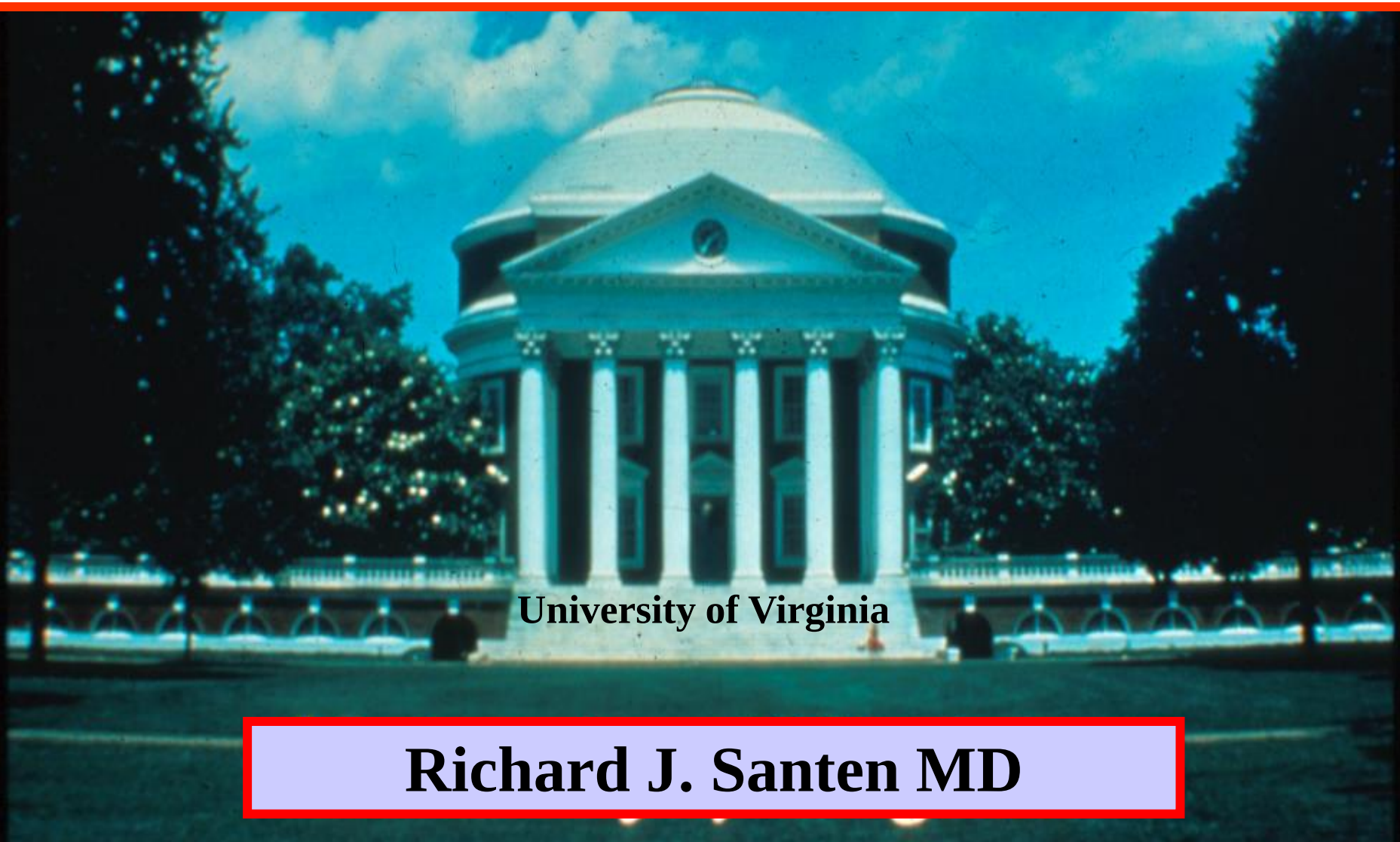
Menopausal Hormone Therapy and Breast Cancer



Richard J. Santen MD

Disclosures

- **Current Grant Funding: Pfizer**
- **This presentation represents my research and does not present the views of the Endocrine Society in my role as President**

I will first examine data on the effects of Menopausal Hormone Therapy (MHT) as reported from the only randomized controlled trial

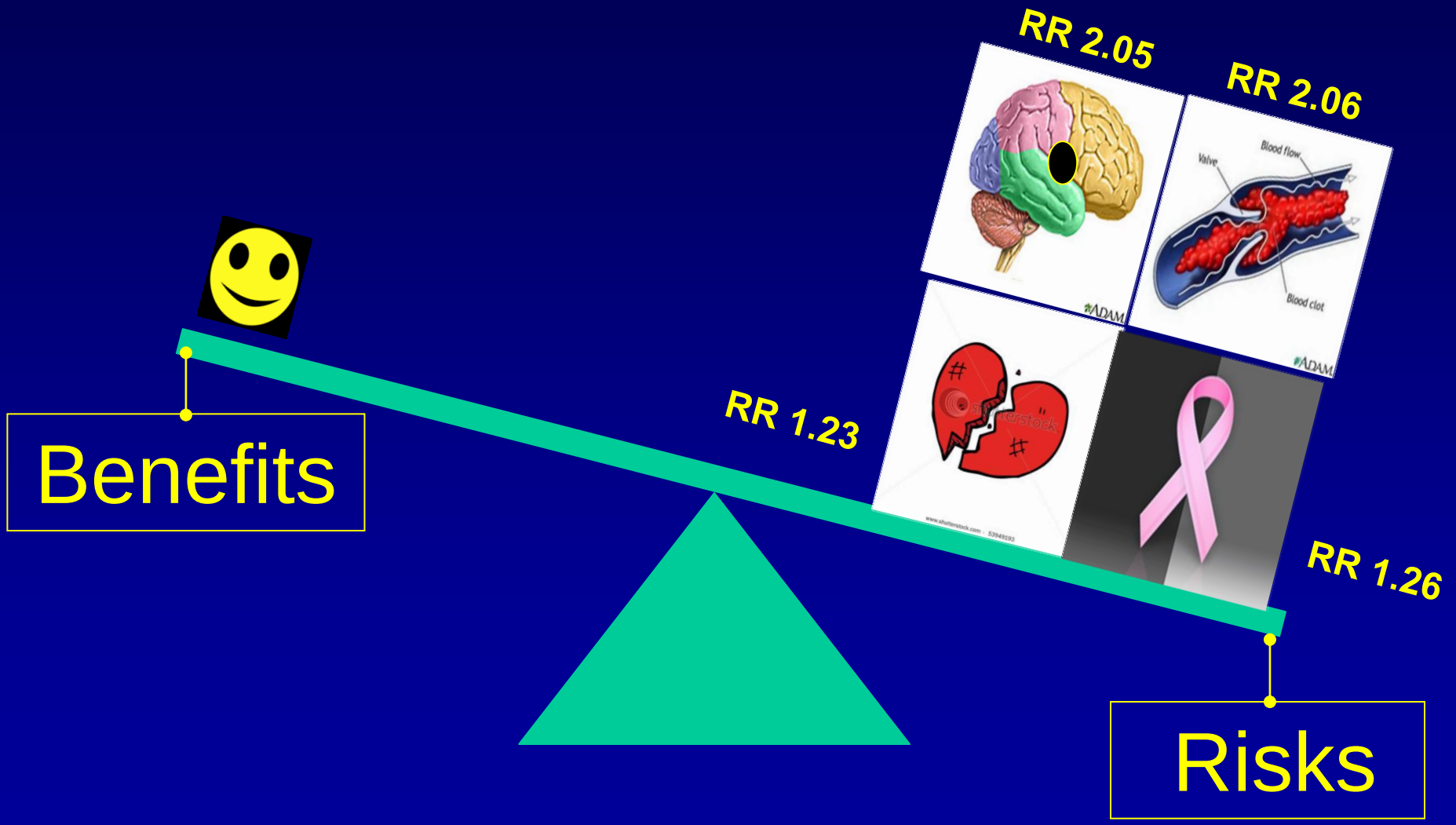
Women's Health Initiative Study in USA

- 27,000 healthy women entered
- Average age 63
- Two arms
  - Placebo versus estrogen (E)
  - Placebo versus estrogen plus progestin (E+P)
- Randomized Controlled Trial
- Treatment for 6 years

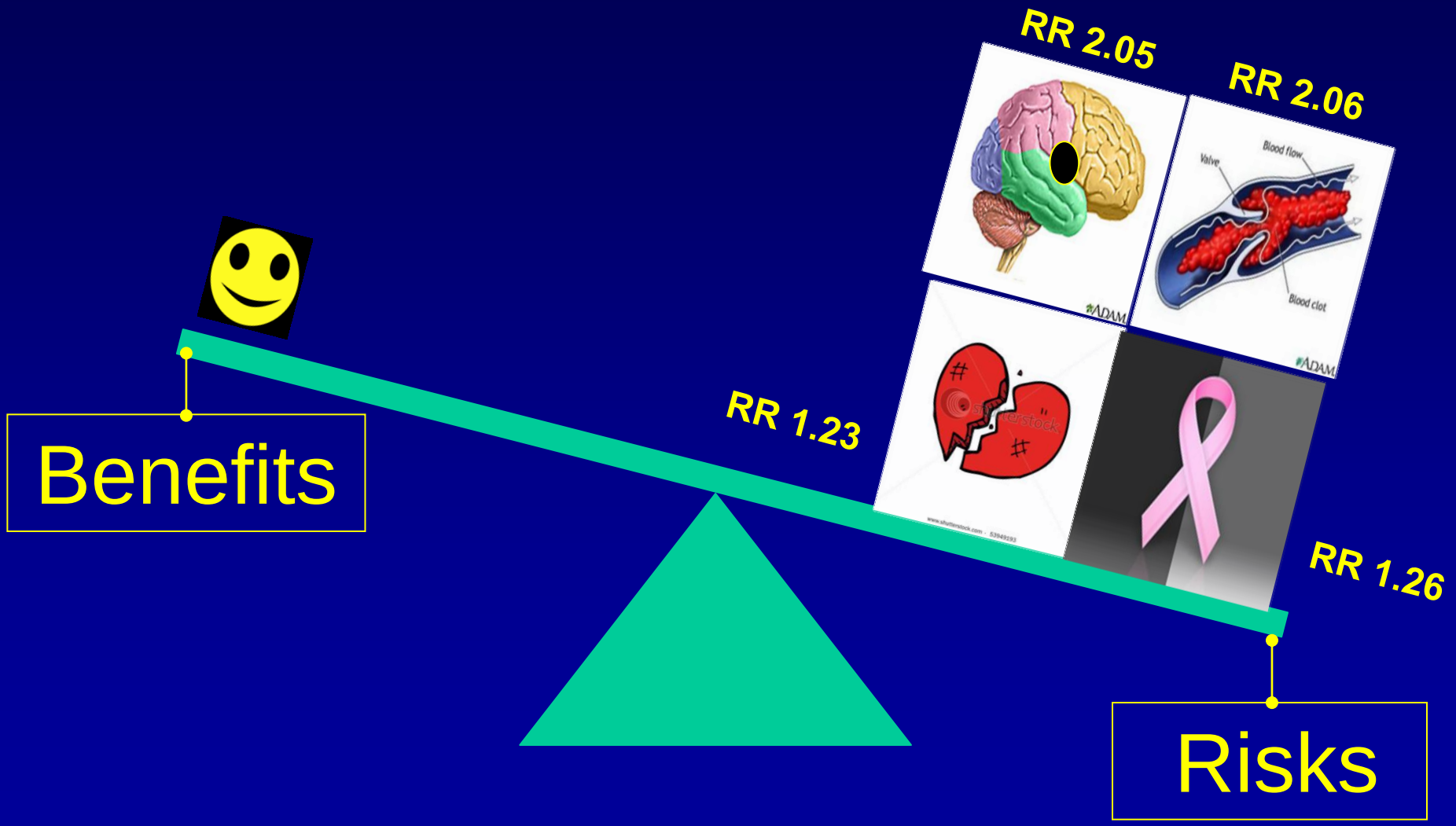
WHI E+P

ages 50-79

2002



Average Age 63



Women make a decision about menopausal hormone therapy shortly after menopause and commonly plan to use for about five years

Reanalysis of WHI

Post-hoc Reanalysis WHI

- October 2, 2013 Manson JA et al JAMA 310:1353-1368, 2013

Post-hoc Reanalysis WHI

- October 2, 2013 Manson JA et al JAMA 310:1353-1368, 2013
- Recognized that relative risk data can be misleading

Relative vs Absolute Risk

- Example of relative risk
  - One flight by plane from Lima to New York City---one chance in 10 million of death in a plane crash
  - Five flights from Lima to New York City--- five chances in one million of death in a plane crash
  - This is a 500% increase in *relative risk*
- Example of absolute risk
  - One in five 10 million chance of dying with five flights
  - absolute risk is very small even though relative risk is 500 %

Post-hoc Reanalysis WHI

- October 2, 2013 Manson JA et al JAMA 310:1353-1368, 2013
- Recognized that relative risk data can be misleading
- Reported excess risks and benefits

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- Calculated the difference in rates between placebo group and CEE plus MPA or CEE alone

