

# Prevention and Early Detection of Breast Cancer: Weighing the Risks and Benefits

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# Outline

- **Prevention of Breast Cancer**
  - ◆ **Consideration of Risks and Benefits**
- **New Screening Modalities – the role of MRI**

## **U. S. Preventive Services Task Force**

- **convened by the U.S. Public Health Service**
- **Overseen by The Center for Practice and Technology Assessment (CPTA), Agency for Healthcare Research and Quality (AHRQ)**
- **Publishes the Guide to Clinical Preventive Services – now online**

**<http://www.ahrq.gov/clinic/uspstfix.htm>**

# Chemoprevention of Breast Cancer

## USPSTF Recommendations

- The USPSTF recommends that clinicians discuss chemoprevention with women at high risk for breast cancer and at low risk for adverse effects of chemoprevention. Clinicians should inform patients of the potential benefits and harms of chemoprevention. B recommendation.
- *Based on fair evidence that treatment with tamoxifen can significantly reduce the risk for invasive estrogen-receptor-positive breast cancer in women at high risk for breast cancer and that the likelihood of benefit increases as the risk for breast cancer increases.. The USPSTF concluded that the balance of benefits and harms may be favorable for some high-risk women but will depend on breast cancer risk, risk for potential harms, and individual patient preferences.*
  - ◆ All women

2.5

# Chemoprevention of Breast Cancer

## U.S. Preventive Services Task Force

- The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of tamoxifen or raloxifene for the primary prevention of breast cancer in women at low or average risk for breast cancer **D recommendation.**

- The USPSTF found fair evidence that tamoxifen and raloxifene may prevent some breast cancers in women at low or average risk for breast cancer, based on extrapolation from studies of women at higher risk .... however, the potential harms of chemoprevention may outweigh the potential benefits in women who are not at high risk for breast cancer.*

## Definition of High Risk?

Entry Criteria for the Breast Cancer Prevention Trials: who is at “high risk”?

