

Breast Cancer

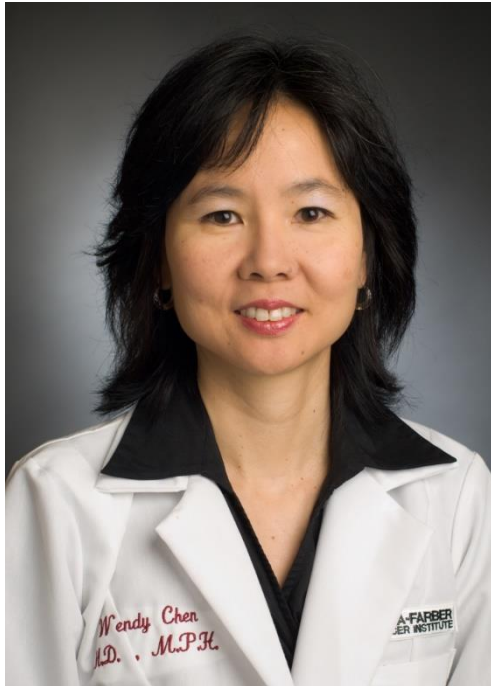
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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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 - Research focus: Cancer epidemiology

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- **Disclosures:**
 - **None related to this presentation**

Learning objectives

- *Review current breast cancer screening recommendations*
- *Review key breast cancer risk factors*
- *Review options for breast cancer prevention*
- *Counsel patients regarding genetic testing*
- *Review current treatment trends*





Breast	321,910	32%
Lung & bronchus	118,500	12%
Colon & rectum	74,690	7%
Uterine corpus	68,270	7%
Melanoma of the skin	46,600	5%
Non-Hodgkin lymphoma	35,550	3%
Pancreas	32,340	3%
Thyroid	32,000	3%
Kidney & renal pelvis	29,680	3%
Leukemia	28,720	3%
All sites	1,020,780	

Cancer cases



Lung & bronchus	61,950	21%
Breast	42,140	14%
Pancreas	25,510	9%
Colon & rectum	25,120	8%
Uterine corpus	14,450	5%
Ovary	12,450	4%
Liver & intrahepatic bile duct	11,330	4%
Leukemia	10,010	3%
Brain & other nervous system	8,380	3%
Non-Hodgkin lymphoma	8,260	3%
All sites	298,850	

Cancer deaths

Screening mammography

Current screening guidelines



Screening question

45 y.o. woman wants to know more about breast cancer screening. You advise her that:

- A. Mammograms do not reduce mortality for women aged 40-49
- B. MRI reduce breast cancer mortality more than mammograms
- C. Breast density decreases with higher body mass index
- D. Ultrasound is superior to mammography as screening tool for dense breasts

Answer to screening question

55 y.o. woman wants to know more about breast cancer screening. You advise her that:

- A. Mammograms **DO** reduce mortality for women aged 40-49.
- B. MRI has **NOT** been shown to reduce breast cancer mortality
- C. *Breast density decreases with higher BMI*
- D. Ultrasound is **NOT** superior to mammography as screening tool for dense breasts

Why the controversy about mammograms?

- **2024 USPSTF guidelines - Women aged 40-74 should get routine screening mammogram**
 - Randomized controlled trials and meta-analyses => 15-20% ↓↓ mortality
 - Recommended screening interval 2 years
- **Why age 50 before?**
 - Breast cancer less common < age 50 so absolute benefits smaller
 - More false positives in women 40-50
- **What changed?**
 - Breast cancer ↑↑ 2% per year in women aged 40-50
 - Black women earlier age at dx and higher mortality

When to stop screening?

- **No large RCT enrolled women > 75 yrs**
 - RR breast cancer mortality 1.12 (95% CI 0.73-1.72) for Swedish trial with ~5000 women aged 70-74
- **Annual Medicare costs for screening, diagnosis, and treatment ~ \$1.36 billion**
 - \$410 million spent on women aged 75+
- **Guidelines vary when to stop screening**
 - Screening detects small cancers that are unlikely to lead to death

Different society guidelines

	USPSTF	American Cancer Society	American College of Radiology
Age to start screening	40	45	40
Age to stop screening	75	<10 years life expectancy	Stop when severe comorbidity
Screening interval	2 yrs	Annual 45-54 Biennial 55+	Annual

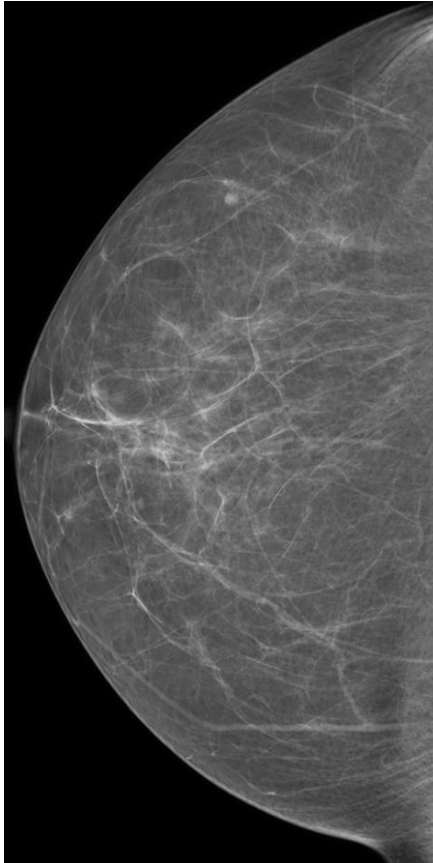
Breast density

- **Breast density associated with ↑↑ breast cancer risk**
 - Biology unclear since breast density not correlated with known risk factors, e.g. decreases with age and higher BMI
- **Unclear what screening modality best**
 - Breast density notification now mandated by FDA
 - Ultrasound best for targeted areas, not whole breast
 - MRI high rate of false positives and not been shown to impact mortality

