Risk Factor&
Risk Reduction of
Breast Cancer

دکتر کبیری

بیمارستان گلستان

بخش جراحی

How is breast screening done:
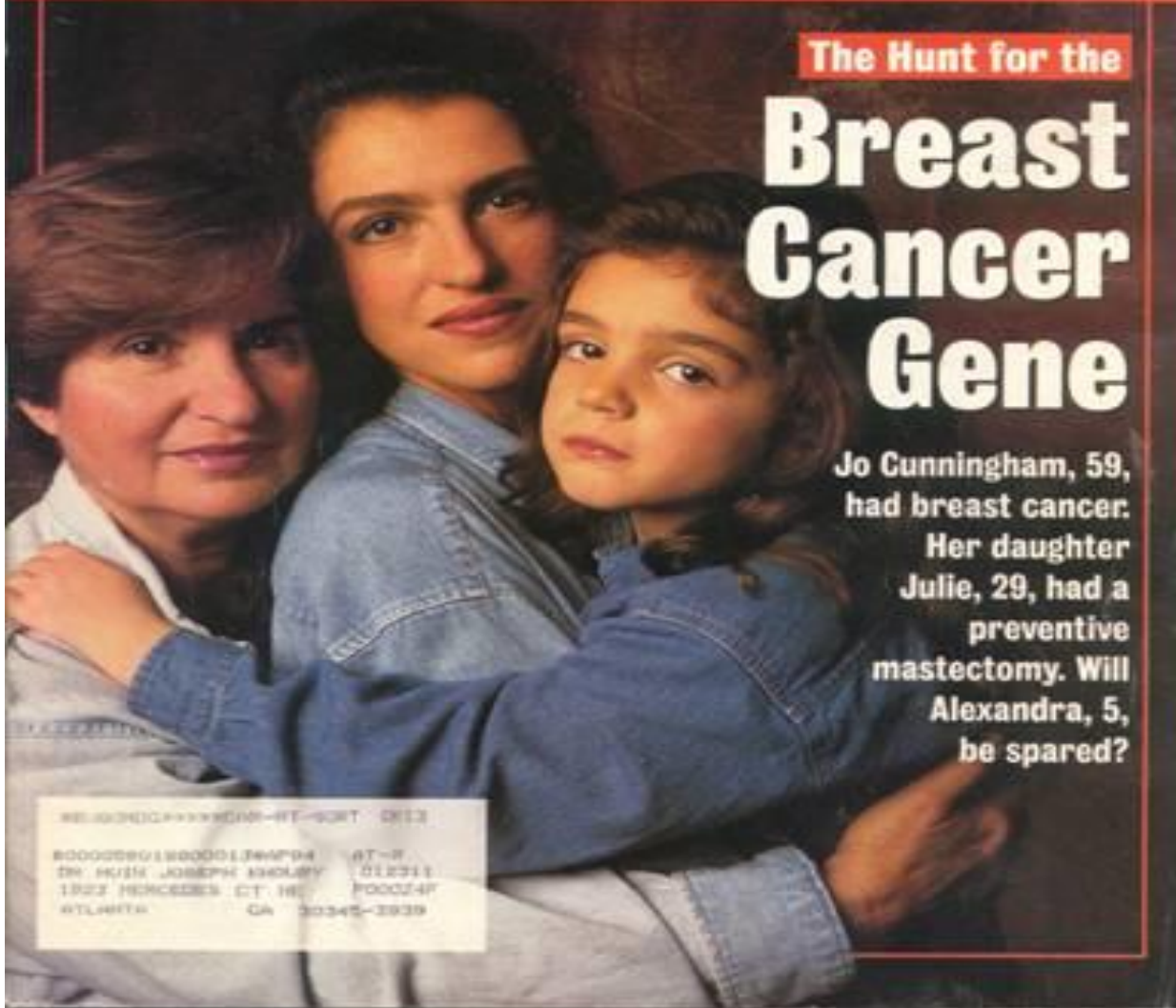
Invasive:

QUESTION:

RISK REDUCTION:

بیماری اظهار میدارد که:مادرش "خواهرش" دخترش"
و یا فامیل درجه دوم مبتلا دارد

چگونه ریسک بیمار را تعیین کنیم؟؟؟؟؟

RETIREMENT BLUES: HOW SAFE IS YOUR PENSION?

Newsweek

December 6, 1993 · $2.95

The Hunt for the

Breast Cancer Gene

Jo Cunningham, 59, had breast cancer. Her daughter Julie, 29, had a preventive mastectomy. Will Alexandra, 5, be spared?