5 year risk of breast cancer of at least  
1.66%

# **Chemoprevention of Breast Cancer Options for High Risk Women**

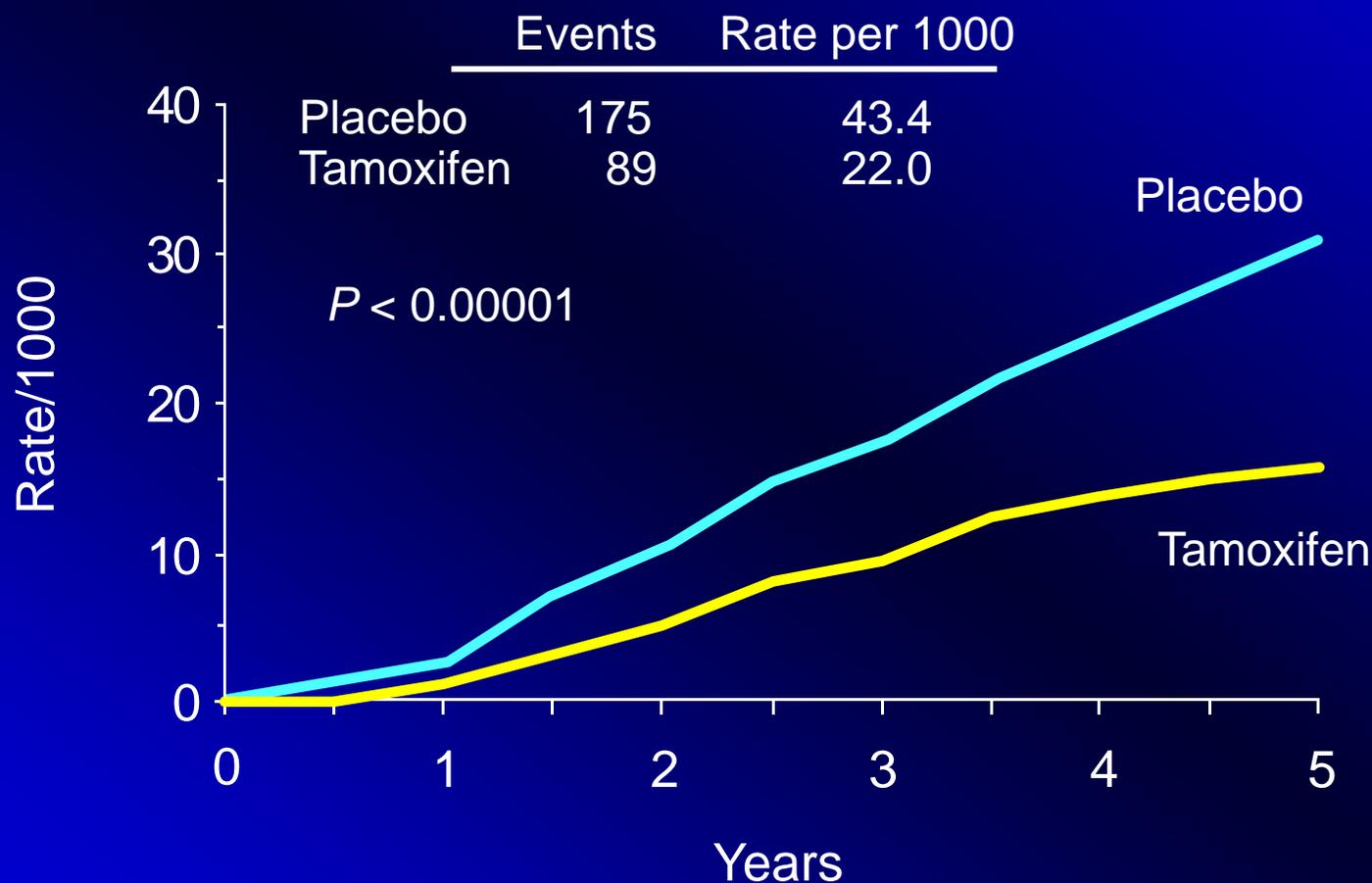
- **Chemoprevention with SERMs (e.g. tamoxifen (FDA approved indication))**
- **Participation in trials using aromatase inhibitors**
- **Early phase trials using Cox 2 inhibitors**

# Balancing Risks and Benefits



# The Benefits

# BCPT Results: Cumulative Rate of Invasive Breast Cancer



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

# Benefits of tamoxifen from the BCPT

● Breast cancer	RR
◆ Invasive	0.5
◆ <i>In-situ</i>	0.5
● Hip fracture	0.55
● Colles/spine fx	0.7