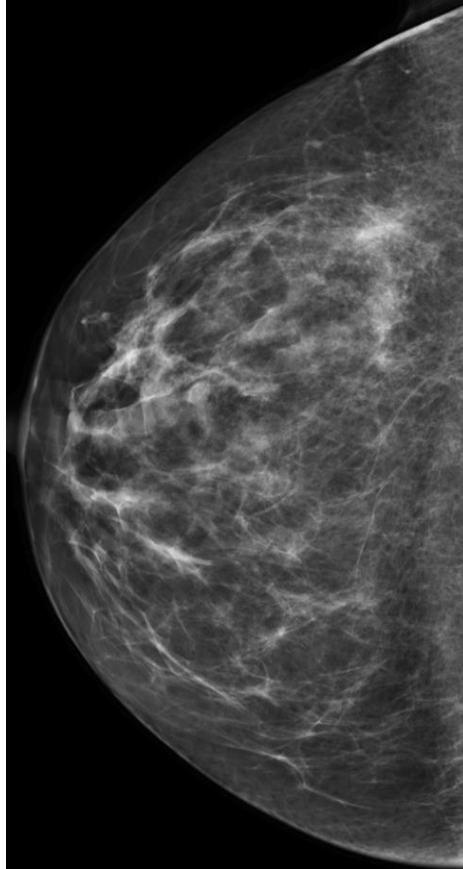


Breast density categories

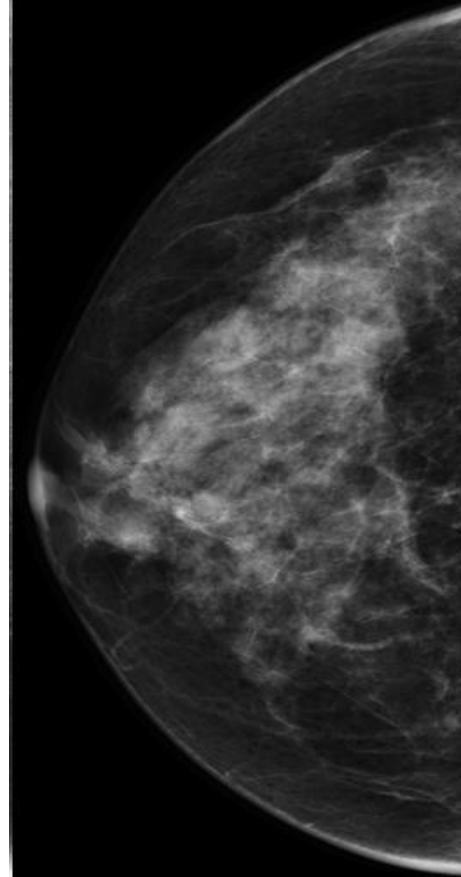
A



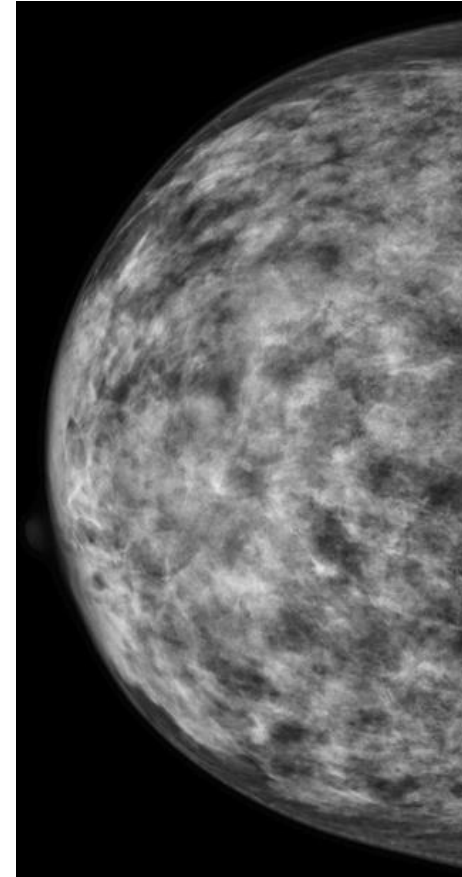
B



C



D



**Almost
entirely fatty**

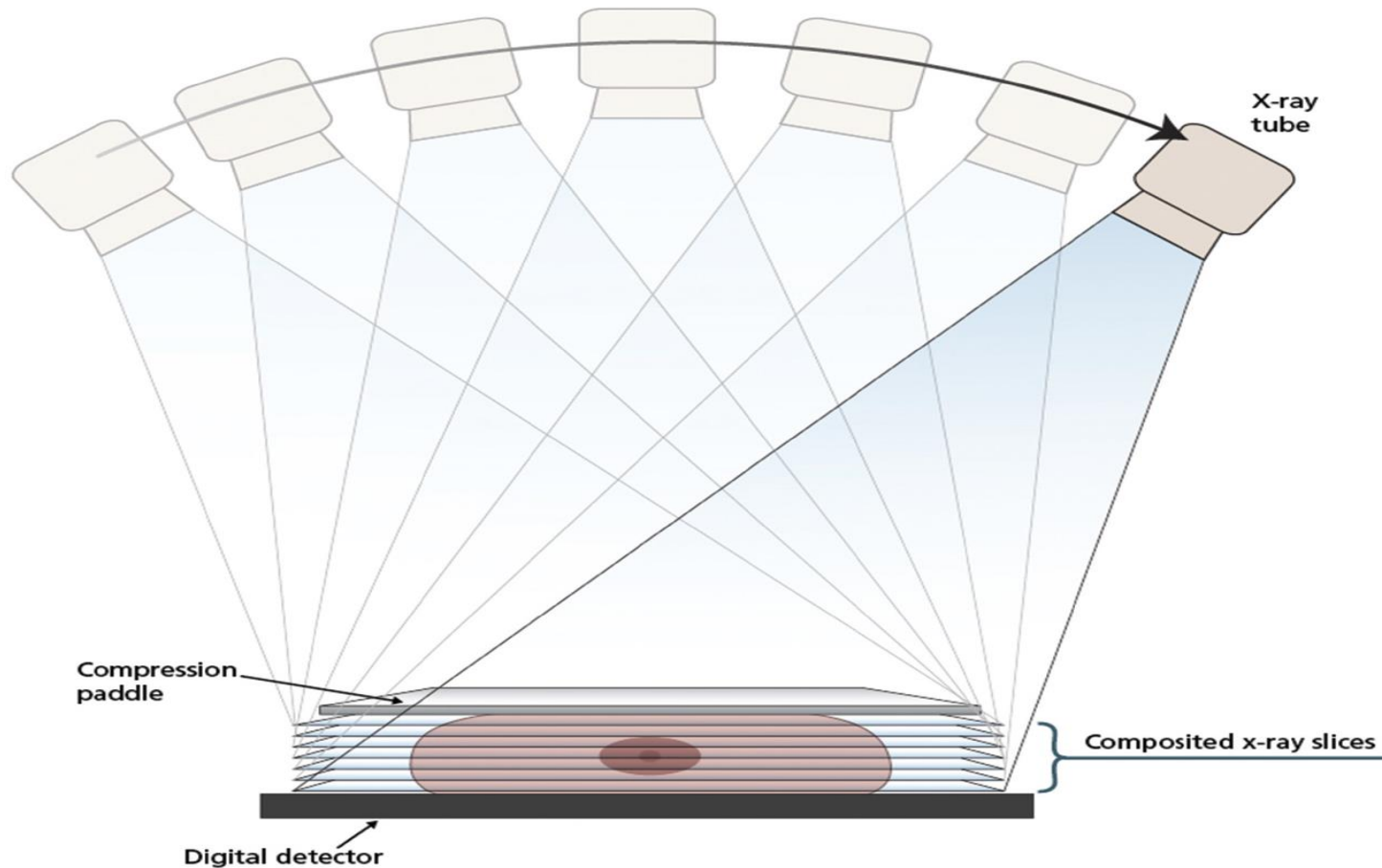
**Scattered areas of
fibroglandular
density**

**Heterogeneously
dense**

**Extremely
dense**

Breast tomosynthesis (3-D mammo)

Breast stays in place and x-ray machine moves to take multiple images of breast



Breast MRI

- **More sensitive – especially in young women**
 - Does not replace mammograms
 - Many more false positives
 - Requires IV gadolinium
 - Impractical as screening tool
 - **Annual MRI screening recommended**
 - Breast cancer germline genetic mutations
 - Radiation to chest between ages 10 and 30
 - Lifetime risk of >20-25%
 - NCCN and ACR also recommend for dense breasts
- = >Never been shown to reduce mortality**

Contrast enhanced mammo

- IV contrast prior to standard mammo
- **BRAID** randomized trial of supplemental screening for women with dense breasts and normal mammo

	Cancer detection rate per 1000 (95% CI)
Abbreviated MRI	17.4 (12.2–23.9)
Automated u/s	4.2 (1.9–8.0)
Contrast mammo	19.2 (13.7–26.1)

- **Current FDA approval for diagnostic imaging**
 - Availability limited and reimbursement still unclear

Established breast cancer risk factors

- Age
- Overweight
- Alcohol use
- Physical activity
- Menopausal hormone use
- Late age at first birth (> 30 y.o.)
- Early age at menarche
- Late age at menopause
- *BRCA1/2*, *genetics*, and Family history

Established breast cancer risk factors

- Age
- **Overweight**
- **Alcohol use**
- **Physical activity**
- Menopausal hormone use
- Late age at first birth (> 30 y.o.)
- Early age at menarche
- Late age at menopause
- ***BRCA1/2, genetics, and Family history***

