Endocrine Therapies in Non-Invasive Breast Cancer: Less vs More

11th Annual San Antonio Breast Cancer Symposium Review

5 March 2019

Rick Zinke, MD

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Overview

Case presentation: Patty

Types of breast cancer

Estrogen in breast cancer

Endocrine therapies

Current standards in DCIS

New data for endocrine therapies in DCIS

Conclusions

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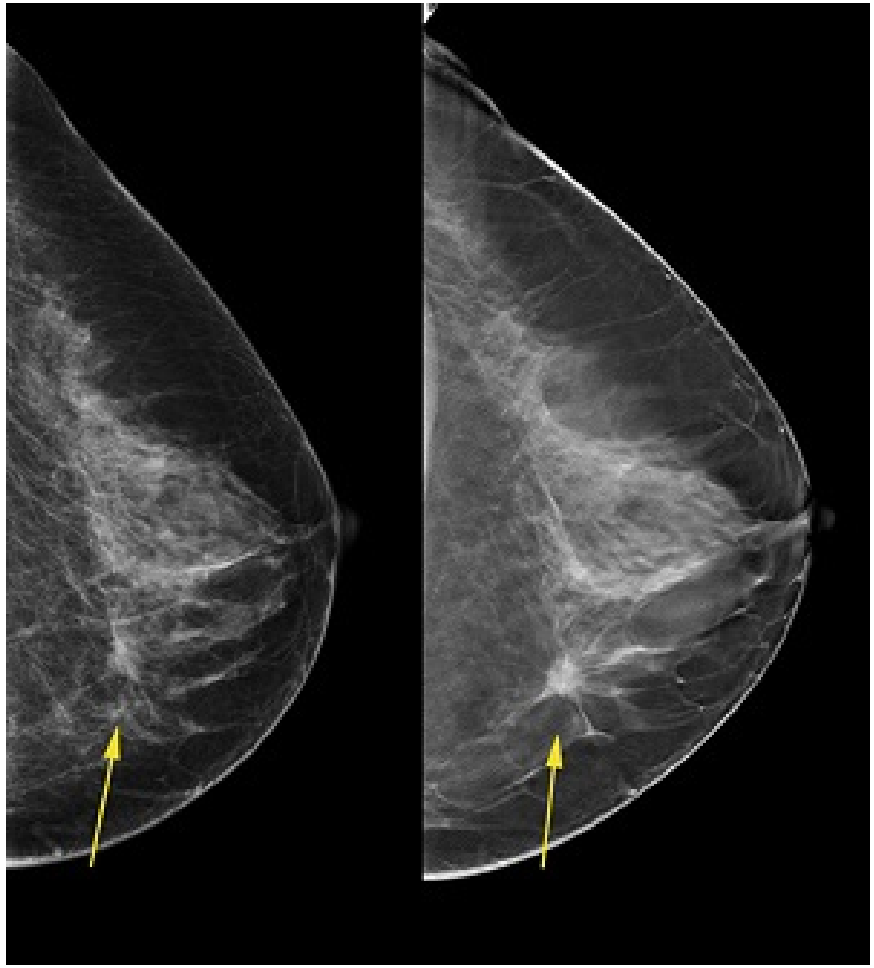
Patty—a 50 year old female

Undergoes routine screening 3D mammogram, which demonstrates a new asymmetric finding in the left breast concerning for possible malignancy.

Left breast diagnostic mammogram and U/S confirm the suspicious lesion.

U/S-guided biopsy is recommended.



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At the time of diagnosis, we need to know…

1. Type of breast cancer:
    - DCIS, invasive ductal carcinoma, etc.
    - The subtype based on receptor status: ER, PR, HER2
    - Other features

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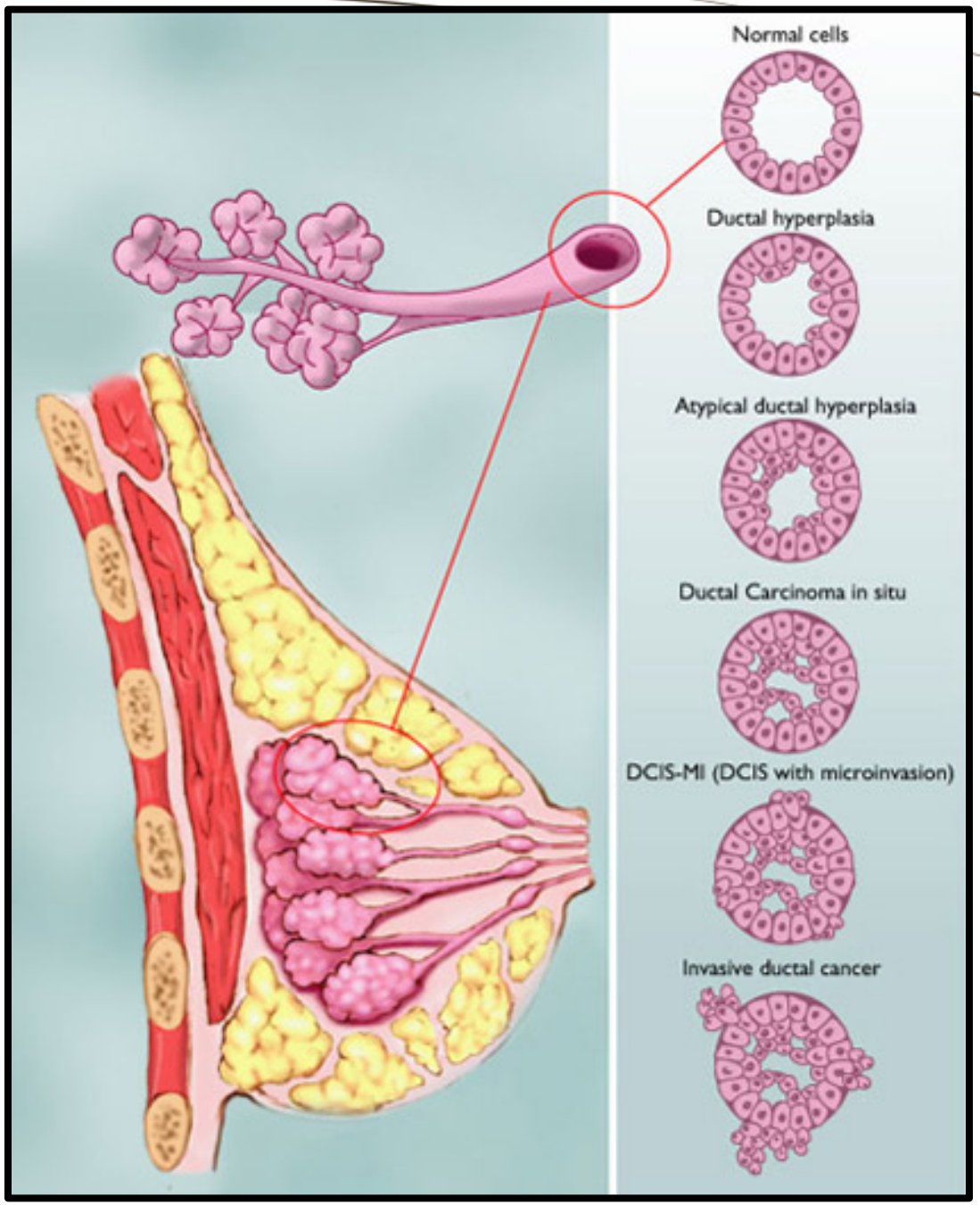
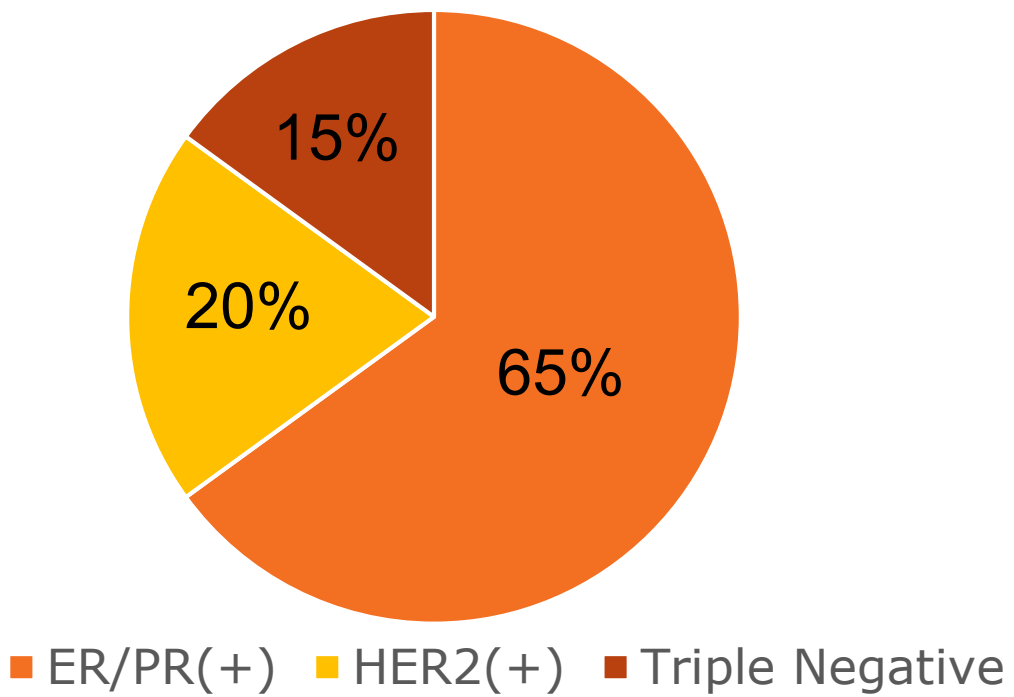
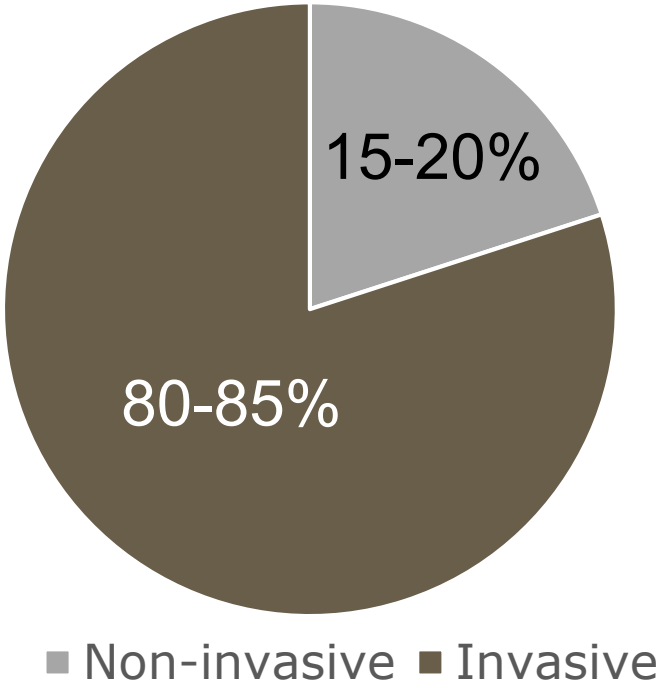
Evolution of Breast cancer



