

24 GIUGNO 2015
**CARCINOMA MAMMARIO:
quando la DONNA
è GIOVANE**

Presidente: Dr.ssa **Stefania Gori**

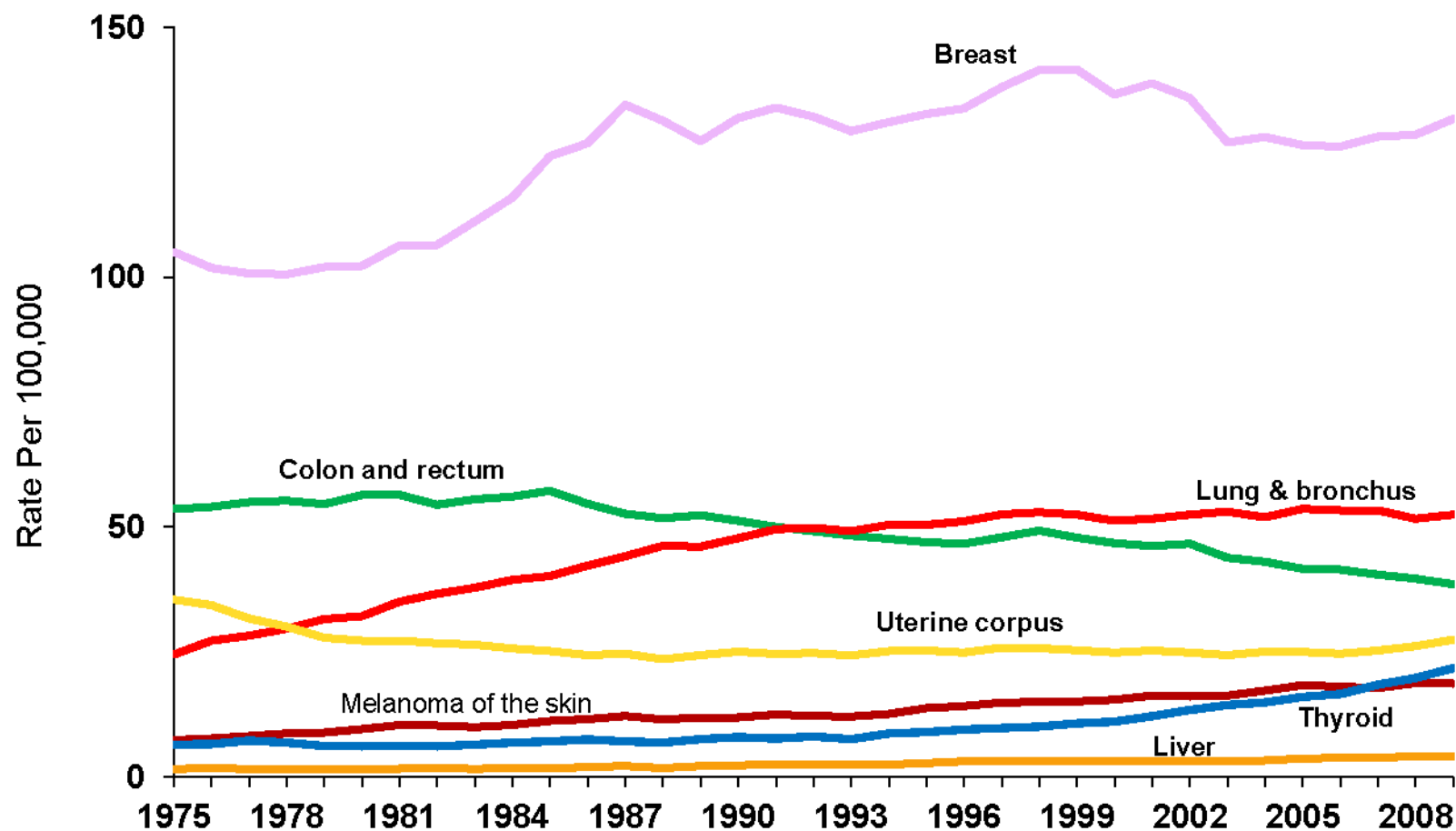
CENTRO FORMAZIONE
**Ospedale Sacro Cuore - Don Calabria
NEGRAR**

con il patrocinio di  **GOIRC**
GRUPPO ONCOLOGICO ITALIANO
DI INFERENZA CLINICA

Epidemiologia, Fattori di Rischio, Stili di Vita

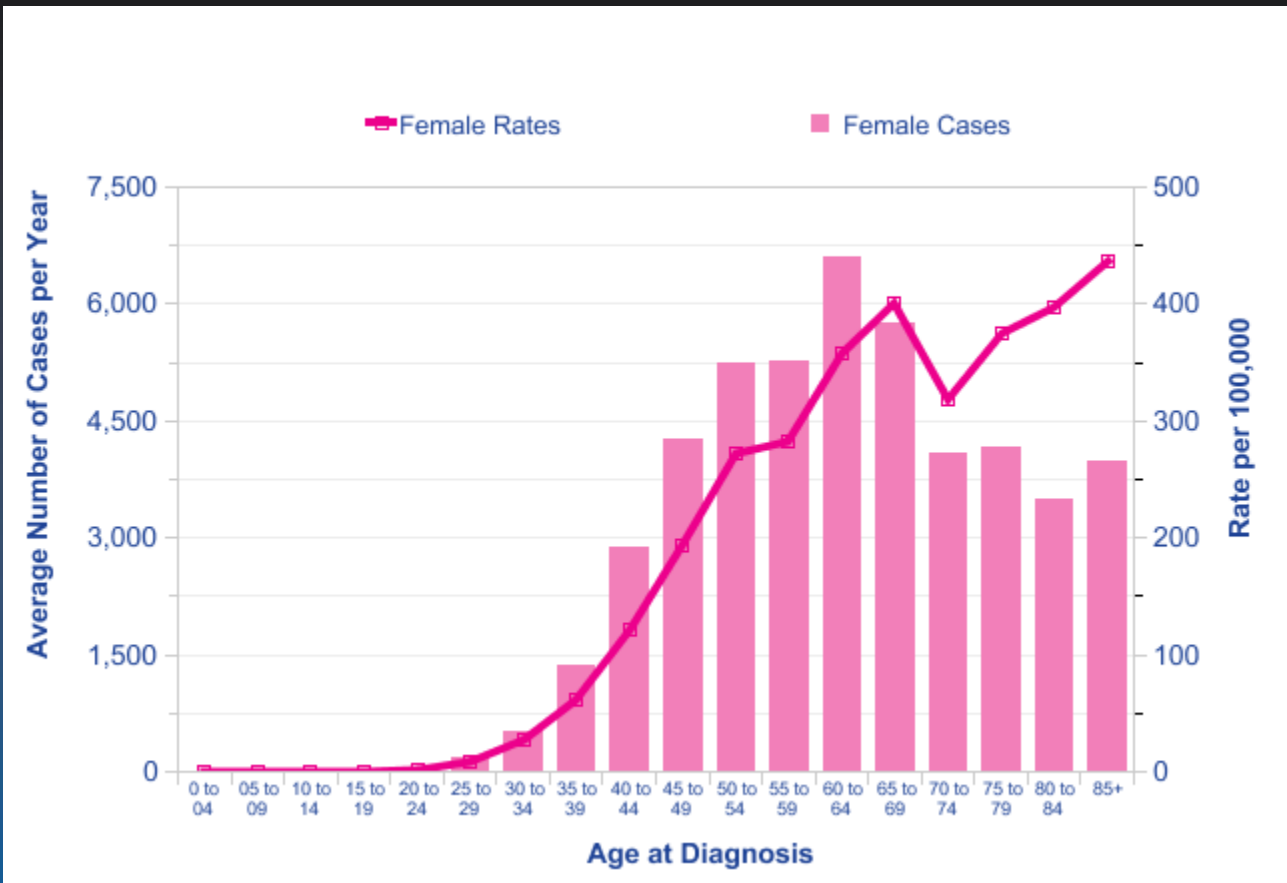
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Cancer Incidence Rates* Among Women, US, 1975-2009