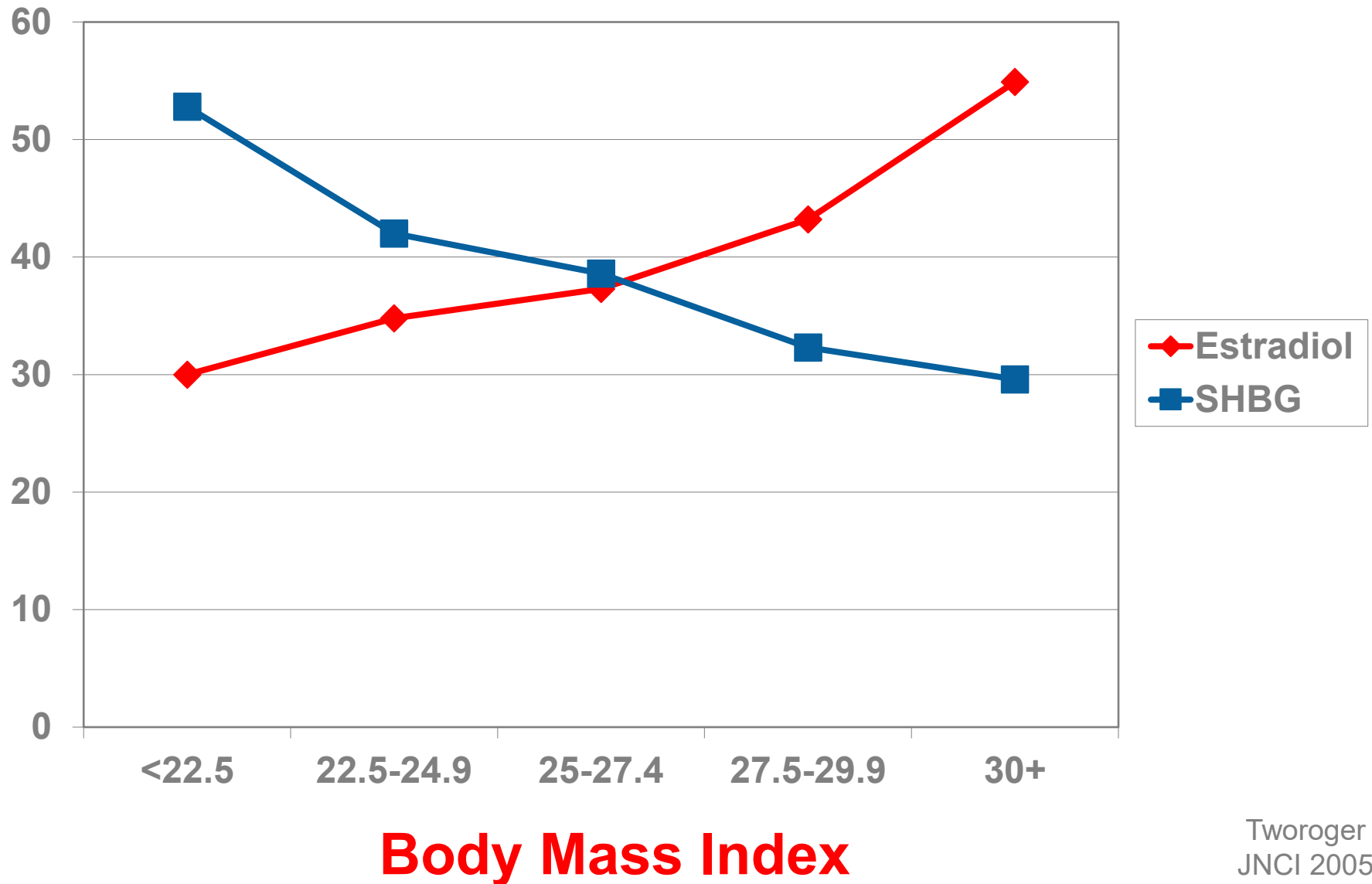
Body mass index and breast cancer



Body mass index

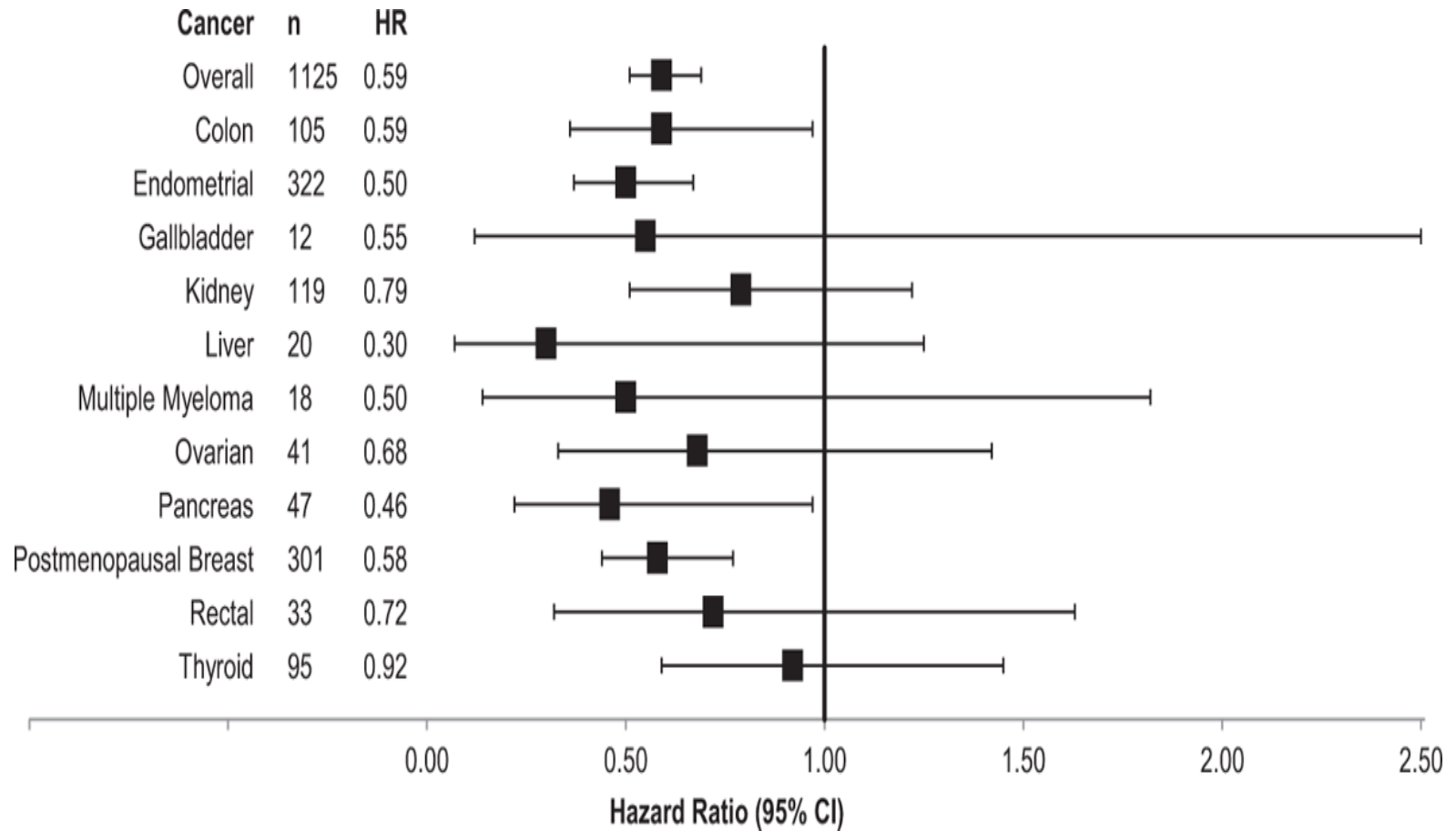
- **↑↑ Postmenopausal breast cancer risk**
 - 20-30% with **↑↑ BMI > 30**
 - 10% **↑↑** with 5 kg/m² increase BMI
- *Main source of estrogen after menopause = peripheral conversion of androgens into estrogens by aromatase in adipose tissue*