Breast Cancer Subtypes





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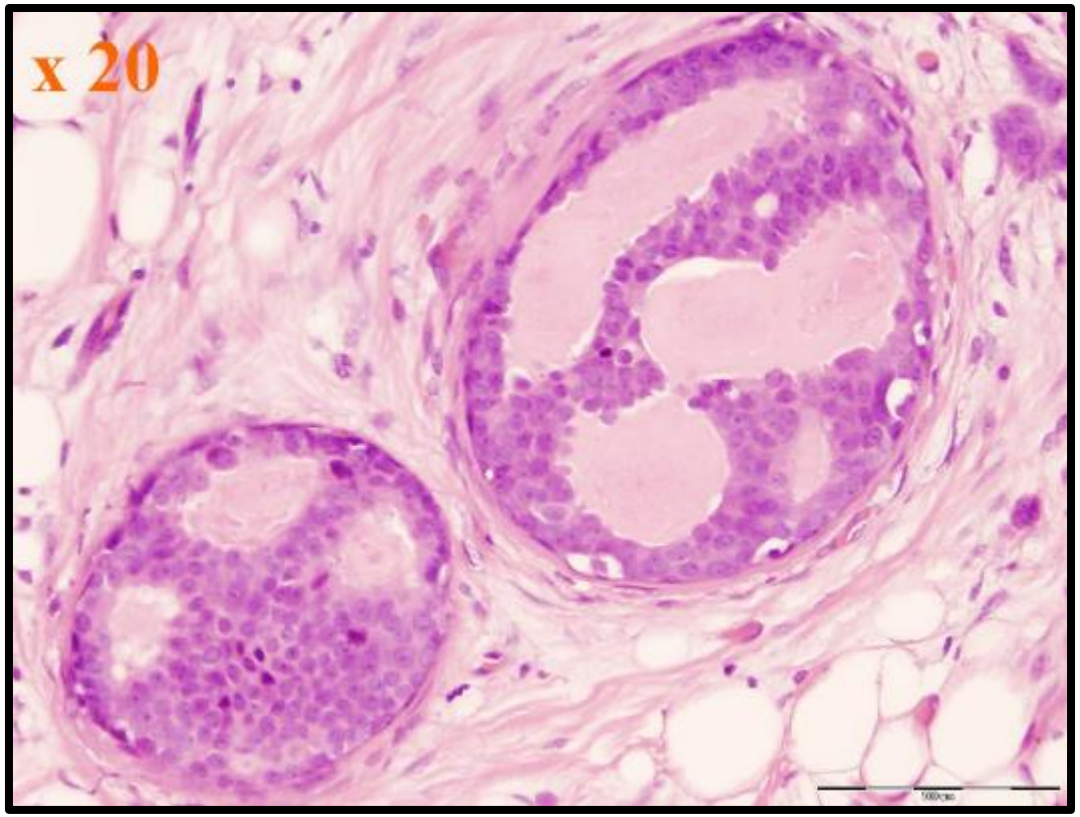
Back to Patty

Biopsy shows presence of ER/PR(+) ductal carcinoma in situ (DCIS)



At the time of diagnosis we need to know…

1. Type of breast cancer:
   - DCIS, invasive ductal carcinoma, etc.
   - The subtype based on receptor status: ER, PR, HER2
   - Other features