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

Incidence of Breast Cancer by Age

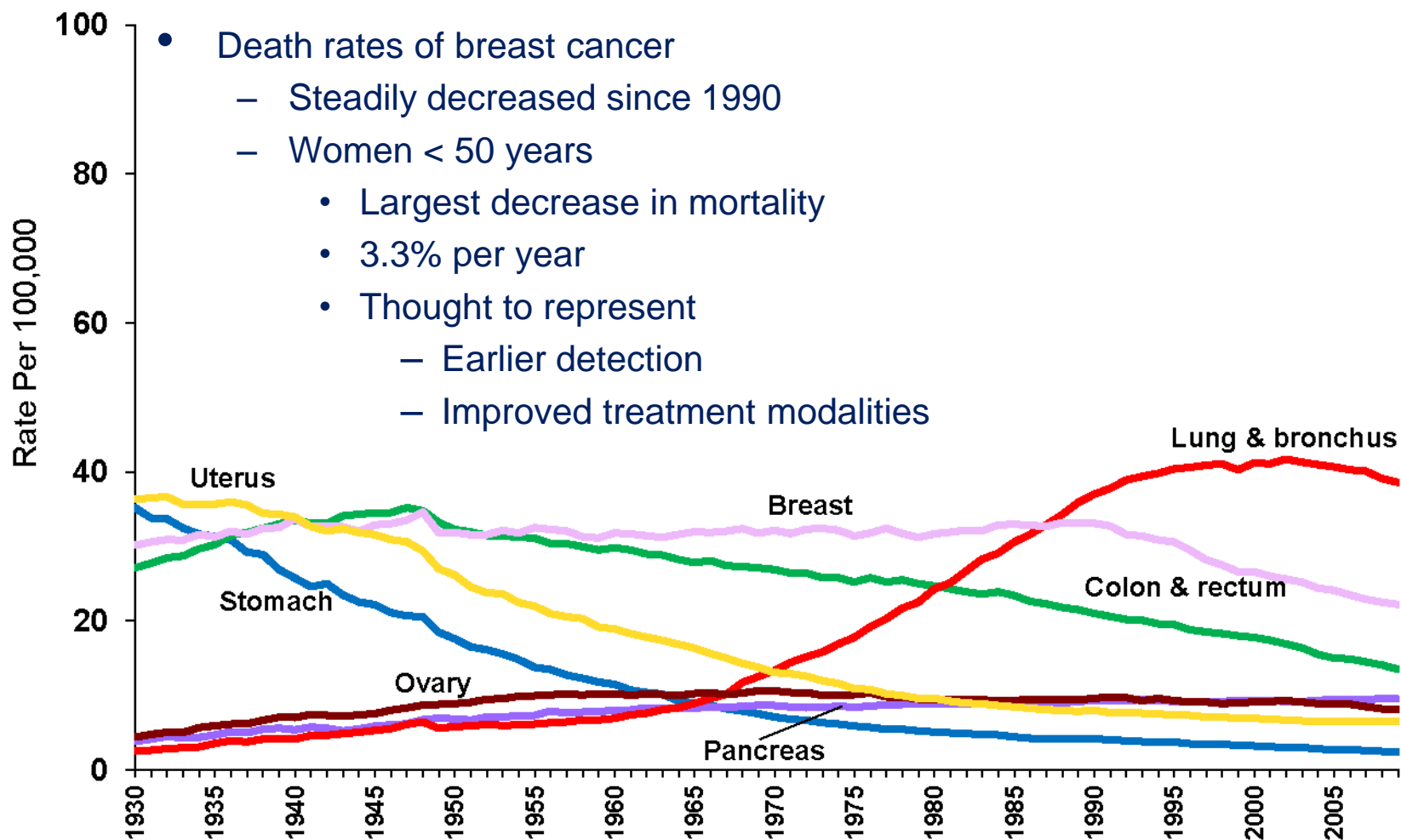


Breast Cancer is the Most Common Cancer in Women Starting at Age 30

Top 5 Cancers by Age Group

15-19	20-24	25-29	30-34	35-39
Testis	Testis	Testis	Breast / Testis	Breast
Hodgkin Lymphoma	Thyroid	Thyroid	Thyroid	Thyroid
Leukemia	Hodgkin Lymphoma	Melanoma	Cervix Uteri	Cervix Uteri
Brain and Other CNS / Thyroid	Melanoma	Cervix Uteri	Melanoma	Melanoma
Non-Hodgkin Lymphoma	Leukemia	Breast	Non-Hodgkin Lymphoma	Testis

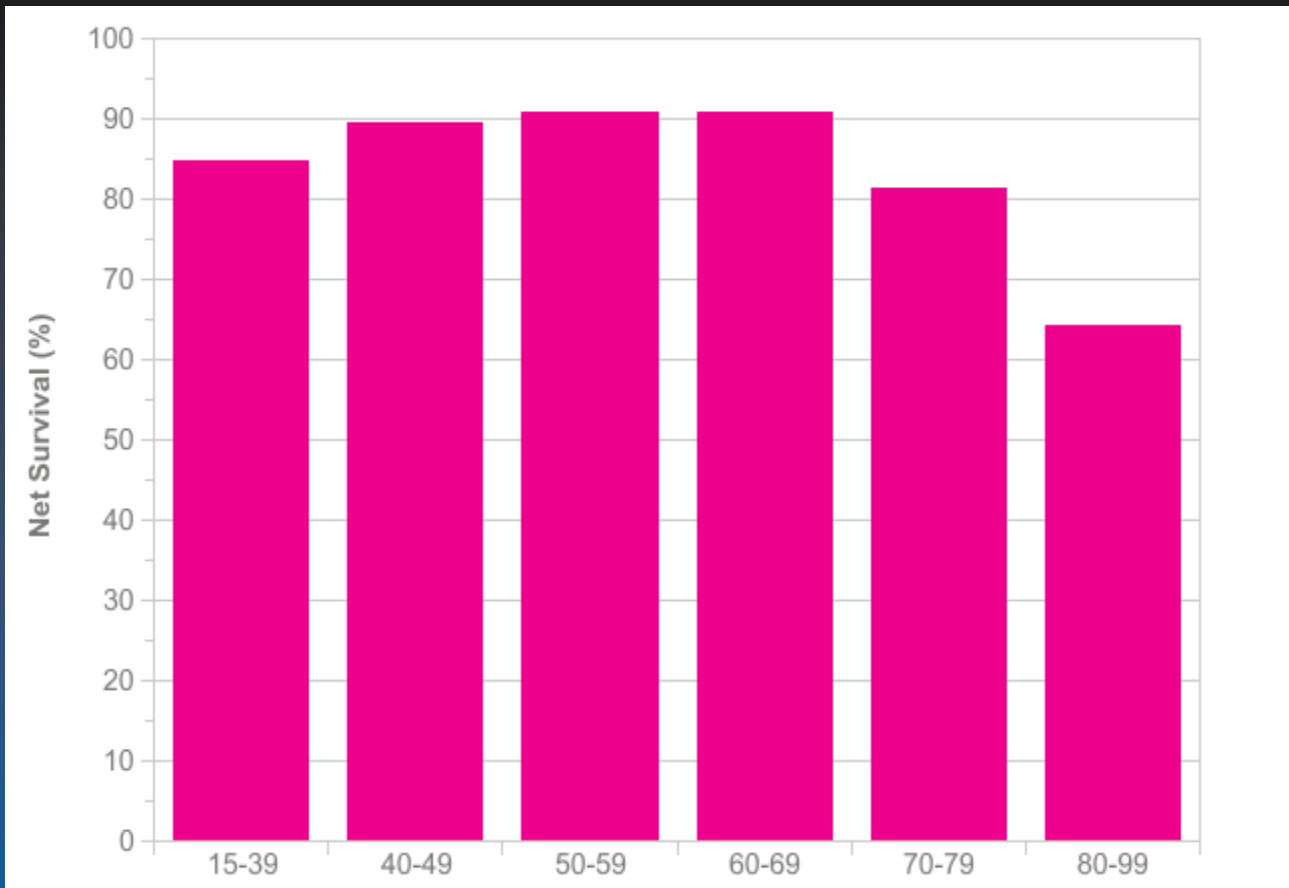
Cancer Death Rates* Among Women, US, 1930-2009