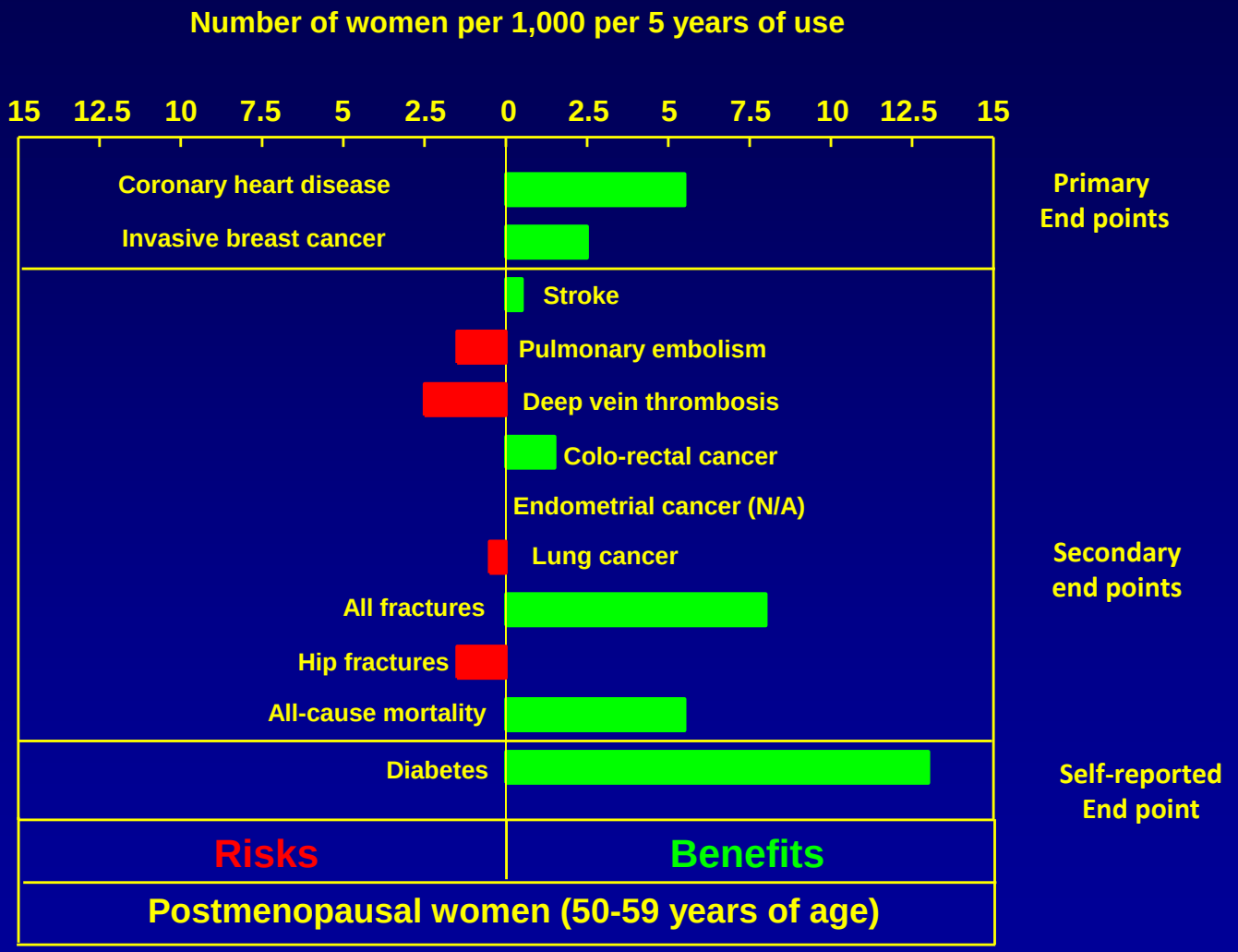
Example of Calculation of Excess Risk

- Without menopausal hormone therapy the incidence of breast cancer is 4 per 1000 women
- With hormone therapy the incidence is 7 per 1000 women
- The excess risk would be 3 per 1000

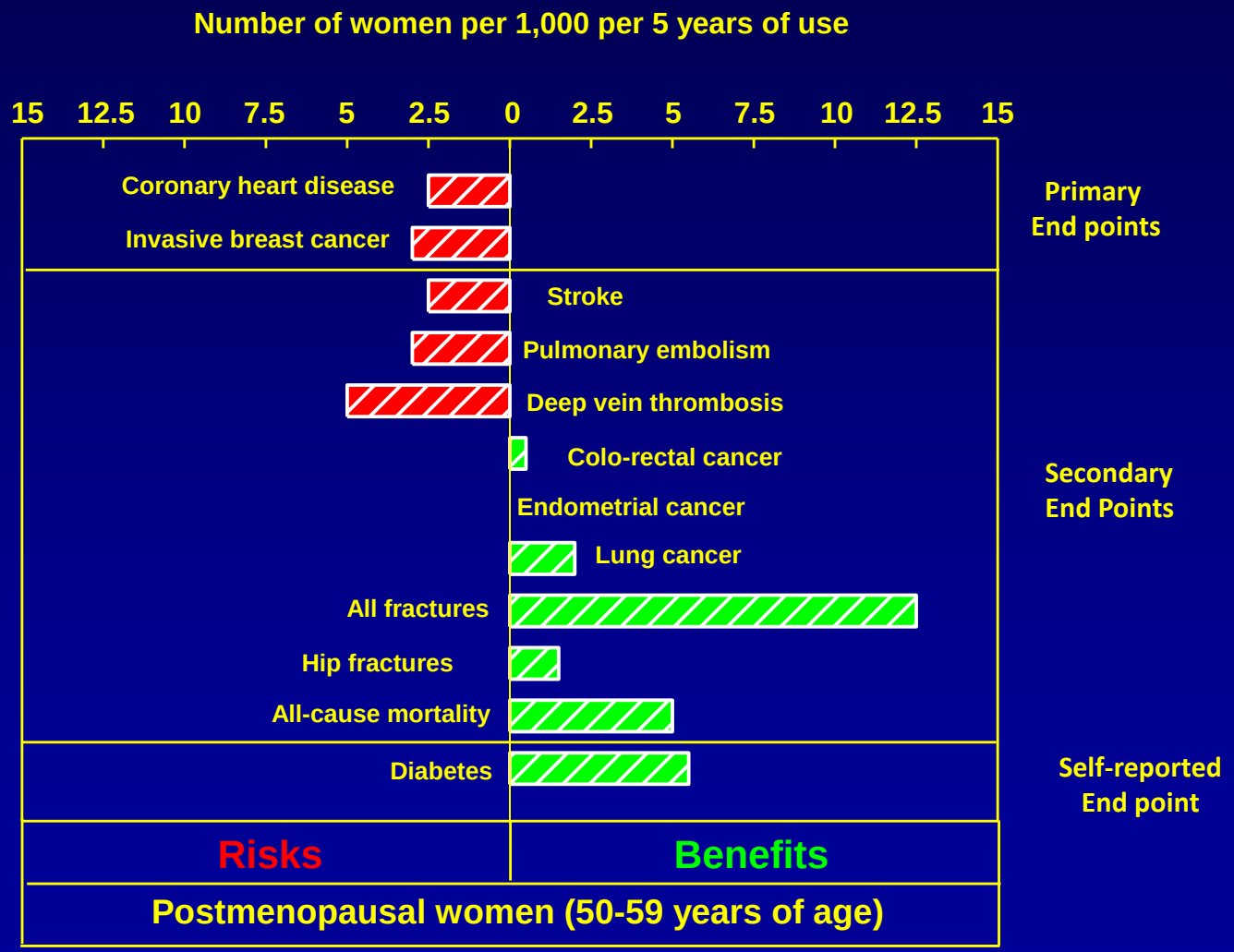
Post-hoc Reanalysis WHI

- October 2, 2013 Manson JA et al JAMA 310:1353-1368, 2013
- Recognized that relative risk data can be misleading
- Reported excess risks and benefits
- Calculated the difference in rates between placebo group and CEE plus MPA or CEE alone
- Analyzed subgroup of women ages 50-59

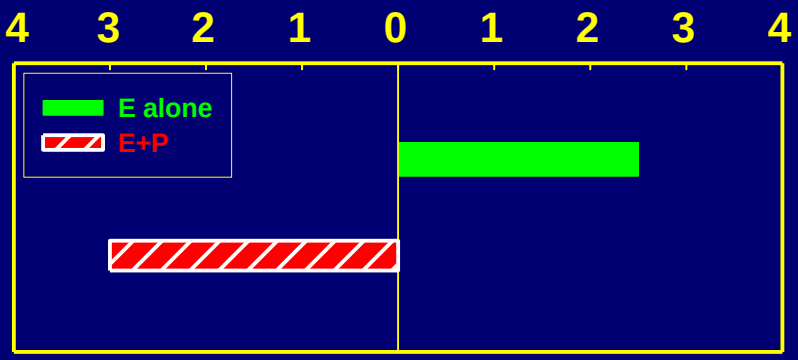
CEE alone during intervention



CEE plus MPA during intervention



Number of women
per 1,000 per 5 years of use



Risk

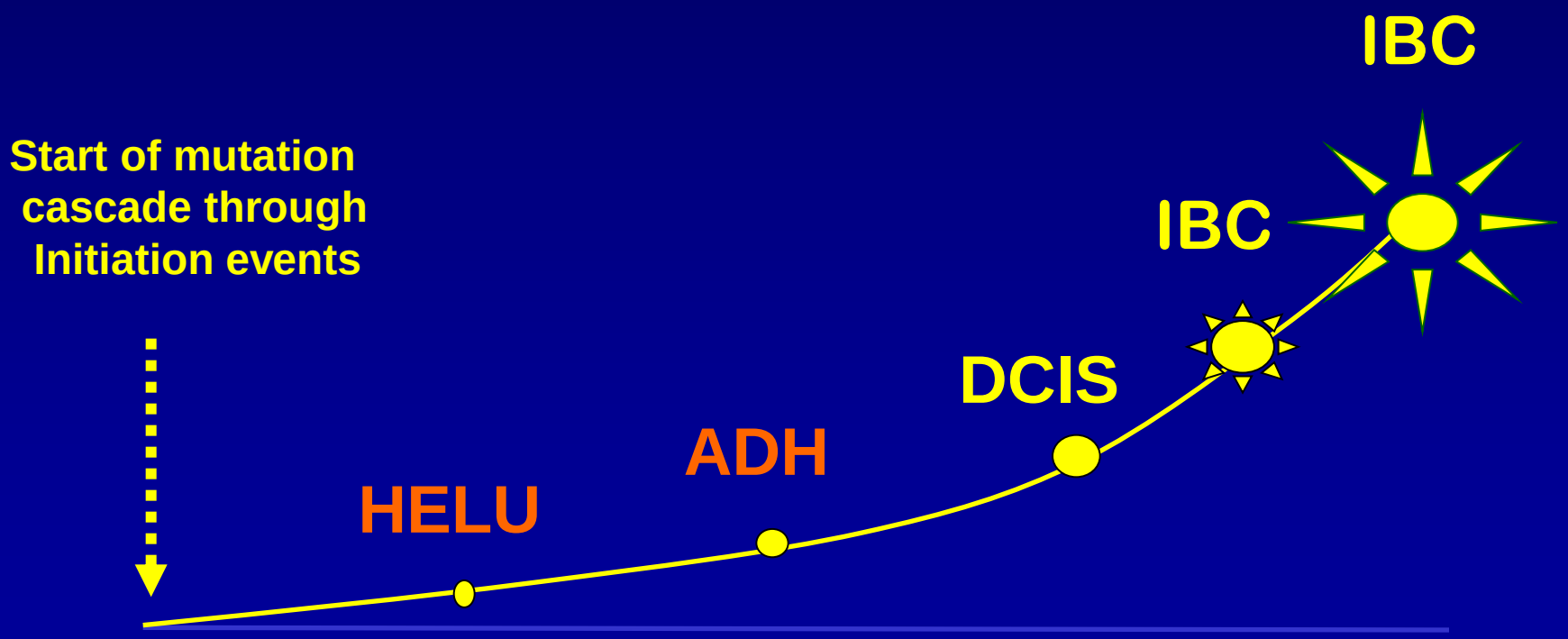
Benefit

How can E+P increase the risk of breast cancer and E alone reduce the risk?

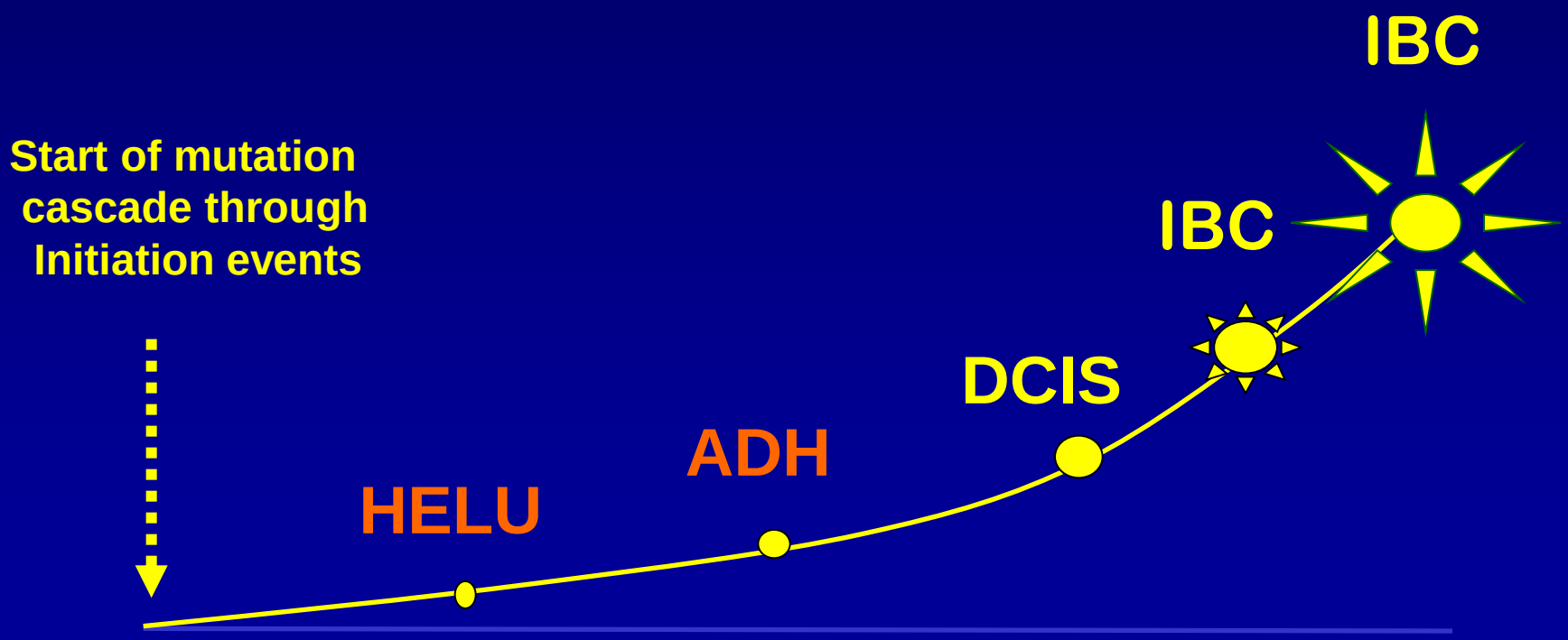
We developed a biologically based and a computer based models to address the question

Modeling of the Growth Kinetics of Occult Breast Tumors: Role in Interpretation of Studies of Prevention and Menopausal Hormone Therapy, Cancer Epidemiology Biomarkers and Prevention 21:1038-48,2012 Santen RJ, Yue W, Heitjan D