Body mass index and sex steroid levels



Weight Loss Lowers Cancer Risk

Bariatric surgery – 22,198 pts and 66,427 controls



Physical activity

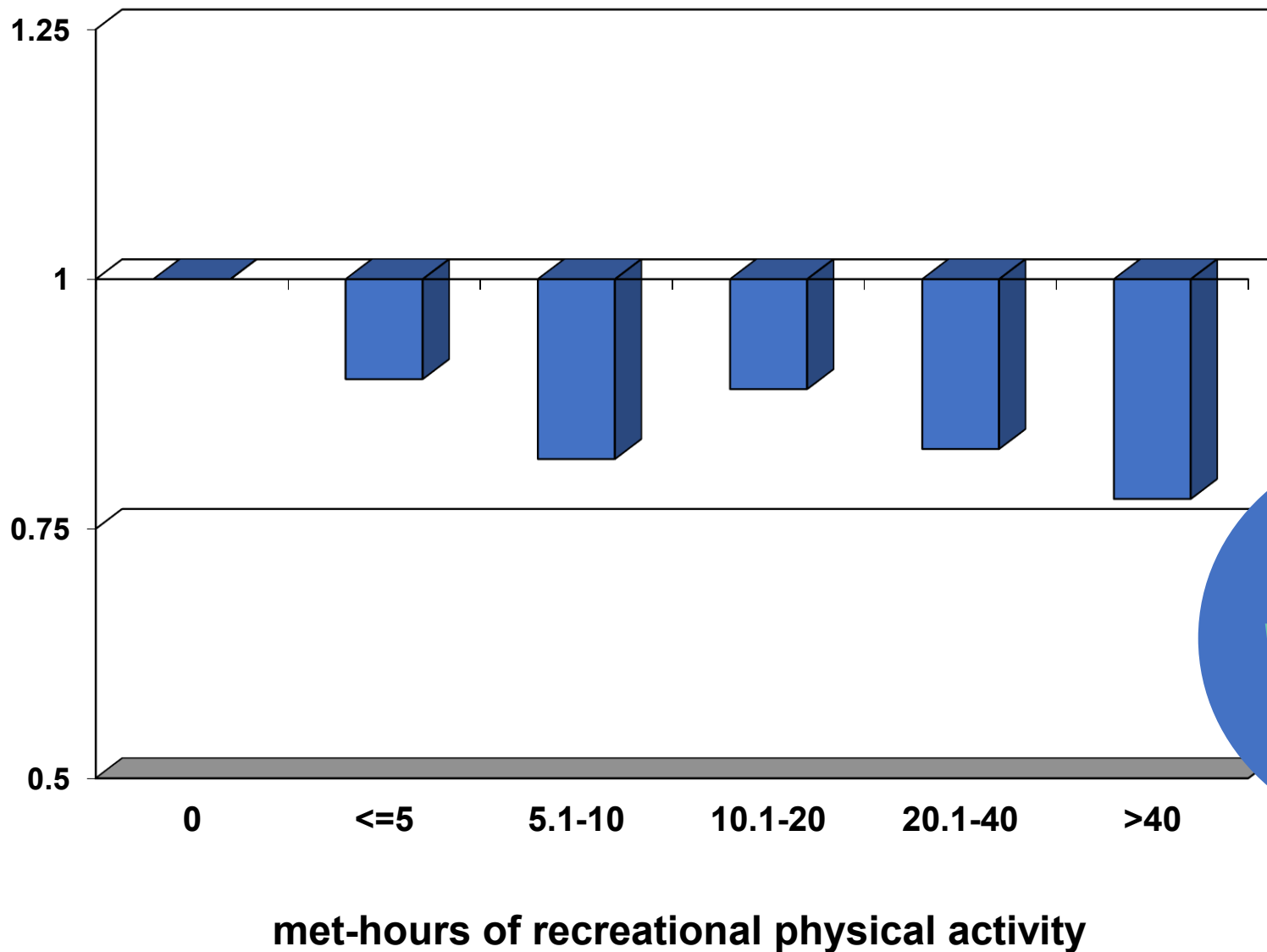


Physical activity and breast cancer

- ↓↓ **Breast cancer risk with physical activity**
 - Prevent weight gain and ↓ body fat
 - ↓ estradiol, estrone, and free estradiol and
↑ sex hormone binding globulin
 - ↓ insulin levels



Exercise and postmenopausal breast ca



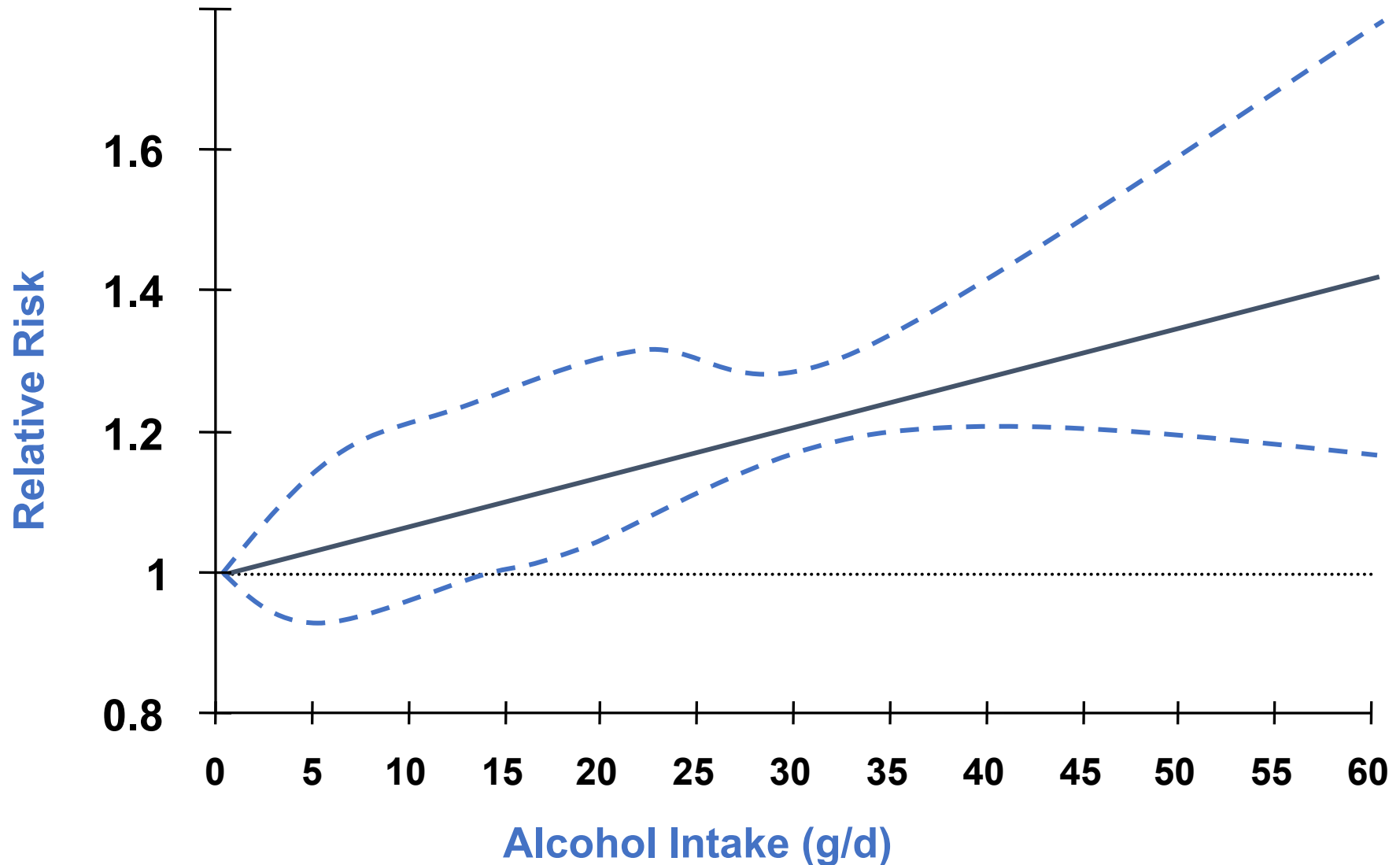
=> No strong association with moderate or strenuous activity

Alcohol

Multiple studies show association between alcohol and breast cancer

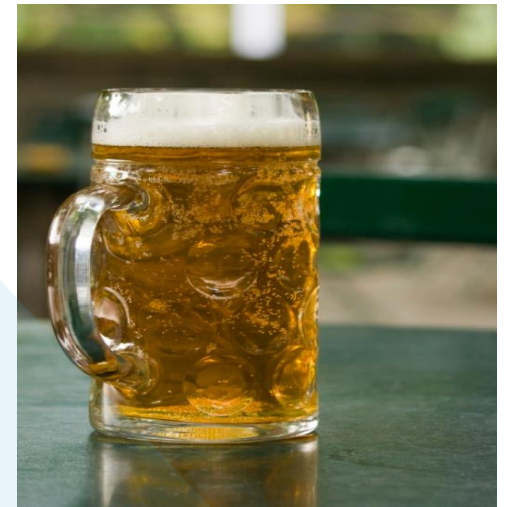


Alcohol Intake and Breast Cancer



Alcohol and breast cancer

- **No difference by type of alcoholic beverage**
 - Wine vs. beer. vs. liquor
- **Cumulative intake best measure**
- **2-3 servings per week OK**



Nutrition and Breast Cancer



Challenges to studying nutrition and cancer

- **Many food items inter-related**
 - People who eat more meat, eat less vegetables
- **Nutrition related to other health behaviors**
 - People who eat healthier often thinner and more physically active
- **Long-term trends more important than short-term**



**=> Beware
of findings
from small
individual
studies!**

Nutrition and breast cancer risk



- **Modest benefit of fruit and vegetable intake on breast cancer**
 - ✓ Results stronger for estrogen negative cancers



- **Modest increased risk with red meat and breast cancer**

No strong associations between breast cancer and fish, fiber, or caffeine intake

Why the interest in soy

- **Soy high in isoflavones – phytoestrogens**
 - Structurally similar to estradiol and bind ER
- **Modest ↓↓ breast cancer risk with soy**
 - Meta-analysis: OR 0.78 (highest vs lowest intake)
 - Asian studies show strongest effect
- **Asian and western soy intake differ**
 - Types of soy – whole vs processed soy
 - Timing of soy exposure – early vs late life



Family History/Genetics



Who should get BRCA1/2 testing?