*Age-adjusted to the 2000 US standard population.

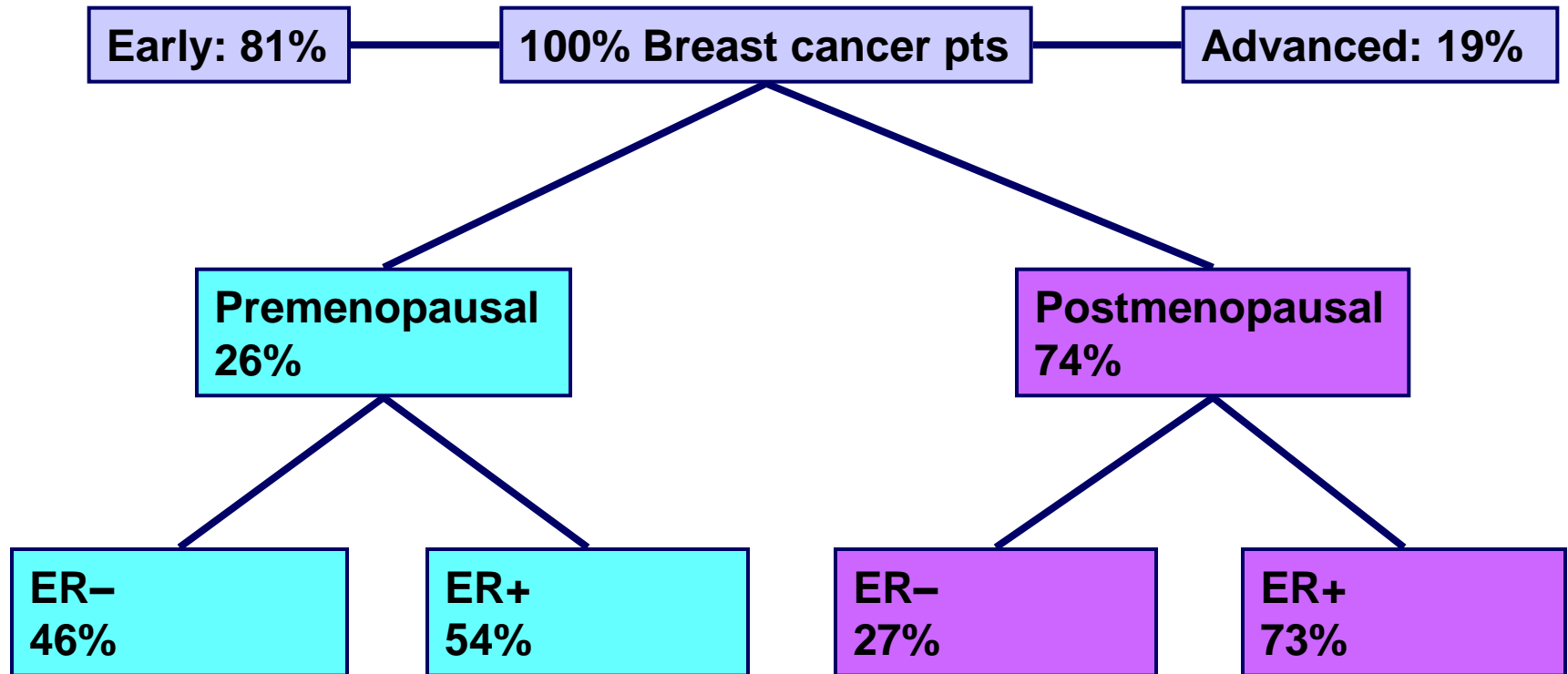
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

Survival of Breast Cancer by Age



www.cancerresearchuk.org/cancer-info/cancerstats/

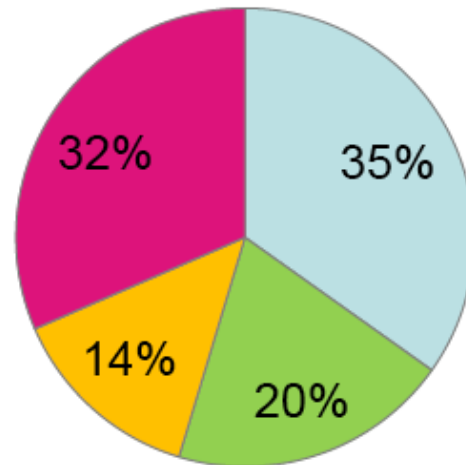
BREAST CANCER PATIENTS



~25% of breast cancer patients are pre-menopausal (15% pts <45 yrs) at the time of diagnosis

