than those with high breast density and **no** family history of breast cancer
- Women with **atypical** hyperplasia and **high breast density** have a **higher risk** of breast cancer compared to women with **atypia** and **low breast density**

Breast cancer screening should be individualized

- *Breast cancer risk assessment*

Three Step Approach

Breast cancer cases



Breast cancer cases

- **Hereditary breast cancer**:
  High penetrance genotype (autosomal dominant)
  Vertical transmission
  Early age at diagnosis
  Association with *other types of tumors*

- **Familial breast cancer**:
  Multiple family members, *without an obvious inheritance* pattern, age of onset is similar to general population
  Chance clustering, environmental, low penetrance genes

- **Sporadic breast cancer**:
  Environmental, personal risk factors, older age, no particular inheritance pattern.

Highly penetrant hereditary breast cancer

- **HBOC**-1:400-1:800, 1:40 in Ashkenazi Jews
  - *Causative genes*-**BRCA1**, **BRCA2**
  - *Associated malignancies*-breast, ovarian, male breast, prostate, pancreatic, melanoma, colon

- **Li-Fraumeni** syndrome-very rare
  - *Causative gene*-**TP53**
  - *Associated malignancies*-breast, sarcoma, leukemia, lymphoma, melanoma, colorectal, pancreas, brain

- **Cowden syndrome**-1:250,000
  - *Causative gene*-**PTEN**
  - Associated malignancies-breast, thyroid, endometrial, colorectal, melanoma, renal

- **Peutz-Jeghers syndrome**-1:280,000, **STK11** mutation, assoc. with GI malignancies, breast, ovarian, uterine

- **Hereditary diffuse gastric ca-**prevalence unknown, **CDH1** assoc. with

BRCA population estimates

General population	Ashkenazi Jewish population
1 in 400	1 in 40
Women with breast ca (any age) 1 in 50	Women with breast ca (any age) 1 in 10
Women with breast ca (<40) 1 in 10	Women with breast ca (<40) 1 in 3
Men with breast cancer : 1 in 20	Men with breast cancer : 1 in 5
Women with ovarian cancer : 1 in 8	Women with ovarian cancer : 1 in 3

Breast cancer risk assessment

Step 1-**Family History**

- Identify women who have a family history which raises concern for an **inherited predisposition** for breast cancer

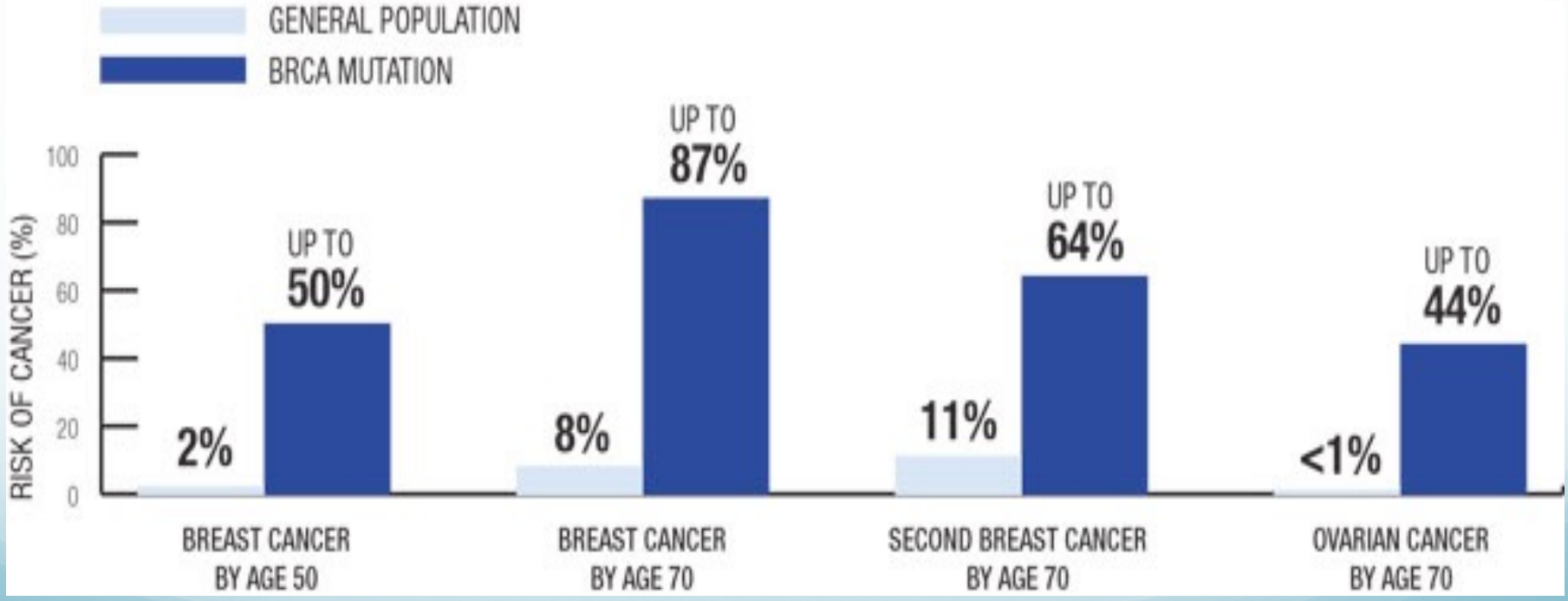
Features that suggest an **increased** likelihood of having a **BRCA** mutation