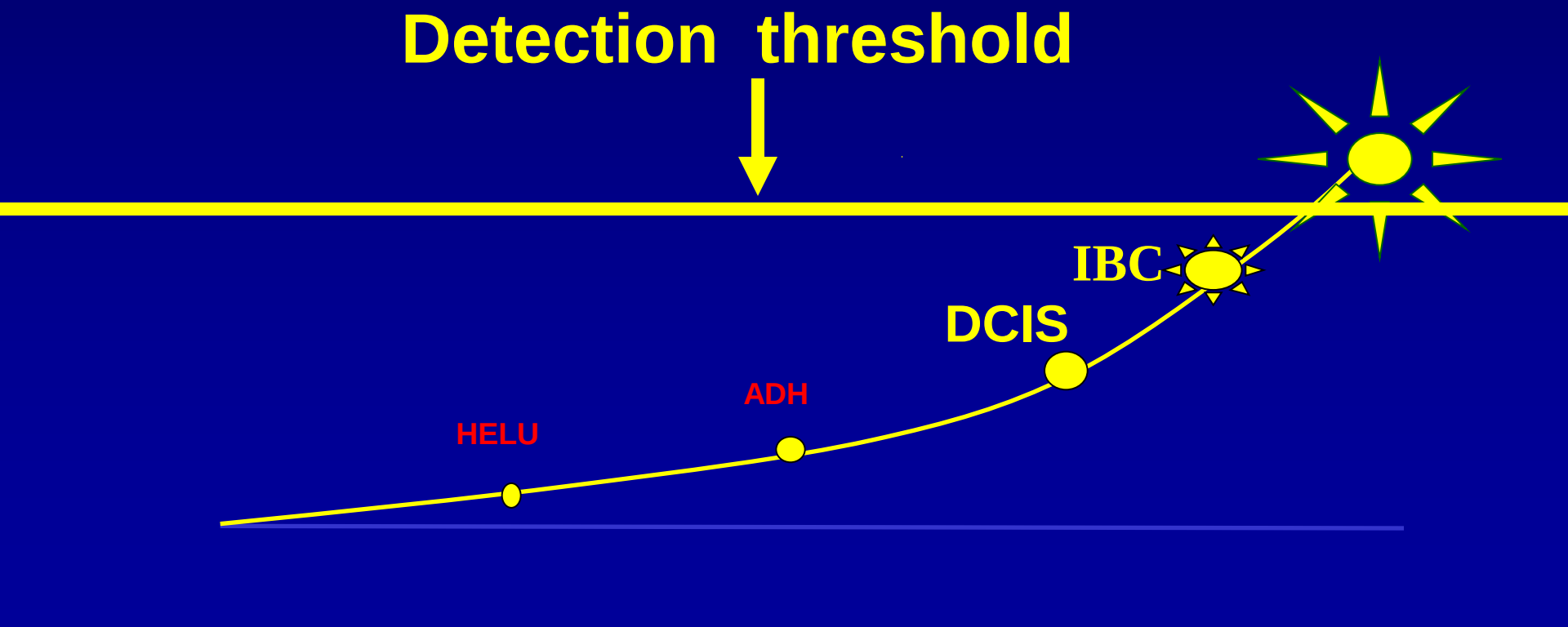
Life History of a Breast Tumor



Average of 11 mutations



For diagnosis, the tumor must exceed the detection threshold



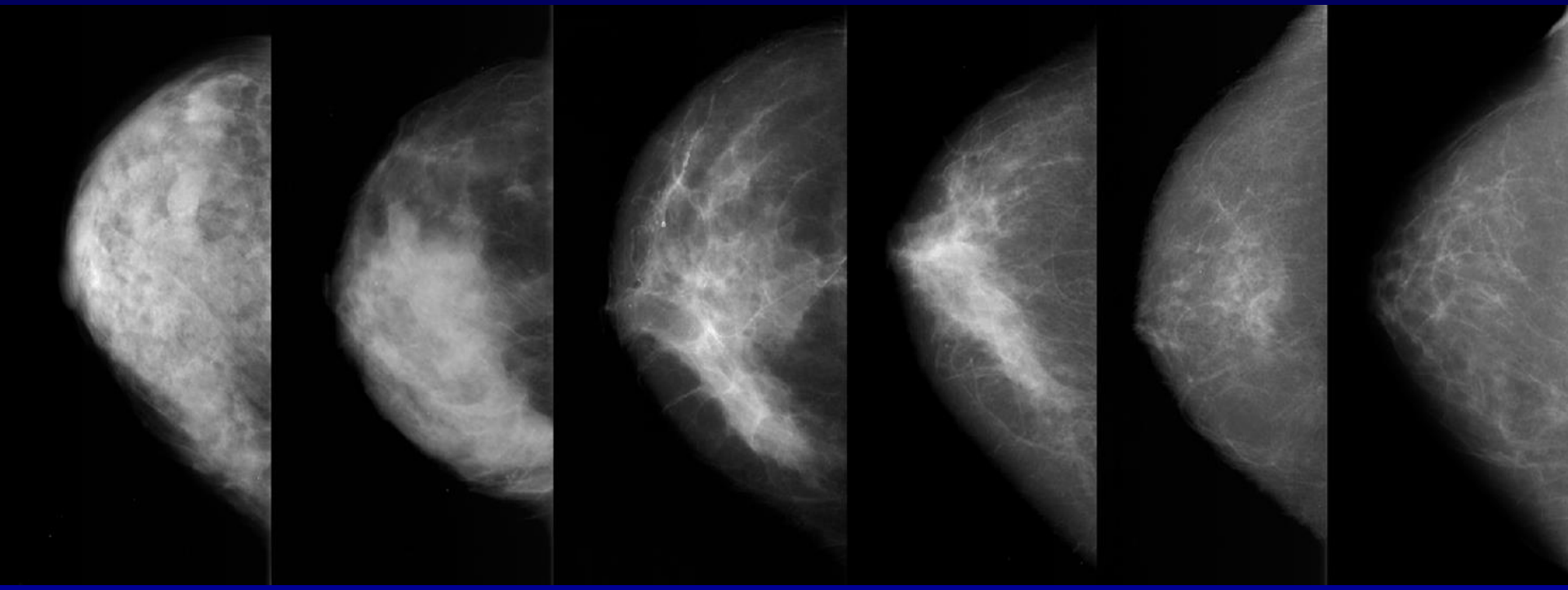
What determines the detection threshold?