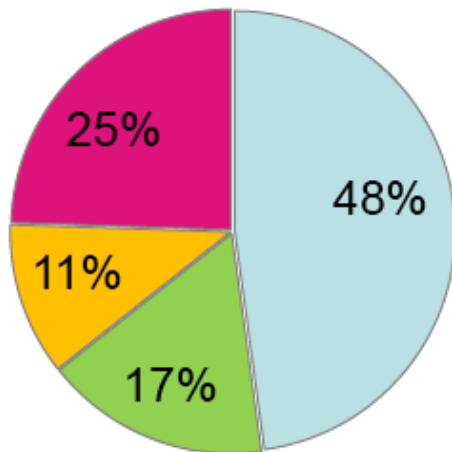
Breast Cancer Subtypes According to Age

≤ 35

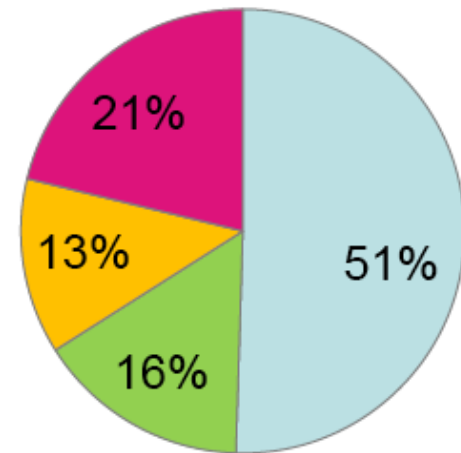


- HR+/HER2-
- HR+/HER2+
- HR-/HER2+
- TNBC

36-50



≥ 51



Long History of Studying Breast Cancer Causes

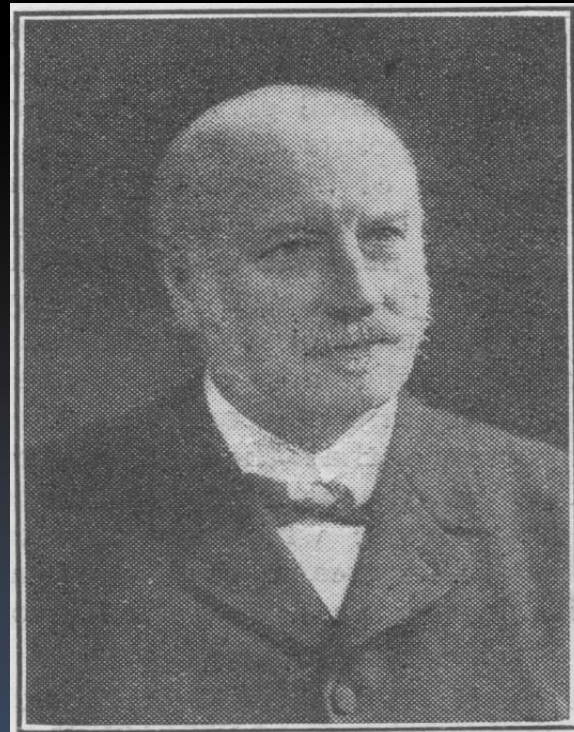
- 1850's family history
- 1920's reproductive risk factors
 - Lane-Clayton, 1926 case-control study
- 1950's menopause
- 1970 – onwards oral contraceptives, postmenopausal hormones, diet, physical activity, obesity, endogenous hormones, SERMs

Classics in Oncology

On The Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases

George Thomas Beatson, M.D.

Lancet 2:104-107, 1896.



It was clear to me that the changes that take place in the mammary gland in the process of lactation are almost identical, up to a certain point, with what takes place in a cancerous mamma.

Is cancer of the mamma due to some ovarian irritation, as from some defective steps in the cycle of ovarian changes; and if so, would the cell proliferation be brought to a standstill, or would the cells go on to the fatty degeneration seen in lactation were the ovaries to be removed?

Do We Know Causes of Breast Cancer?

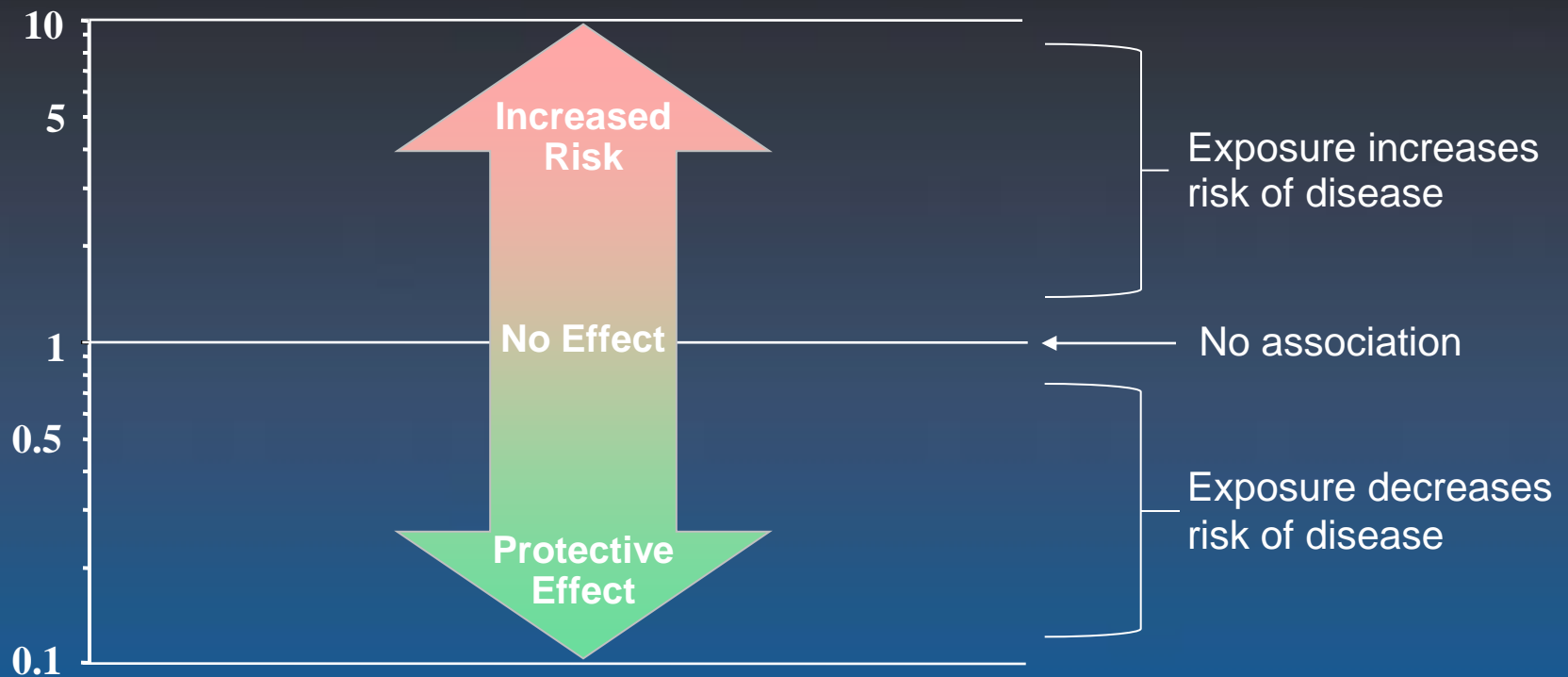
- At the population level:

$$\text{Relative Risk} = \frac{\text{Probability of developing condition X in exposed population}}{\text{Probability of developing condition X in unexposed population}}$$

Understanding Relative Risk

Risk Versus Protection

Relative Risk Log Scale



Risk factors

- Age
- Gender
- Family history
- Benign breast disease
- Reproductive factors
- Endogenous hormones
- Exogenous hormones
- Adiposity
- Diet
- Physical activity
- Alcohol
- Radiation