2. Stage: 0 to IV

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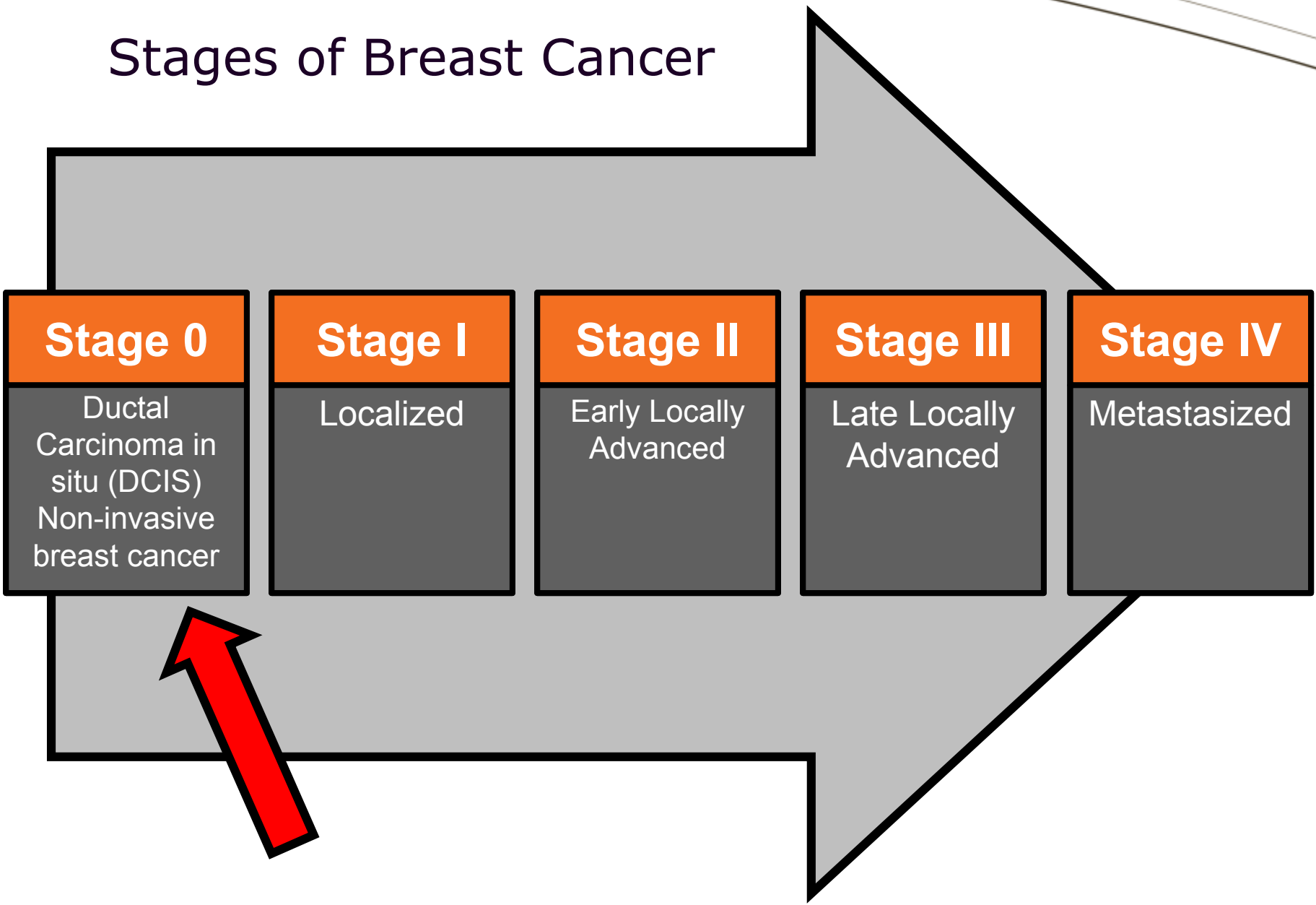
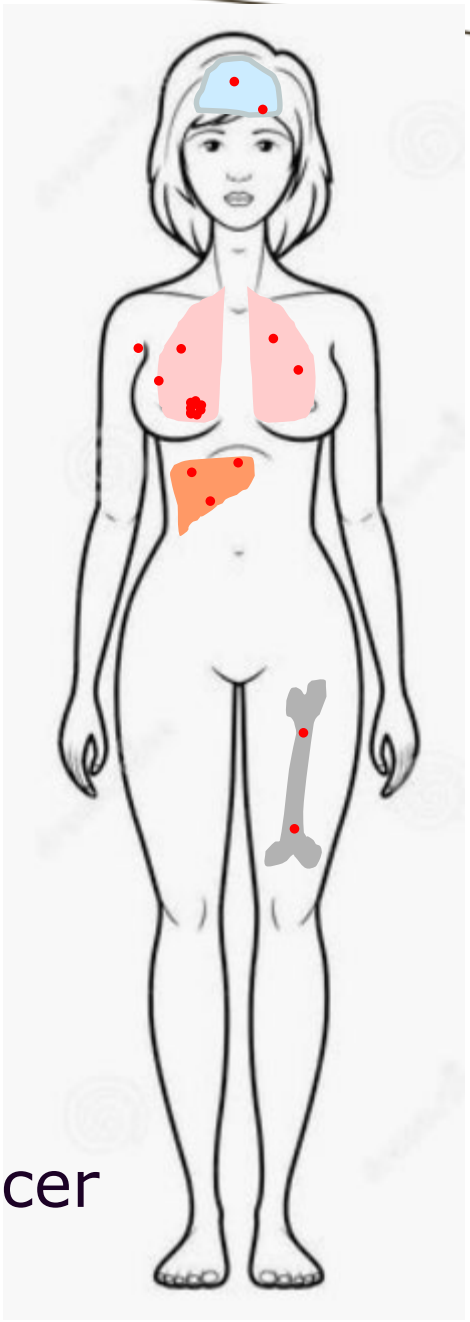
Stages of Breast Cancer





Invasive Breast Cancer

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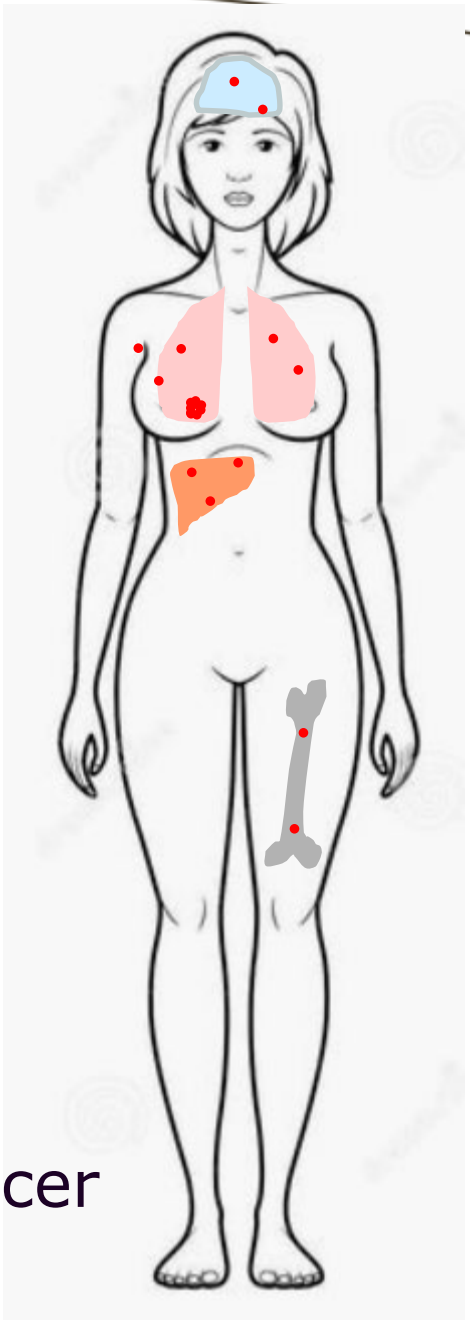
Removal of
Visible Disease

Surgery

Lumpectomy
Mastectomy



Invasive Breast Cancer

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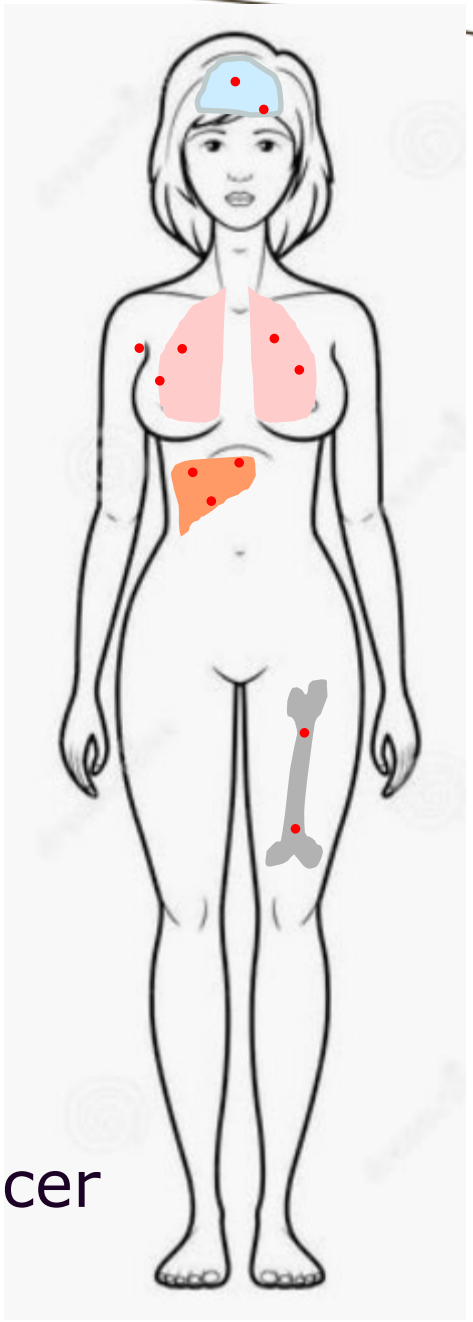

Removal of
Non-visible Disease

Other Therapies

Chemotherapy
Targeted Therapy
Hormonal Therapy
Radiation Therapy

Invasive Breast Cancer

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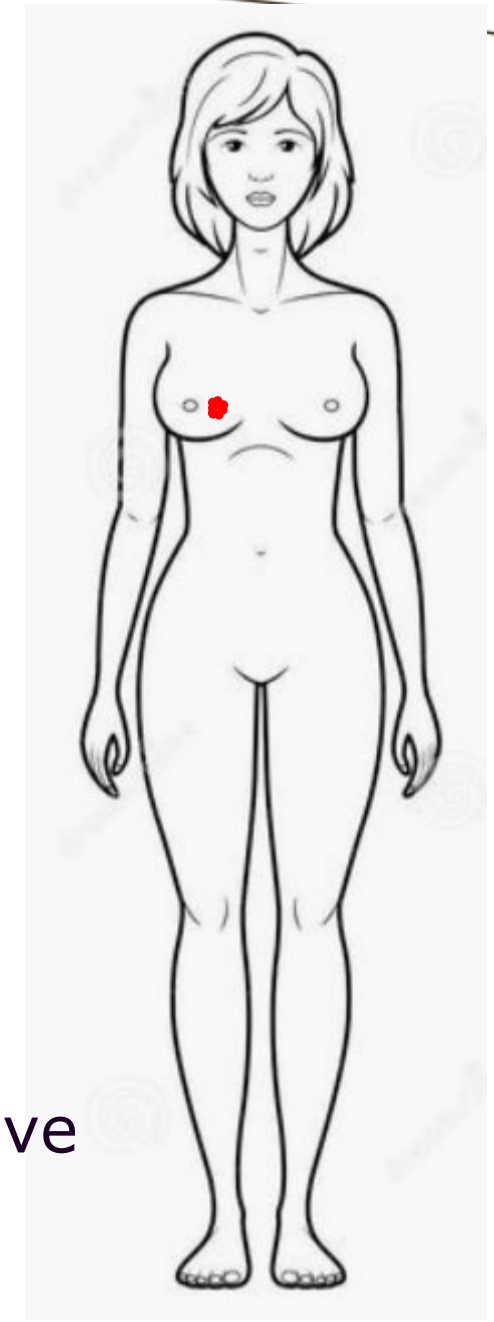
Removal of
Visible Disease

