MEDICATIONS TO PREVENT BREAST CANCER

Journal Club – 2/11/2021 – Alexa Waters, PGY3

DISCLOSURES

None

WHY THIS TOPIC?

LEARNING OBJECTIVES

1. Review USPSTF recommendations for the use of medications to prevent breast cancer in high-risk women
2. Identify breast cancer risk calculation tools
3. Recall mechanism of action of aromatase inhibitors
4. Explore a journal article supporting the use of anastrozole to prevent breast cancer in high-risk post-menopausal women
5. Review and apply Odds Ratios (ORs)
6. Consider how this journal article may influence our practice

OUTLINE

- Background
- USPSTF recommendations
- Estimating breast cancer risk
- Mechanism of action: aromatase inhibitors
- Article
  - Methods
  - Statistics Detour: Odds Ratios
  - Results
  - Discussion
- Implications for Practice

SCOPE

- We will not discuss…
  - Details of estimating breast cancer risk
  - Details of estimating risk of adverse effects from medications used to prevent breast cancer
  - Use of tamoxifen, raloxifene, or non-anastrazole aromatase inhibitors for prevention of breast cancer

BACKGROUND

- Breast cancer is the most common nonskin cancer among women in the U.S. and the 2nd leading cause of cancer death
- Median age at diagnosis = 62 years
- An estimated 1 in 8 women will develop breast cancer at some point in their lifetime
- Medications can be used to prevent breast cancer in high-risk women

USPSTF (2019)

USPSTF RECOMMENDATIONS

Breast Cancer: Medication Use to Reduce Risk

September 03, 2019

Recommendation Summary

Population	Recommendation	Grade
Women at increased risk for breast cancer aged 35 years or older	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects.	B

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Women not at increased risk for breast cancer aged 35 years or older	The USPSTF recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer.	D

USPSTF (2019)

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What is the evidence behind use of these medications?

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How do we estimate breast cancer risk?

USPSTF (2019)

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How do we estimate risk for adverse effects?

USPSTF (2019)

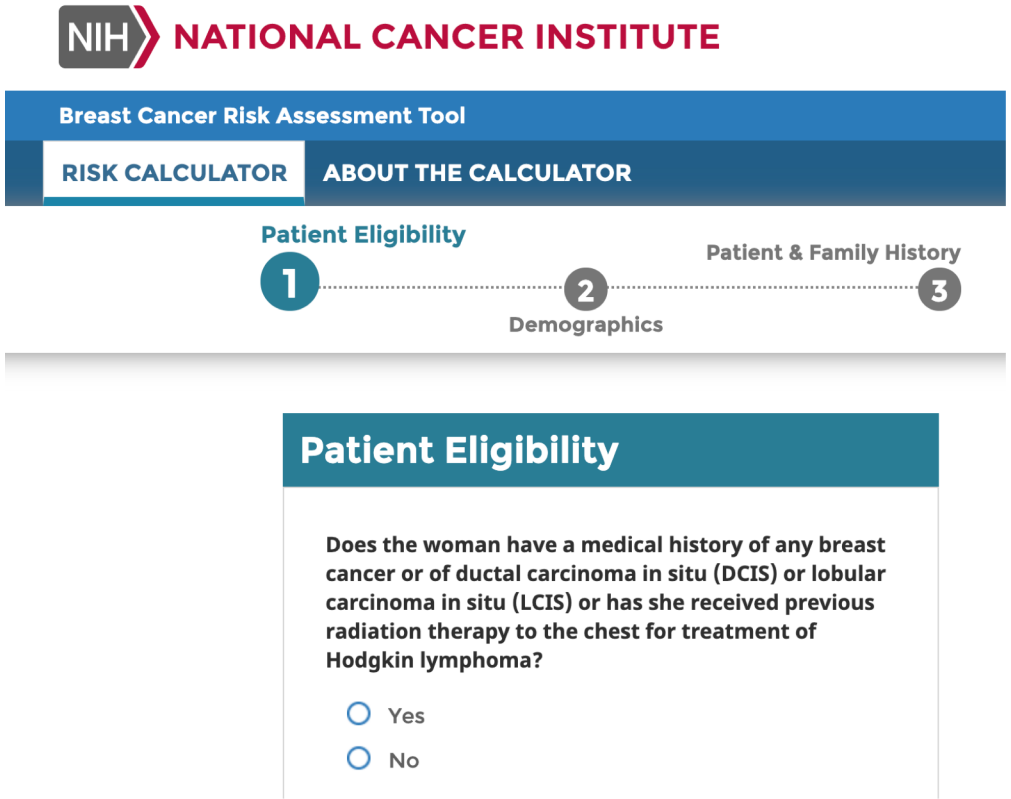
ESTIMATING BREAST CANCER RISK

- Many methods available (tools vs. clinical estimation)
- USPSTF does not endorse any particular tool

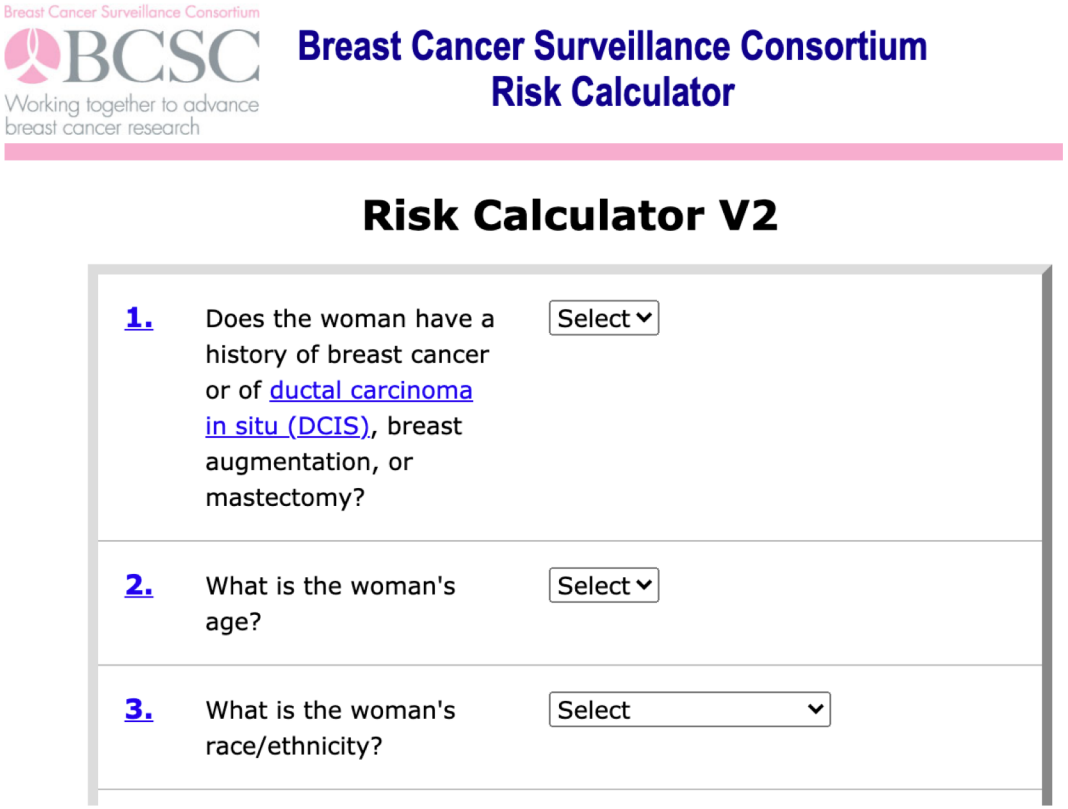
  → 2 U.S. Population-based tools:
  - The National Cancer Institute Breast Cancer Risk Assessment Tool
  - Breast Cancer Surveillance Consortium Risk Calculator
- Clinicians may use combination of risk factors to estimate risk
  - E.g., age 65+ with 1 first-degree relative with breast cancer