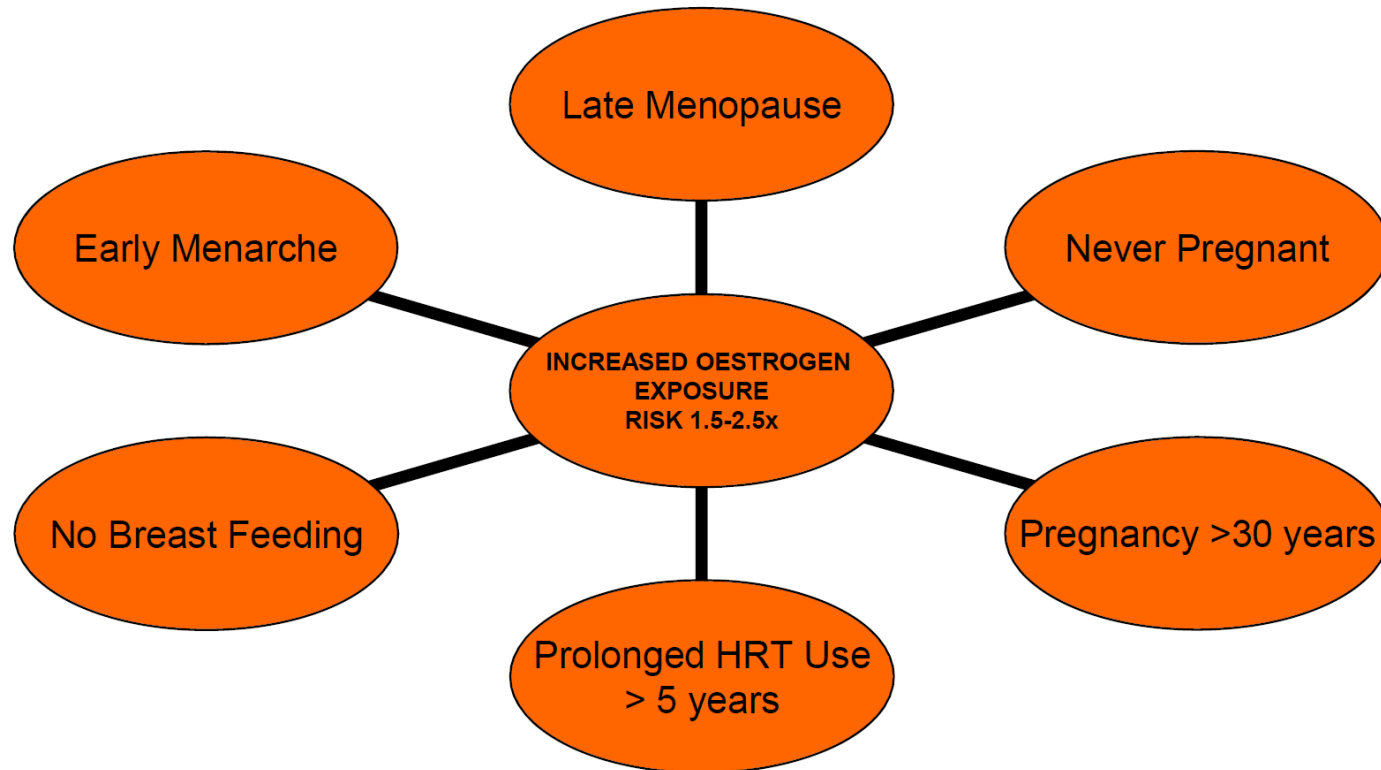
Age and Breast Cancer

- Cumulative incidence:

By Age 45	By Age 70
1.19%	9.67%

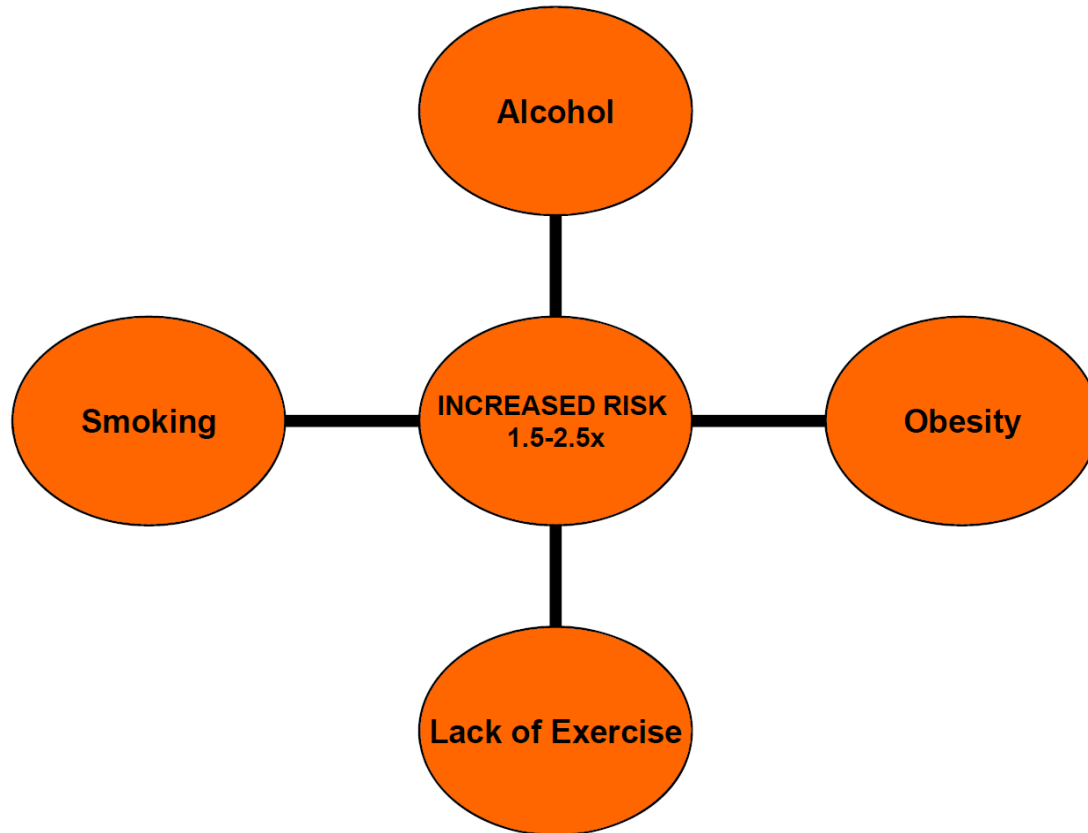
- Relative risk (≥ 50 vs. < 50 yr): **6.5**

Hormonal risk factors



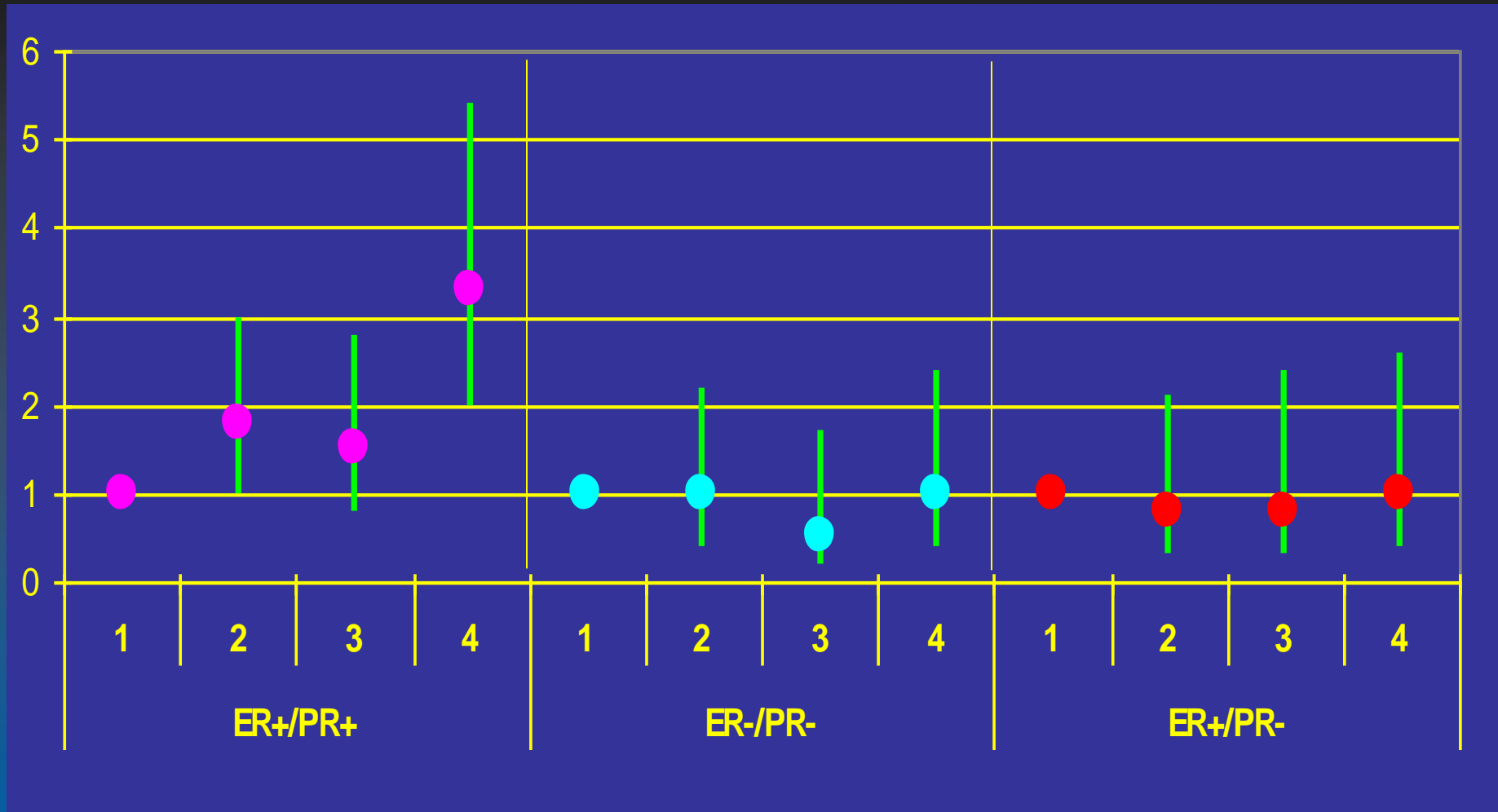
- Oral contraceptives (OCs)
 - 1.25 increased risk among current users of OCs
 - Risk appears to decrease
 - As age and time from oral contraceptive discontinuation increases
 - Breast cancer risk returns to that of the average population after approximately 10 years following cessation of oral contraceptives