Influence of Age on Detection Threshold

- <40 1.63 cm
- 40-49 1.44 cm
- 50-59 1.25 cm
- 60-69 1.07 cm
- >70 0.88 cm

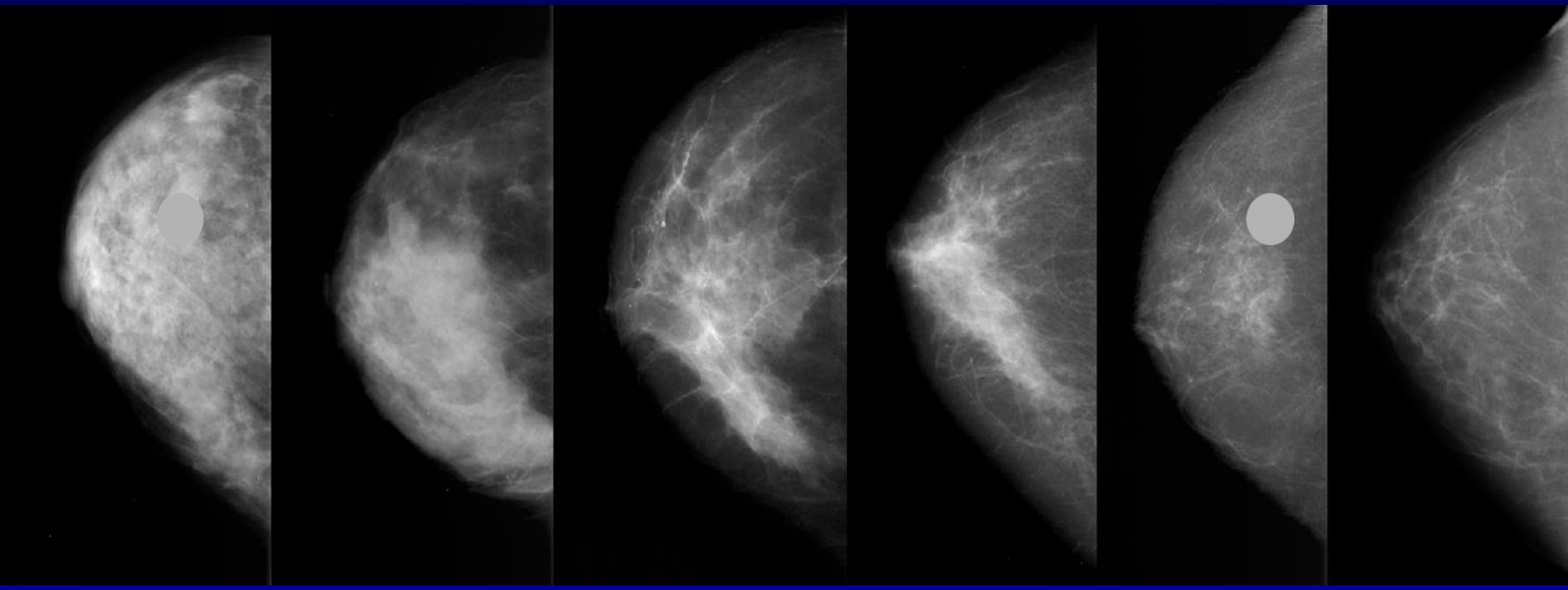
Average for the WHI age 50-69 1.16 cm

Change in mammographic density with age



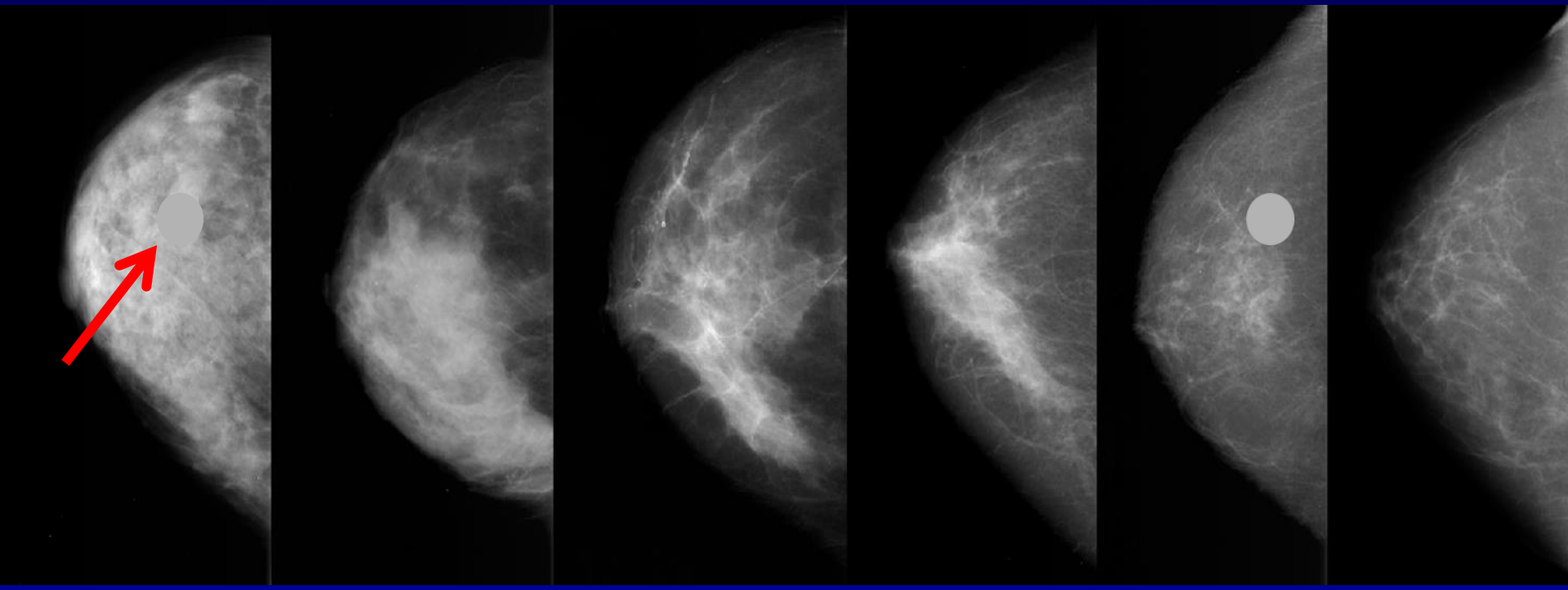
30 40 50 60 70 80

Change in mammographic density with age



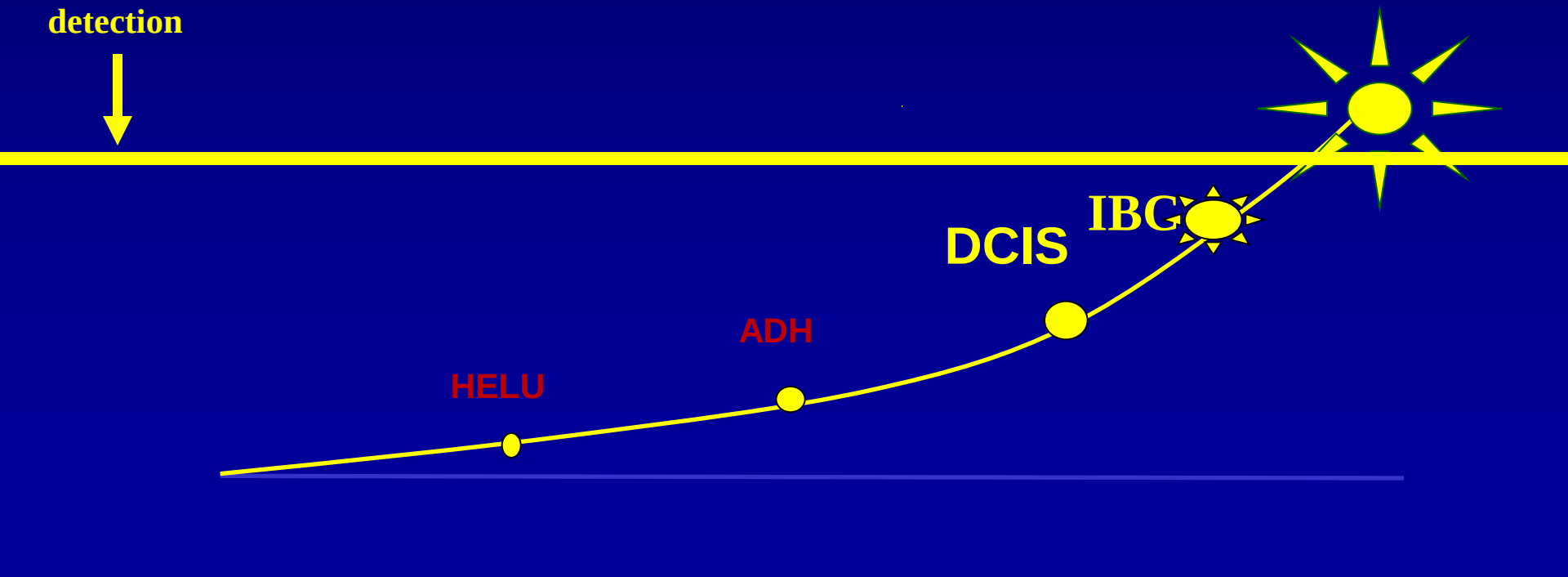
30 40 50 60 70 80

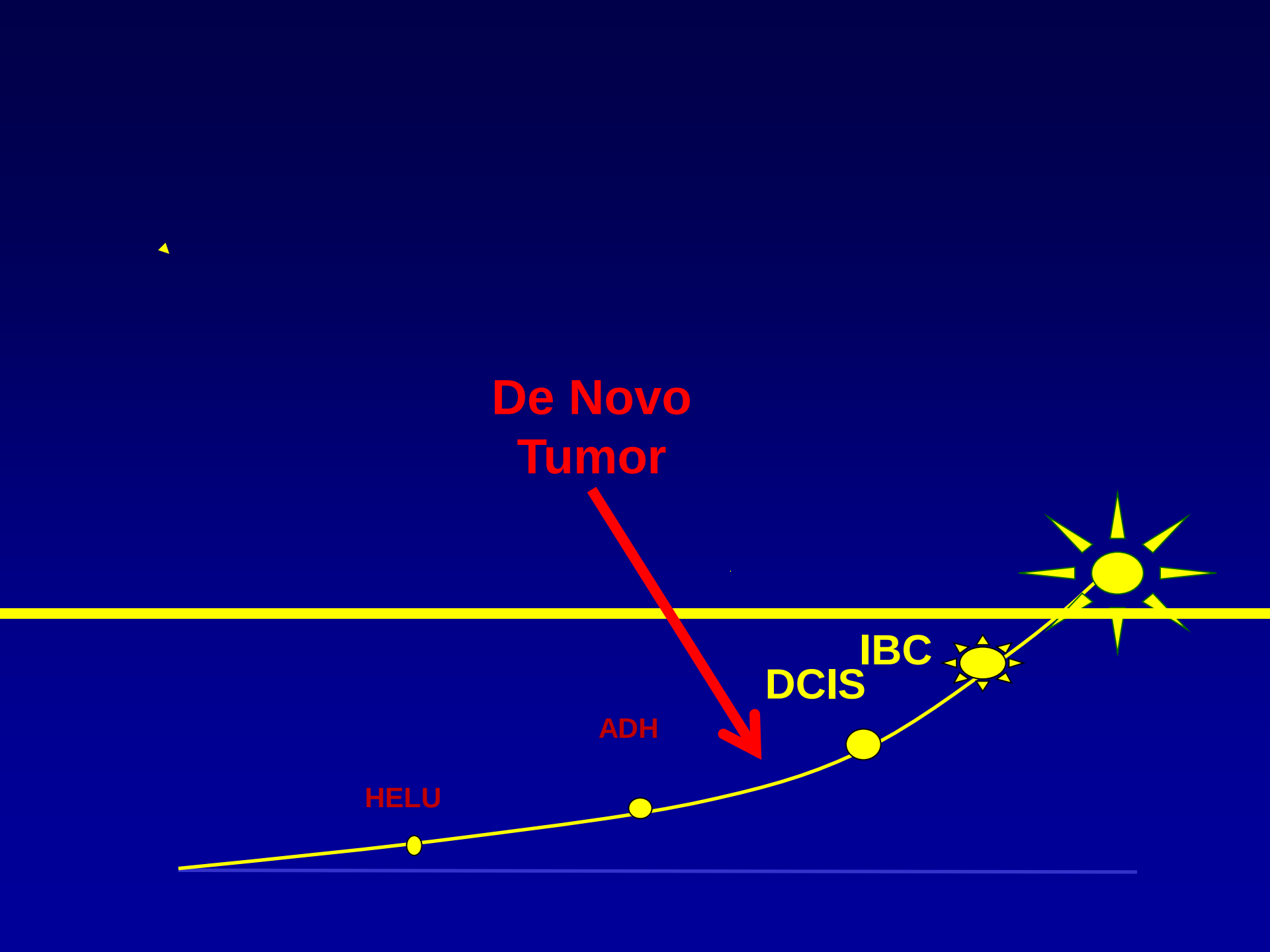
Change in mammographic density with age



30 40 50 60 70 80

How long does it take for a de novo tumor to reach the detection threshold?



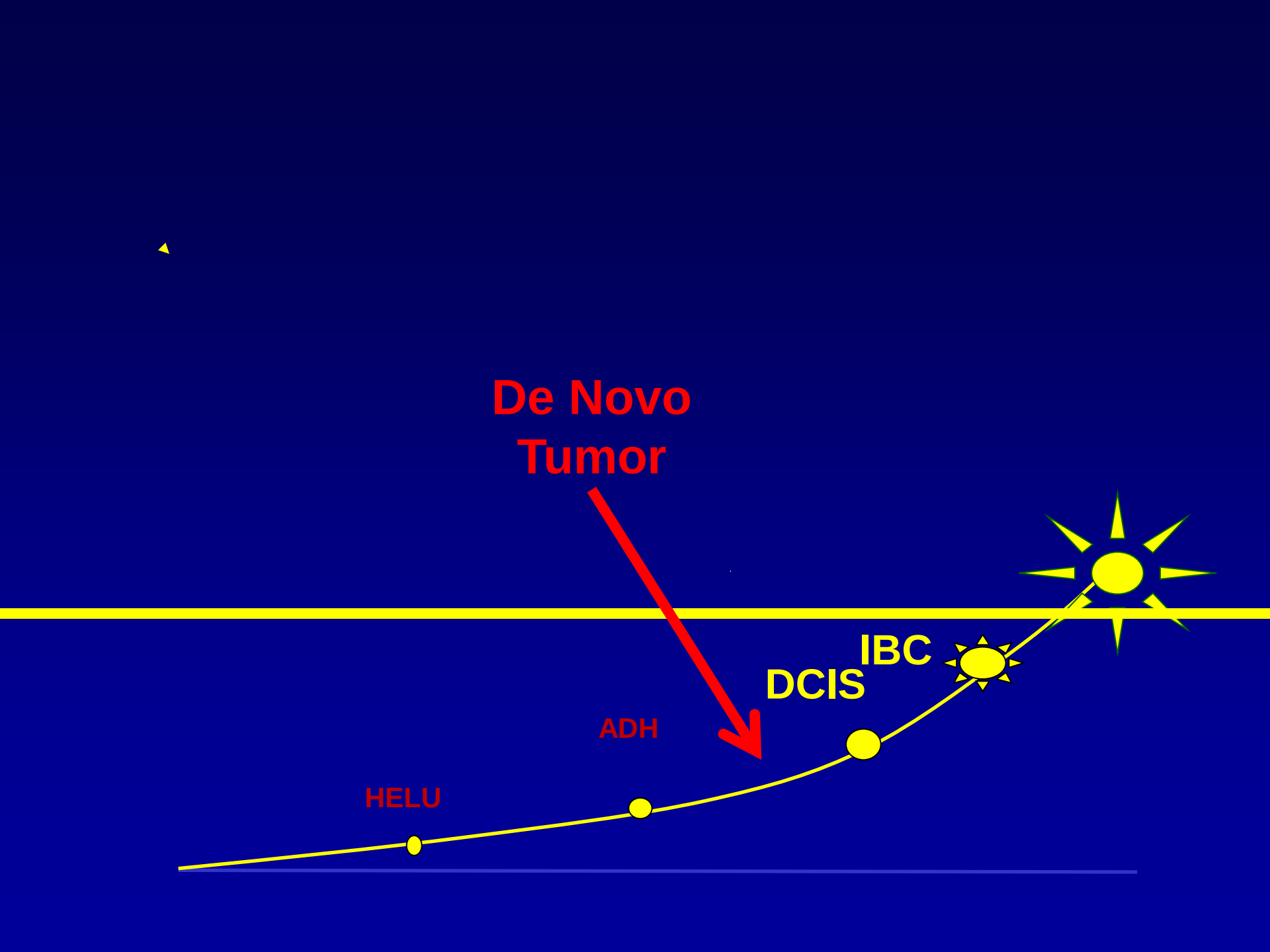

De Novo
Tumor
IBC
DCIS
ADH
HELU

Depends on the doubling time

It takes 30 doublings for a tumor to go from one cancerous cell to a tumor of a billion cells, the number needed to reach a size of 1 cm in diameter

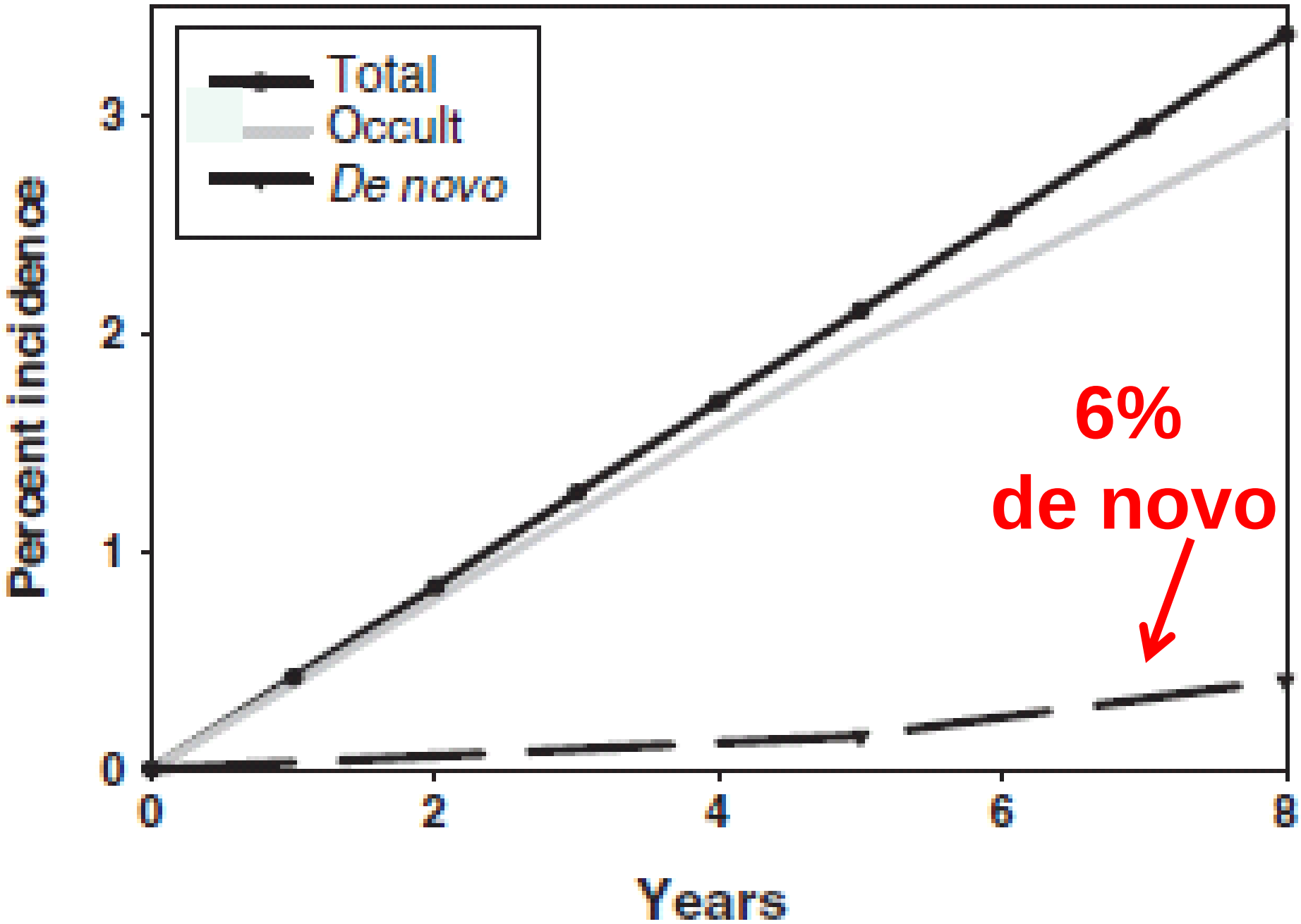
The average tumor doubling time in post-menopausal women is 200 days

How many de novo tumors would have reached the diagnostic threshold within the 5.6 year duration of the WHI E+P study ?


De Novo
Tumor
IBC
DCIS
ADH
HELU

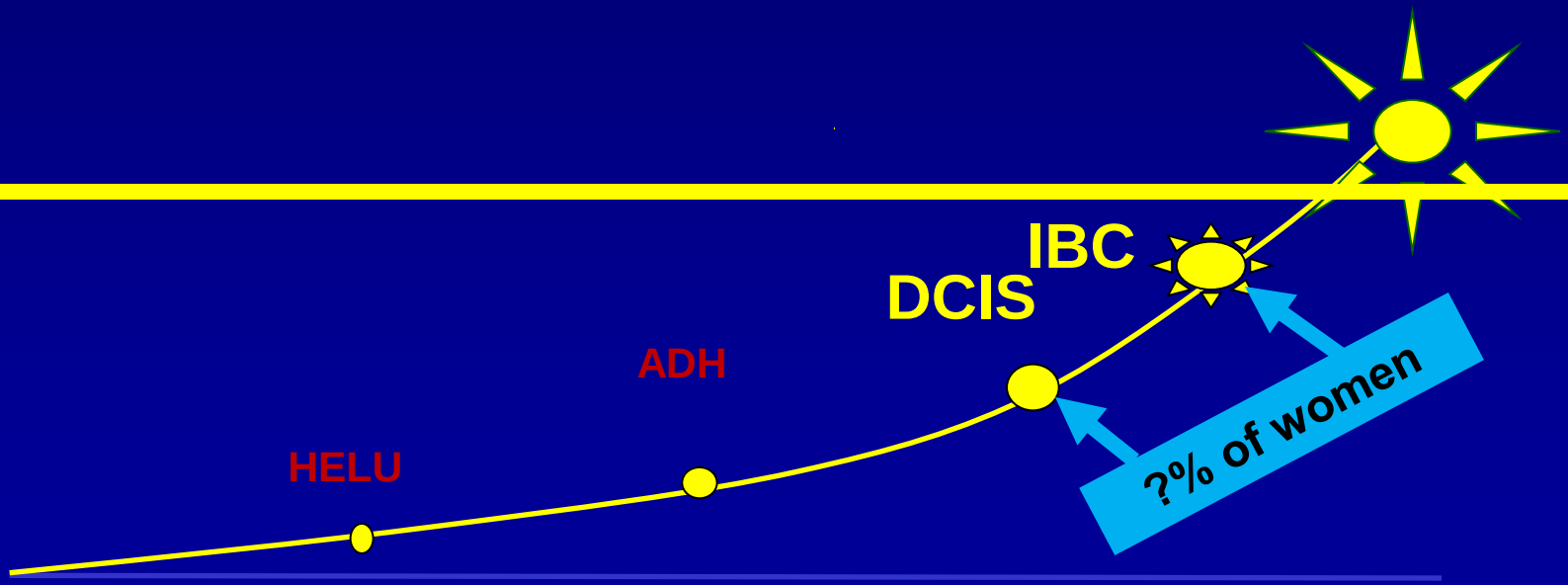
Only tumors with a doubling time of 50 days or less

94 % of tumors were pre-existing and only 6% de novo



Therefor nearly all of the effects
of menopausal hormone therapy in the WHI
were on pre-existing occult tumors

What was prevalence of pre-existing, occult tumors at start of WHI Study?