USPSTF (2019)

ESTIMATING BREAST CANCER RISK



bcrisktool.cancer.gov/calculator.html



tools.bcsc-scc.org/BC5yearRisk/calculator.htm

CONSIDERING RISK-REDUCING MEDICATIONS

When considering risk-reducing medications, the potential benefit of risk reduction of breast cancer must be weighed against the potential harms of adverse medication effects

USPSTF (2019)

CONSIDERING RISK-REDUCING MEDICATIONS

When considering risk-reducing medications, the potential benefit of risk reduction of breast cancer must be weighed against the potential harms of adverse medication effects

Potential Benefits of Risk-Reducing Medications

The USPSTF found convincing evidence that risk-reducing medications (tamoxifen, raloxifene, or aromatase inhibitors) provide at least a moderate benefit in reducing risk for invasive estrogen receptor (ER)–positive breast cancer in postmenopausal women at increased risk for breast cancer

Both tamoxifen and raloxifene can reduce risk of some types of skeletal fractures, independent from the risk of breast cancer.

The USPSTF found that the benefits of taking tamoxifen, raloxifene, and aromatase inhibitors to reduce risk for breast cancer are no greater than small in women not at increased risk for the disease.

USPSTF (2019)

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Potential Harms of Risk-Reducing Medications

The USPSTF found convincing evidence that tamoxifen and raloxifene are associated with small to moderate harms. Tamoxifen and raloxifene increase risk for venous thromboembolic events (VTEs); tamoxifen increases risk more than raloxifene (Table), and the potential for harms are greater in older women than in younger women. The USPSTF also found adequate evidence that tamoxifen, but not raloxifene, increases risk for endometrial cancer in women with a uterus. Tamoxifen also increases risk of cataracts. Vasomotor symptoms (hot flashes) are a common adverse effect of both medications.

The USPSTF found adequate evidence that the harms of aromatase inhibitors are also small to moderate. These harms include vasomotor symptoms, gastrointestinal symptoms, musculoskeletal pain, and possible cardiovascular events, such as stroke. Aromatase inhibitors do not reduce, and may even increase, risk of fractures.

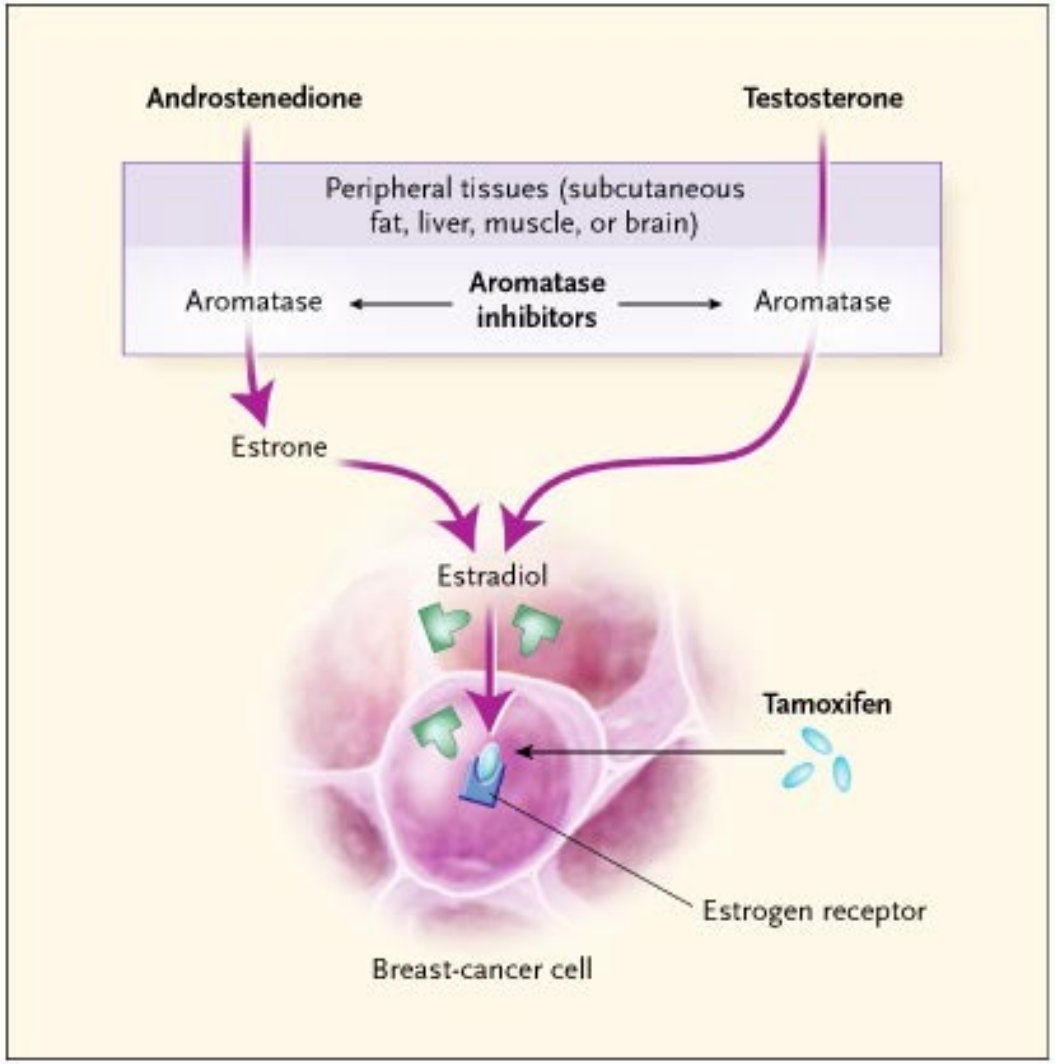
USPSTF (2019)

ANASTROZOLE: MECHANISM OF ACTION

- Anastrozole: an aromatase inhibitor
- Inhibits aromatase enzyme through reversible binding
- Blocks production of estrogen
  - After menopause, residual estrogen production is solely from non-glandular sources – mostly subcutaneous fat