Lifestyle risk factors

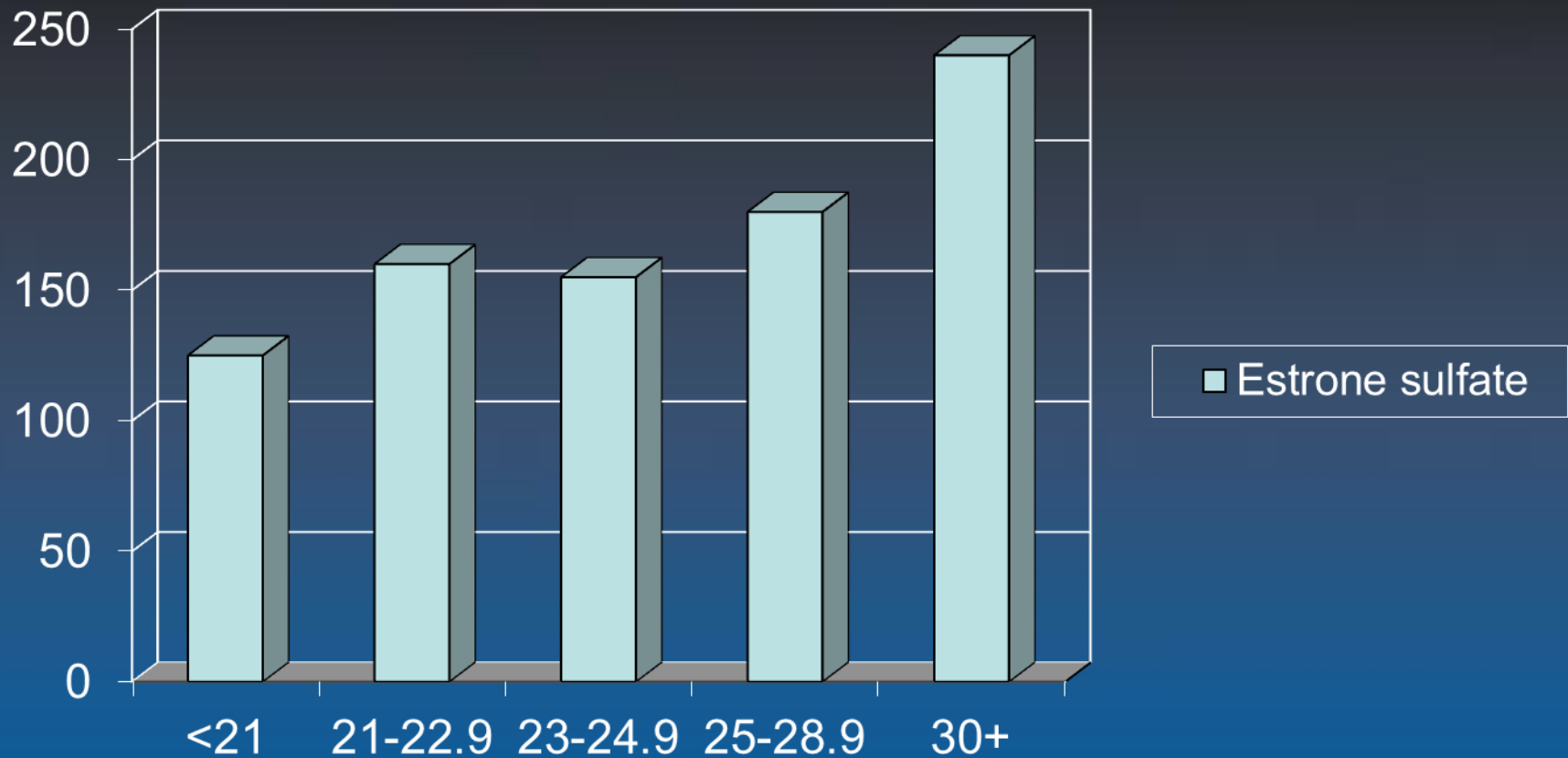


Risk of Breast Cancer by Plasma Estradiol Levels by Tumor Receptor Status

P for heterogeneity = < 0.001



Body Mass Index and Estrone Sulfate



Breast Cancer Risk Factors: Lifestyle

Risk Factor	High Risk Category	Referent Group	Relative Risk
Obesity (postmenopausal)	> 35 BMI	< 25	1.2-1.5
Physical Activity	Inactive	Regular activity	1.25-1.7
Alcohol Use	>2 drinks/day	Non drinkers	1.5

McTiernan, Oncologist 2003; Hamijima, Br J Ca 2002

Weight loss and breast cancer incidence

Cohort studies	Population	Weight loss	RR
Harvie <i>et al</i> 2005 IWHS	34,000 postmenopausal women	>5% ~3.5 kg	0.61 (0.46 – 0.80)
Eliassen <i>et al</i> 2006 NHS	87,000 postmenopausal women	>10kg ~15%	0.43 (0.25 – 0.86)
Teras <i>et al</i> , 2011 CPS-II	13,055 overweight & obese postmenopausal women	>5 kg ~7%	0.78 (0.55 – 1.10)
RCT			
Prentice <i>et al</i> , 2006 WHI	48,835 postmenopausal women	2 kg ~3%	0.91 (0.83 – 1.01)

Physical Activity and Breast Cancer Risk

Women's Health Initiative (WHI)

- Patients: 74,171 women ages 50-79
 - 1,780 cases of breast cancer diagnosed over 5 yrs
- Study: Evaluated incidence of breast cancer correlated to physical activity at age 18, 35, 50
- Results:
 - Regular strenuous physical activity at age 35 had 14% reduction in breast cancer risk (similar at age 18, 50)
 - 1.25-2.5 hrs/wk brisk walking had 18% decreased risk
 - Greatest reduction seen with >10 hrs/wk brisk walking

Exercise and Survival After Breast Cancer Diagnosis (Nurses Health Study)