Risk for BRCA1/2 mutation is greater if:

Age $\leq$ 50 at diagnosis

Bilateral breast cancer

Male breast cancer

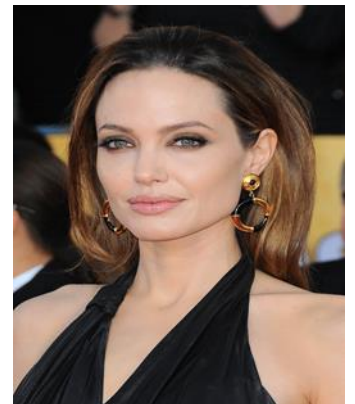
Ovarian or pancreatic or met prostate cancer

Triple negative breast cancer

=> *Person with cancer should be tested first*

BRCA 1 & 2

- ↑↑ lifetime risk of breast/ovarian cancer
- **BRCA1**
 - >60% breast , 40-60% ovarian ca
 - ↑ prostate and pancreatic cancer
- **BRCA2**
 - >60% breast , 10-25% ovarian ca
 - ↑↑ male breast, pancreatic, prostate, melanoma
- Explains 5-10% of breast cancers
 - More common in Ashkenazi Jewish



Multigene/Expanded Panel test

- **BRCA1/2 testing alone rarely done**
- **Expanded panel testing**
 - Breast ca - ATM, BARD1, CDH1, CHEK2, NF1, PALB2, pTEN, RAD51, STK11, TP53
- **Breast ca risk vary**
 - Generally lower than BRCA1/2
 - Clinical recommendations vary depending on risk
- **Risk of other cancers vary**
 - CDH1 gastric ca



Breast Cancer Prevention



Prevention question

A healthy 45 y.o. premenopausal woman has a mother who was diagnosed with breast cancer at age 60 and passed away at 65 with metastatic disease. She would like to discuss breast cancer prevention. You recommend that she consider:

- A. Aromatase inhibitor
- B. Raloxifene
- C. Tamoxifen
- D. All of the above depending upon side effects

Answer to Prevention question

A healthy 45 y.o. premenopausal woman has a mother who was diagnosed with breast cancer at age 60 and passed away at 65 with metastatic disease. She would like to discuss breast cancer prevention. You recommend that she consider:

A. Aromatase inhibitor

B. Raloxifene

C. Tamoxifen

D. All of the above depending upon side effects

Randomized prevention trials

- **Tamoxifen, raloxifene, aromatase inhibitors** ↓↓
breast ca risk ~50% compared to placebo
 - Only prevents ER+ breast cancer
 - No survival benefit seen
 - Raloxifene and AI's only after menopause
 - Low dose tamoxifen (5 mg daily) fewer side effects
 - Option for prevention (not breast cancer treatment)
- **Why are these drugs not used more?**
 - Absolute risk of breast cancer low
 - Side effects
 - Screening available for breast cancer

Who should consider risk reducing meds?

- **Aged 35 and older with increased risk of breast cancer**
 - 1st degree relative with breast cancer
 - Personal history of lobular carcinoma in situ or atypical hyperplasia
 - 5 yr predicted risk of breast cancer $>1.66\%$ (Gail model)

<http://bcrisktool.cancer.gov>



Tamoxifen vs Raloxifene vs AI

	Tamoxifen	Raloxifene	Aromatase inhibitors
Hot Flashes	Yes	Yes	No
Uterine effects	Yes	No	No
Bone Density	↑↑	↑↑	↓↓
Thrombotic risk	Yes	Yes	No
Premenopausal use	Yes	No	No

Breast Cancer Treatment



Treatment question

60 y.o. woman was diagnosed with a 1.5 cm grade 2, node negative, ER positive, HER2 negative breast cancer and had a mastectomy. What will have the biggest impact on 10-year breast cancer specific survival?

A. Hormonal therapy

B. Radiation

C. Chemotherapy

D. Trastuzumab

Adjuvant hormonal therapy

- **1st targeted therapy**

- ↓↓ breast cancer mortality by 1/3
- ↓↓ contralateral breast cancer by 1/2
- 5 yrs for node negative, 8-10 yrs for node positive

- **Tamoxifen**

- Can be used for both pre and postmenopausal
- No data for raloxifene in adjuvant setting