Occult breast cancers diagnosed at autopsy Ages 40-80

TABLE 9. Incidence of breast cancer in autopsy studies of women not known to have breast cancer

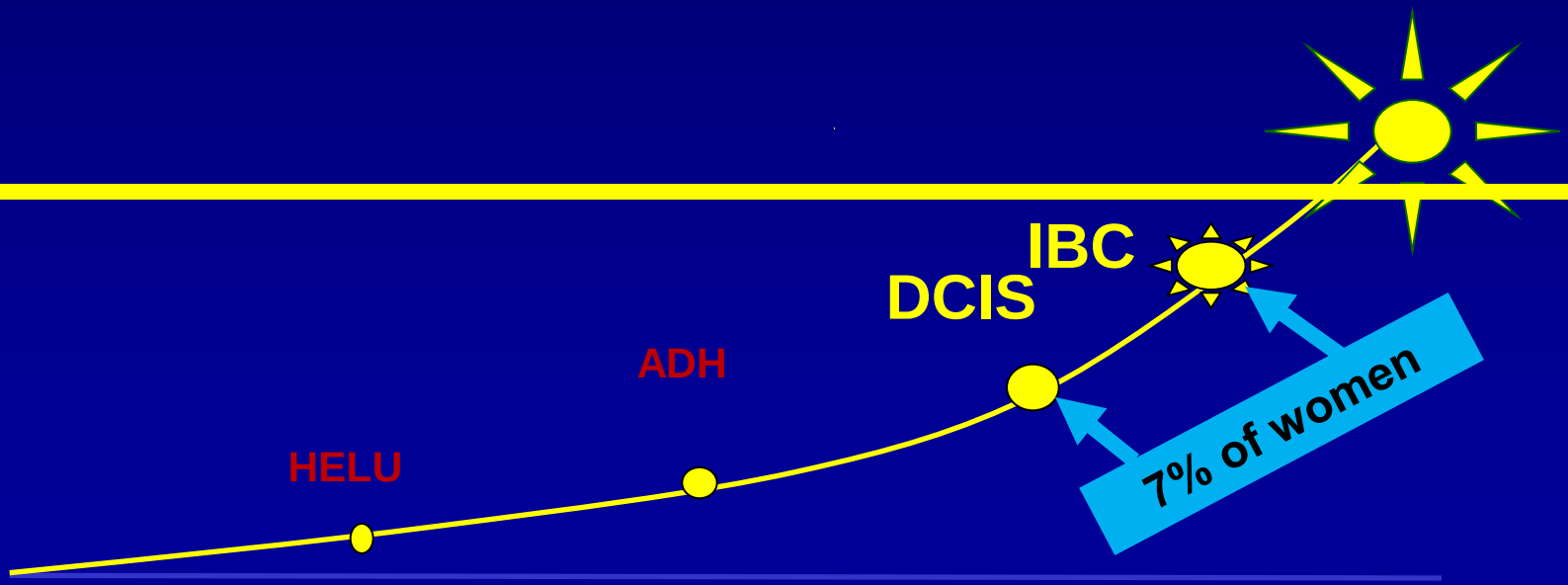
Author	No. of cases	Autopsy setting	% Occult DCIS (all ages)	% Occult IBC (all ages)	% Occult DCIS or IBC (age ≥40 yr)	Refs.
Ryan	200	Hospital	0	0	0% (40–100 yr)	214
Kramer	70	Hospital	4.3	1.4	4.3% (DCIS), 1.4% (IBC) (all >70 yr)	211
Wellings	67	Hospital	4.5	0	10% (DCIS) (50–70 yr)	206
Nielsen	77	Hospital	14.3	1.3	Not available	212
Alpers	101	Hospital	8.9	0	13% (DCIS) (40–70 yr)	208
Bhathal	207	Forensic	12.1	1.4	Not available	210
Bartow	221	Forensic	0	1.8	7% (IBC) (45–54 yr)	209
Nielsen	109	Forensic	14.7	0.9	39% (DCIS) (40–49 yr)	213

In Situ 6% **Invasive 1%** **Total 7%**

This is the same situation as for prostate cancer. At age 50, about 15% of men have prostate cancers too small to detect.

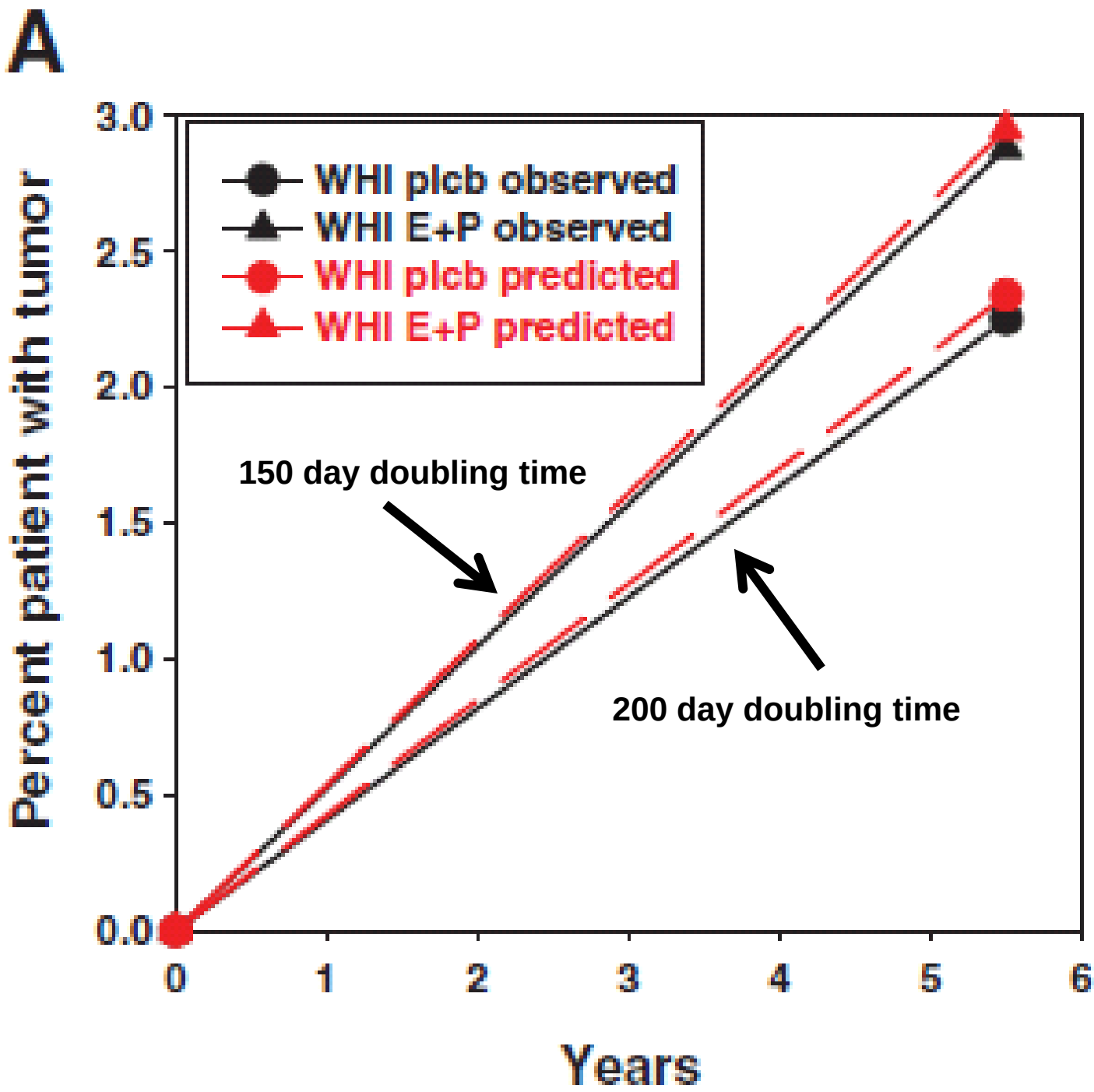
We then used our model to re-analyze the WHI data

Effect of estrogen plus a progestogen on these occult tumors



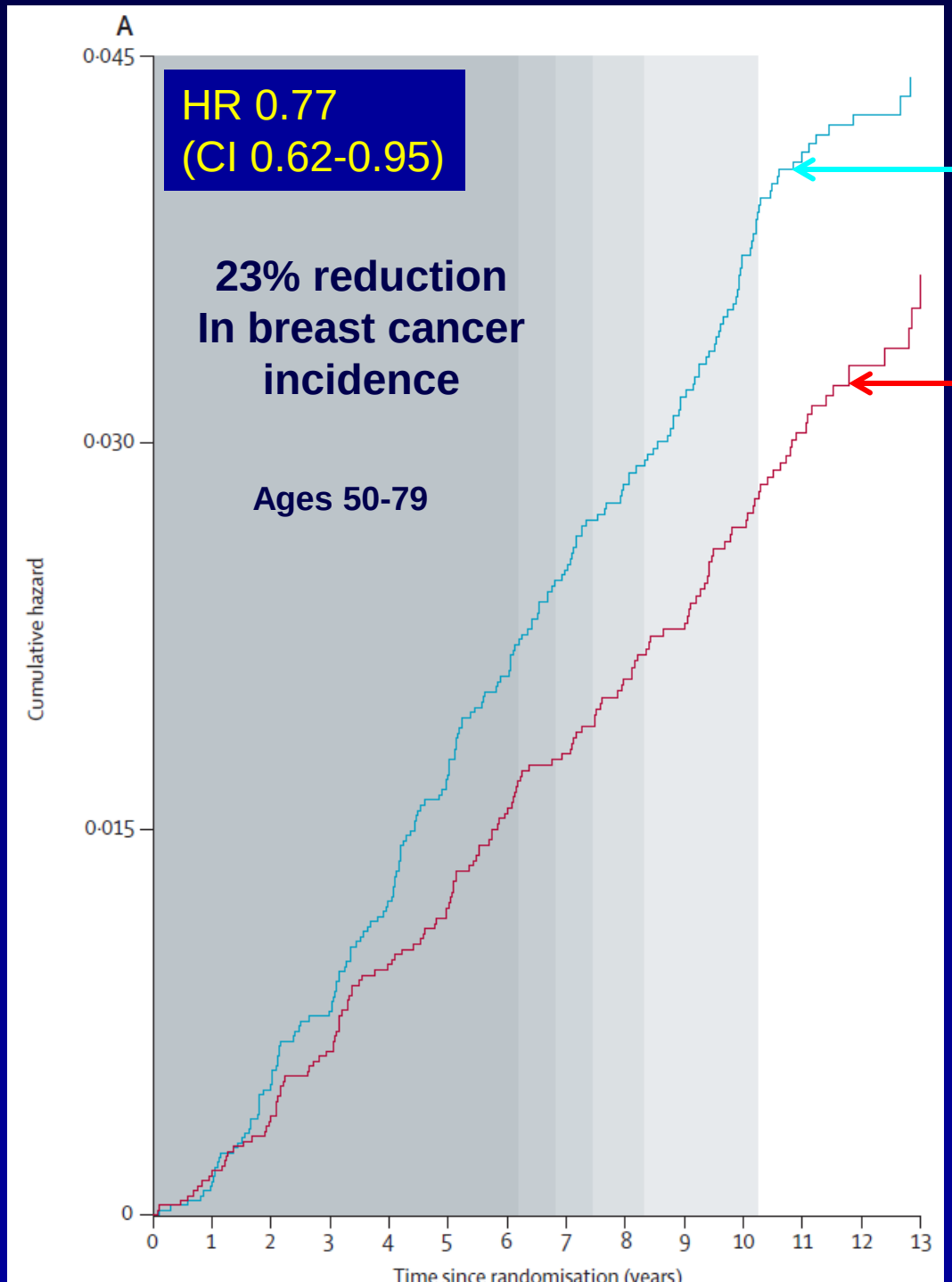
Estrogen plus a progestogen

- We assumed that this combination caused occult, pre-existing tumors to grow more rapidly
- We used our growth model to examine
- We examined the effects of tumor doubling times of 180 days, 150 days, and 120 days


A
Percent patient with tumor
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
Years
WHI plcb observed
WHI E+P observed
WHI plcb predicted
WHI E+P predicted
150 day doubling time
200 day doubling time

How do we explain the effects of estrogen alone?

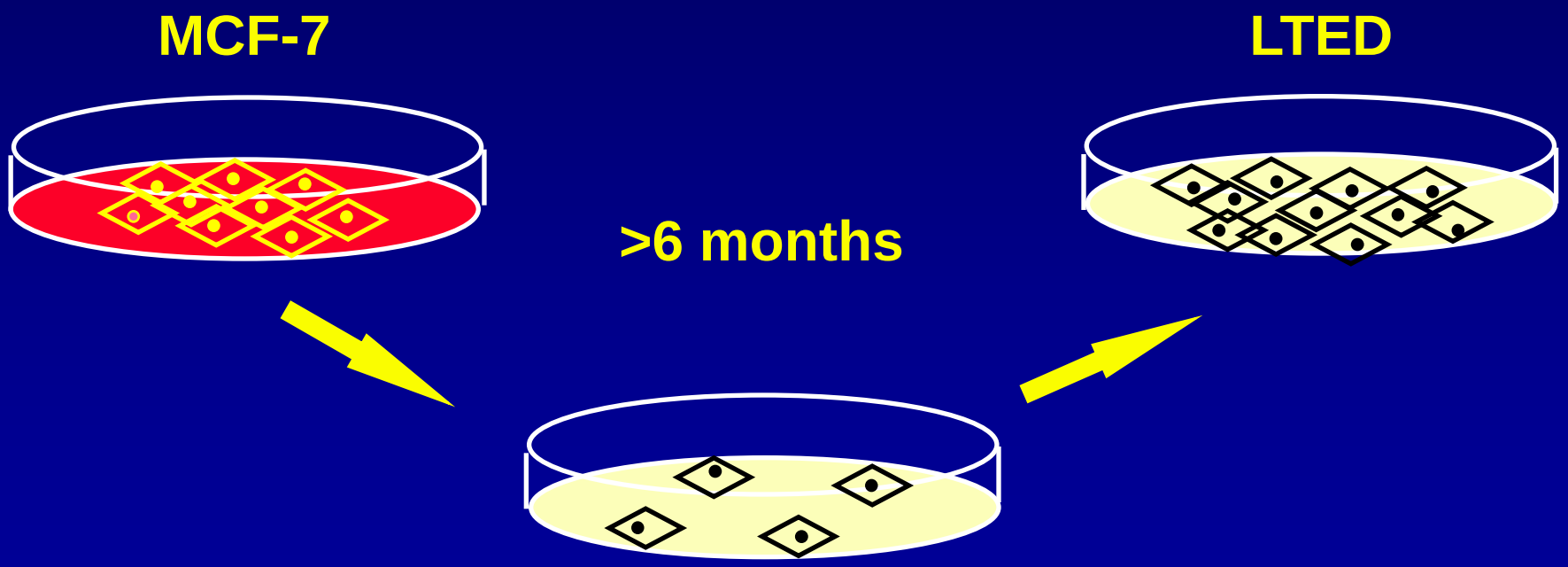
CEE alone arm of the WHI


A
0·045
0·030
0·015
0
Cumulative hazard
HR 0.77
(CI 0.62-0.95)
23% reduction
In breast cancer
incidence
Ages 50-79
placebo
CEE
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Time since randomisation (years)