Patients: 2,987 nurses with early stage breast cancer

Physical activity categories:

- LOW: < 3 MET hours per week
- LOW/MED: 3-8.9 MET hours/week
- MED/HIGH: 9-14.9 MET hours/week
- HIGH: > 24 MET hours/week

(3 MET hours/week equal to walking average pace of 2-3 miles per hour for 1 hour)

- Results: Compared to women with LOW physical activity, risk of dying of breast cancer was:
 - 20% less for LOW/MED exercise
 - 40-50% less for MED/HIGH and HIGH exercise (at least 3 hours per week walking at average pace)

Low Fat Diet RCTs for BC

- | | <u>RR (95% CI)</u> |
|--|--------------------|
| • WHI:
– Primary prevention
– 25% of total calories | 0.91 (0.86-1.01) |
| • WINS:
– Secondary prevention
– 20% of total calories | 0.76 (0.60-0.98) |
| • WHEL:
– Secondary prevention | 0.96 (0.80-1.14) |

WINS and WHEL Comparison

	WINS	WHEL
Patients	Postmenopausal only	Pre and Postmenopausal
Systemic Therapy	Protocol defined	Up to institution
Entry	< 1 yr diagnosis	< 4 yrs from diagnosis
Average entry from diagnosis	7 months	24 months
Fruit/Vegetable	No	Yes
Dietary Fat ↓	Yes	Marginal/No
Weight loss	Yes	No
Intervention result	RFS 0.76 (0.60-0.98, p=0.34)	DFS 0.99 (0.83-1.17, p=.63)

The WHEL protocol entered different patients at a different time in their disease course, had limited long term influence and fat intake and there was no weight loss difference between groups. The WHEL results provide no direct test of the WINS findings.

Healthy diet does not reduce cancer or CVD mortality in obese women

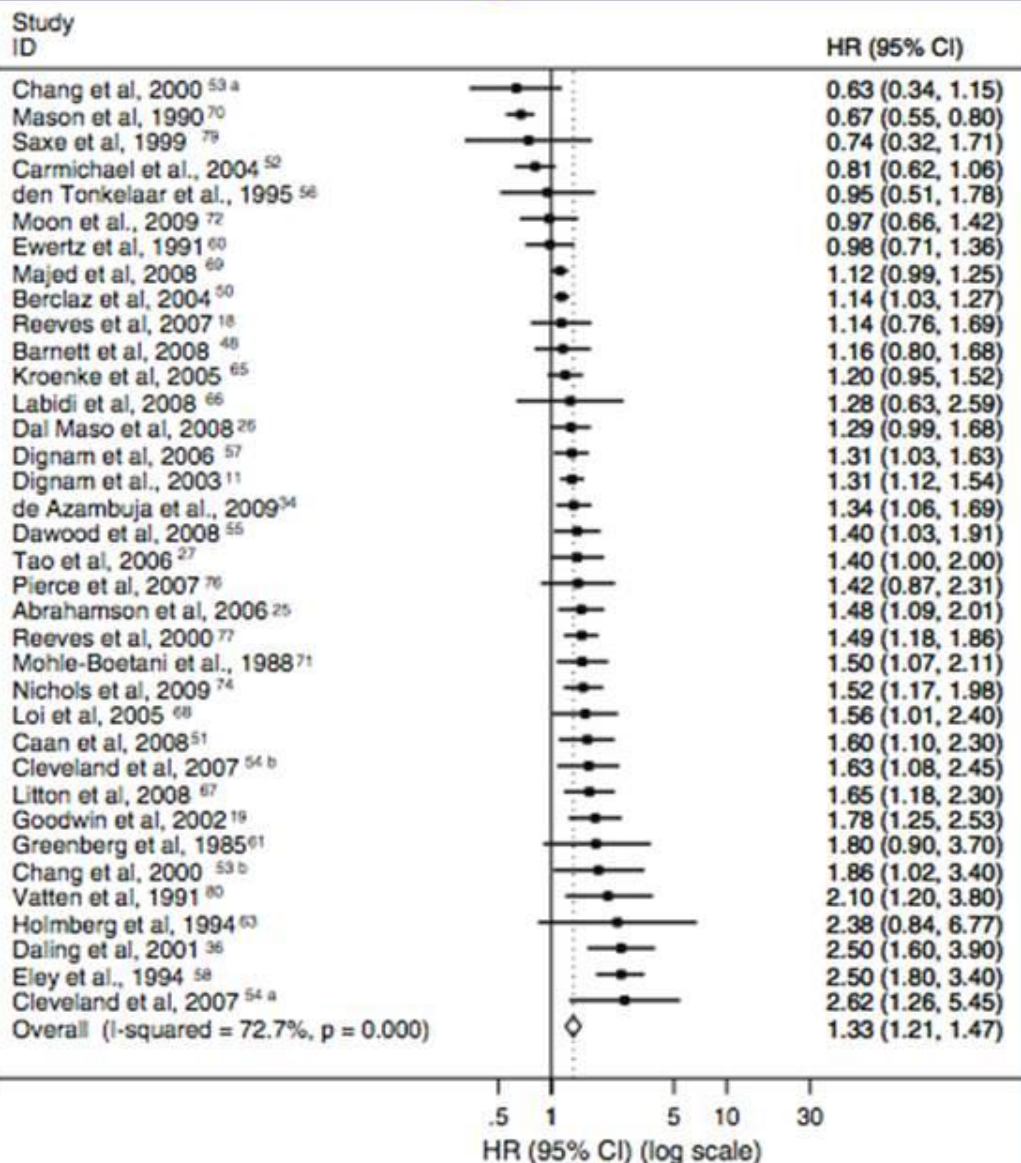
n = 63,805 Women's Health Initiative Observational Study



	BMI <25 (n = 26,551)		BMI 25–29.9 (n = 21,628)		BMI ≥30 (n = 14,936)	
	HR	P	HR	P	HR	P
All causes	0.72 0.62, 0.82	<0.0001	0.84 0.73, 0.98	0.022	0.81 0.67, 0.97	0.023
CVD	0.74 0.56, 0.98	0.038	0.72 0.52, 1.00	0.047	0.87 0.61, 1.23	0.420
Cancer	0.79 0.64, 0.97	0.027	0.68 0.53, 0.86	0.001	0.90 0.68, 1.18	0.438

George Am J Epidemiol 2014;180(6):616– 625

Obesity and Breast Cancer Mortality



Overall HR=1.33 (1.21-1.47)

Protani et al. (2012) Breast Cancer Res Treat (2010) 123:627-635

Effect of obesity on prognosis in pre-menopausal, ER+ early breast cancer

EBCTCG data on 80,000 patients in 70 trials

Hongchao PAN & Richard GRAY,
University of Oxford, UK

for the Early Breast Cancer Trialists' Collaborative Group
(EBCTCG)