Surgery
Lumpectomy Mastectomy



Removal of
Non-visible Disease

Other Therapies
Hormonal Therapy Radiation Therapy

DCIS: Non-invasive Breast Cancer

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ER/PR(+) Breast Cancers

In general, ER/PR(+) breast cancers:

- Are less aggressive
- Have a better prognosis
- Are more common in elderly woman

Can be treated with hormonal therapies:

- Only effective when the tumor is ER(+) and/or PR(+)
- Remain a critical aspect of treatment in this setting (Often more effective than chemotherapy)

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The Effects of Estrogen

Brain

Body temp regulation

Protects against memory loss

Breast

Programs mild production

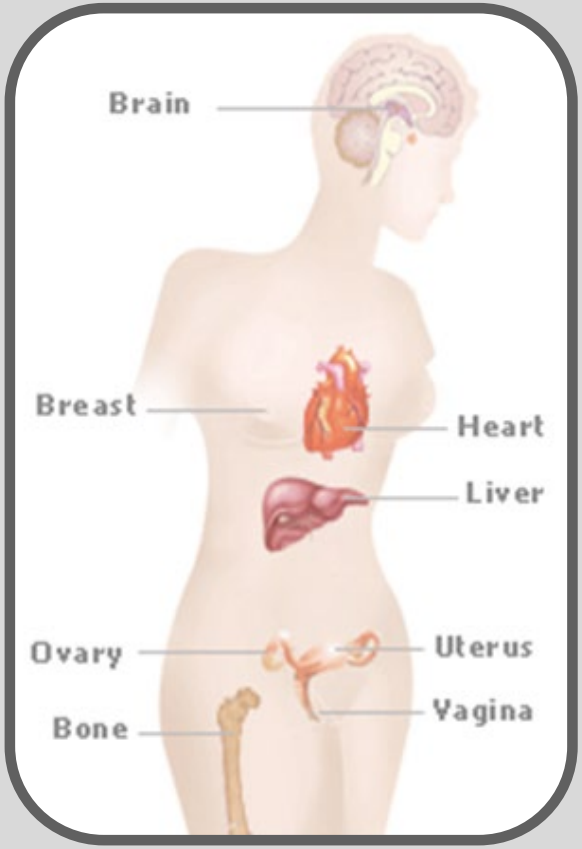
Ovary

Stimulates maturation

Triggers start of menstrual cycle

Bone

Preserves bone density



Liver & Heart

Increase HDL (good cholesterol)

Lower LDL (bad cholesterol)