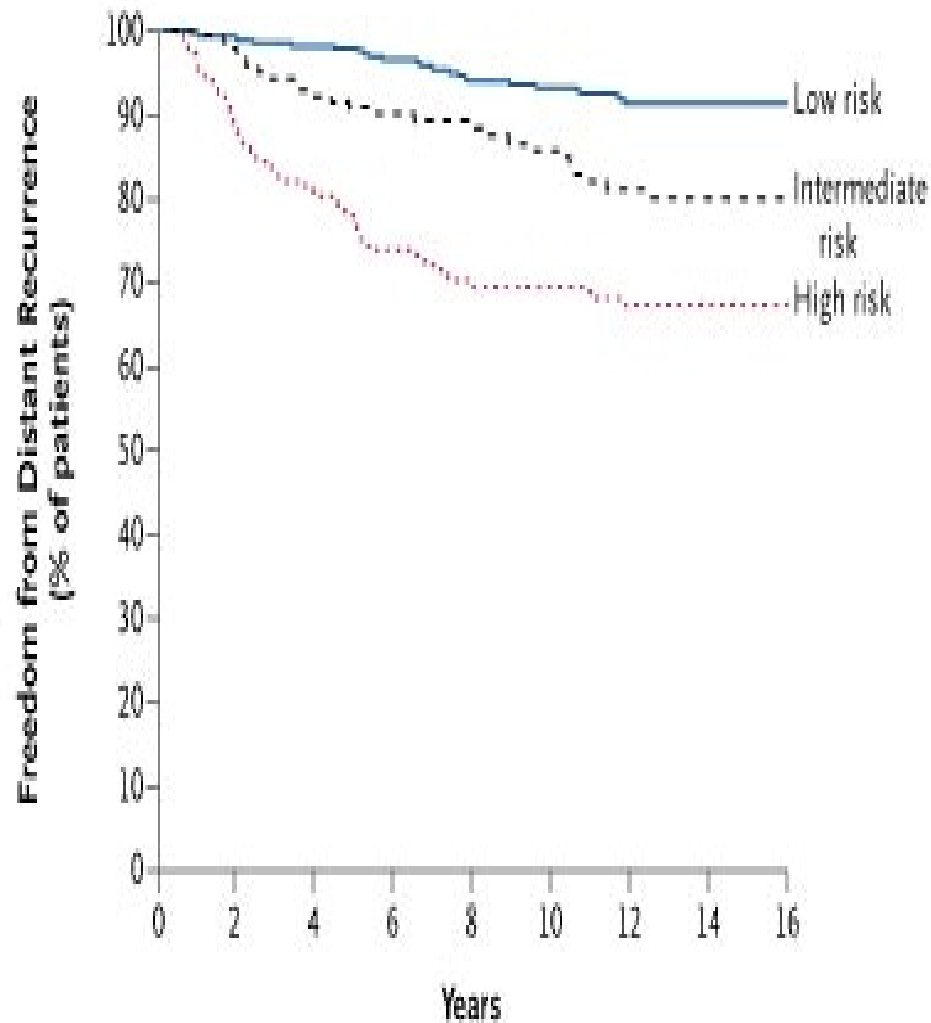
- **Aromatase inhibitor**

- Preferred for postmenopausal women

- **Ovarian suppression**

- Considered for higher risk

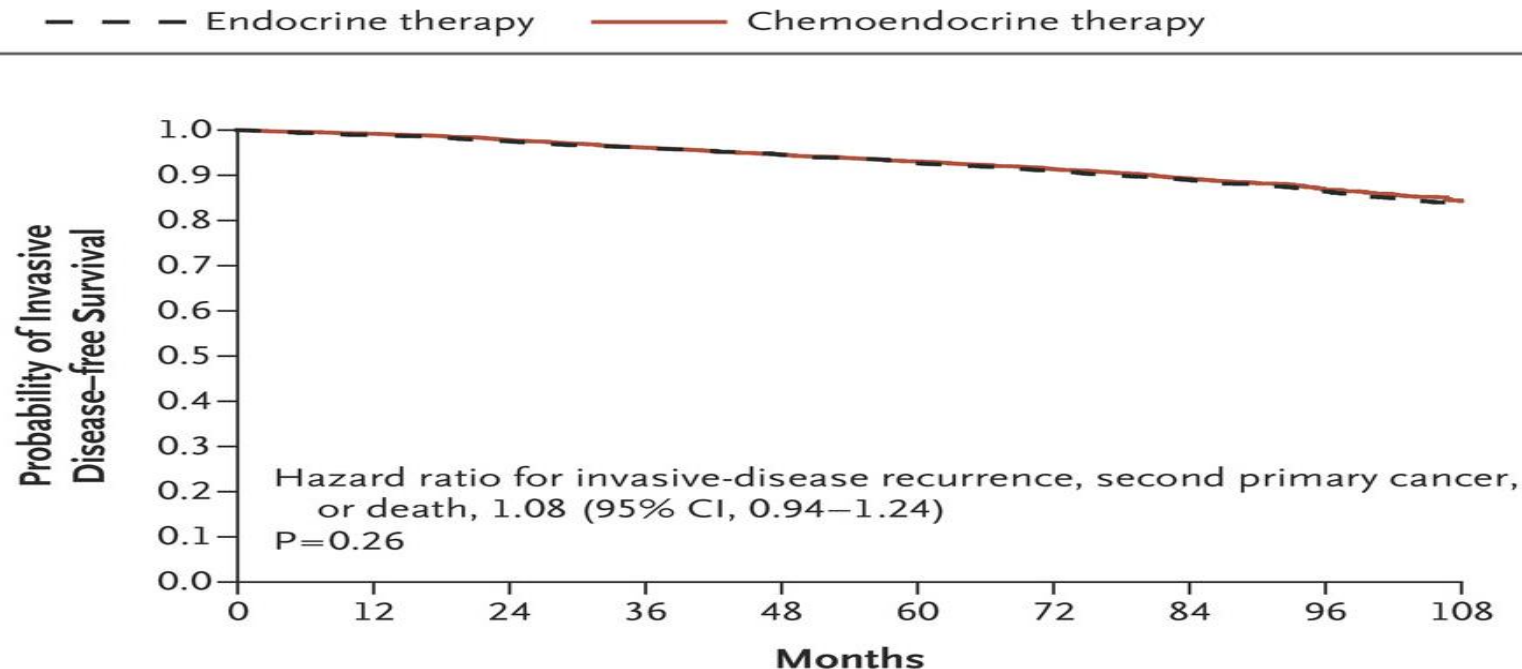
OncotypeDX[®] for prognosis



- **RT-PCR gene expression array**
 - Estimate recurrence risk from clinical trial data
 - ER positive and HER2 negative
 - Node-negative and 1-3 positive lymph node
- **Low score is good!**
 - Cutoff for low varies
- **Node negative**
 - 9 yr Distant met < 1%
- **Node positive**
 - 5 yr distant mets < 5%

OncotypeDX® for prediction

- TAILORx randomized 10,273 ER pos, node neg with OncotypeDX 11-25 to hormonal rx +/- chemo
 - Overall survival 93.9 vs 93.8% (median f/u 8 yrs)
 - No benefit to chemo for women > 50 yrs
 - ?Chemo benefit for women < 50 yrs and score 16-25 but could chemo effect be due to ovarian suppression?



Adjuvant breast cancer chemo

- **Important trends**

- Less chemo for ER positive
- If chemo given, often before surgery to shrink tumor and assess response
 - For ER negative and HER2 positive, residual disease after chemo strongly related to prognosis

- **Biology, not stage, drive chemo recs**

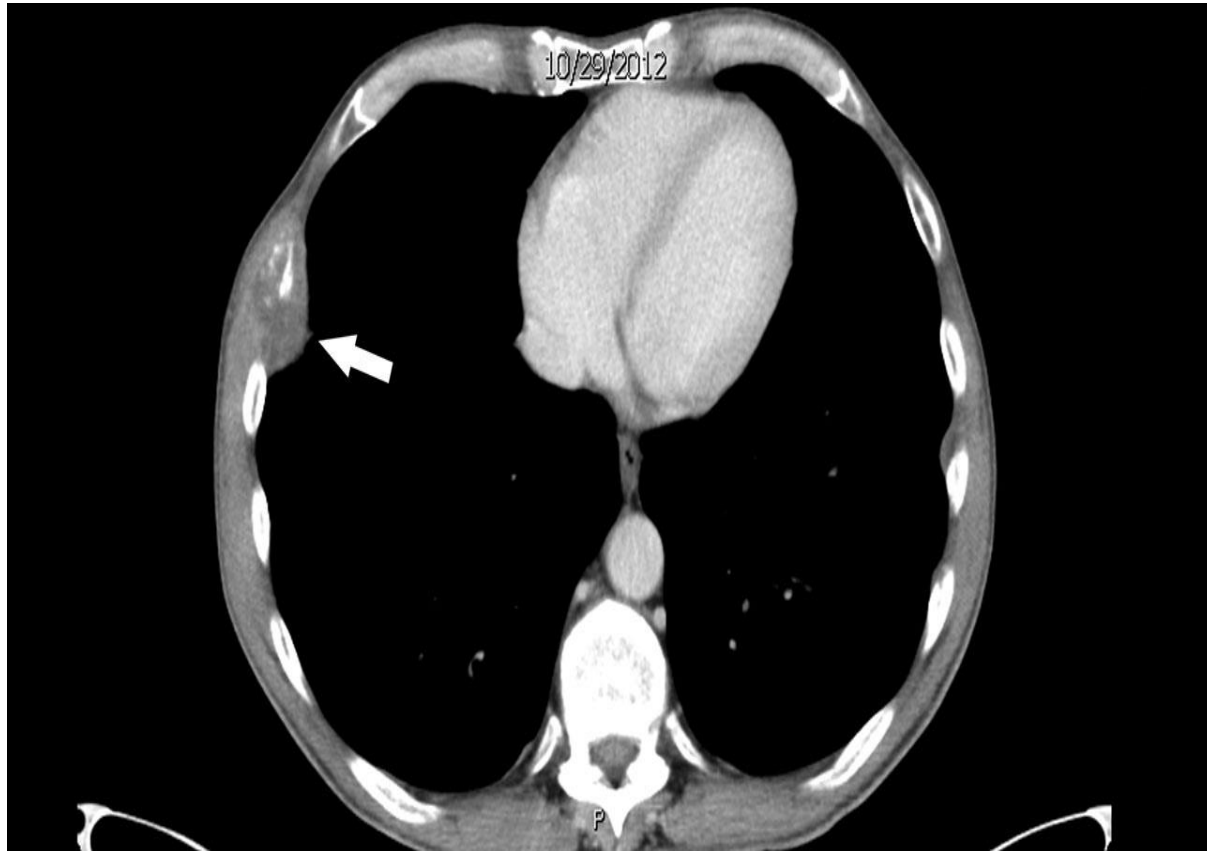
- Triple negative with chemo + immunotherapy
- HER2 positive with trastuzumab
- ER positive if high risk or multiple positive lymph nodes