Introduction:

1) In 2020, there were 2.26 million new cases and 685,000 deaths per year worldwide

2) IN USA : 330,840 new cases of breast cancer are estimated in 2021, of which 261,550 are expected to be   invasive   carcinomas, 49,290 ductal carcinomas in situ (DCIS), and 43,600 deaths

3) OF these new cases, 45,280 are estimated to occur in women aged 40- 49 years

4) The incidence of breast cancer is greater in more developed countries, with the highest rates in Australia/New Zealand,Western and Northern Europe, and Northern America

developing countries====developed countries

17% higher mortality rates

About 90% of breast cancers are due to genetic abnormalities that happen as a result of the aging process and life in general, not to inherited mutations.
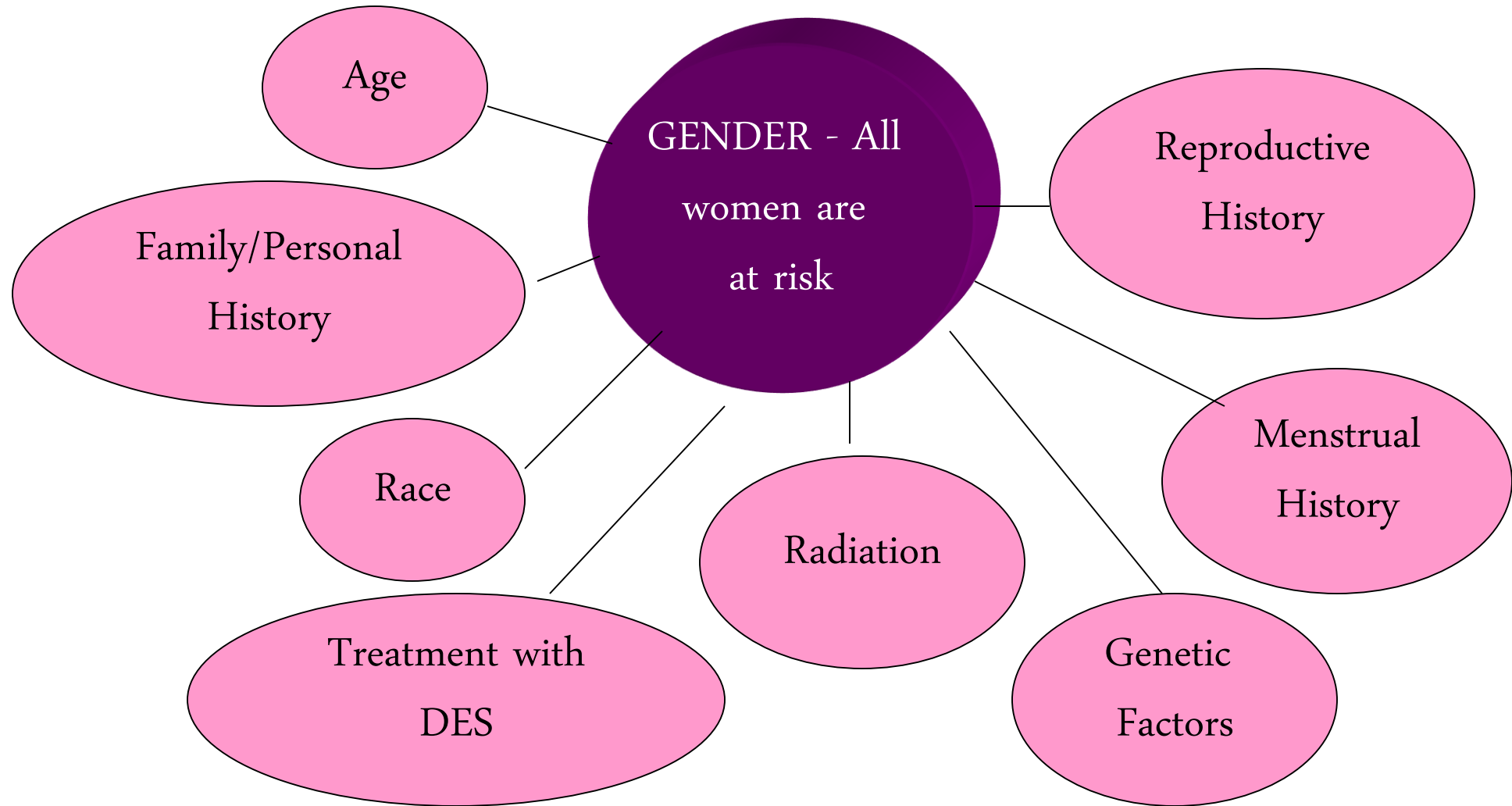
Probabilities of Developing Invasive Breast Cancer Based on Age

Current Age	Probability of breast cancer in next 10 years
20	0.05% or 1 in 1,837
30	0.43% or 1 in 234
40	1.43% or 1 in 70
50	2.51% or 1 in 40
60	3.51% or 1 in 28
70	3.88% or 1 in 26