→ Reduced risk for development of estrogen-responsive breast cancers

- Also reduces estrogen's actions on other organs and body functions (bone/muscles, cardiovascular system, endometrium, etc.)
- Potential adverse effects include: CV events including stroke, myalgias, arthralgias, fractures, vasomotor symptoms



N Engl J Med (2013)

ARTICLE:

THE LANCET

Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial

*Jack Cuzick, Ivana Sestak, John F Forbes, Mitch Dowsett, Simon Cawthorn, Robert E Mansel, Sibylle Loibl, Bernardo Bonanni, D Gareth Evans, Anthony Howell, on behalf of the IBIS-II investigators**

Lancet (2020)

STUDY BACKGROUND

- 2 large clinical trials have studied the use of aromatase inhibitors to reduce risk of breast cancer in high-risk women, with favorable results within a 5 yr period of medication use
  - MAP.3 (N Engl J Med, 2011)
  - International Breast Cancer Intervention Study II (IBIS-II; Lancet, 2013)

- This article: blinded, long-term follow-up results for the IBIS-II trial, which compared anastrozole with placebo
  - Goal: Determine the efficacy of anastrozole for preventing breast cancer in the post-treatment (after 5 yr) period

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METHODS: STUDY DESIGN

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- Randomized, double-blinded placebo-controlled trial
- International

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METHODS: PARTICIPANTS

- Post-menopausal women at high risk for breast cancer
- Age 40-70
- Recruited in a 9-year period between 2003 and 2012
- From 153 breast cancer treatment centers across 18 countries

Lancet (2020)

METHODS: INCLUSION CRITERIA

POST-MENOPAUSAL

- Age ≥60
- S/p bilateral oophorectomy
- Age <60 with a uterus and amenorrhea for >12 mo
- Age <60 without a uterus, with FSH >30 IU/L

+

HIGH RISK

For breast cancer, compared to the general population (RR = relative risk)

- Age 40-45 with RR ≥4x higher
- Age 45-60 with RR ≥2x higher
- Age 60-70 with RR ≥1.5x higher

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How do we estimate breast cancer risk?

Supplementary Table 1: Entry criteria and distribution by treatment allocation.

For women aged 45-70	Anastrozole (N=1920)	Placebo (N=1944)
First degree relative who developed breast cancer at age 50 or less.	677 (35.3%)	655 (33.7%)
First degree relative who developed bilateral cancer.	164 (8.5%)	141 (7.3%)
Two or more first or second degree relatives who developed breast or ovarian cancer.	952 (49.6%)	933 (48.0%)
Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer.	211 (11.0%)	207 (10.6%)
Benign biopsy with proliferative disease and first degree relative who developed breast cancer.	21 (1.1%)	33 (1.7%)
Mammographic opacity covering at least 50% of the breast	7 (0.4%)	10 (0.5%)
First degree relative with breast cancer at any age.	488 (25.4%)	499 (25.7%)
Age at menopause 55 years or more.	45 (2.3%)	38 (2.0%)
Nulliparous or age 30 or above at first birth.	86 (4.5%)	83 (4.3%)
For women aged 40-44		
Two or more first or second degree relatives who developed breast cancer or ovarian cancer at age 50 or less.	8 (4.2%)	8 (0.4%)
First degree relative with bilateral breast cancer who developed first breast cancer at age 50 or less.	2 (0.1%)	0
Nulliparous or age 30 or above at first birth, and first degree relative who developed breast cancer at age 40 or less.	0	2 (0.1%)
Benign biopsy with proliferative disease and first degree relative who developed breast cancer at age 40 or less.	0	0
For women in all age groups		
Lobular carcinoma in situ (LCIS)	50 (2.6%)	55 (2.8%)
Atypical ductal or lobular hyperplasia in a benign lesion.	104 (5.4%)	135 (6.9%)
DCIS (ER-positive) diagnosed within last 6 months with completed adequate local treatment.	160 (8.3%)	166 (8.5%)
Women with a clearly apparent family history indicating appropriate increased risk	34 (1.8%)	38 (2.0%

ER = Oestrogen Receptor, LCIS = Lobular Carcinoma In Situ, DCIS = Ductal Carcinoma In Situ

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METHODS: EXCLUSION CRITERIA

- Premenopausal
- Previous breast cancer including DCIS dx >6 mo before trial entry
- Previous invasive cancer in past 5 yr (except non-melanoma skin cancer or cervical cancer)
- Current or previous use of selective estrogen receptor modulators (SERMs) for >6 mo
- Intention to continue hormone replacement therapy
- Prophylactic mastectomy
- Evidence of severe osteoporosis (T score <-4, or >2 vertebral fractures)
- Life expectancy <10 yr

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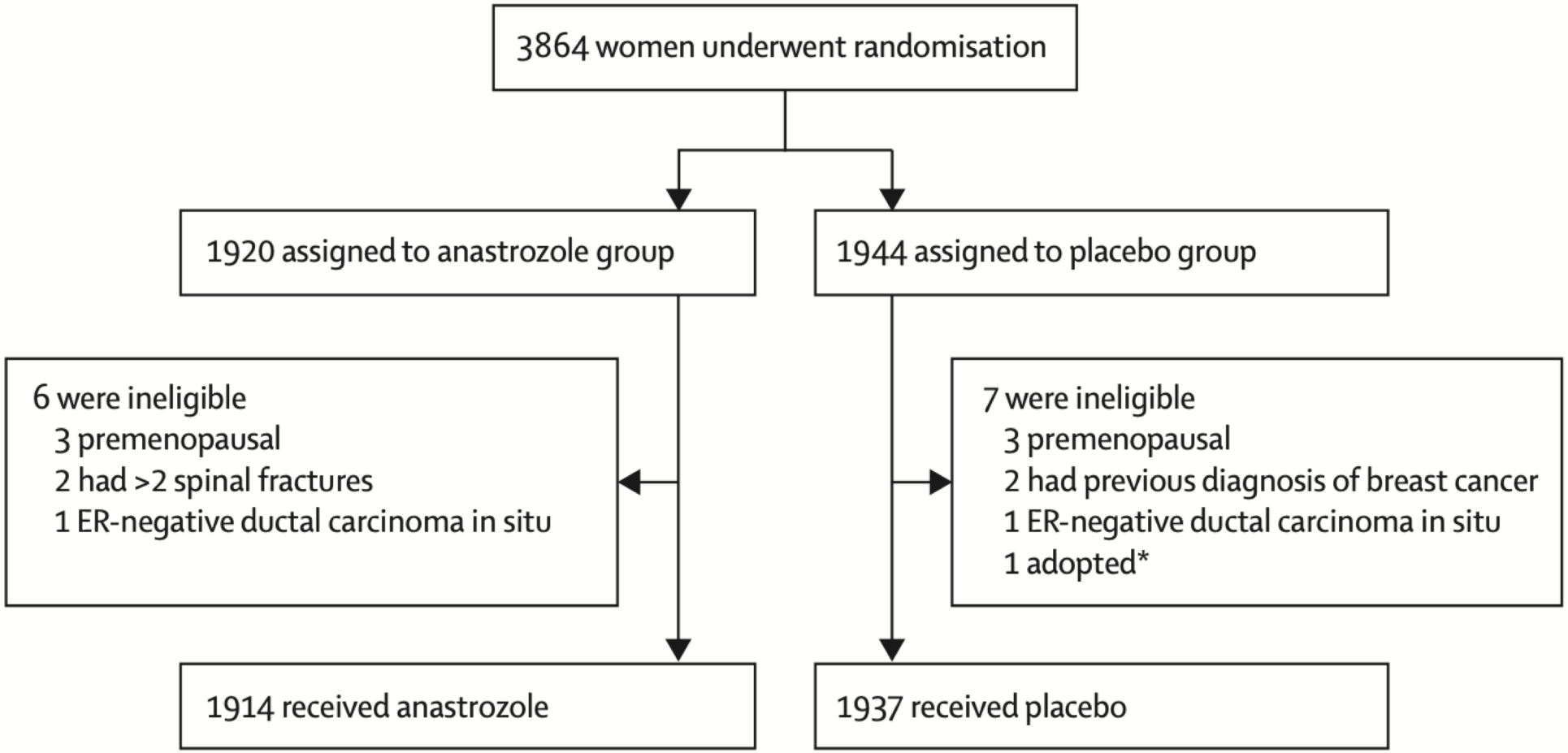
METHODS: RANDOMIZATION