Uterus

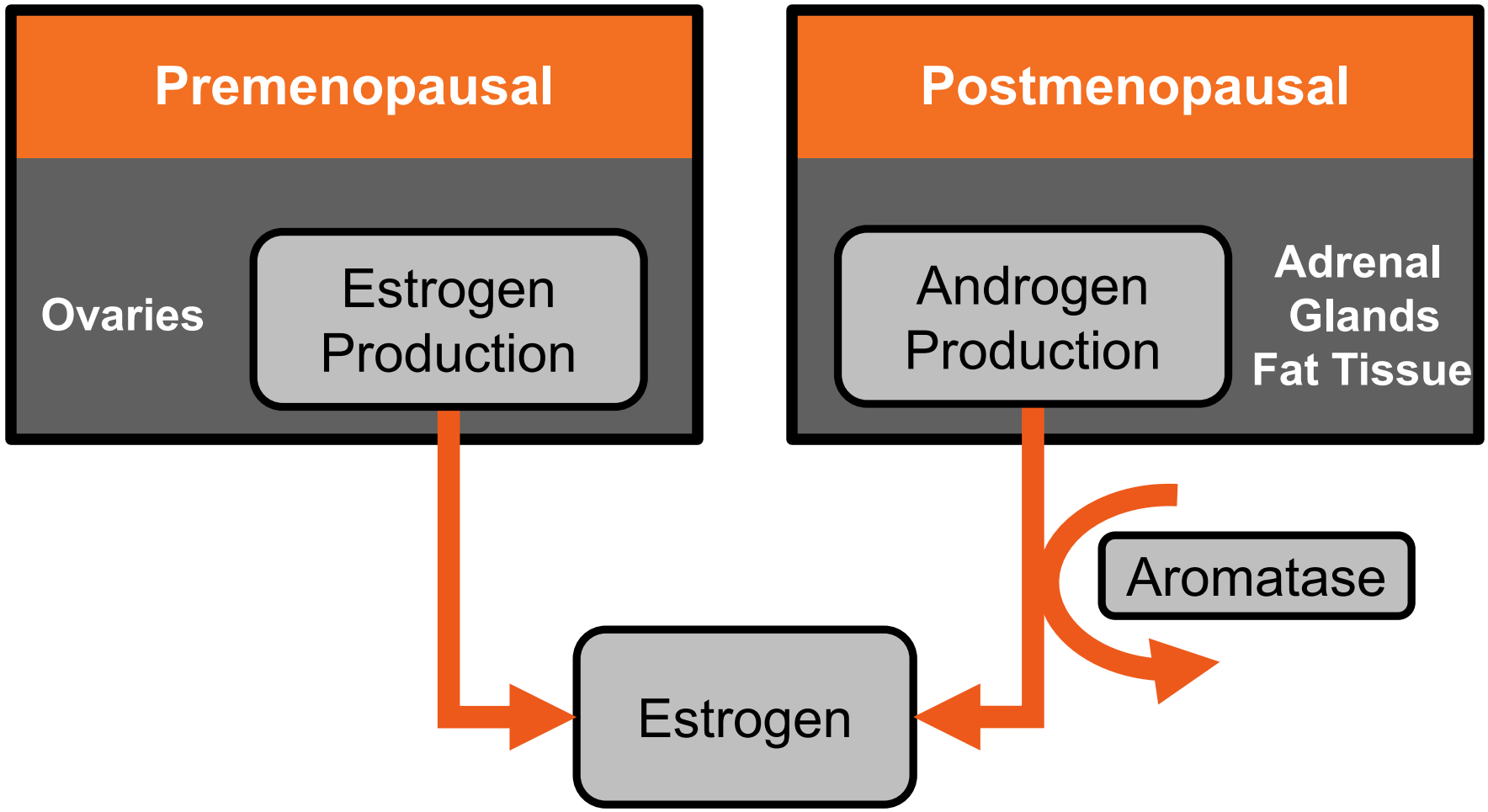
Prepares lining for pregnancy

Increased risk of uterine cancer

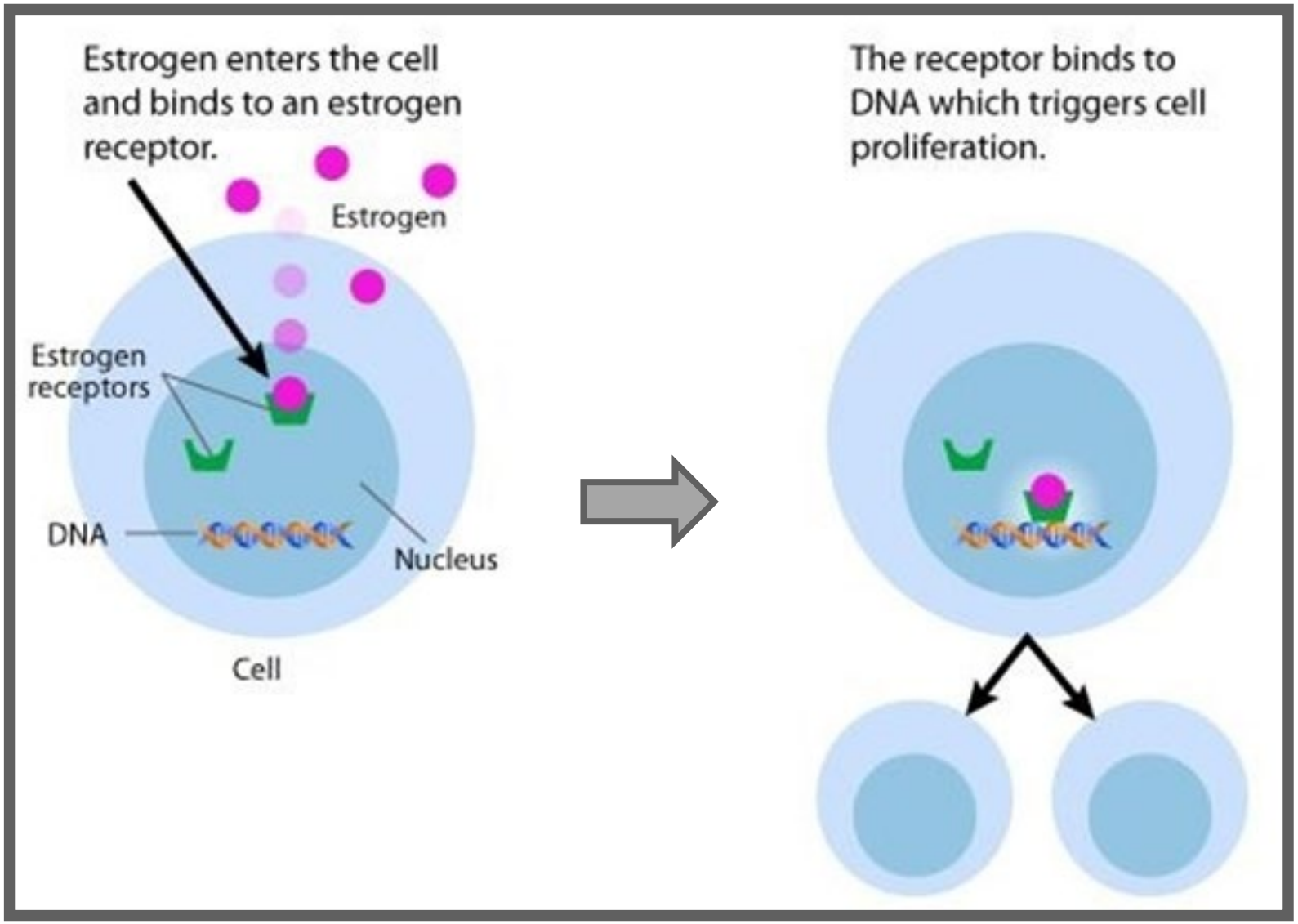
Vagina

Helps maintain a thick & lubricated vaginal lining

Sources of Estrogen



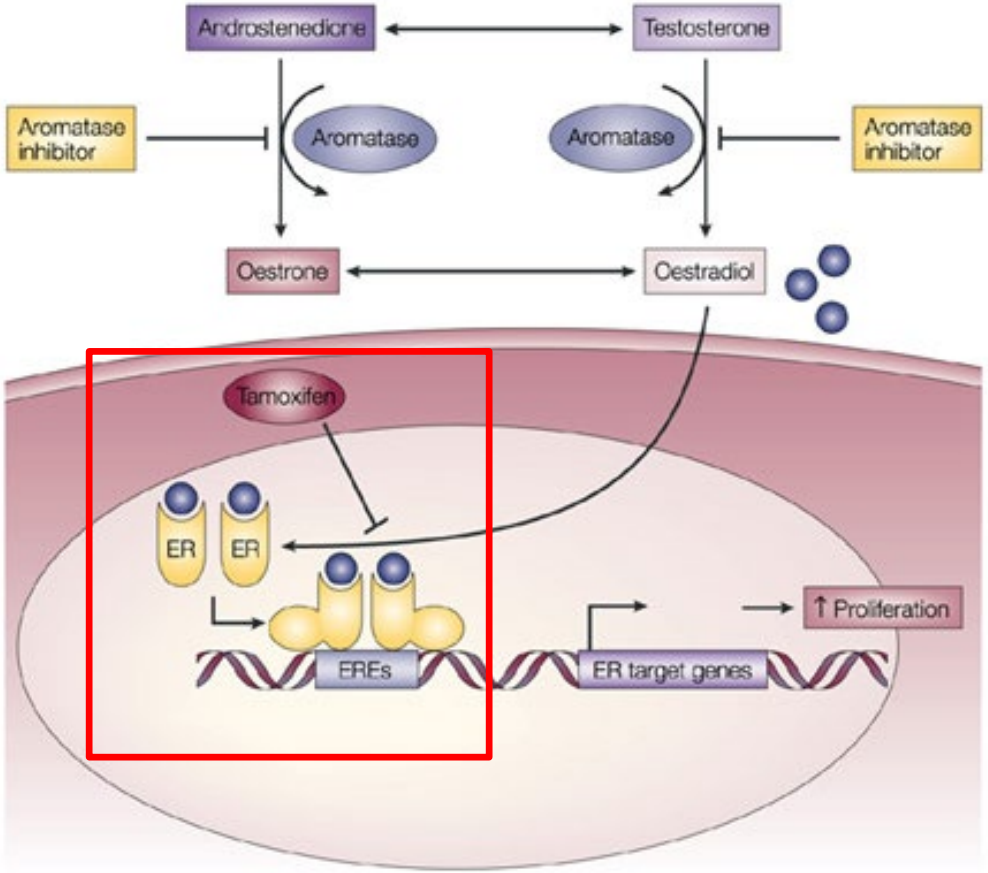
Estrogen Receptor Activity



Endocrine Therapies

Block Estrogen Action

- Tamoxifen:
  - Binds estrogen receptor and alters its shape
  - Prevents estrogen from binding
  - Similar meds: raloxifene, toremifene (not as effective)
- Fulvestrant:
  - Down regulates the ER
  - Fewer around for binding of estrogen
  - Used only in stage IV disease



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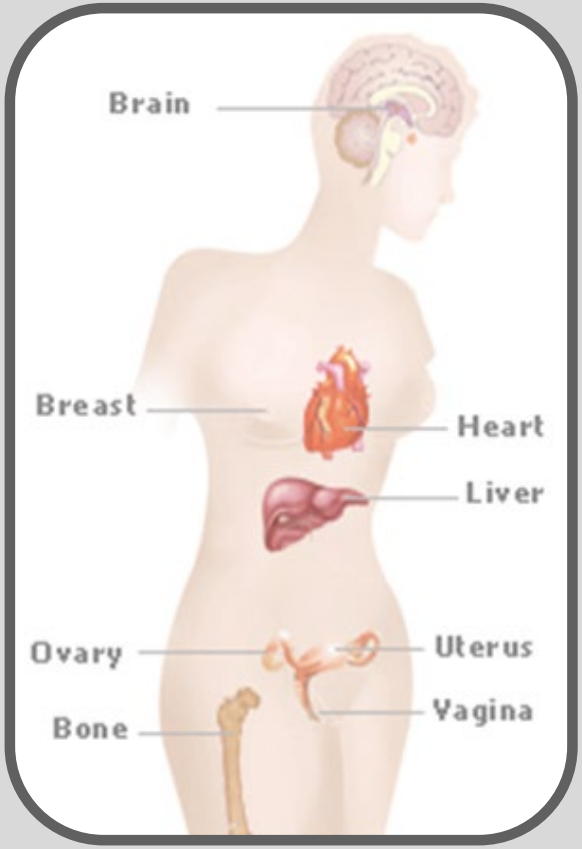
The Effects of Tamoxifen

Brain
Hot Flashes

Breast
Reduces breast cancer risk (ER Antagonist)

Bone
Preserves bone density (ER Agonist)

Other
Increased risk of venous thromboembolism (blood clots)