Lifetime risk: 12.28%; 1 in 8 women

Breast Cancer Risk Factors

that cannot be changed

Age

GENDER - All women are at risk

Reproductive History

Family/Personal History

Race

Radiation

Menstrual History

Treatment with DES

Genetic Factors

Breast Cancer Risk Factors
that can be *controlled*

Obesity

Exercise

Breastfeeding

Alcohol

All women are at risk

Hormone Replacement Therapy

Not having children

Birth Control Pills
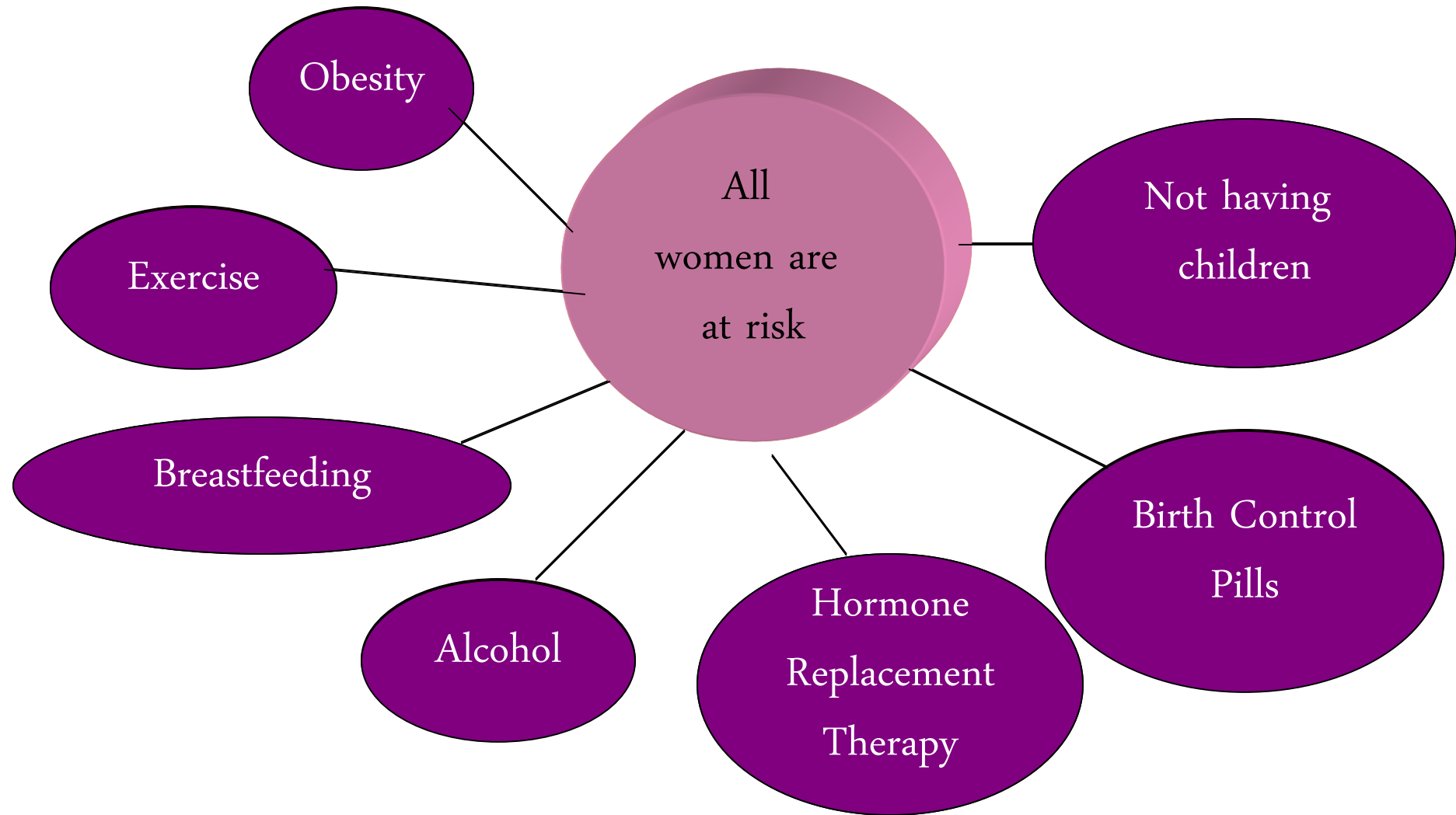
Current medical efforts:

1) PREVENTION → **HRT**

2) INCREASED AWARNESS → **BSE**

3) EARLY DETECTION WITH SCREENING → **MAMMOGRAPHY**

4) TREATMENT

- IN USA:SCREENING and treatment:>41% mortality reduction since
- 1990 has been recorded