- **Multiple** cases of early onset breast cancer $\leq$ **50**
- **Ovarian** cancer
- **Breast** and **ovarian** cancer in the same woman
- **Bilateral** breast cancer
- **Triple negative** breast cancer

Features that suggest an **increased** likelihood of having a **BRCA** mutation

- **Male** breast cancer
- **Ashkenazi Jewish** ancestry with breast cancer at any age
- **Breast cancer at any age** with **≥2** close relatives with *pancreatic* or *aggressive prostate cancer*.

BRCA mutation carriers



Breast cancer risk assessment **Step 2**:

- Identify other groups of women known to be at *increased risk*
  - History of previous biopsies, especially **atypia** and **LCIS**
  - History of **previous breast cancer**
  - **Dense breasts**

Breast cancer risk assessment **Step 3A**

- **Gail model** risk assessment
  - For women **>35** years old **without** a strong family history of breast cancer or history of **LCIS**

Gail model

- **Risk factors** in the Gail Model:
  - Current **age**
  - Age at **menarche**
  - Age at **first live birth** or nulliparity
  - Number of **first degree** relatives with breast cancer
  - Number of **previous breast biopsies**
  - Presence of **atypia**?
  - **race**

Gail model

- Calculates the **risk** of developing breast cancer in one's **lifetime**
- Calculates the **risk** of developing breast cancer over the **next 5 years**
- **Comparison** of woman of the same age and race

Gail model

- **NCCN Breast Cancer Risk Reduction panel** uses a **5 yr** risk of **≥1.7%** as defined by the **Gail Model** to identify women eligible to consider the use of **risk reduction strategies**
- This value was used to identify women eligible for the **NSABP BCPT** and the study of *tamoxifen* and *raloxifene* (**STAR** trial)