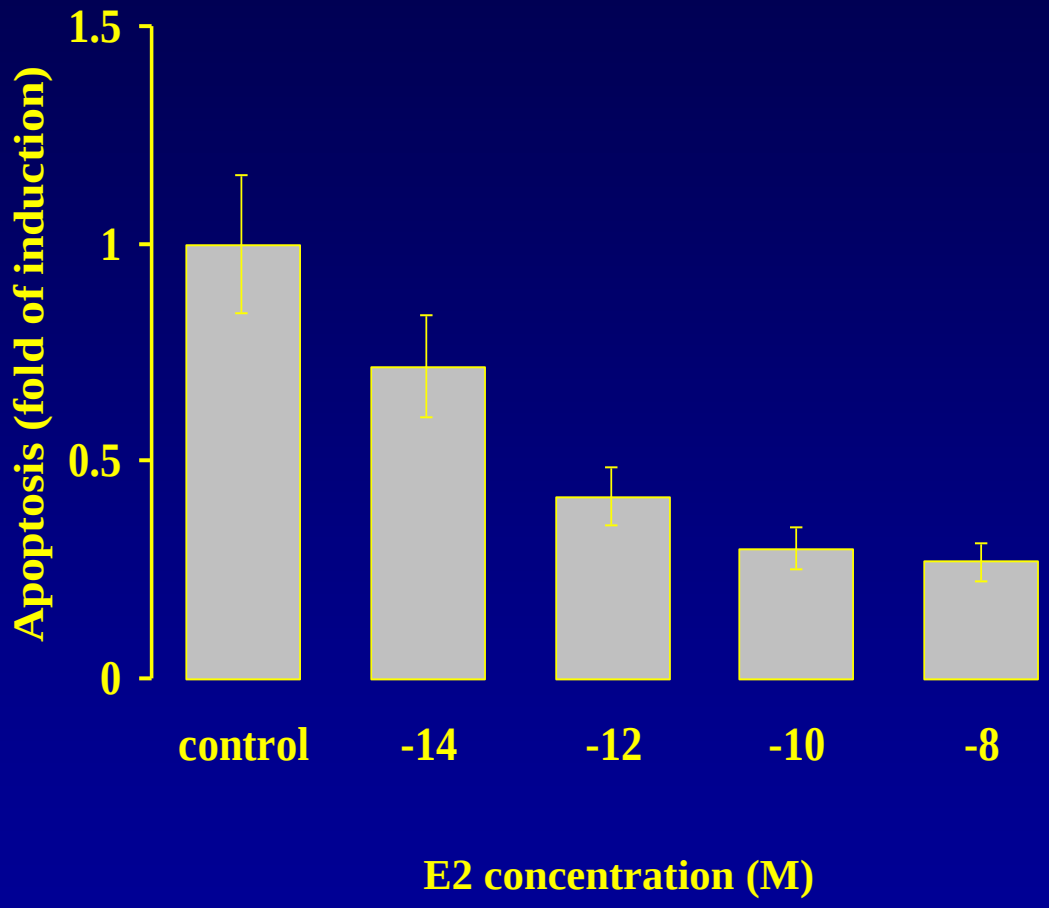
Hypothesis

- Conjugated equine estrogens caused apoptosis of occult tumors
- Long term deprivation of estrogen causes breast cancer cells to undergo apoptosis in response to estrogen
- The average age of women in the WHI was 63, 12 years after the average age of menopause

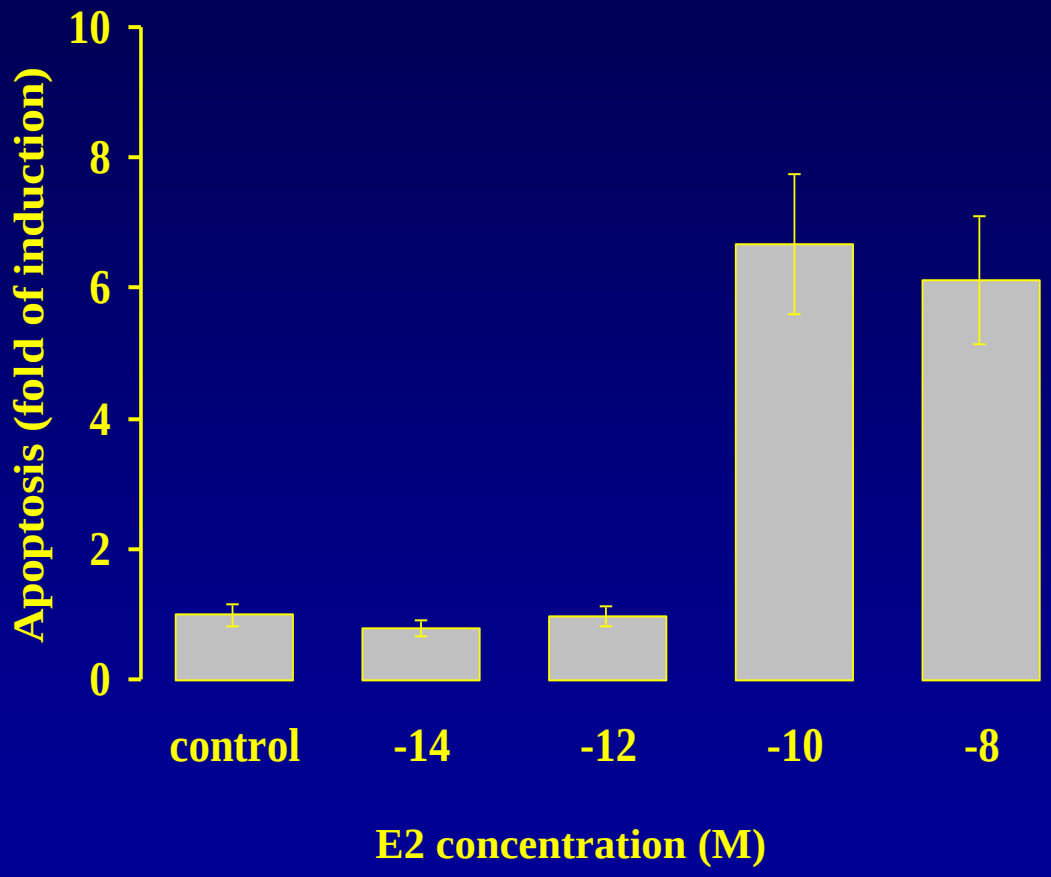
In Vitro Model of Long Term Estrogen Deprivation



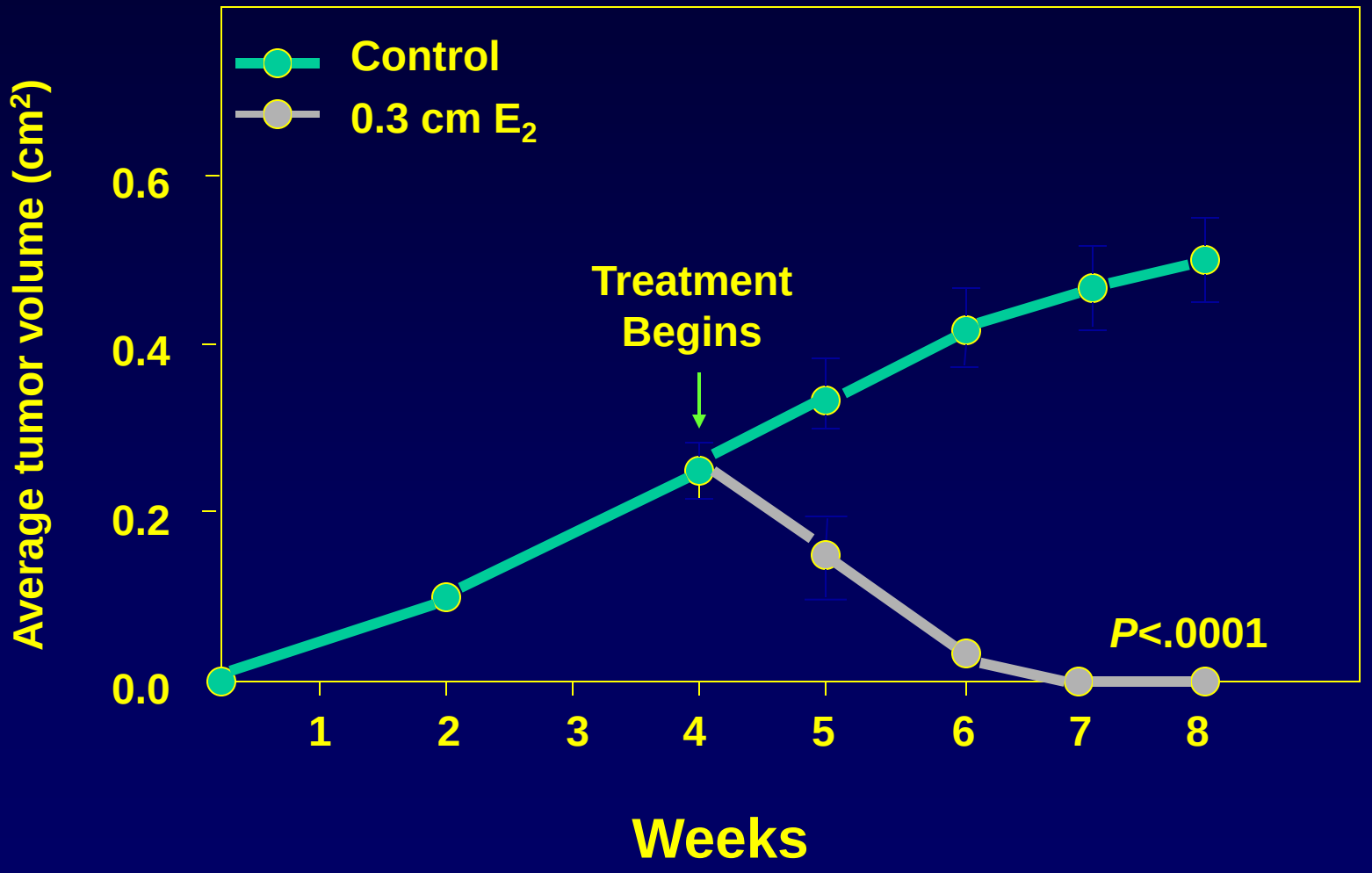
Wild Type Cells



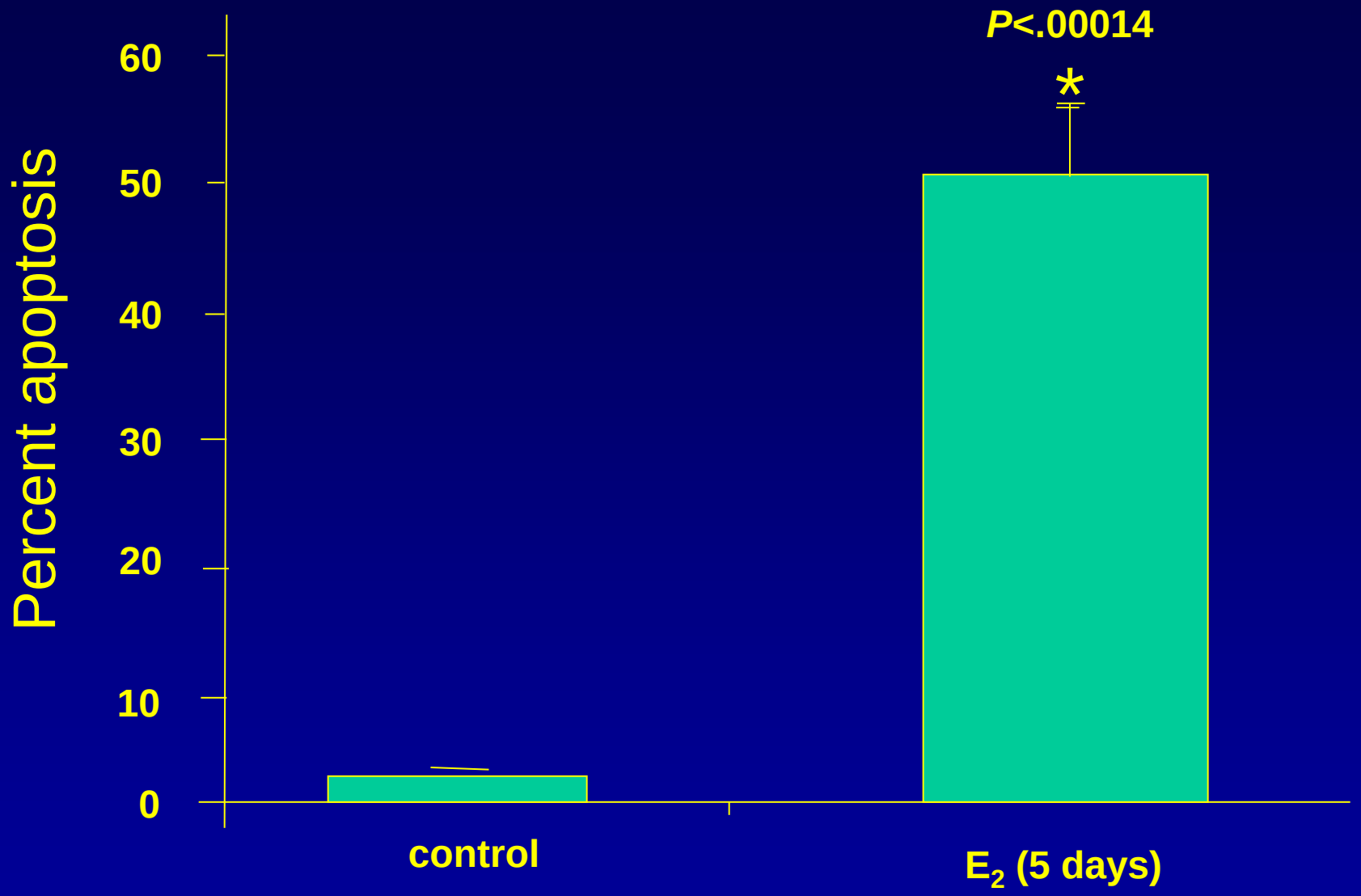
LTED Cells


Apoptosis (fold of induction)
10
8
6
4
2
0
control
-14
-12
-10
-8
E2 concentration (M)