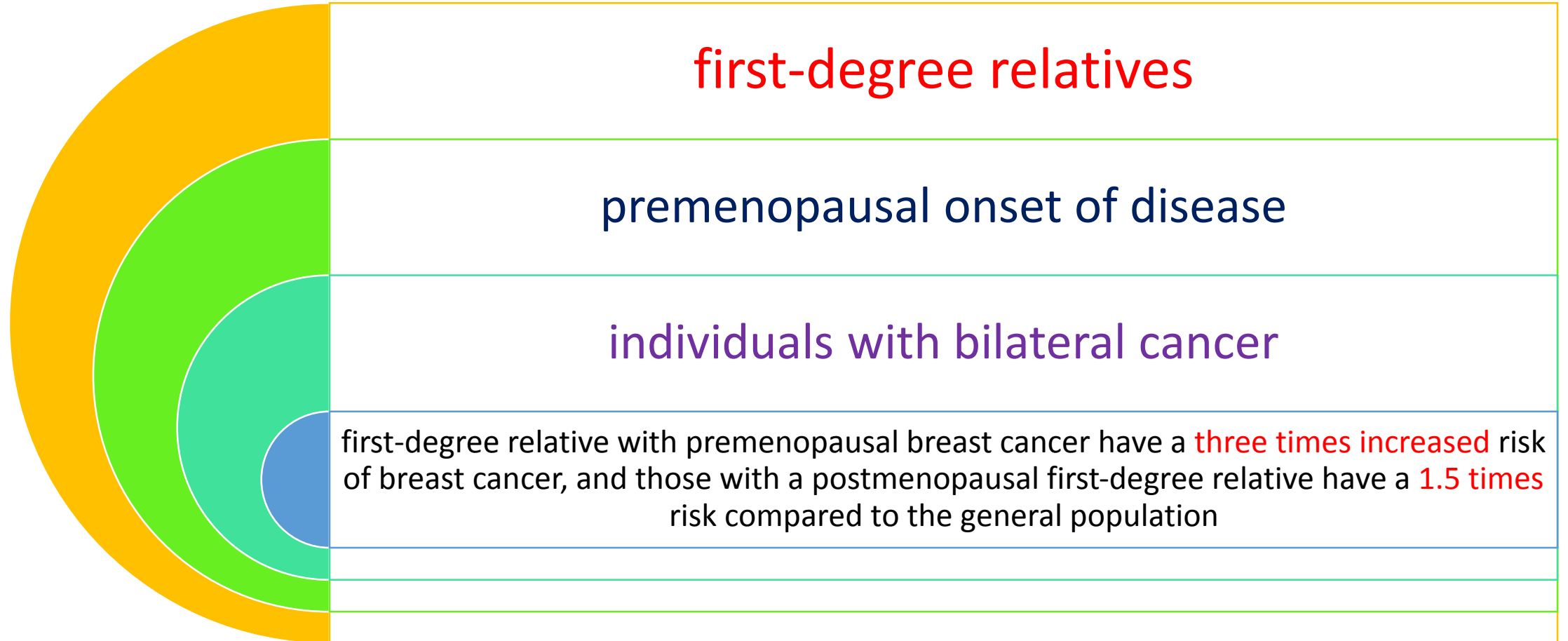# Risk identification:

Family history

Genetic testing

Prior biopsy

Thoracic radiation

Lifestyle

Reproductive factors

Combination of ALL

Family history:

first-degree relatives

premenopausal onset of disease

individuals with bilateral cancer

first-degree relative with premenopausal breast cancer have a three times increased risk of breast cancer, and those with a postmenopausal first-degree relative have a 1.5 times risk compared to the general population

genetic testing indications:

1. As of 2021 in persons with a relative with a known pathogenic variant

2. first- or second-degree relative with breast cancer at age 50 or less

3. ovarian cancer

4. pancreatic cancer

5. male breast cancer

6. or multiple relatives with Cancer

Inherited Genes

BRCA1 (Breast Cancer 1)