Liver & Heart
Increase HDL
Lower LDL

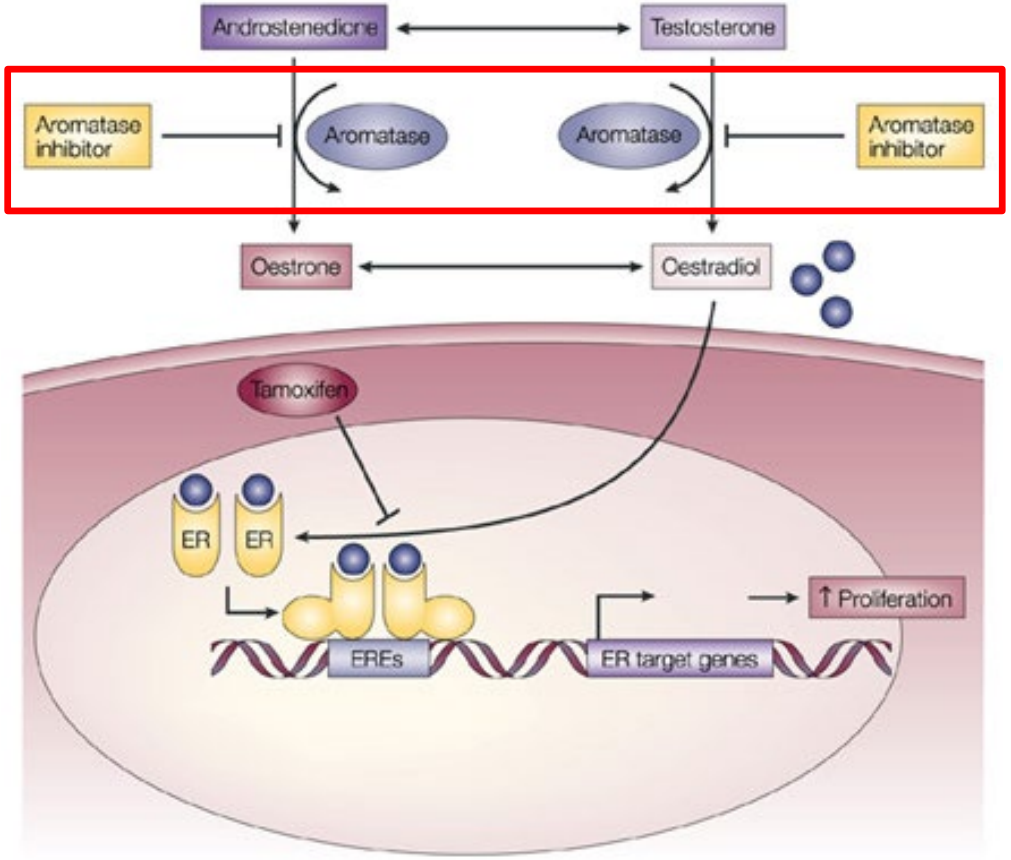
Uterus
Increased risk of uterine cancer (ER Agonist)

Vagina
Vaginal bleeding
Vaginal discharge

Endocrine Therapies

Block Estrogen Production

- Ovarian Ablation:
  - Surgical: oopherectomy
  - Medical: LHRH agonists
- Aromatase Inhibitors (AIs):
  - Inhibit conversion of androgens into estrogens
  - **Anastrozole** (Arimidex)
  - **Letrozole** (Femara)
  - **Exemestane** (Aromasin)



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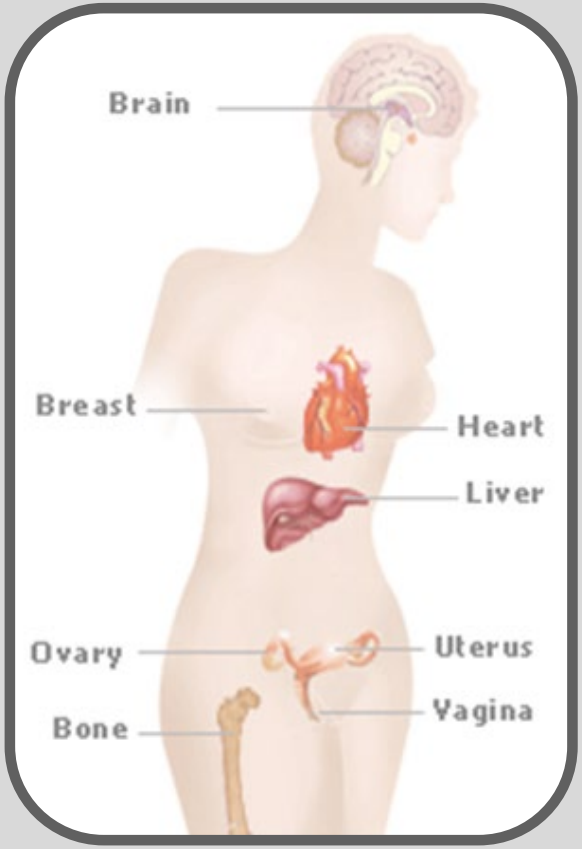
The Effects of Aromatase Inhibitors (AIs)