# The Risks

## BCPT Quality of Life Data

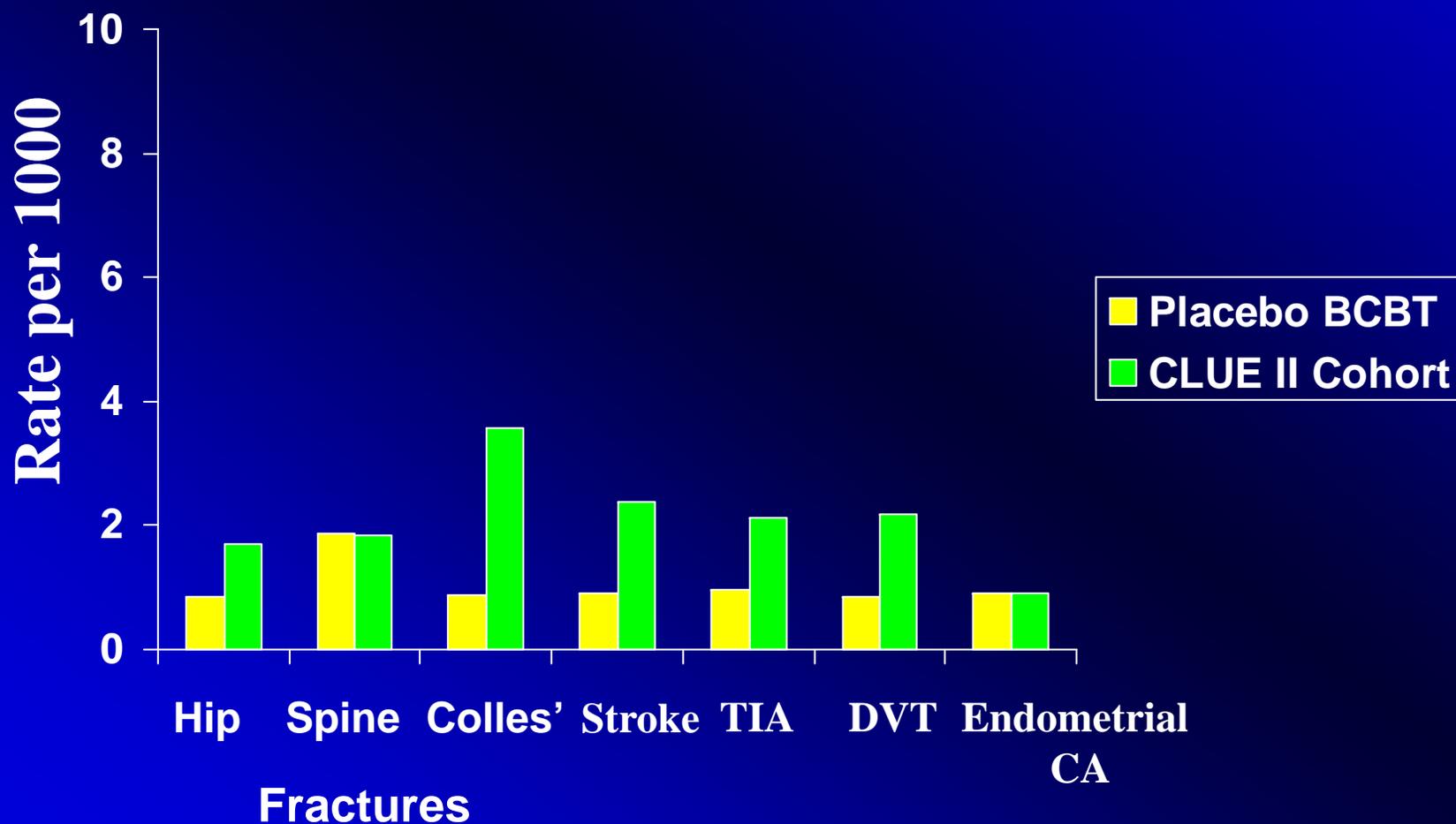
<b>Symptom</b>	<b>%</b>		<b>Risk Ratio</b>
	<b>Tamoxifen</b>	<b>Placebo</b>	
<b>Vaginal discharge</b>	55	34	1.60
<b>Cold sweats</b>	21	15	1.45
<b>Genital itching</b>	47	38	1.23
<b>Night sweats</b>	67	55	1.22
<b>Hot flashes</b>	78	65	1.19
<b>Pain with intercourse</b>	28	24	1.17

Day et al. *J Clin Oncol* 1999 (under submission).

## Risks of tamoxifen from the BCPT

● Endometrial Cancer	RR
◆ Women $\geq$ 50	4.0
● Stroke	1.6
● DVT	1.6
● Pulmonary embolus	3.0
● Cataracts	1.14

Annual incidence of adverse health events in a community-based cohort among women 40 to 70 years old compared to rates for women on the placebo arm, BCPT



**Number needed to treat to prevent**

## Number Needed to Treat with Tamoxifen for Harm, Per Year

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	RR (BCPT)	Number Needed BCPT	Number Needed in Community
Endometrial Cancer	2.53	617	710
Stroke	1.59	1886	715
Deep Vein Thrombosis	1.60	2000	761
Cataracts	1.14	322	312

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## Number Needed to Treat with Tamoxifen for Benefit, Per Year