HER2neu and trastuzumab

- **HER2/neu protein**
 - Member of EGFR family
 - 20-25% of breast cancers overexpress HER2
- **Trastuzumab - monoclonal antibody to HER2**
 - Can cause congestive heart failure
 - Most effective when given with chemo
- **HER2 positive tumors have worse prognosis, *if not treated with trastuzumab***
 - With treatment, prognosis similar or better to HER2 negative

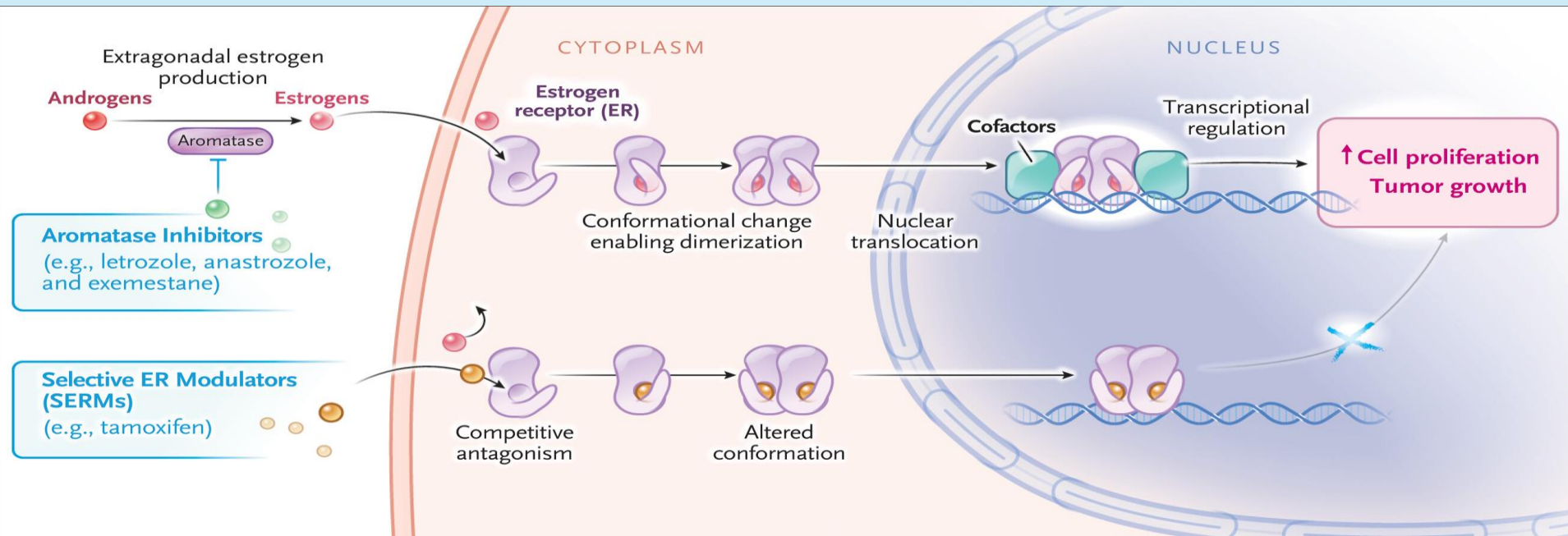
Metastatic Breast Cancer



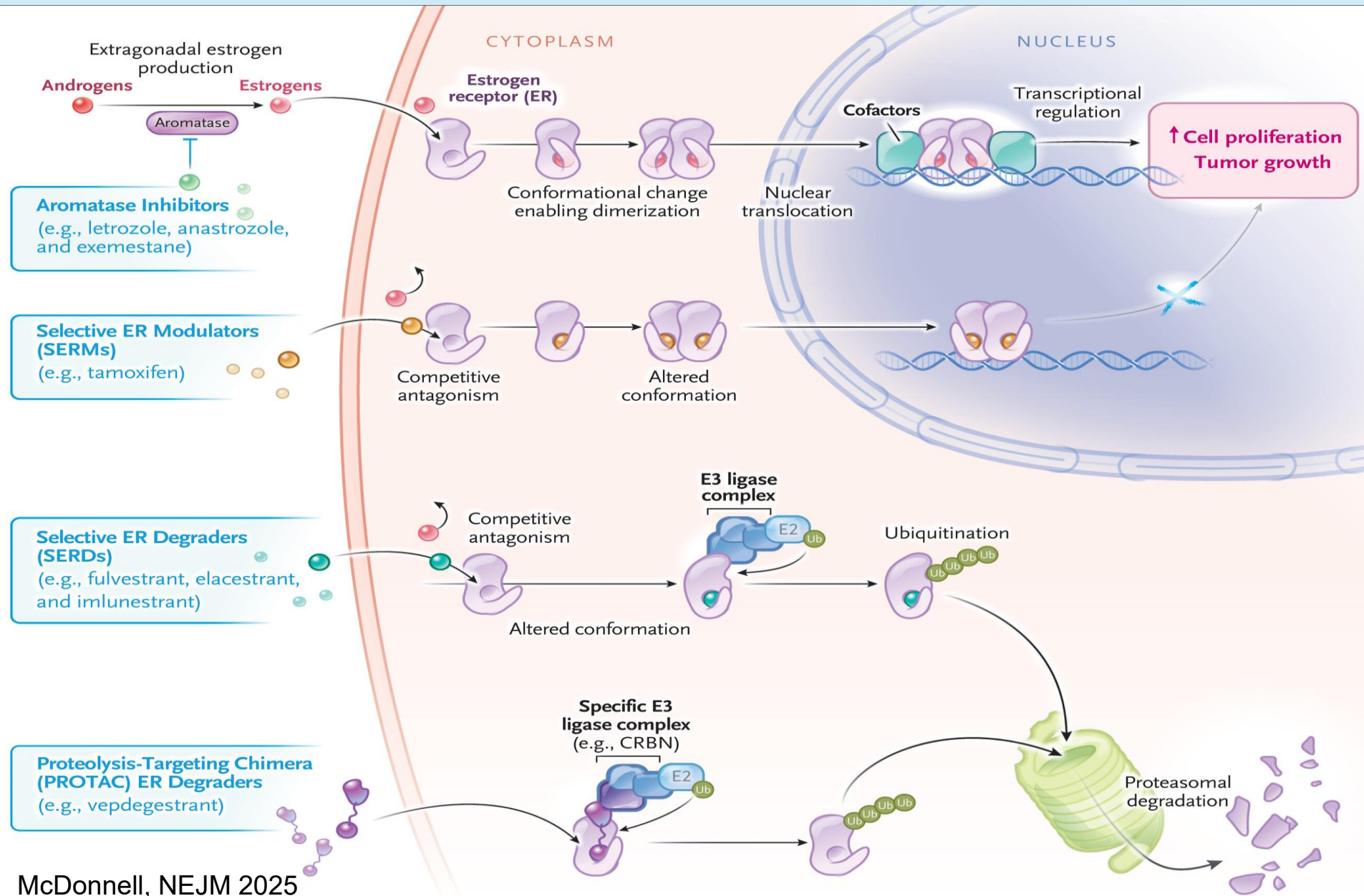
Metastatic breast cancer overview

- **Survival continues to improve**
 - >1/3 alive at 5 yrs, but varies by subtype
- **Hormone receptor positive/HER2 negative**
 - Oral hormonal therapy first before chemo
- **Triple negative**
 - Chemo + immunotherapy first if tumor PDL1 positive
- **HER2 positive**
 - HER2 directed therapy followed by maintenance antibody therapy for responders