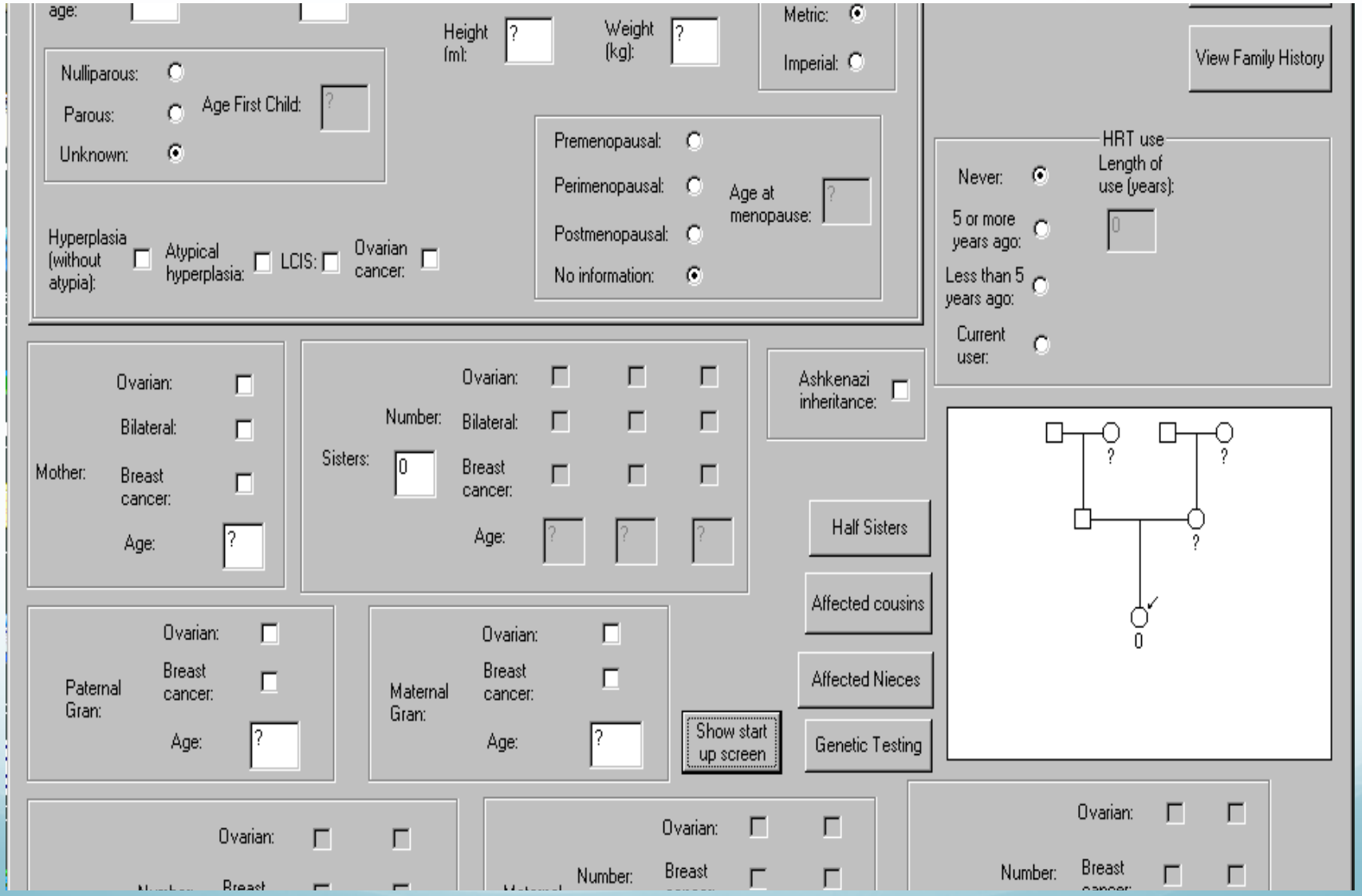
Gail model

- **Limitations**: does **not** include *ovarian cancer* or *breast cancer* in **second degree** relatives (aunts, cousins, and grandparents)

Step 3B: **IBIS risk evaluator**

- For woman with a more **extensive family history** of breast cancer or a family history of **ovarian cancer**
- **IBIS** calculates the **lifetime risk** of breast cancer and the probability of being a **BRCA** carrier

IBIS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View Family History
Nulliparous:
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HRT use
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5 or more years ago:
Less than 5 years ago:
Current user:
Length of use (years):
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Hyperplasia (without atypia):
Atypical hyperplasia:
LCIS:
Ovarian cancer:
Mother:
Ovarian:
Bilateral:
Breast cancer:
Age:
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Sisters:
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Breast cancer:
Age:
Ashkenazi inheritance:
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Screening for breast cancer