	RR (BCPT)	Number Needed Based on BCPT	Number Needed in Community
<b>Invasive Breast Cancer</b>	<b>0.51</b>	<b>300</b>	<b>375</b>
<b>Fractures</b>			
<b>Hip</b>	<b>0.55</b>	<b>2631</b>	<b>1299</b>
<b>Spine</b>	<b>0.74</b>	<b>3333</b>	<b>2079</b>
<b>Colles</b>	<b>0.61</b>	<b>2941</b>	<b>716</b>

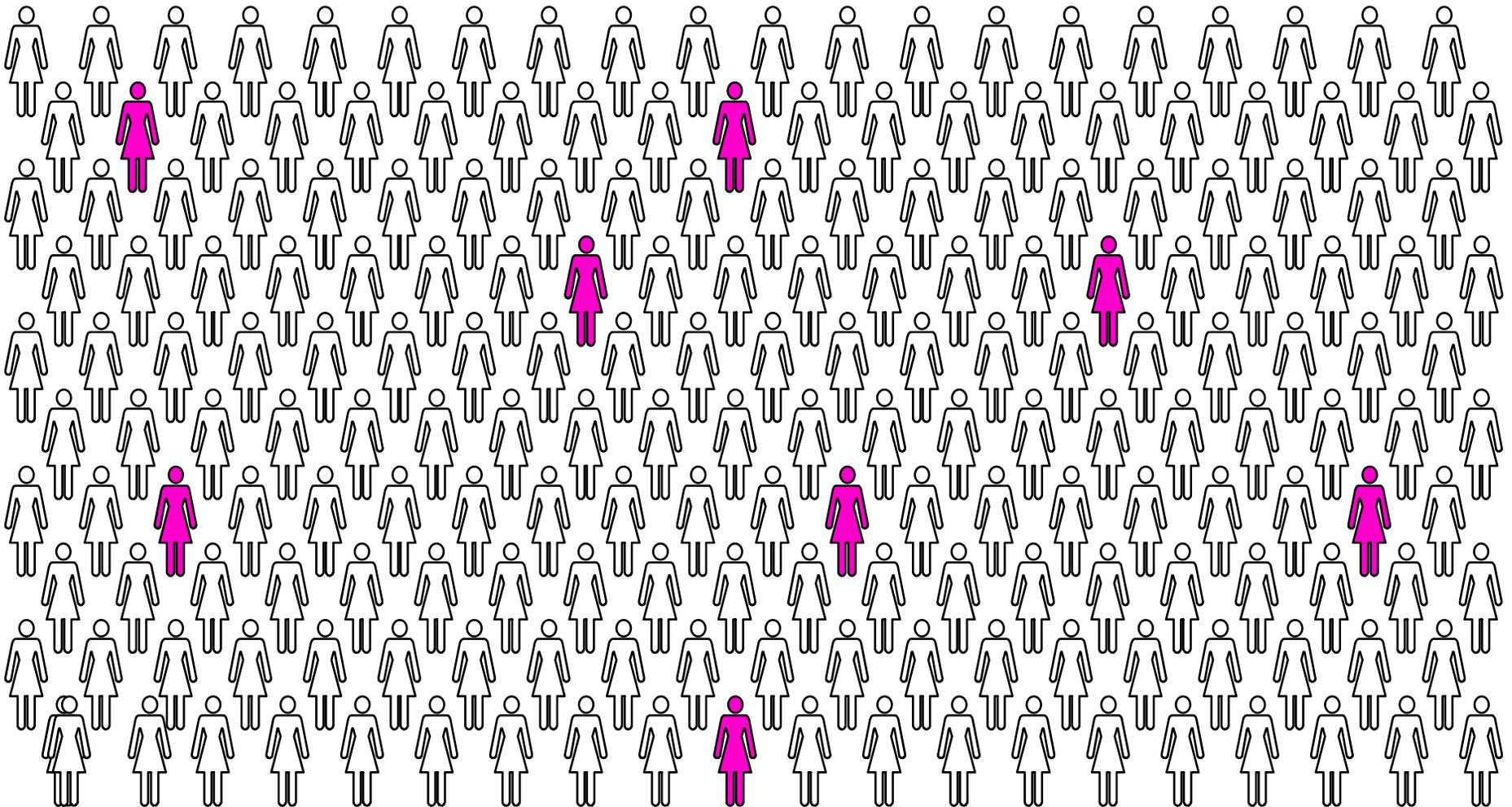
# Aspirin for the primary prevention of cardiovascular events:

Who is at high risk?

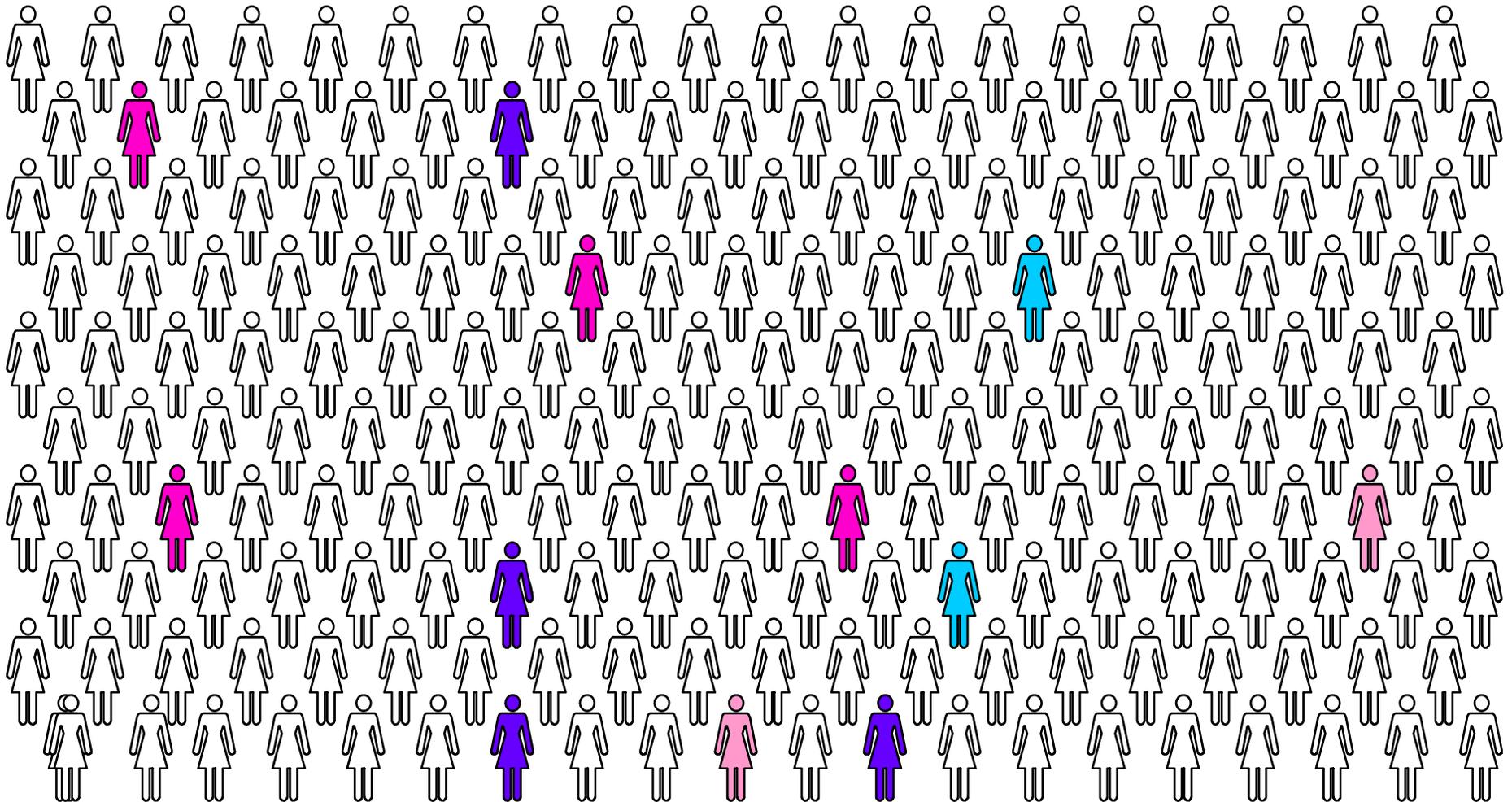
10 year risk of coronary heart disease of at least 10 %