Long term anti-estrogen treated xenografts

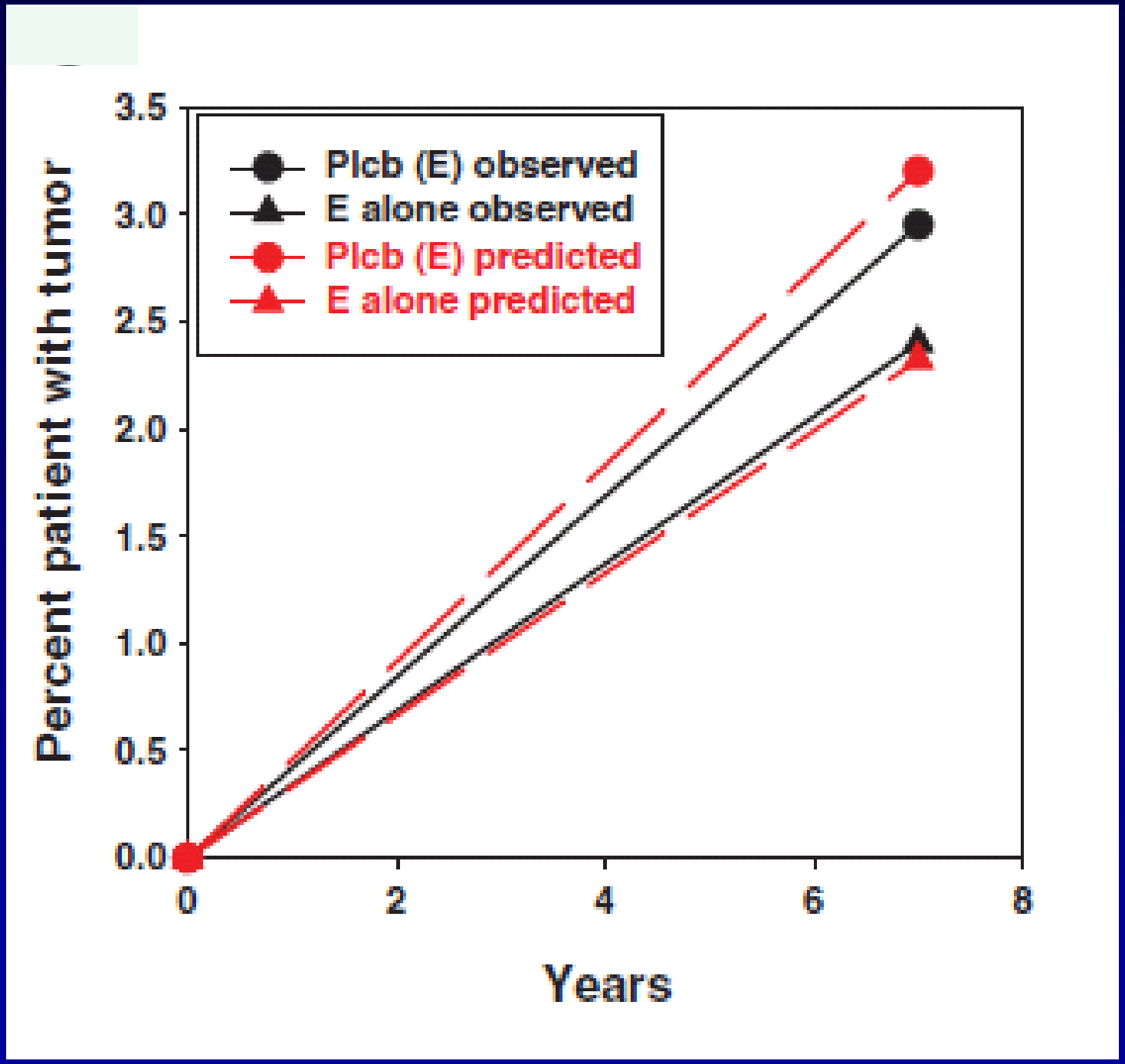


Data of VC Jordan



Jordan et al

Model based on apoptosis used to predict effect of estrogen alone on breast cancer risk


Plcb (E) observed
E alone observed
Plcb (E) predicted
E alone predicted
Percent patient with tumor
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
2
4
6
8
Years

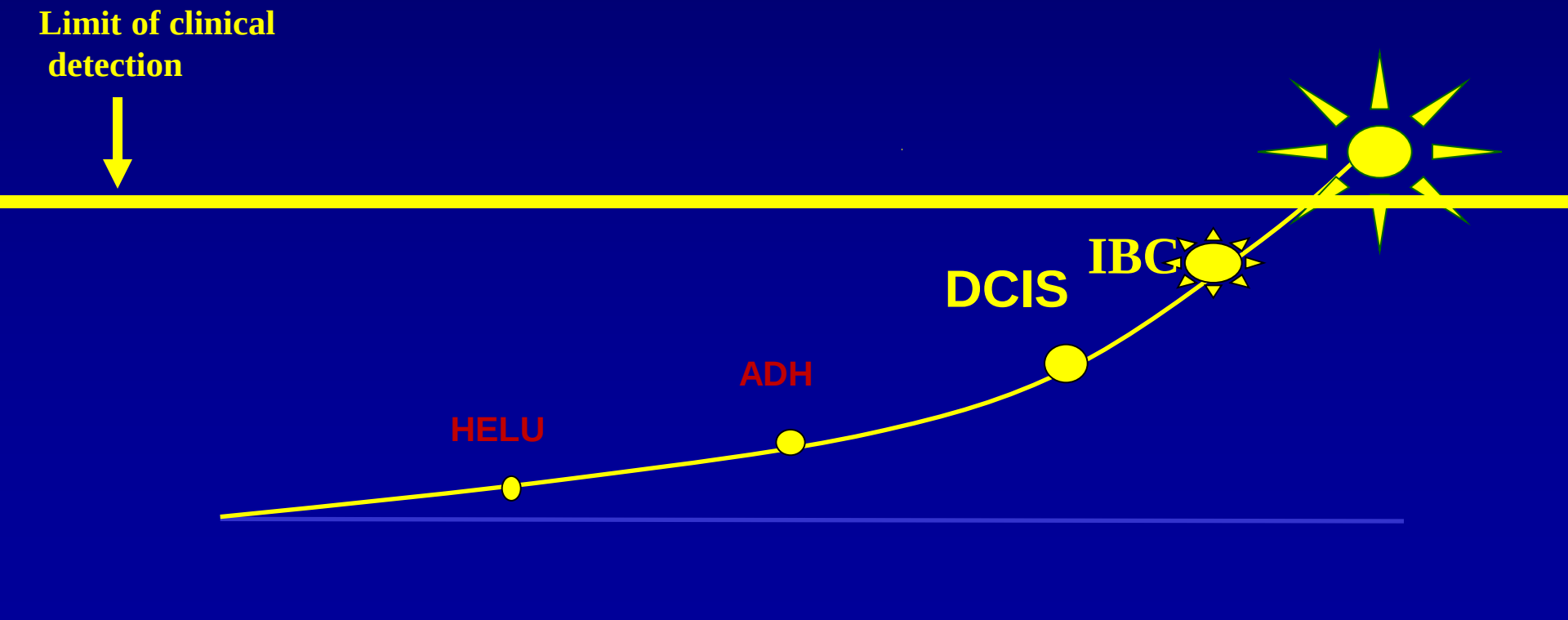
Historical Footnote

- High dose estrogen was used to treat metastatic breast cancer
- Only effective in women at least 5 years postmenopausal
- Recent studies indicate that physiologic doses of estradiol also cause tumor regression in 30% of postmenopausal women with metastatic breast cancer

Implications

- Need to treat these occult breast cancer lesions before they become clinically detectable
- A form of hormone therapy for menopausal women which prevents these occult lesions from growing but relieves menopausal symptoms would be ideal

Treatment before diagnostic threshold reached



Emerging approach

New class of hormonal agents

TSEC

(tissue selective estrogen complex)

TSEC

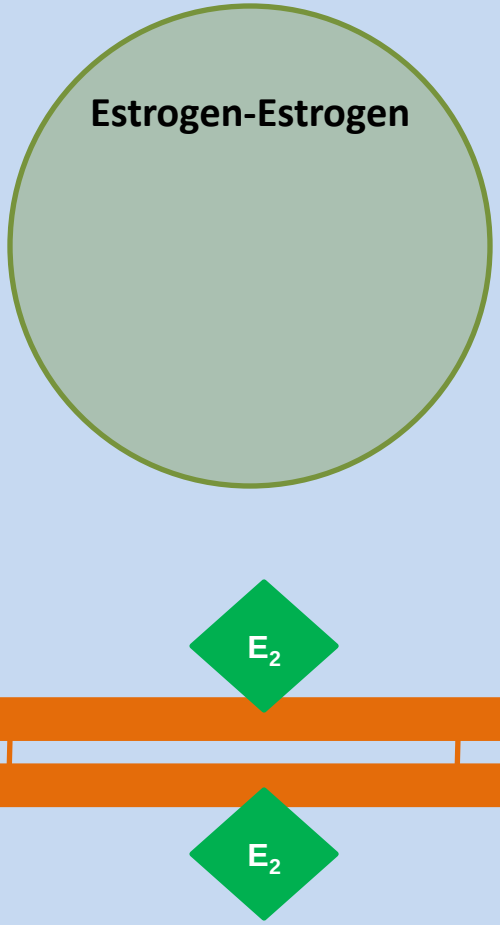
- A combination of a SERM (selective estrogen receptor modulator) plus an estrogen
- A new combination approved in USA –the SERM bazedoxifene in combination with conjugated equine estrogen
- Treats symptoms of menopause but is breast neutral
- 7000 women studied in clinical trials

BZA/CEE

- Avoids need to use a progestogen
- Treats hot flashes, vulvovaginal atrophy, osteopenia/osteoporosis
- No uterine stimulation
- In underpowered trials, no cardiac disease or CVA and low incidence VTE
- Preclinical data—decrease in breast caner

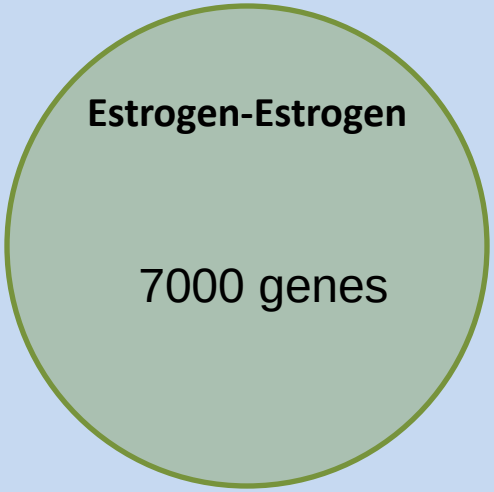
How does the TSEC work ?