Lancet (2020)

METHODS: PROCEDURES & OUTCOMES

Anastrozole group
(*n* = 1920)

Placebo group
(*n* = 1944)

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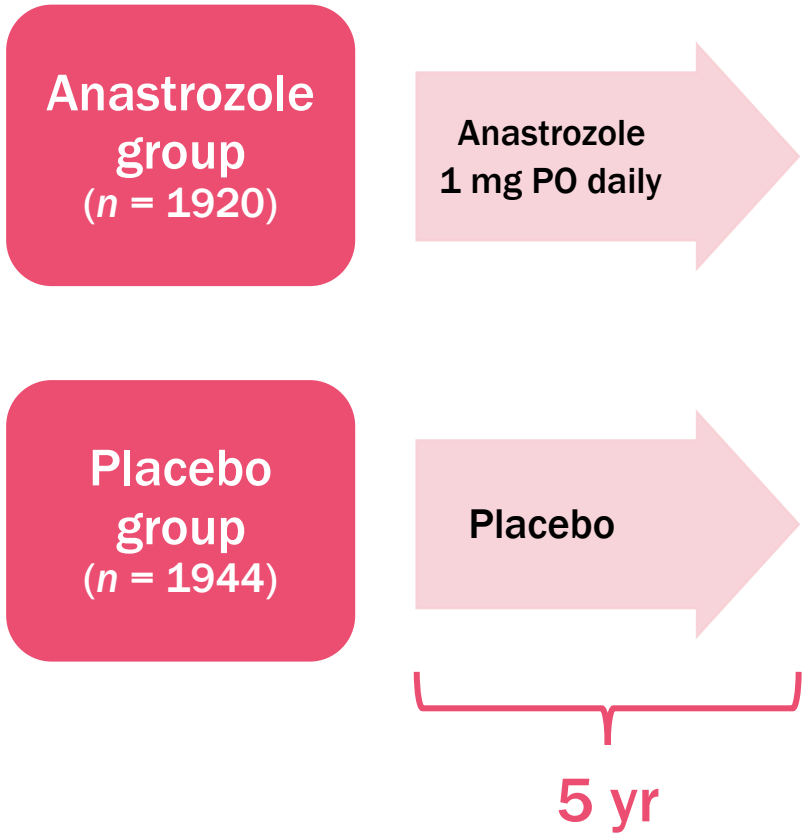
METHODS: PROCEDURES & OUTCOMES



Lancet (2020)

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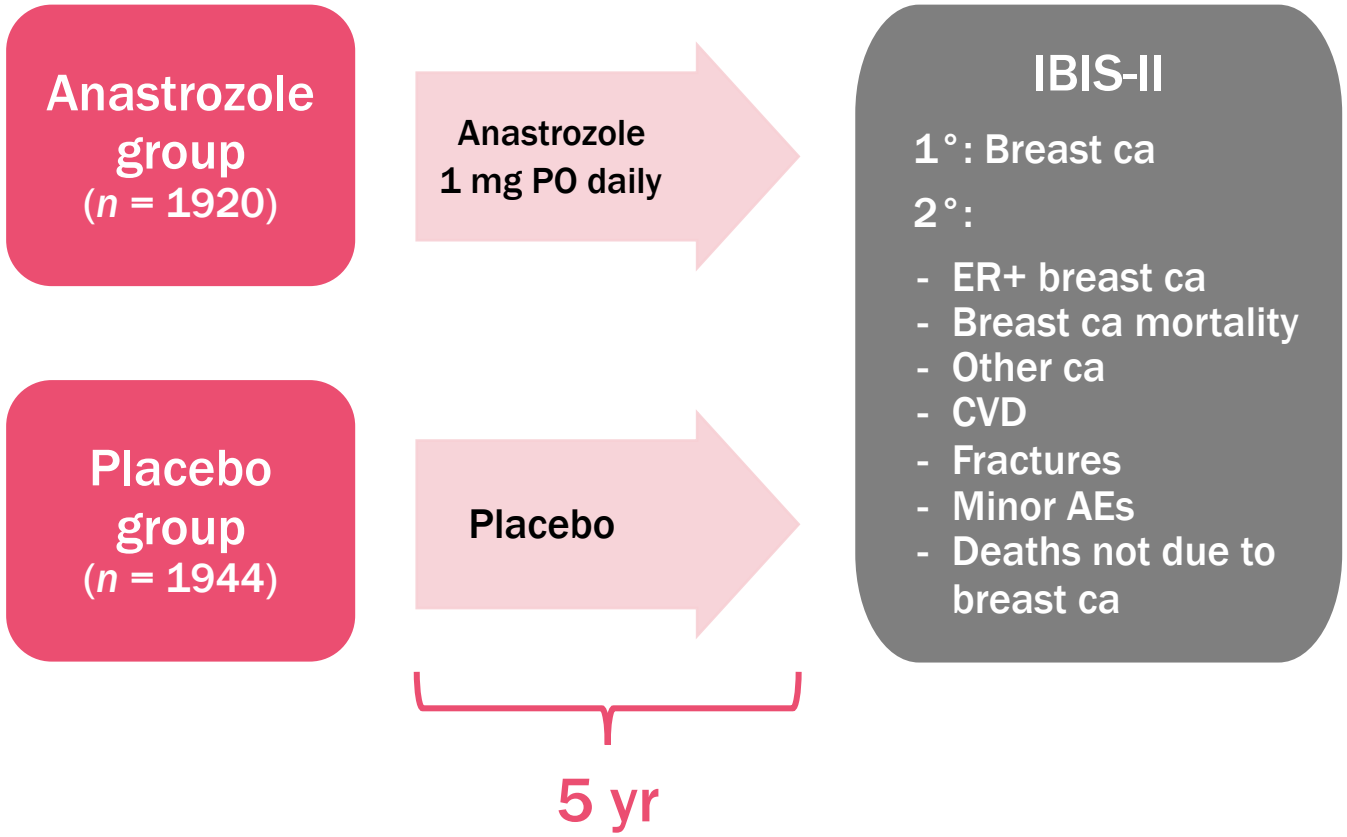