BRCA2 (Breast Cancer 2)
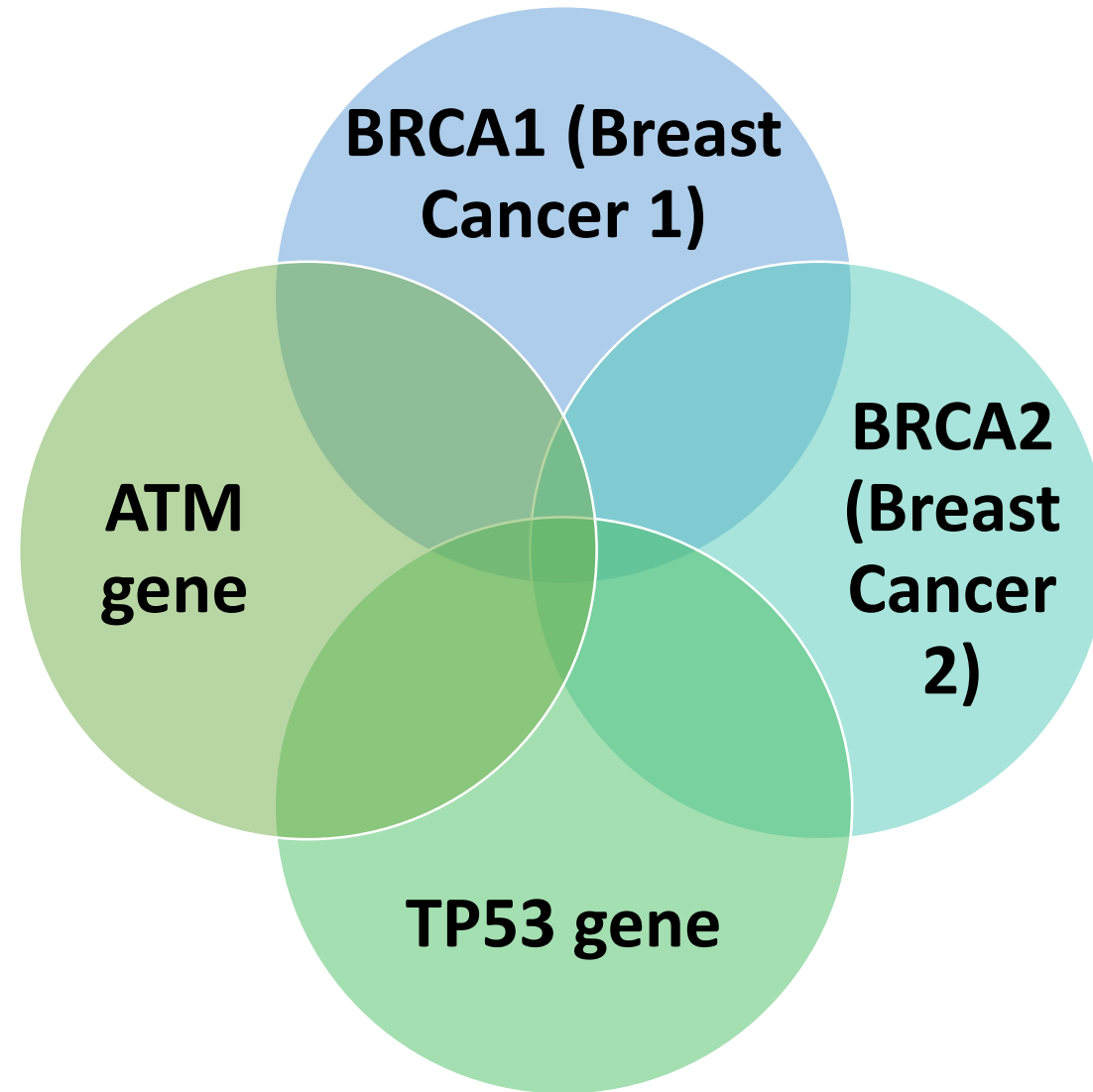
ATM gene

TP53 gene
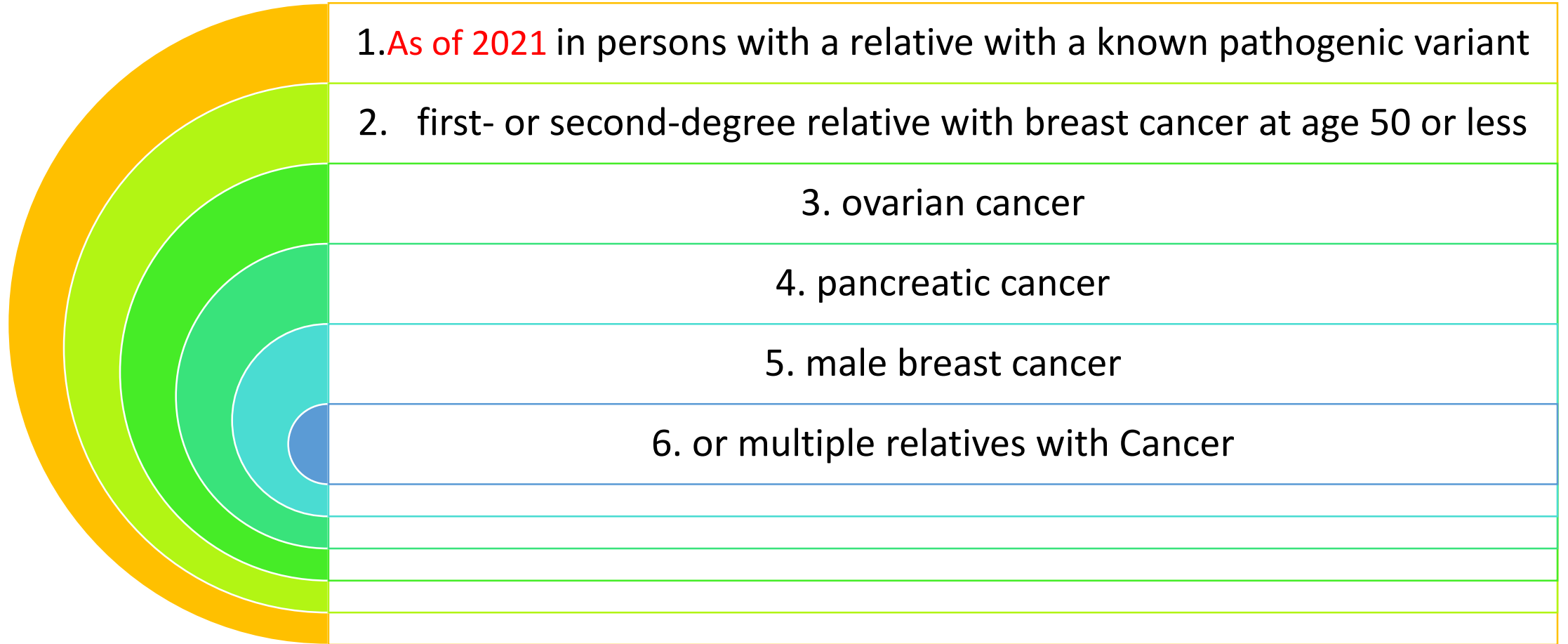
BRCA mutation

The highest risk factor for breast cancer is having a gene mutation in either *BRCA1* or *BRCA2*

- Both are autosomal dominant, high-penetrance genes
- Normally function as a tumor suppressor
- Over 30 known mutations
- 35% to 85% lifetime risk of breast cancer
- 10% to 50% lifetime risk of ovarian cancer

prior breast biopsy: PATHOLOGY

1) **Atypia** have an increased risk of breast cancer.