Brain
Hot Flashes

Breast
Reduces breast cancer risk

Bone
REDUCES bone density

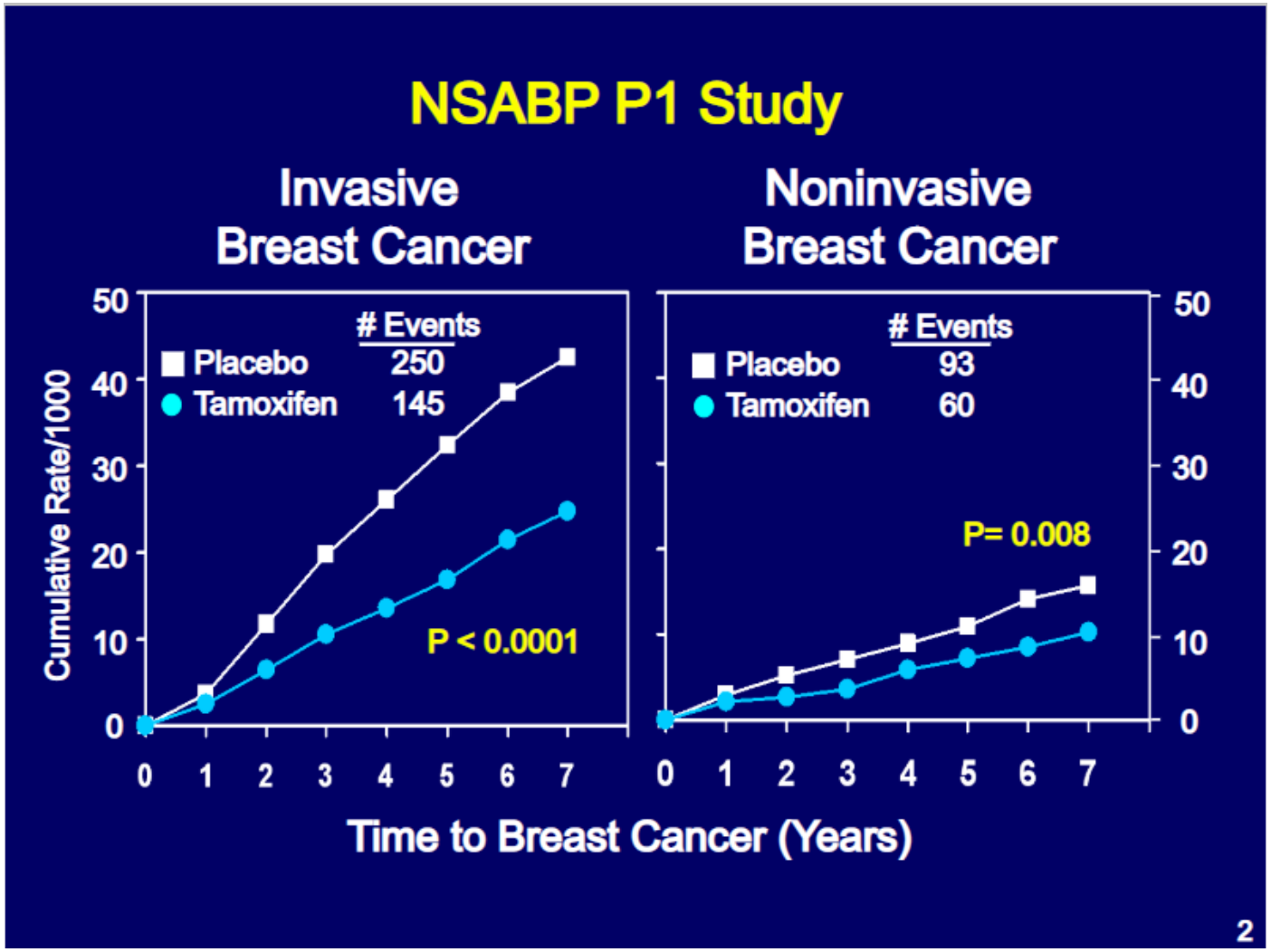


Uterus
NO increased risk of uterine cancer

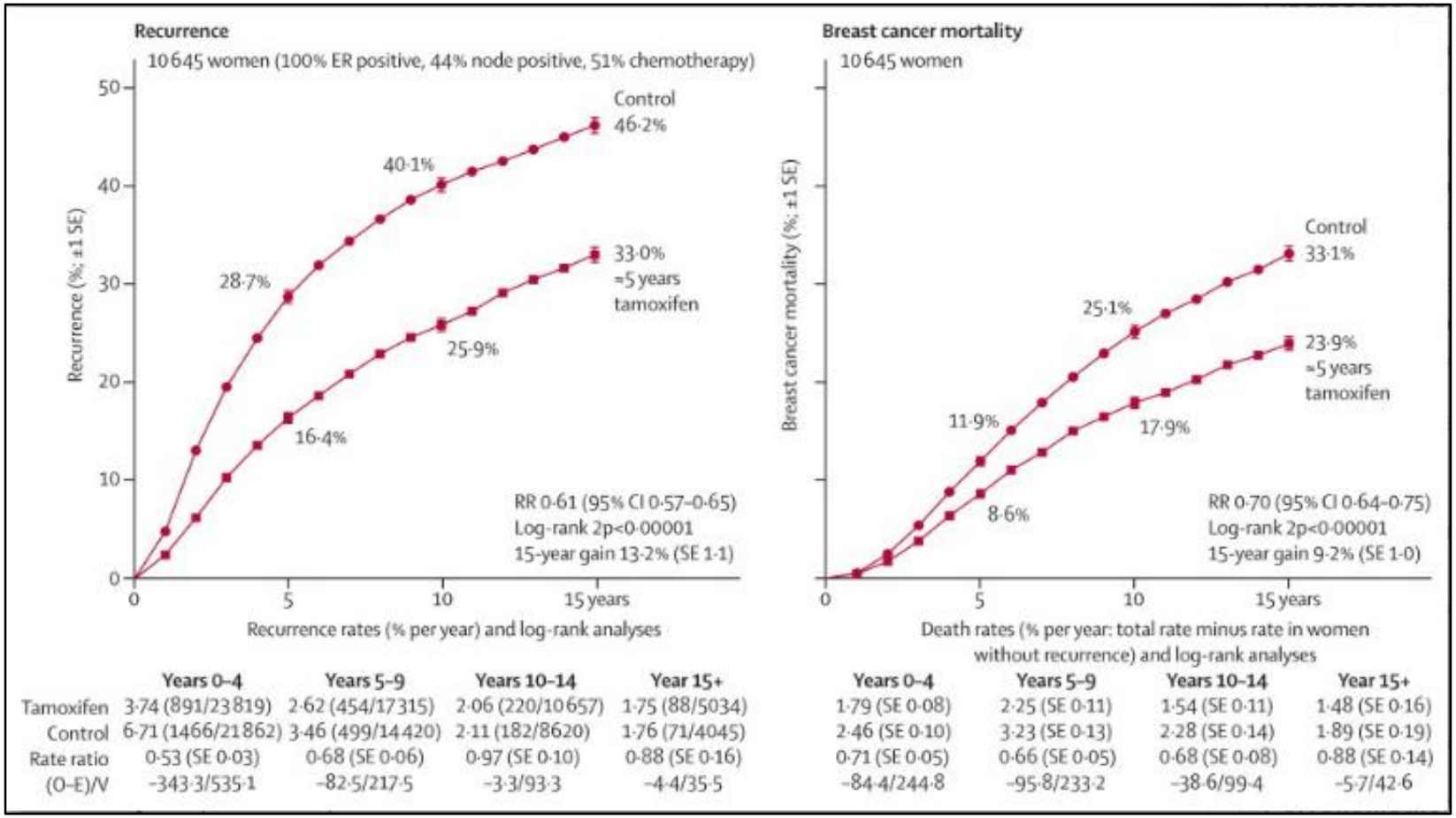
Vagina
Atrophic vaginitis (vaginal dryness/thinning)

Musculoskeletal
Increased risk of arthralgias/myalgias (aches/pains in the muscles and bones/joints)

Anti-estrogen therapy can be used both for PREVENTION and TREATMENT



Tamoxifen for treatment of invasive breast cancer



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

EBCTG, meta-analysis, 2011; 20% noncompliant

DCIS

Stage 0, Non-invasive

Up to 15-20% of cancers diagnosed in a non-invasive phase

Very good prognosis overall but high risk of invasive cancer development.

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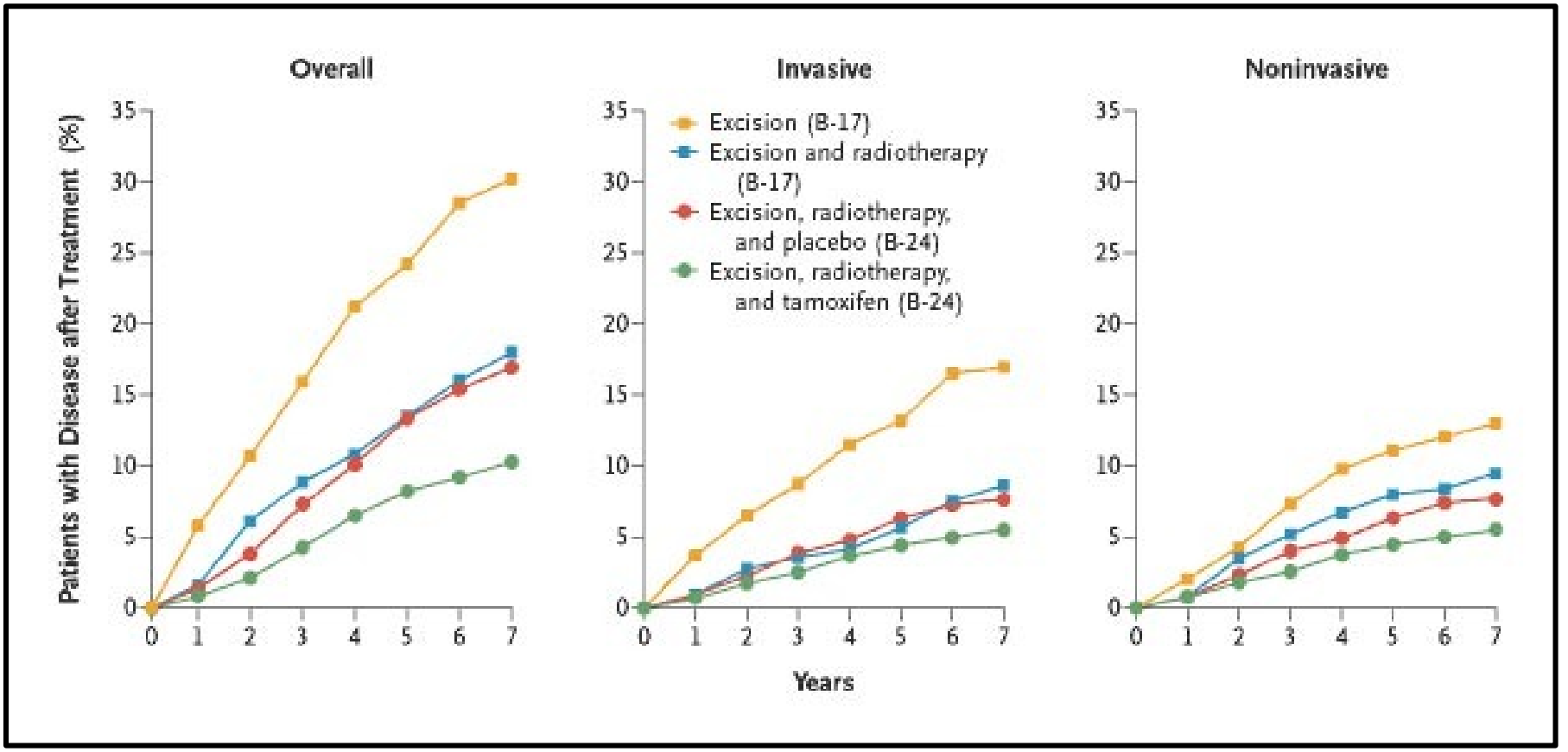
NSABP Trials



Burstein H et al. NEJM 2004;350:1430-1441

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Standard of Care: 3 main options

Lumpectomy
+
Radiation
+
Hormonal Therapy x 5 years*

Mastectomy
+
Consideration of Hormonal Therapy x 5 years

Double Mastectomy

*tamoxifen 20 mg daily x 5 years (or consider an AI if postmenopausal)

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New!