Hormonal therapy

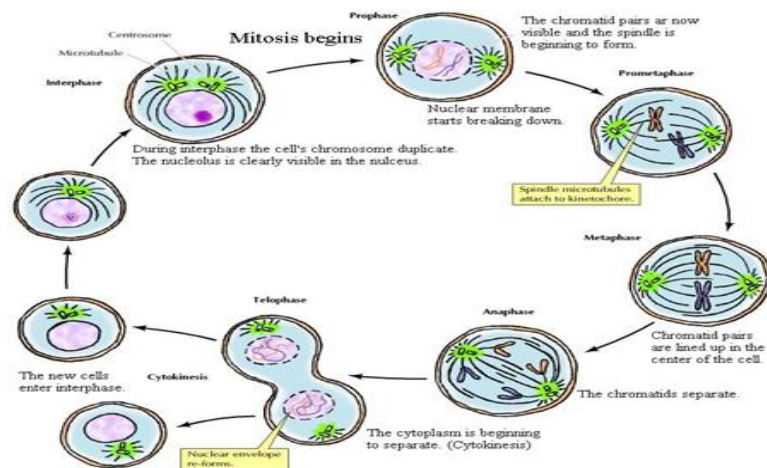


Hormonal therapy



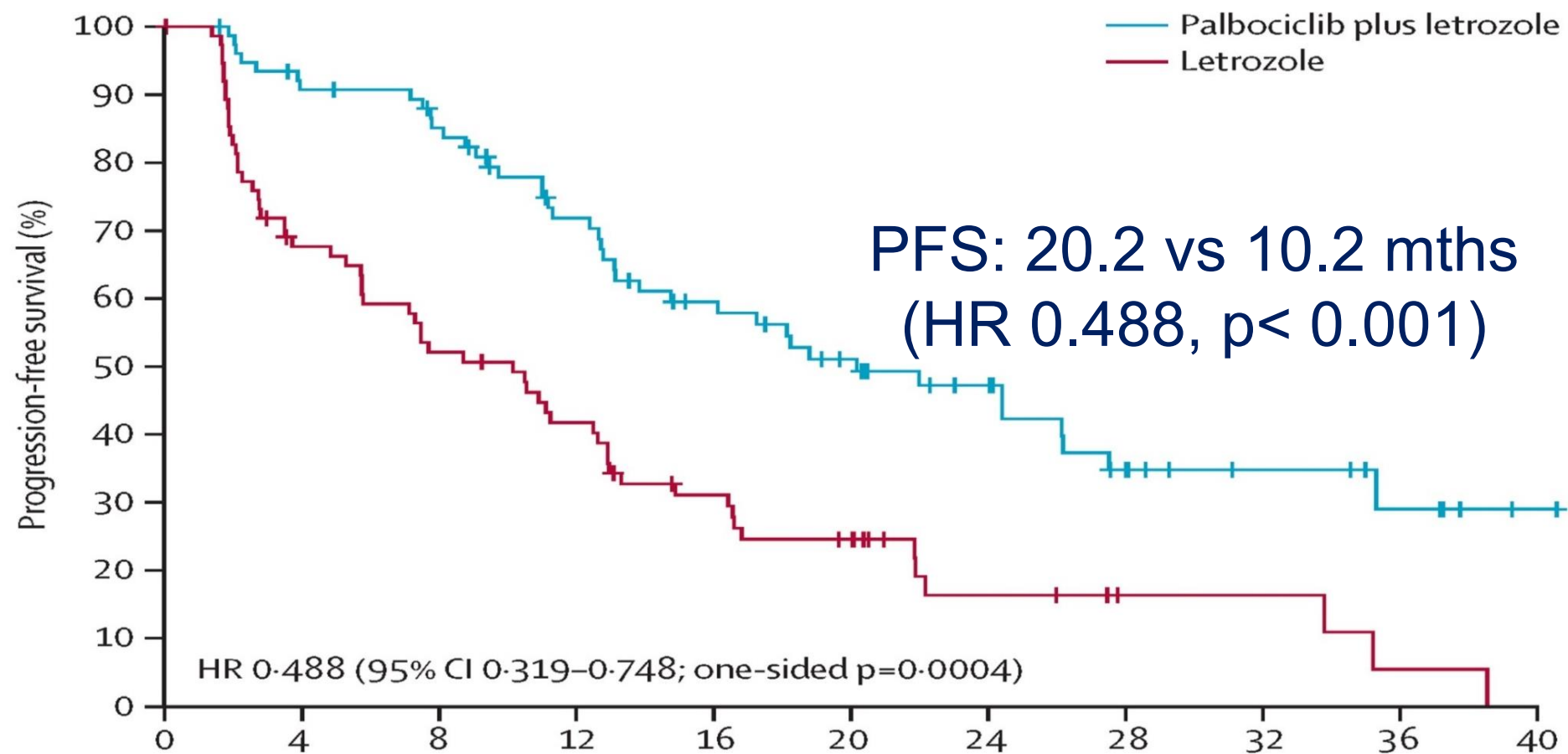
CDK4/6 inhibitor

- Cyclin dependent kinase (CDK) 4/6 mediates G0/G1 => S phase transition
 - CDK4/6 overexpression common in ER+ breast cancer
 - Oral pill combined with hormonal therapy
 - Ribociclib (Kisqali), abemaciclib (Verzenio), palboclib (Ibrance)



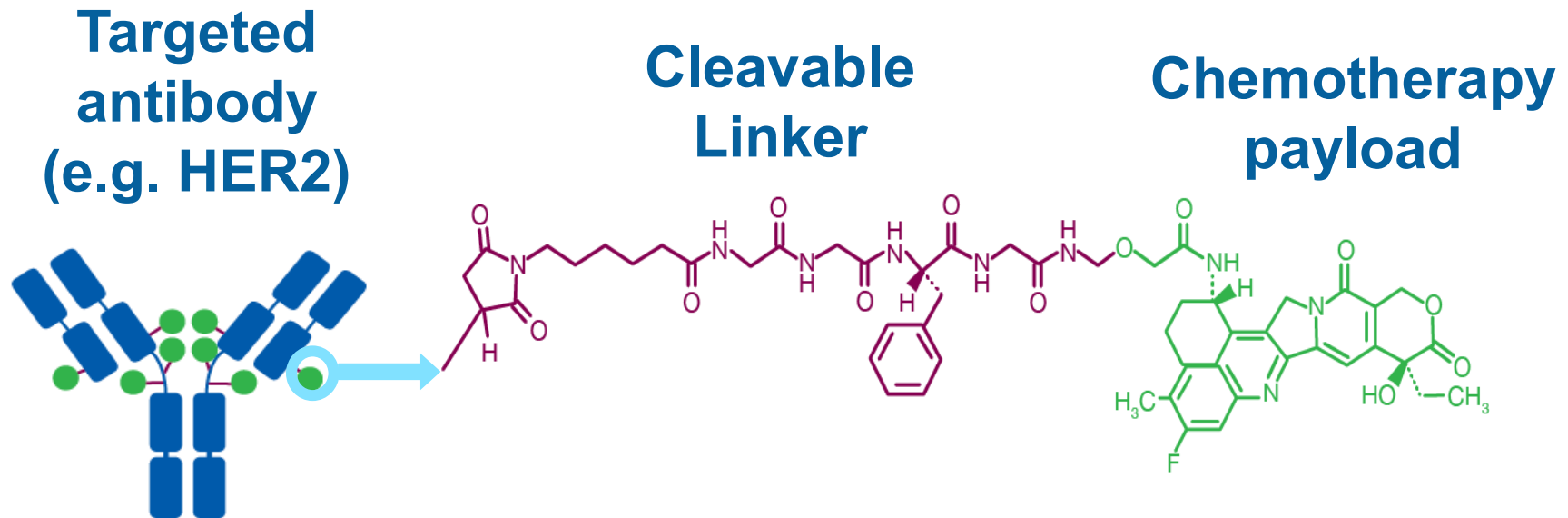
CDK4/6 inhibitor for metastatic breast cancer

- Significantly delays time to chemo and $\uparrow\uparrow$ survival
- Also for adjuvant high risk to prevent recurrence



Antibody drug conjugates

Antibody drug conjugate has 3 components:



Sacituzumab govitecan, trastuzumab deruxtecan, datopotomab deruxtecan –FDA approved for breast cancer

Targeted therapy

- **PI3/AKT inhibitor**

- Alpelisib, capivasertib, and inavolisib

- **PARP inhibitor**

- BRCA1/2 mutation carriers

- **Immunotherapy**

- Pembrolizumab + chemo for PDL1 positive triple negative breast cancer

- **mTOR inhibitor**

- Everolimus



Take home points

- Epidemiology –Overweight and alcohol use ↑↑ breast ca risk, physical activity ↓↓ risk
- Prevention – Tamoxifen , raloxifene, and AI ↓↓ breast ca risk, but no effect on mortality
- Screening – Mammography ↓↓ mortality ages 40-74, but should stop when life expectancy < 10 years
- Treatment – Biology not stage drives treatment

References

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Thank You!