Lancet (2020)

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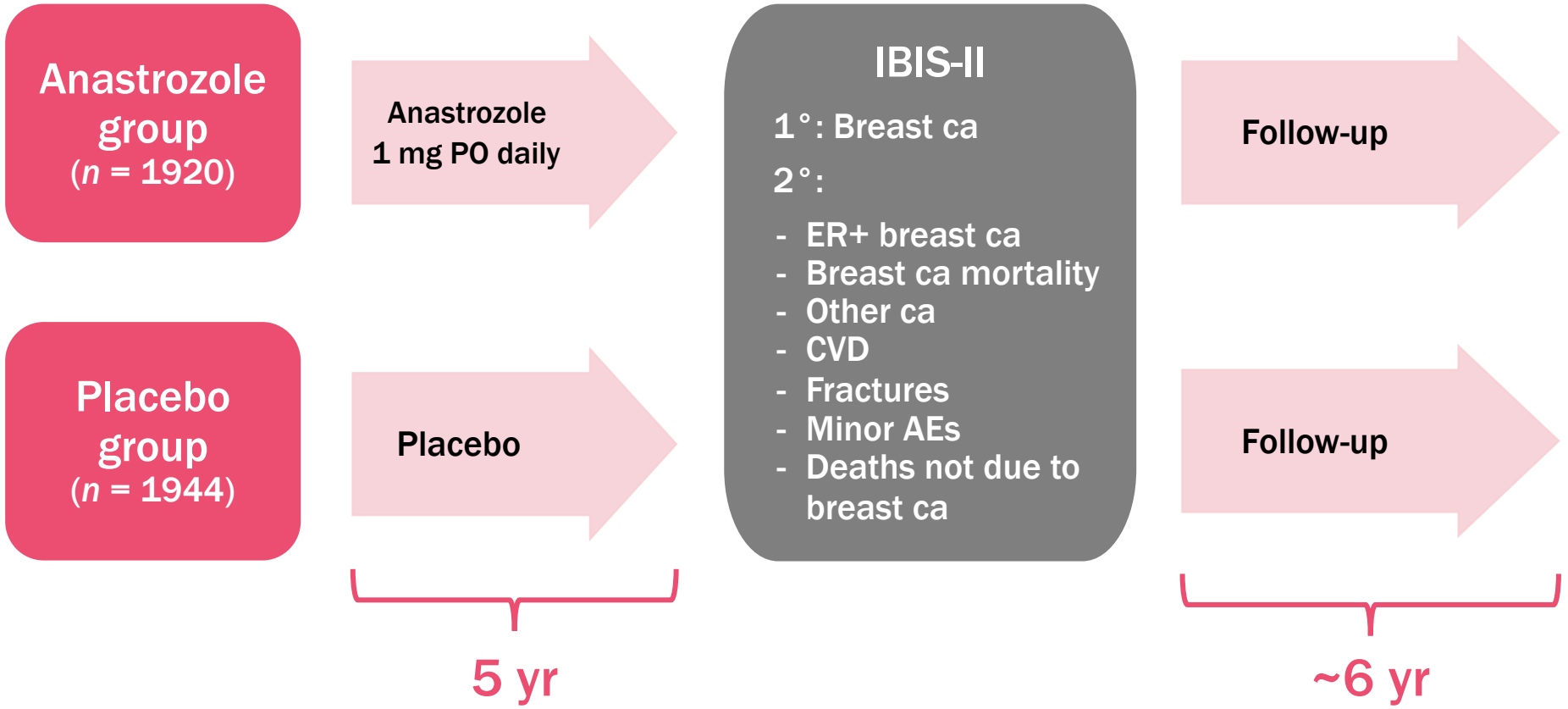

Lancet (2020)

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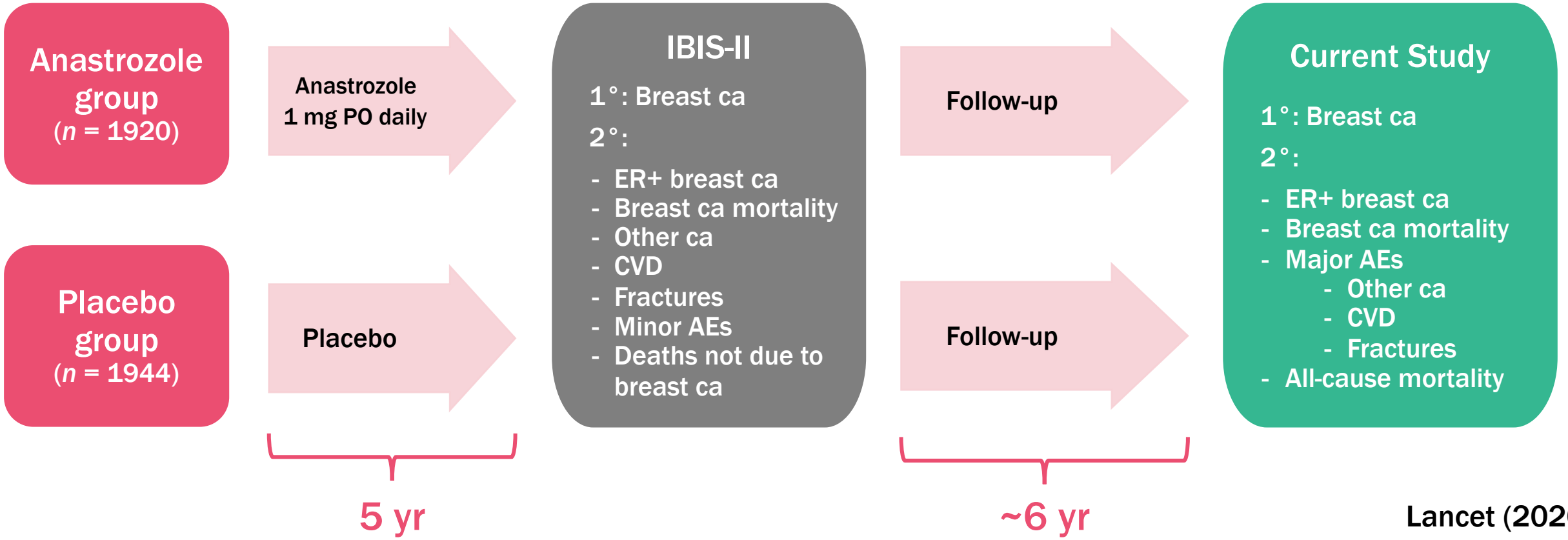

Lancet (2020)

METHODS: STATISTICAL ANALYSIS

- Intention-to-treat analysis
- Efficacy endpoints
  - Hazard ratios (HRs)
- Survival curves
  - Kaplan-Meier method
- Side effects and secondary outcomes
  - Compared between treatment groups using odds ratios (ORs) and Fisher exact significance tests

Lancet (2020)

STATISTICS DETOUR

What is an Odds Ratio (OR)?