- Breast cancer is approximately **4-5 times** more likely among those with atypia on breast biopsy

2) **lobular carcinoma** in situ (LCIS) the risk is even higher, with studies showing a **15%-30%**

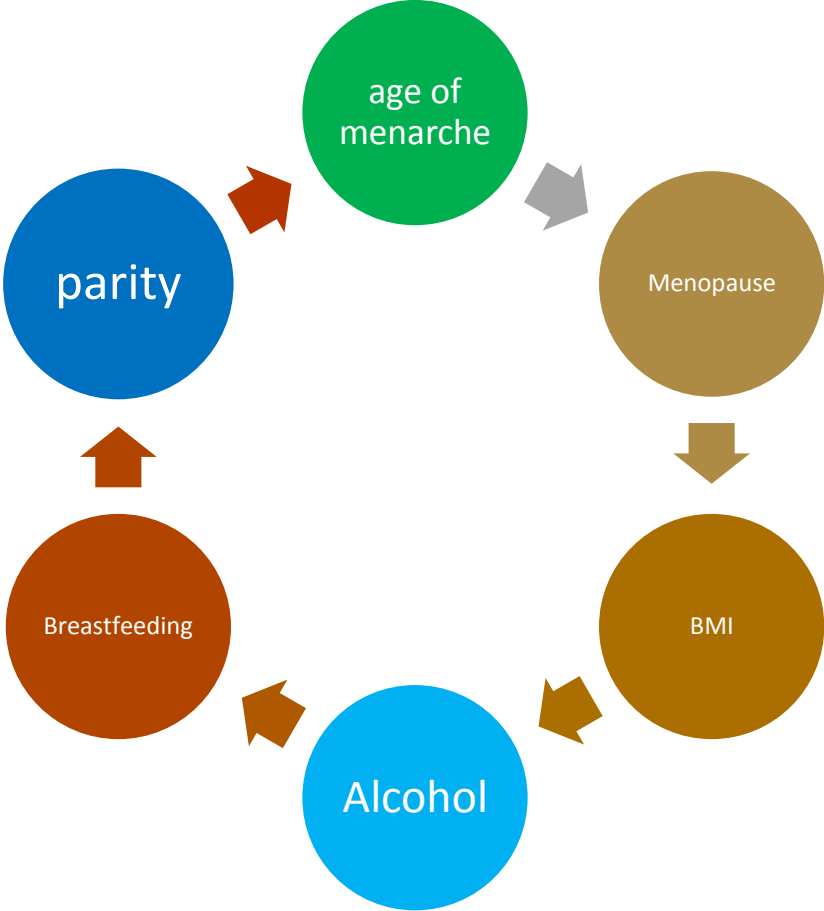- risk of developing breast cancer within 15 years of the biopsy result

chest wall irradiation:

young age (less than 30 years old)

Hodgkin lymphoma

This risk may be as high as 50% for those treated less than age 20

hormonal and lifestyle risk factors:

Health status:

life expectancy of 10 years or less.

Lifetime risks associated with genetic variants.

Population	Gene	Lifetime Risk	Management Recommendations
General Population Risk		12-13%	Screening mammography
Moderate Risk	*ATM*	15-40%	Screening mammography; consider MRI screening
	BARD1		
	CHEK2		
	NF1		
	RAD51C		
	RAD51D		
High Risk	*CDH1*	41-60%	Screening mammography; MRI screening; consider chemoprophylaxis; consider surgical prophylaxis with significant family history
	PALB2		
	STK11		
Very High Risk	*BRCA1*	>60%	Screening mammography; MRI screening; consider chemoprophylaxis; consider surgical prophylaxis
	BRCA2		
	PTEN		
	TP53		

Risk factors for breast cancer.

Risk Factor	Relative Risk
Age >64	5-10
Menarche <11	3
Menopause >54	1.2-2
ADH/ALH	4-5
LCIS	16.4
1st degree relative with breast cancer	1.5-3
Postmenopausal BMI >35	2
Alcohol consumption	1.2
Hormone use >=5 years	1.2

Risk assessment tools: modified Gail:

age

race

menarche

age of first live birth

number of first-degree relatives with breast cancer

and breast biopsy

www.cancer.gov/brcrisktool

- validated for women 35 years of age and older, and is not appropriate for those with strong family history, known high-risk genetic mutations, prior thoracic radiation, or LCIS

Relative risk estimates for the Gail model

VARIABLE	RELATIVE RISK
Age at menarche (years)	
≥14	1.00
12–13	1.10
<12	1.21
Number of biopsy specimens/history of benign breast disease, age <50 y	
0	1.00
1	1.70
≥2	2.88
Number of biopsy specimens/history of benign breast disease, age ≥50 y	
0	1.02
1	1.27
≥2	1.62
Age at first live birth (years)	
<20 y	
Number of first-degree relatives with history of breast cancer	
0	1.00
1	2.61
≥2	6.80
20–24 y	
Number of first-degree relatives with history of breast cancer	
0	1.24
1	2.68
≥2	5.78
25–29 y	
Number of first-degree relatives with history of breast cancer	
0	1.55
1	2.76
≥2	4.91
≥30 y	
Number of first-degree relatives with history of breast cancer	
0	1.93
1	2.83
≥2	4.17