# Challenge in cancer prevention: Treat many to prevent few

Breast cancer cases among 200 women with 5 year breast cancer risk of 4.0%

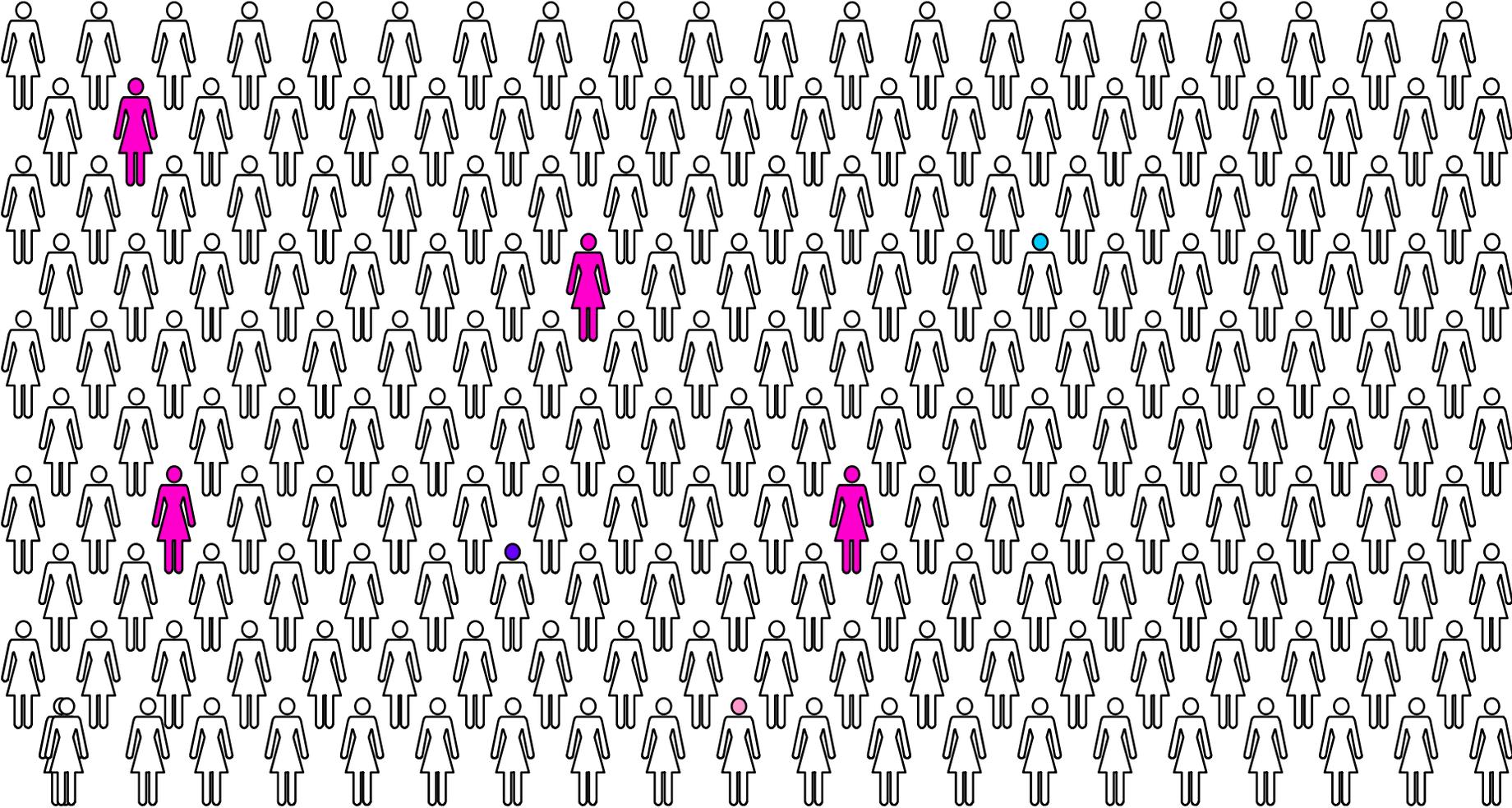


**Benefit/risk index associated with tamoxifen for 200 white women  
(age range 50 to 