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What is an Odds Ratio (OR)?

Odds Ratio: A measure of association between an exposure and an outcome

"The odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of the exposure"

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OR = 1

OR > 1

OR < 1

STATISTICS DETOUR

What is an Odds Ratio (OR)?

Odds Ratio: A measure of association between an exposure and an outcome

"The odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of the exposure"

OR = 1 → Exposure does not affect odds of outcome

OR > 1 → Exposure assoc with higher odds of outcome

OR < 1 → Exposure assoc with lower odds of outcome

STATISTICS DETOUR

Odds Ratio: (OR)

"The odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of the exposure"

		Outcome +	Outcome -
Exposure	+	a	b
	-	c	d

a = exposed cases
b = exposed non-cases
c = unexposed cases
d = unexposed non-cases

STATISTICS DETOUR

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a = exposed cases
b = exposed non-cases
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$$OR = \frac{\text{exposed cases} / \text{unexposed cases}}{\text{exposed non-cases} / \text{unexposed non-cases}}$$

$$OR = \frac{a / c}{b / d}$$

$$OR = \frac{ad}{bc}$$

STATISTICS DETOUR

Odds Ratio: *"The odds of having a fracture in the anastrozole group, compared to the odds of having a fracture in the placebo group"*

		Fracture +	Fracture -	
Anastrozole	+	a	b	1920
	-	c	d	1944

a = exposed cases
b = exposed non-cases
c = unexposed cases
d = unexposed non-cases

RESULTS

- *Intention to treat:*
  - All women (n = 3864) randomly assigned to anastrozole (n = 1920) vs placebo (n = 1944) were included in analysis
  - Treatment adherence for full 5 yr: 75% for anastrozole, 77% for placebo
- After the initial 5-yr treatment period, 3704 (~96%) women were still at risk of developing breast cancer
- Median follow-up was 131 months (10 yr, 11 mo)
- 41,495 women-years accrued, incl. 22,367 after 5-yr treatment period

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DEMOGRAPHICS

	Anastrozole group (n=1920)	Placebo group (n=1944)
Age (years)	59·5 (55·0–63·5)	59·4 (55·1–63·3)
Age at menarche (years)	13·0 (1·2–14·0)	13·0 (12·0–14·0)
Parous	1601 (83%)	1637 (84%)
Age at first child birth (years)	24·0 (21·0–27·0)	24·0 (21·0–27·0)
Age at menopause (years)	50·0 (45·0–52·0)	49·0 (45·0–52·0)
Height (cm)	162·0 (158·0–166·0)	162·2 (158·0–167·0)
Weight (kg)	71·8 (64·0–82·2)	72·1 (64·0–83·5)
Body-mass index (kg/m²)		
<25	581 (30%)	568 (29%)
25–30	699 (36%)	732 (38%)
>30	640 (33%)	644 (33%)
Previous use of hormone replacement therapy	893 (47%)	910 (47%)
Use of hormone replacement therapy within previous 12 months	128 (7%)	152 (8%)
Hysterectomy	631 (33%)	656 (34%)
Two or more first-degree or second-degree relatives with breast or ovarian cancer	956 (50%)	938 (48%)
One first-degree relative with breast cancer at age 50 years or younger	675 (35%)	653 (34%)
One first-degree relative with bilateral breast cancer	164 (9%)	141 (7%)
Lobular carcinoma in situ or atypical hyperplasia	154 (8%)	190 (10%)
Oestrogen-receptor-positive ductal carcinoma in situ treated by mastectomy within 6 months	160 (8%)	166 (9%)
10-year Tyrer-Cuzick risk (%)	7·6% (5·8–9·9)	7·8 (5·1–10·2)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics**

Similar demographics between groups

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BREAST CANCERS

	Number of events, anastrozole *vs* placebo	Hazard ratio (95% CI)	p value	$p_{heterogeneity}$*
Overall	85 *vs* 165	0·51 (0·39–0·66)	<0·0001	..
0–5 years	35 *vs* 89	0·39 (0·27–0·58)	<0·0001	0·087
>5 years	50 *vs* 76	0·64 (0·45–0·91)	0·014	..
Invasive oestrogen receptor-positive	48 *vs* 103	0·46 (0·33–0·65)	<0·0001	..
0–5 years	20 *vs* 51	0·39 (0·23–0·66)	<0·0001	0·43
>5 years	28 *vs* 52	0·52 (0·33–0·83)	0·0062	..
All ductal carcinoma in situ	13 *vs* 31	0·41 (0·22–0·79)	0·0081	..
0–5 years	5 *vs* 17	0·29 (0·11–0·80)	0·016	0·43
>5 years	8 *vs* 14	0·56 (0·23–1·32)	0·18	..

*0–5 years *vs* >5 years.

Table 1: **Number of breast cancer events and hazard ratios**

Hazard ratio: measure of the effect of an intervention on an outcome of interest over time

Lancet (2020)

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Table 1: **Number of breast cancer events and hazard ratios**

49% reduction in all breast cancer
→ 61% ↓ within first 5 yrs
→ 37% ↓ during follow-up

54% reduction in invasive ER+ ca
→ 61% ↓ within first 5 yrs
→ 48% ↓ during follow-up