SABCS 2018: The TAM01 Trial

San Antonio Breast Cancer Symposium®, December 4-8, 2018

Abs GS03-01. Randomized trial of low dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01

A.DeCensi*, M.Puntoni, A.Guerrieri Gonzaga, S.Caviglia, F.Avino, L.Cortesi, M.Donadio, M.Grazia Pacquola, F.Falcini, M.Gulisano, M.Digennaro, A.Carriello, K.Cagossi, G.Pinotti, M.Lazzeroni,D.Serrano, D.Branchi, S.Campora, M.Petrera, T.Buttiron Webber, L.Boni and B.Bonanni

Ospedali Galliera Genova

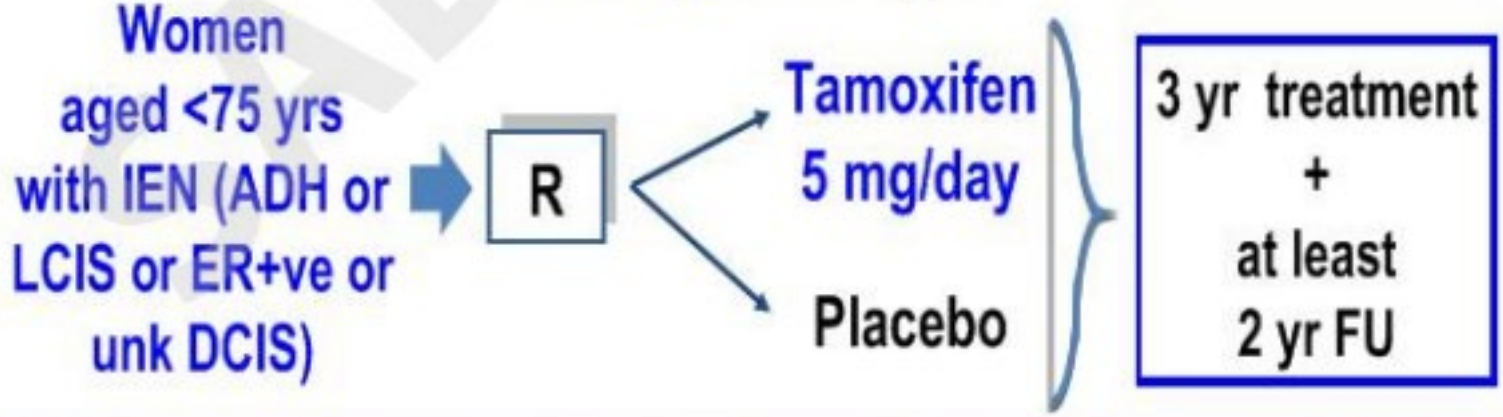
IEO Istituto Europeo di Oncologia

Queen Mary University of London

Barts and The London

EudraCT Number
2007-007740-10
ClinicalTrials.gov
NCT01357772

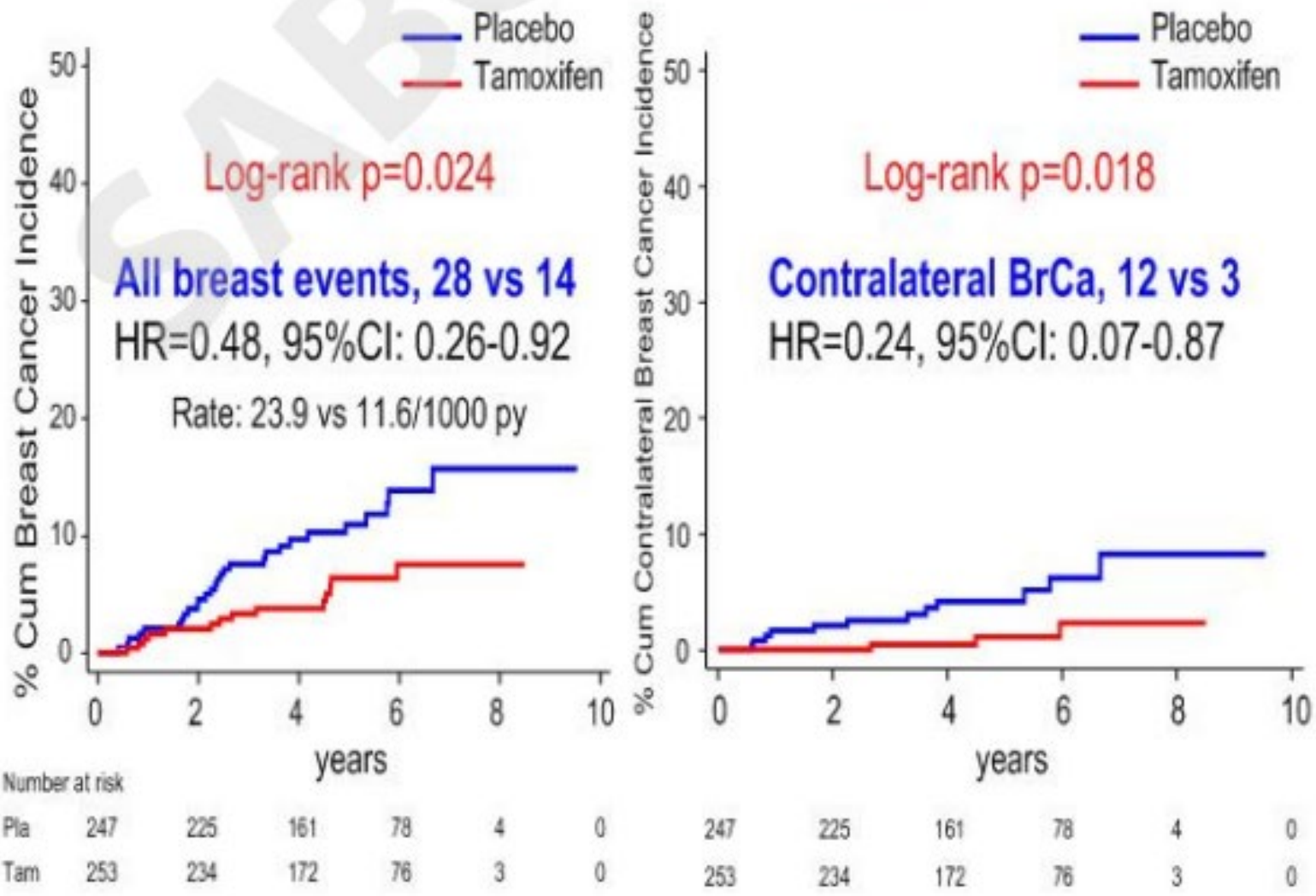
Study Design



Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

San Antonio Breast Cancer Symposium®, December 4-8, 2018



San Antonio Breast Cancer Symposium®, December 4-8, 2018

Main tumor characteristics during the trial (n = 42)

	Tamoxifen (N=14)	Placebo (N=28)
Invasive	3	10
DCIS	11	18
Tumor diameter (mm), median (IQR)	10 (8-17)	16 (6-22)
ER (%), median (IQR)	83 (70-95)	90 (60-95)
PR (%), median (IQR)	60 (5-80)	23 (0-90)
HER2/neu 3+, %	20	16

TAM01 Tolerance

Overall the low dose tamoxifen was very well tolerated.

- Hot Flashes: Median of 1 additional HF per day
- Reports of vaginal dryness, pain with intercourse, and musculoskeletal pain were not significantly different.

Adherence to treatment (use for at least 2.5 years)

- Tamoxifen: 64.8%
- Placebo: 60.7%
- → fairly low overall

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Less vs more? How does it really compare?

	TAM01 (Tamoxifen 5 mg daily x 3 years)	NSABP B24 Trial (Tamoxifen 20 mg daily x 5 years)
Reduction in risk of recurrent breast cancer event	52%	42%

Serious Event	TAM01 (Tamoxifen 5 mg daily x 3 years)	NSABP P1+ NSABP B24 Trials (Tamoxifen 20 mg daily x 5 years)
Endometrial Cancer	1 case	2.7 cases
DVT/PE	1 case Tamoxifen/ 1 case placebo	2.4 cases

TAM01 CONCLUSIONS

In women with DCIS and other forms of intraepithelial neoplasia, low-dose tamoxifen (5 mg daily) given for 3 years reduced the risk of breast cancer development by 52% and breast cancer in the opposite breast by 76%.

Side effects in the tamoxifen arm were not significantly higher than in the placebo arm, except for a borderline effect on hot flashes.

Serious adverse effects (uterine cancer, DVT/PE) were not different from placebo and were 2.5 times lower than 20 mg daily

Low-dose tamoxifen (5 mg daily) may be an effective chemopreventive strategy, with good tolerability, in this population.

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So what does this mean for Patty?

She undergoes lumpectomy followed by radiation therapy and is now faced with a decision regarding hormonal therapy.

Should she be treated with tamoxifen 5 mg daily x 3 years or tamoxifen 20 mg daily x 5 years?

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