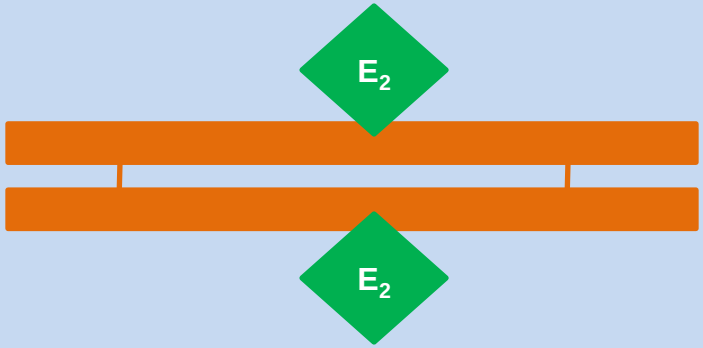
Gene Transcription



Estrogen receptor complex

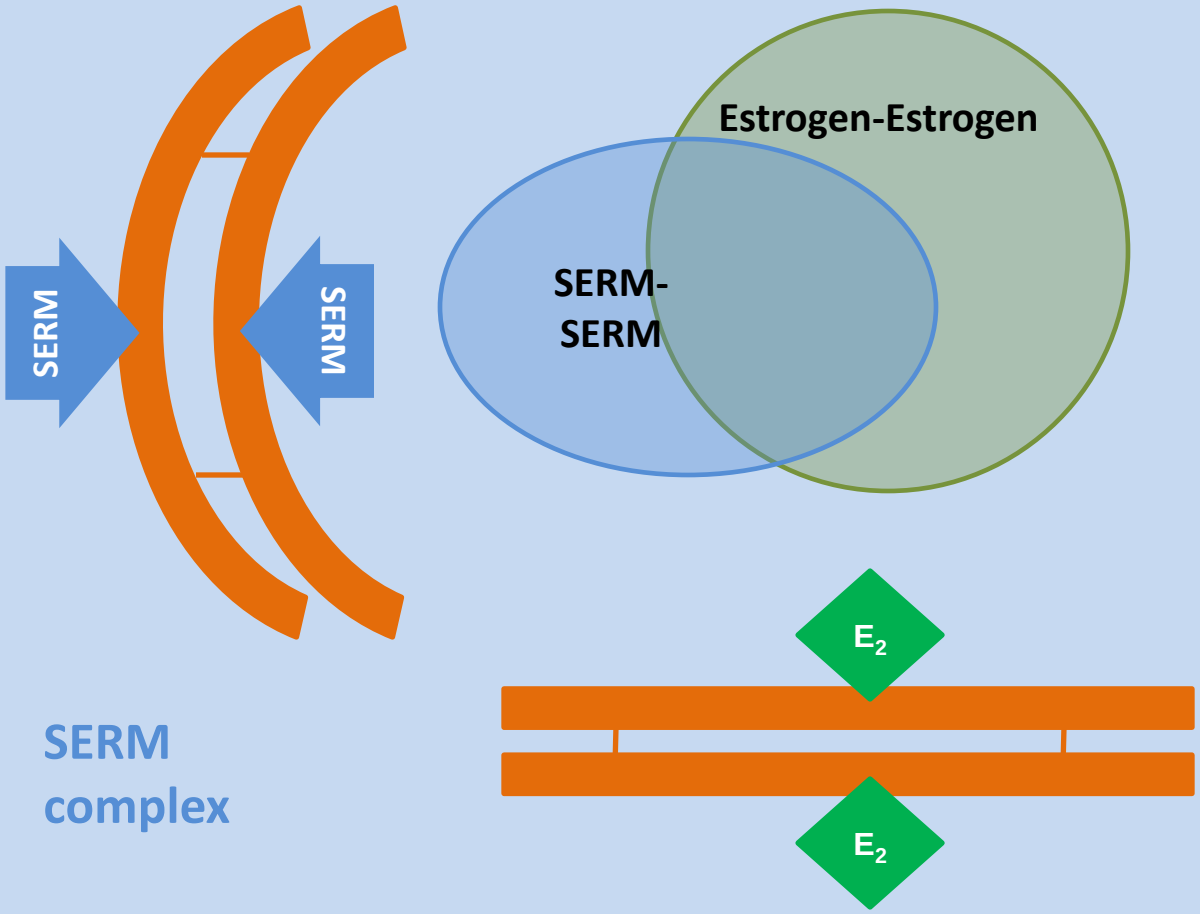
Gene Transcription





Estrogen receptor complex

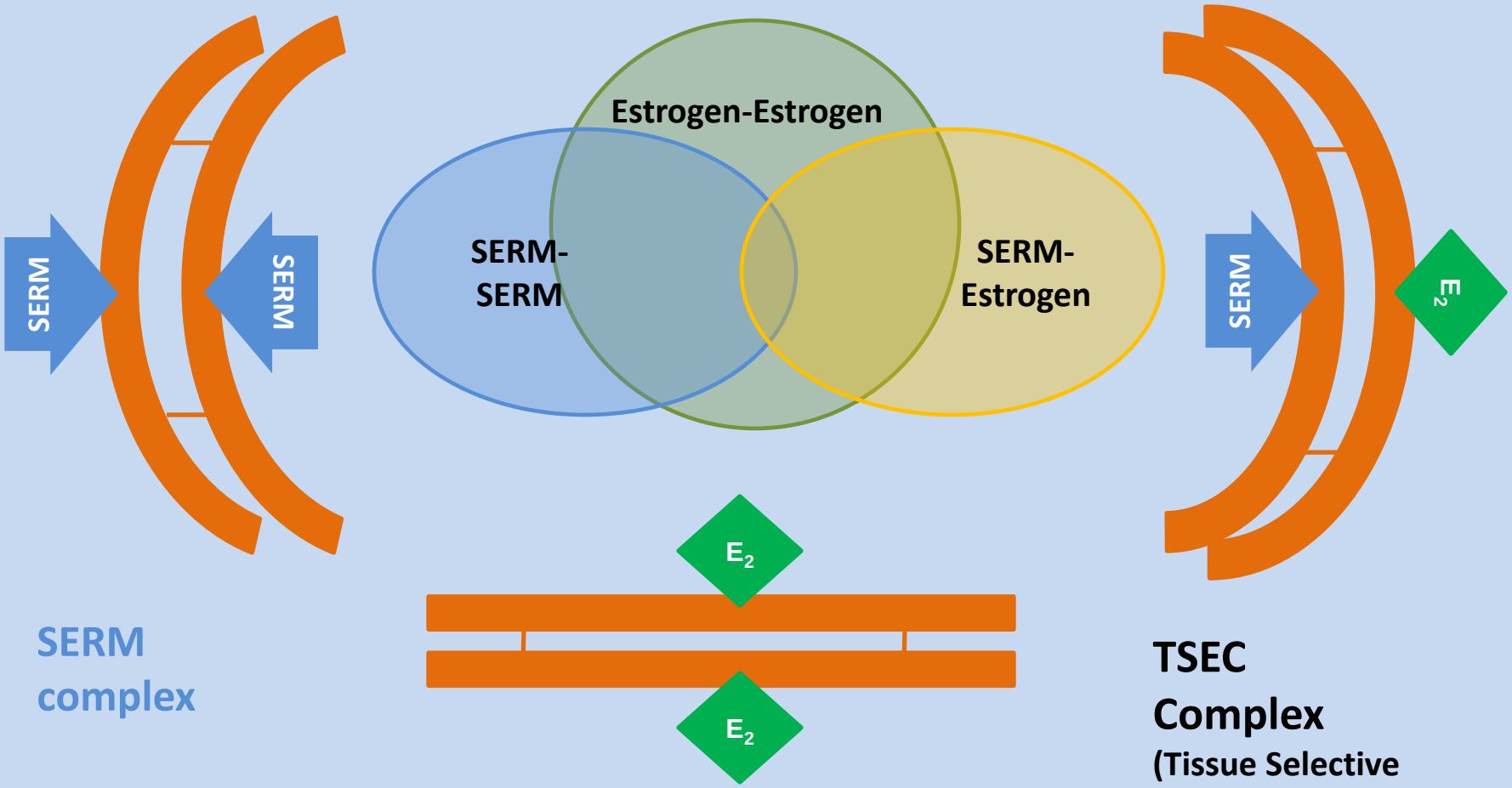
Gene Transcription



SERM complex

Estrogen receptor complex

Gene Transcription

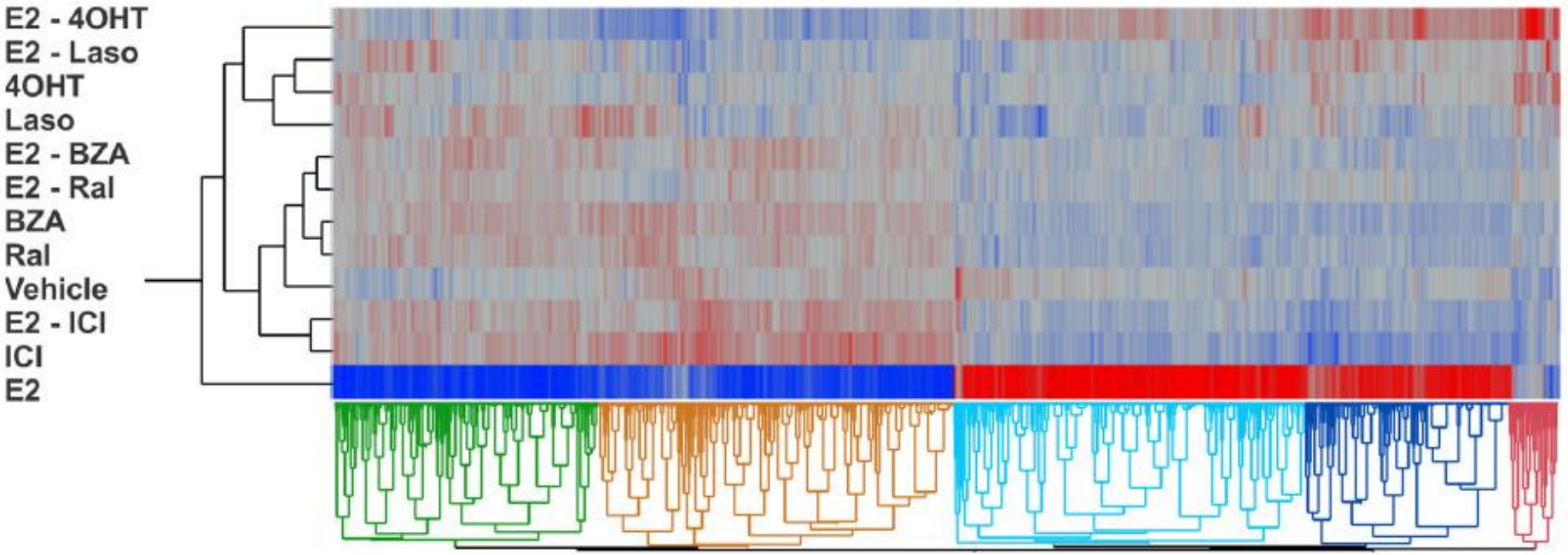


SERM complex

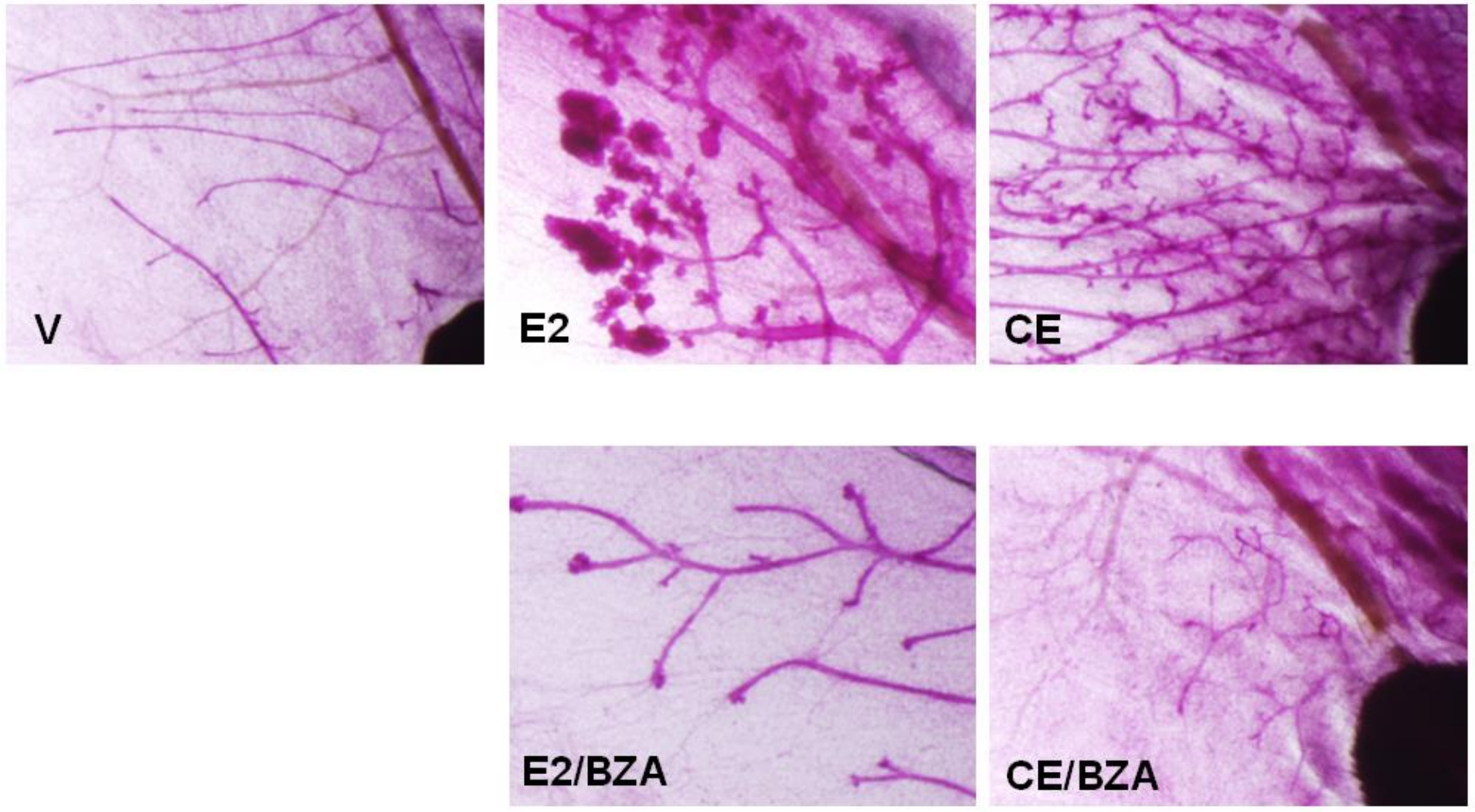
TSEC Complex (Tissue Selective estrogen complex)

Estrogen receptor complex

Wardell SE and McDonnell D
Mol Endo 26:1235-1248,2012



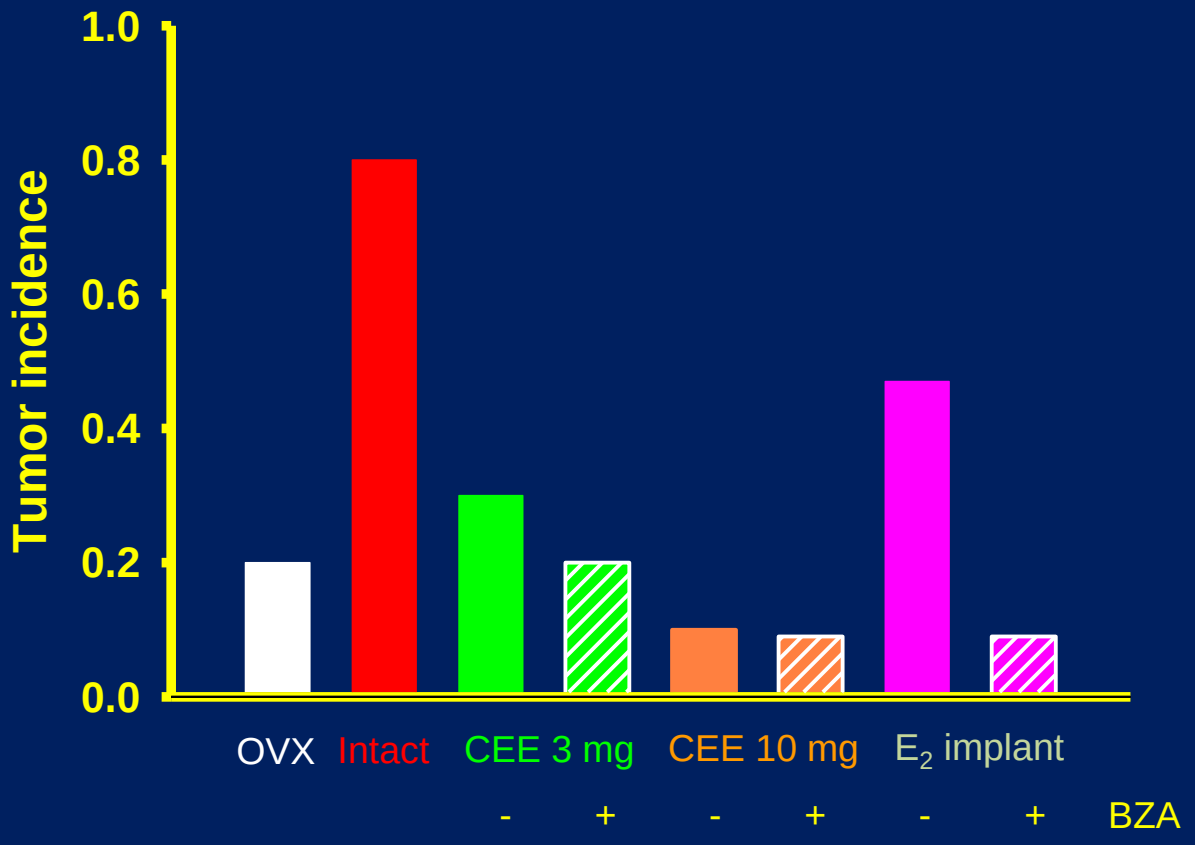
Effects on immature mouse breast



The effects of the TSEC on breast are anti-estrogenic

Carcinogen Induced Tumor Model

(Sprague Dawley Rats, 50 days of age)


Tumor incidence
1.0
0.8
0.6
0.4
0.2
0.0
OVX
Intact
CEE 3 mg
CEE 10 mg
E2 implant
-
+
-
+
-
+
BZA

Summary

- Menopausal hormone therapy with E + P does not cause breast cancer but stimulates the growth of pre-existing small occult tumors.
- E alone reduces risk of breast cancer due to apoptosis
- Emerging therapies are being developed to improve safety with respect to the breast

Conclusions

- The benefits of menopausal hormone therapy outweigh the risks in most women just entering menopause
- Before recommending menopausal hormone therapy, determine the underlying risk of breast cancer and don't recommend if a woman is at moderate or high risk of breast cancer
- TSECs may be used to eliminate the need for a progestogen and may be safer on the breast

Thank you
for your attention