Significant reduction in DCIS

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BREAST CANCERS

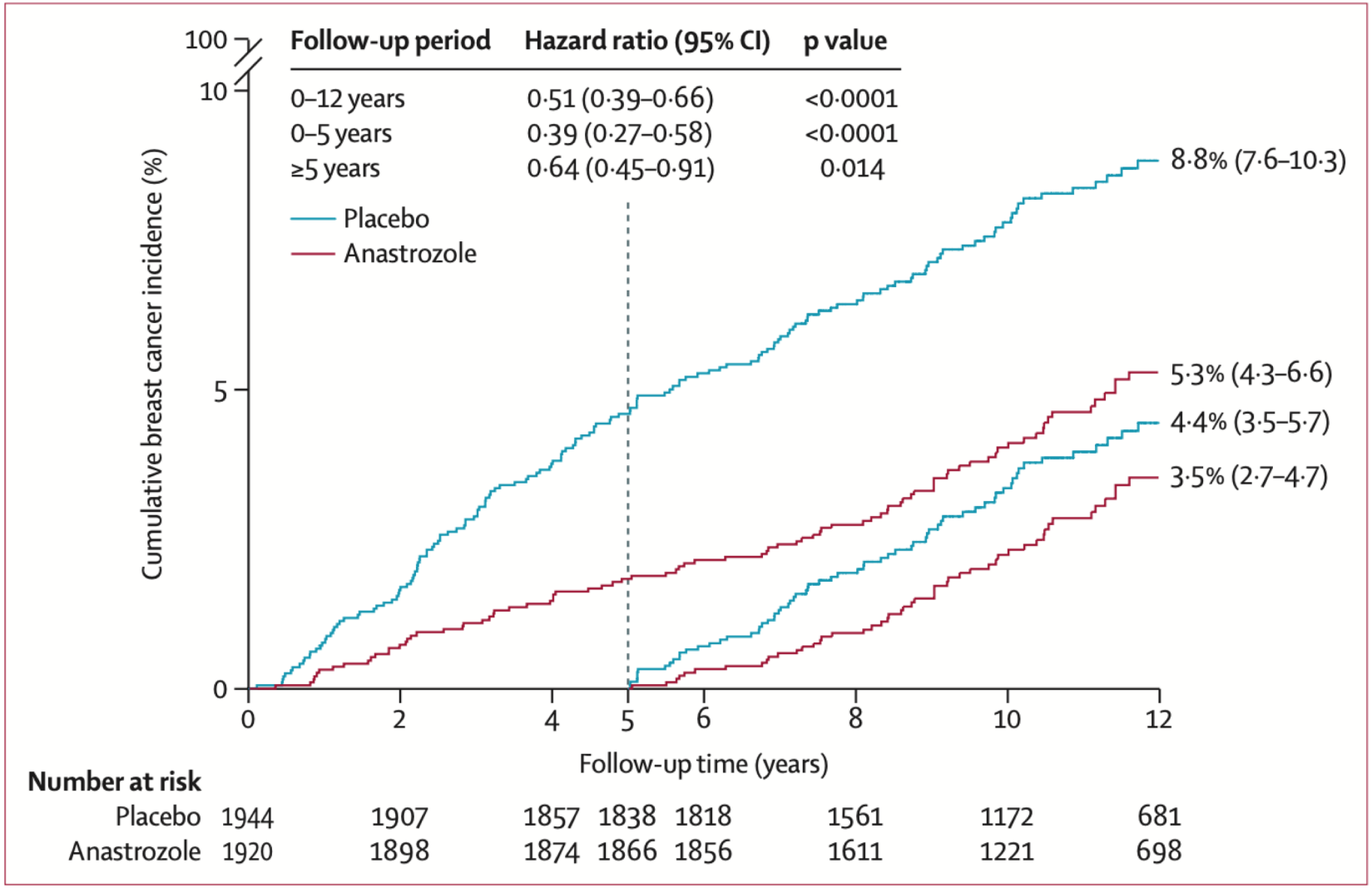

Figure 1: **Cumulative incidence for all breast cancer by treatment allocation and follow-up period**

After 12 yr of follow-up, estimated risk of developing breast cancer:

- 8.8% in placebo group

- 5.3% in anastrozole group

Number needed to treat (NNT) for 5 yr to prevent one breast cancer = 29

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BREAST CANCERS

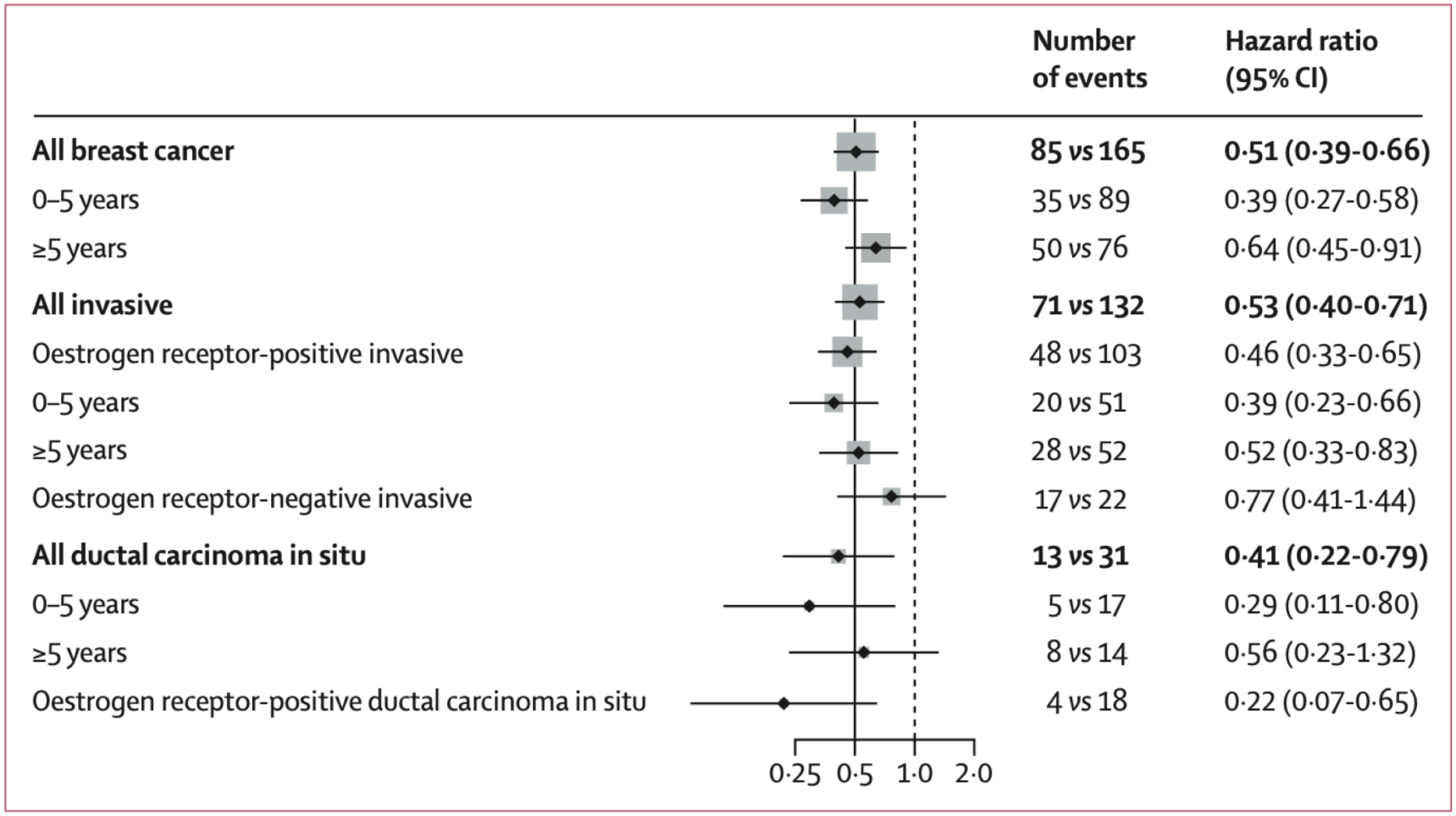

Figure 2: **Hazard ratios for subgroup analyses by follow-up period**
Grey squares indicate the amount of information available for this comparison, largely based on the number of events.