- **Breast awareness**
- **Women** know their breasts better than anyone else
- Almost **half** of breast cancers in women 50-69 are found by the women themselves or their physician
- Instead of focusing on a specific technique, woman should be **aware** of their breasts and **report any changes**

Women at **average risk** for development of breast cancer

- breast awareness
- Healthy lifestyle changes (maintain normal BMI,exercise, limit ETOH)
- **Clinical breast exam** every year
- Screening **mammography yearly** starting at **age 40**-ACS guidelines

Women at **average risk** for development of breast cancer

- The majority of breast cancer seen in women in their **40's** occur in women without significant risk factors
- **71%** *fewer deaths* with **annual** screening compared with screening *every 2 years*

Screening women at **Intermediate risk**

- **Clinical breast exam** every **six** months
- Yearly **mammography** staggered with **breast ultrasound** by **six** months
- Consider **Molecular Breast Imaging**

Women at **highest risk** for developing breast cancer-**lifetime risk of ≥20%**

- Breast awareness
- CBE every 6 months
- Yearly mammogram staggered by 6 months with yearly breast **MRI**
- **Risk reduction**

ACS recommendations for screening breast MRI

- Women with a **gene mutation**
- Woman with a **first degree** relative with a gene mutation
- **Extremely strong family history** of breast cancer
- History of **radiation therapy** to the chest between the ages of 10 thru 30

ACS recommendations for screening **breast MRI**

- **Lifetime risk** of **≥20%**
- **Problem solving-** palpable lesions without an imaging correlate

MRI screening in women at **moderately** increased risk

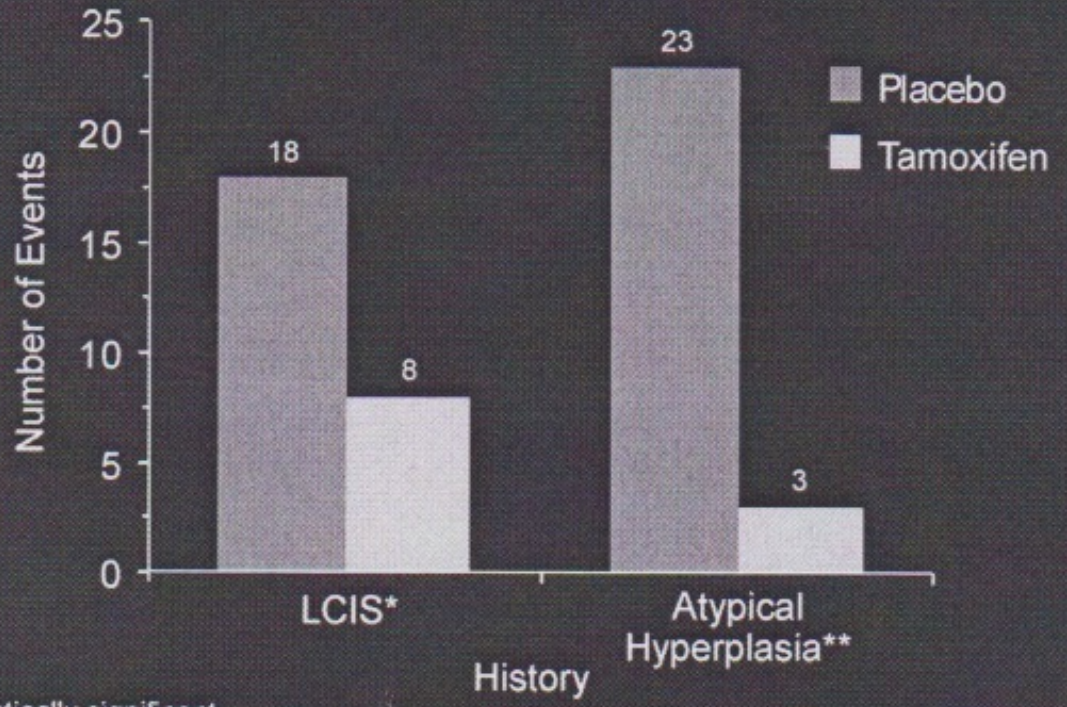
Insufficient evidence to recommend **for or against MRI** screening:

- Lifetime risk of 15-20%
- LCIS
- Atypical ductal or lobular hyperplasia
- Women with a personal h/o breast cancer and DCIS
- Extremely dense breasts

High risk group- **risk reduction**

- **BCPT**: treatment with tamoxifene for 5 years **reduces** the risk of invasive and noninvasive breast cancer up to **50%**
- **Reduction** in invasive breast cancer risk in women with **atypia** is up to **85%**
- Other potential benefits: reduction in osteoporotic fractures

BCPT Results: Invasive Breast Cancer Cases by Previous Pathology



*Not statistically significant.

**AH=ADH or ALH

Fisher B, J Natl Cancer Inst 1998.

Risk reduction

- **STAR Trial-raloxifene** in postmenopausal women was shown to be **as effective** as tamoxifen in reducing risk of invasive breast cancer
- At a medium follow up of 81 months, breast cancer risk reduction is more **durable** with tamoxifen

Risk reduction: SERMS

- Harms:
  - **Less serious**: increased frequency of hot flashes and vaginal discharge
  - **More serious**: endometrial cancer and thromboembolic disease

(raloxifene has a slightly lower incidence of thromboembolic events, and does not effect risk for cataracts)

Risk reduction:
Risk verses Benefits

- **BCPT: Absolute risk reduction** of 2.1 per 100 women
- **NNT-48**

Update-IBIS-I

Medium f/u of 16 years

Now shows the **NNT** is only **22 women** with daily tamoxifen for 5 years to prevent 1 case of breast cancer in the next **20 years**

Risk reduction: Risk verses Benefit

- An absolute increased risk of **1.4** cases of **endometrial cancer** per 1000 women per year was seen in women taking tamoxifen (no increased risk with raloxifene)

Or:

- For each **714** women taking tamoxifen for 5 years, **1** woman would be newly diagnosed with endometrial cancer

Chemoprevention Risk verses Benefit

- **Thromboembolic**-Absolute increase in risk (BCPT) was 0.5 cases per 1,000 women per year

Or:

- For each 2,000 women taking tamoxifen for 5 years, one woman would develop a **DVT** and one would suffer a **PE**

	Endometrial ca	PE	DVT
Women ≤ 49y	1.3/1000	0.2/1000	1.1/1000
Women ≥ 50y	3.1/1000	1.0/1000	1.5/1000

Woman of all ages had **similar reductions in breast cancer incidence**

Postmenopausal women **were more at risk** for endometrial ca, DVT and PE than **premenopausal** women

Risk reduction: additional options

Postmenopausal Options	Premenopausal Options
Tamoxifen (FDA approved)	Tamoxifen (FDA approved)
Raloxifen (FDA approved)	
Exemestane (not FDA approved)	
Anastrozole (not FDA approved)	

Exemestane decreased risk of both invasive and noninvasive breast cancer by **65%** (MAP 3)
Anastrozole decreased risk by **53 %** (IBIS-II)

Risk reduction: In High risk women

- Complicated decision
- **Balance** of benefits verses harms
- Consider **individual risk profiles** and **age**
- **Respect** patient's preferences and values
- Women at **higher risk** will have **greater absolute benefit** and **fewer harms** and women at **low risk** will have **lower absolute benefit** and **greater harms**

Optimal breast cancer screening

- Screening must be increasing tailored to an **individual's** risk and optimized through patient specific imaging and risk reduction strategies.
- Significant opportunities exist to **reduce breast cancer incidence**

- “Knowledge, like air, is vital to life. Like air, no one should be denied it.”
  - Alan Moore, author