59) with a 5 yr breast cancer risk of 4.0%**



# Benefit/risk index associated with aspirin use for 200 individuals

With a 4% 5 yr risk of coronary heart disease



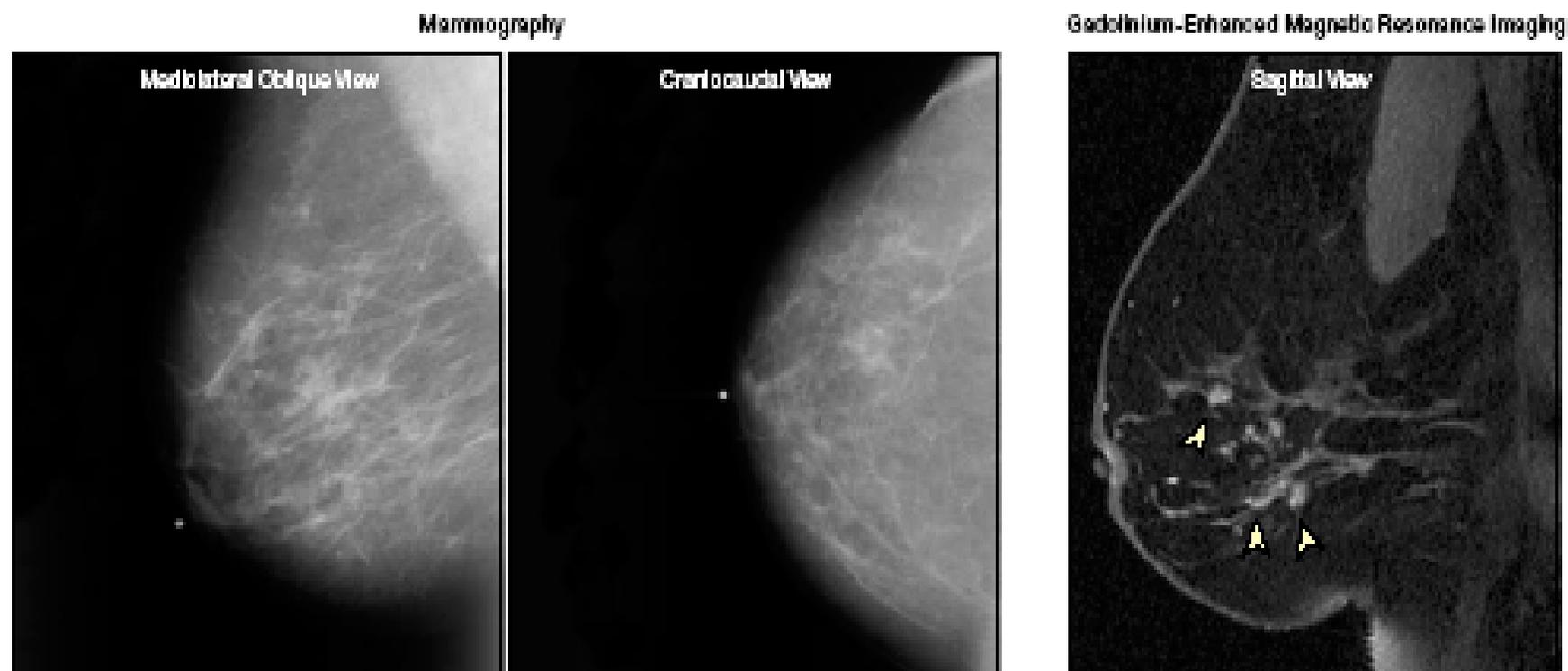
# Imaging Modalities for the Early Detection of Breast Cancer