Lancet (2020)

NON-BREAST CANCERS

	Anastrozole N=1920, n (%)	Placebo, N=1944, n (%)	Odds ratio (95% CI)
Total	147 (7·1%)	200 (9·8%)	0·72 (0·57–0·91)
Skin	52 (2·7%)	85 (4·4%)	0·61 (0·42–0·88)
Non-melanoma	43 (2·2%)	73 (3·8%)	0·59 (0·39–0·87)
Melanoma	9 (0·5%)	12 (0·6%)	0·76 (0·28–1·97)
Gynaecological	14 (0·7%)	20 (1·0%)	0·71 (0·33–1·47)
Endometrial	5 (0·3%)	7 (0·4%)	0·72 (0·18–2·65)
Ovarian	7 (0·4%)	10 (0·5%)	0·71 (0·23–2·06)
Respiratory	13 (0·7%)	13 (0·7%)	1·01 (0·43–2·38)
Lung	11 (0·6%)	12 (0·6%)	0·93 (0·37–2·30)
Gastrointestinal	24 (1·3%)	33 (1·7%)	0·81 (0·45–1·43)
Colorectal	11 (0·6%)	16 (0·8%)	0·69 (0·29–1·60)

Table 2: **Cancers other than breast**

28% reduction in all non-breast cancers

→ Mostly driven by a reduction in the incidence of non-melanoma skin cancer

→ No significant effect on other cancers

Interestingly, no reduction in endometrial cancer (estrogen thought to be a major driver)

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MAJOR ADVERSE EVENTS

	Anastrozole, N=1920, all years (>5 years)	Placebo, N=1944, all years (>5 years)	Odds ratio (95% CI), all years
Fractures	380 (182)	373 (186)	1·04 (0·88–1·22)
Myocardial infarction	16 (8)	14 (8)	..
Deep vein thrombosis*	13 (6)	17 (5)	..
Pulmonary embolism	17 (11)	12 (7)	..
Transient ischaemic attack†	24 (14)	20 (9)	..
Stroke	23 (15)	17 (9)	..

*In the absence of pulmonary embolism. †In the absence of stroke. Numbers in parentheses refer to events occurring in the post-treatment period (>5 year follow-up).

***Table 3:* Major adverse events**

No significant effect seen on any major adverse event

- No excess of fractures
- Overall small number of other events

Lancet (2020)

STATISTICS DETOUR

Odds Ratio: *"The odds of having a fracture in the anastrozole group, compared to the odds of having a fracture in the placebo group"*

		Fracture +	Fracture -	
Anastrozole	+	380	b	1920
	-	373	d	1944

a = exposed cases
b = exposed non-cases
c = unexposed cases
d = unexposed non-cases

STATISTICS DETOUR

Odds Ratio: *"The odds of having a fracture in the anastrozole group, compared to the odds of having a fracture in the placebo group"*

		Fracture +	Fracture -	
Anastrozole	+	380	1540	1920
	-	373	1571	1944

a = exposed cases
b = exposed non-cases
c = unexposed cases
d = unexposed non-cases

$$OR = \frac{ad}{bc} = 1.04\ (95\%\ CI\ 0.88–1.22)$$

No significant increase in fracture risk in patients treated with anastrozole vs placebo

MORTALITY

	Anastrozole, N=1920, n (%)	Placebo, N=1944, n (%)	Hazard ratio (95% CI)
All	69 (3·6%)	70 (3·6%)	0·96 (0·69–1·34)
Breast cancer	2 (0·1%)	3 (0·2%)	0·64 (0·11–3·88)
Other cancer	27 (1·4%)	34 (1·8%)	0·77 (0·47–1·28)
Cardiovascular	13 (0·7%)	9 (0·5%)	1·41 (0·60–3·31)
Other or unknown	27 (1·4%)	24 (1·2%)	1·10 (0·63–1·91)

Table 4: **Specific causes of death**

No significant difference in deaths between anastrozole and placebo groups, either from breast cancer or other causes

- Numbers are small overall

→ Will need longer follow-up to determine whether anastrozole affects breast cancer and other cause mortality

Lancet (2020)

DISCUSSION

- Study supports the use of anastrozole in breast cancer prevention for high-risk post-menopausal women
- Benefits of anastrozole for breast cancer risk reduction extend beyond the 5-yr treatment period
  - NNT during first 12 yr of follow-up for anastrozole = 29
  - NNT during first 12 yr of follow-up for tamoxifen = 58
- Reduction in breast cancer seen was mostly for ER+ cancers
  - Interestingly, also saw reduction in receptor-negative cancers
    → needs further validation

Lancet (2020)

DISCUSSION

- Too early to glean meaningful information about breast cancer-related deaths → need longer follow-up
- No excess side effects identified with longer follow-up
  - 11% excess of fractures during the active treatment period did not continue after 5 yr of follow-up
  - Did not measure minor adverse effects after the 5-yr treatment period

Lancet (2020)

LIMITATIONS

- How diverse was the patient population? External validity?
  No mention of race/ethnicity, though was an international study
- Duration of follow up
  - Need longer-term data re: mortality
- Did not measure minor adverse effects in follow-up period
  - Some minor effects may have important implications for QOL (e.g., hot flashes, arthralgias)
- Need better tools to evaluate risk for breast cancer and risk for adverse effects of medications to prevent breast cancer

SUMMARY

- For women aged ≥35 yr at increased risk for breast cancer, USPSTF recommends we offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to patients who are at low-risk for adverse effects of this treatment
- Breast cancer risk calculation tools:
  NCI Breast Cancer Risk Assessment Tool & BSCS risk calculator
- Aromatase inhibitors block the production of estrogen, thereby reducing risk for breast cancer (particularly ER+ cancer)
- Cuzick et al (2020) study provides longer-term data to support the use of anastrozole to prevent breast cancer in high-risk post-menopausal women

HOW WILL THIS KNOWLEDGE INFLUENCE YOUR PRACTICE?

IMPLICATIONS FOR PRACTICE?

- More careful history to assess women ≥35 for risk of breast cancer
  - Risk factors:
    - **Age, menarche, parity, age of first birth, race/ethnicity, first- and second-degree relatives with hx of breast ca, age of relatives' dx, prior breast bx, breast density**
  - Consider use of risk calculator
  - Consider need for BRCA testing in women with strong FHx
  - Think about these issues at well adult visits, when ordering mammograms, and even before age 40!
- If considering medication to prevent breast cancer, also consider risk for adverse effects of medication:
  - History of or risk for osteoporosis, endometrial cancer, VTE, CV events, etc.
  - Tamoxifen, raloxifene, and aromatase inhibitors have overlapping yet somewhat different side effect profiles

QUESTIONS?

TEST YOUR KNOWLEDGE

https://www.aafp.org/afp/2020/0315/p373.html

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