Tyrer-Cuzick model:

- considering the risk of BRCA mutation and can be used for women 20 years of age and older.

ibis.ikonopedia.com/

- As opposed to the Gail model, the Tyrer-Cuzick model may overestimate the risk of cancer for women with atypia or LCIS

- Other tools:

- Claus

- Breast Cancer Surveillance Consortium (BCSC)

- Stanford Decision Tool for Women with BRCA Mutations can provide estimates of benefit of various screening and risk reduction interventions

NOTE:

- There are no tools to assess the risk of male breast cancer or breast cancer in a transgender population
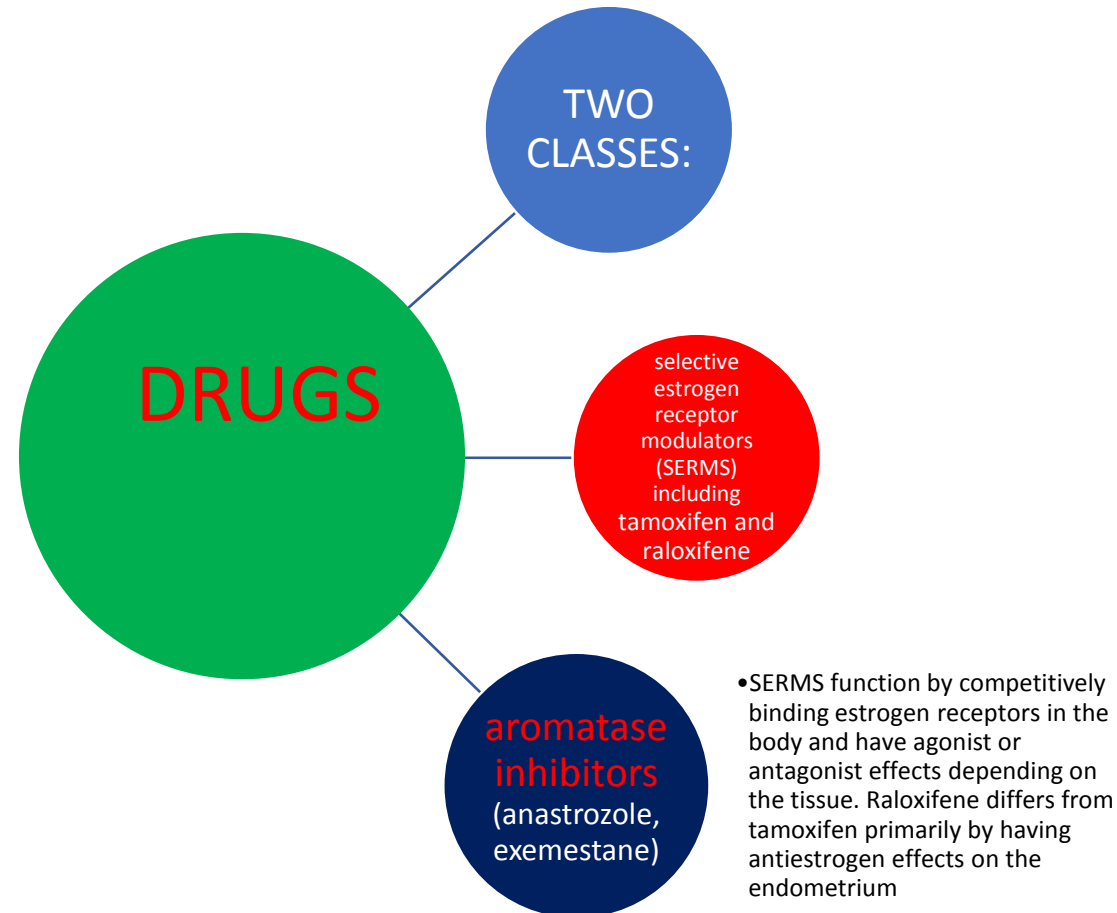
Interventions:

medical therapies

surgical risk reduction

increased surveillance

intervention is driven by quantitative risk assessments or known risk factors that place individuals at significantly increased risk of breast cancer above the general population lifetime risk of 12.9%

Chemoprophylaxis:AGENTS:

TWO CLASSES:

DRUGS

selective estrogen receptor modulators (SERMS) including tamoxifen and raloxifene

aromatase inhibitors (anastrozole, exemestane)

- SERMS function by competitively binding estrogen receptors in the body and have agonist or antagonist effects depending on the tissue. Raloxifene differs from tamoxifen primarily by having antiestrogen effects on the endometrium

TAMOXIFEN:

- 5 –years of 20 mg of tamoxifen in a high-risk population Tamoxifen reduced the risk of invasive breast cancer and non-invasive breast cancer by approximately 50% (invasive cancer RR 0.51, 95%

non-invasive cancer RR 0.50, 95%

IF
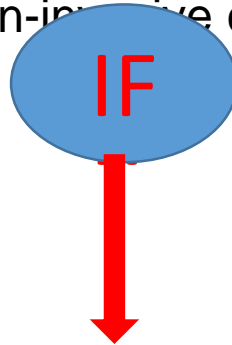
durable with decreased risk 10 years after use

Risks associated with tamoxifen:

- Endometrial cancer among postmenopausal women and an

- increased risk of pulmonary embolism

- cataracts, hot flushes, night sweats, vaginal discharge, and itching

NO OBSERVED:

↓

weight gain, depression, heart disease, stroke, or fracture

Despite the strong evidence for risk reduction, there has been a relatively low uptake of these medications for prophylaxis. Fear of adverse effects, the lack of mortality benefit, and the daily, longterm dosing may all contribute to the poor uptake

Surgical risk reduction:

- **bilateral mastectomy** should be reserved for patients with very high risk of breast cancer due to significant surgical risks and impact on quality of life

- risk of breast cancer is reduced by approximately 90%??????

- BRCA1 and BRCA2 mutations are frequently offered risk-reducing mastectomy

- **Simple mastectomy** has traditionally been performed for risk reduction

- **Bilateral oophorectomy:** risk of breast cancer up to 50%

Risk driven screening:

- **MRI:** greater than **20% lifetime risk** of breast cancer more sensitivity for detection and lower stage at diagnosis; however, there are limited data showing improvement in mortality Compared with mammography, MRI has **increased sensitivity** but **decreased specificity**, resulting in higher **false**-positive rates Initiation of screening should start with MRI 10 years prior to the youngest family member's cancer diagnosis, but not before age 25, and for mammography to start 10 years prior to the youngest family member, but not before age 30

Lifestyle modifications:

1. Many factors that increase the risk of breast cancer are not modifiable strongest link between alcohol intake and increased BMI for postmenopausal women alcohol consumption

1) with a 10% increase in breast cancer risk for each 10 g of alcohol consumed daily regardless of menopausal status

2) increased BMI after menopause as a risk factor

3)elevated BMI prior to menopause appears protective

- BMI of 28 kg/m2 or higher there was a 26% higher chance of breast cancer compared to normal-weight women

Guidelines for clinical practice.

Organization	Guideline	Comment
United States Preventative Services Task Force	Chemoprophylaxis	Risk reducing medication recommended for those at high risk
American Society for Clinical Oncology	Chemoprophylaxis	Risk reducing medication recommended for those at high risk
National Comprehensive Cancer Network	Chemoprophylaxis	Risk reducing medication recommended for those at high risk
National Institute for Health Care Excellence	Chemoprophylaxis	Risk reducing medication recommended for those at high risk
United States Preventative Services Task Force	Genetic testing	Screening tools should be used to refer to genetic testing
National Comprehensive Cancer Network	Genetic testing and management	Criteria for referral to genetic testing; recommended management for results
National Institute for Health Care Excellence	Genetic testing and management	Criteria for referral to genetic testing; management for limited results
American Cancer Society	Screening	Mammogram and MRI screening recommendations for those at elevated risk
National Comprehensive Cancer Network	Screening	Mammogram and MRI screening recommendations for those at elevated risk
National Institute for Health Care Excellence	Screening	Mammogram and MRI screening recommendations for those at elevated risk; cessation of screening recommendations

Guidelines for practice:

- (USPSTF) and American Society of Clinical Oncology (ASCO) both have published guidelines on the use of medications for breast cancer risk reduction

- ASCO recommends consideration of tamoxifen 20 mg per day for 5 years for women who are premenopausal, with no history of deep vein thrombosis, use of hormone therapy, or those pregnant or breastfeeding

American Cancer Society:

- ACS recommends the addition of MRI to mammography yearly starting typically at age 30 for women identified as high risk, including high-risk genetic mutation carriers, chest radiation between 10 and 30 years of age, and a lifetime risk calculated using tools that account for family history of 20-25% or greater

interventions may be undertaken to decrease risk of developing disease or the stage at which it is detected. Although some interventions, such as screening MRI and prophylactic mastectomy for BRCA carriers and other genes that place women at high risk have increased in their acceptance and use, others such as medical prophylaxis have not

Summary:

1) identified based on tools identifying risk family history or personal factors, genetic testing results, atypia on biopsy, or exposure to chest

2) radiation at young age Medications recommended to decrease the risk of breast cancer consist of tamoxifen, raloxifene, and exemestane showing a 50% reduction in invasive cancer Surgical risk reduction should generally be reserved for those with genetic mutations conferring very high risk, history of LCIS, or chest irradiation due to Hodgkin lymphoma

Practice points

- All patients should be assessed for risk factors for developing breast cancer.
- Quantitative tools can be used to estimate the risk of breast cancer, which can direct prevention measures.
- Patients with family history suggestive of genetic predisposition should be offered and referred for genetic counseling and testing.
- Patients at significantly increased risk should be engaged in shared decision-making regarding increased screening and prevention strategies.

- In the year 2008, there were about 2.5 million women in the U.S. who considered themselves breast cancer survivors.

Celebrating Our Survivors