- Mammography
- Ultrasound
- MRI

# **Magnetic Resonance Imaging (MRI)**

- **Provides information on vasuclarity**
- **Higher sensitivity but lower specificity (more false positives)**
- **Not affected by breast density**
- **Evaluated in women at high risk of breast cancer (BRCA1/2 mutation carriers) where screening begins at younger ages**

Figure 2. Mammography and Magnetic Resonance Imaging in BRCA2 Mutation Carrier With Less Than 25% Fibroglandular Density



False-negative mammograms in a 63-year-old BRCA2 mutation carrier demonstrating normal-appearing breasts that are composed of mostly fat (<25% fibroglandular density), classified as Breast Imaging Reporting and Data System (BI-RADS) 1. Sagittal, gadolinium-enhanced, fat-suppressed 3-dimensional spoiled gradient recalled magnetic resonance image of the right breast reveals clumped enhancement of more than 3.4 cm in a ductal distribution (arrowheads), classified as BI-RADS 4. Magnetic resonance imaging-guided wire localization and excisional biopsy revealed ductal carcinoma in situ.

**63 y.o. BRCA2 mutation carrier:  
Mammogram BI-RADS 1; MRI 3.4 cm DCIS (arrows)**

**Surveillance of BRCA1/2 mutation carriers with MRI,  
US, mammography and CBE  
Warner et al JAMA 292:1317-1325**

- **236 women screened with all modalities**
- **22 cancers detected (any suspicious (BI-RADS 4 or 5) lesions were biopsied)**

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	<b>Sensitivity</b>	<b>Specificity</b>
<b>MRI</b>	<b>77.0%</b>	<b>95.4%</b>
<b>Mammography</b>	<b>36.0%</b>	<b>99.8%</b>
<b>Ultrasound</b>	<b>33.0%</b>	<b>96.0%</b>
<b>CBE</b>	<b>9.1%</b>	<b>99.3%</b>

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Warner et al JAMA 2004; 292:1317-1325

**MRI, Mammography, CBE among women with a  
familial of genetic predisposition  
Kriege et al NEJM 2004;351:427-437**

- **1909 women; 358 carriers of BRCA1/2 mutations**
- **51 breast tumors; 44 invasive breast cancers**
- **Biopsy or cytology for any BI-RADS 4 or 5; BI-RADS 3 – additional examinations (US or repeat MRI)**

## **Sensitivity and Specificity for detecting invasive and non-invasive breast cancer**

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	<b>Sensitivity</b>	<b>Specificity</b>
<b>MRI</b>	<b>71.1%</b>	<b>89.8%</b>
<b>Mammography</b>	<b>40.0%</b>	<b>95.0%</b>
<b>CBE</b>	<b>17.8%</b>	<b>98.1%</b>

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**Kriege et al NEJM 2004; 292:1317-1325**

# Who should consider having BREAST MRI in conjunction with mammography?

- Women at high risk – documented or suspected genetic predisposition (high prevalence improves predictive value of positive test)
- BC/BS Technology Assessment – supports the rationale for MRI screening of BRCA mutation carriers and others at high hereditary risk
- Concerns –
  - ◆ high false positive
  - ◆ Translation of research findings to all clinical settings
  - ◆ Determining what to biopsy
  - ◆ Cost

# Balancing Risks and Benefits



# The Perils of Prevention

By SHANNON BROWNLEE  
NY Times Magazine 3/16/03