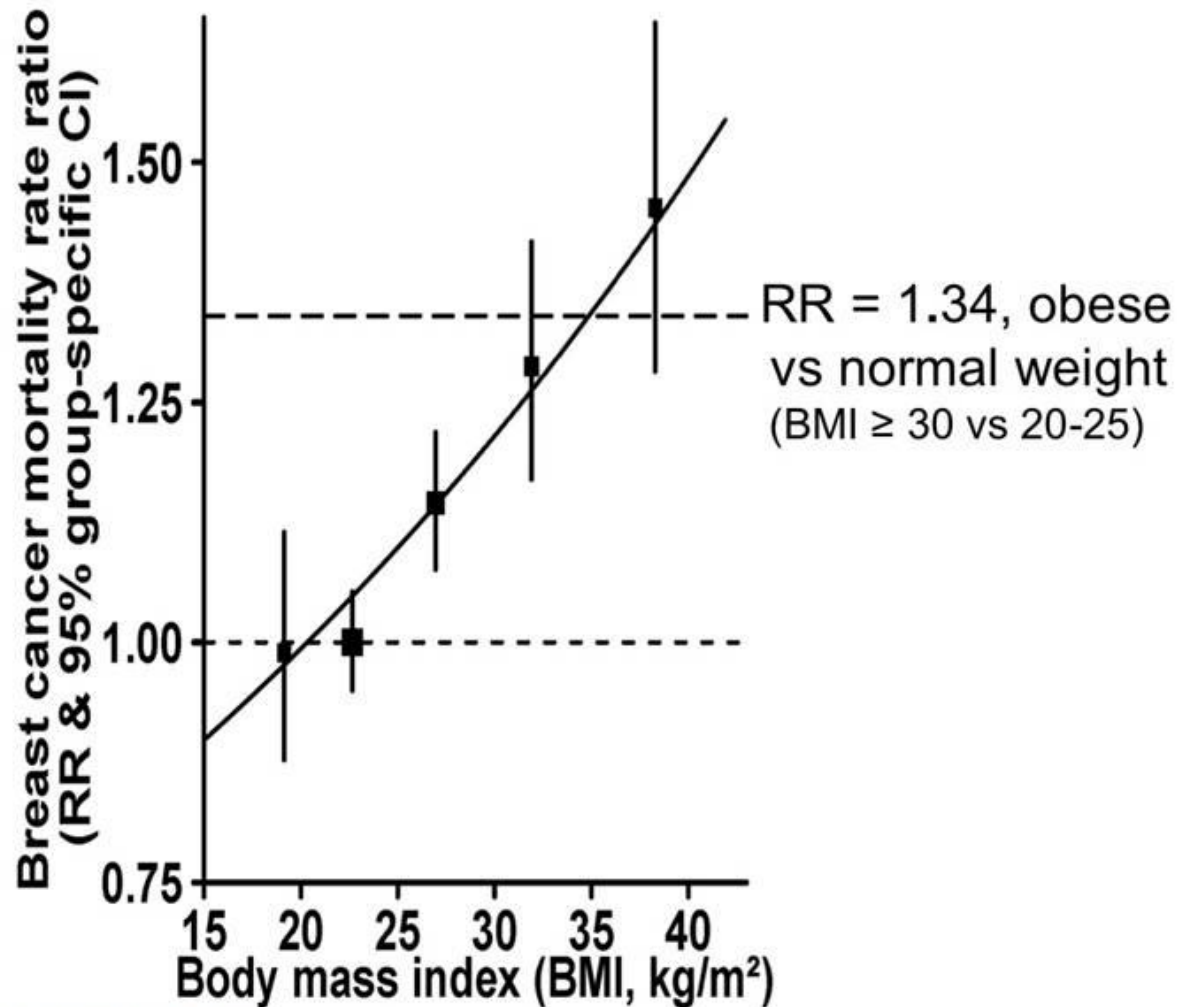
Findings

**Definite, independent adverse effect of obesity
on breast cancer mortality only in
pre-menopausal* ER+ disease**

* Defined to include peri-menopausal

Pre-menopausal ER+ disease: 20,000 women

Breast cancer mortality by 5 BMI groups

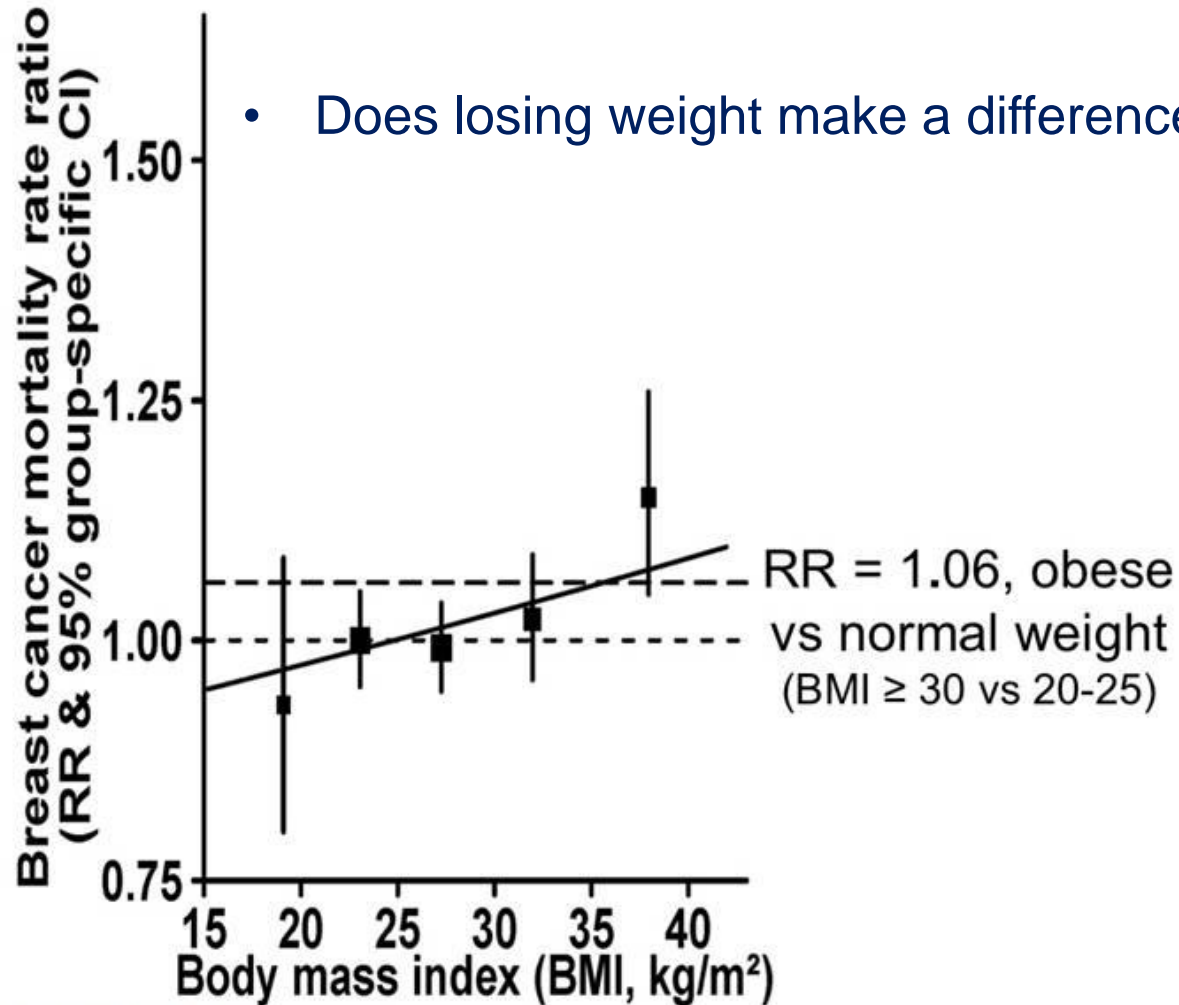


American Society of Clinical Oncology
Making a world of difference in cancer care

BMI: <20 20-25 25-30 30-35 35+
Patients: 1913 10189 5983 2348 1286

Post-menopausal ER+ disease: 40,000 women

Breast cancer mortality by 5 BMI groups



Further Epidemiologic Research of Breast Cancer

- Identification of causes of the substantial proportion of BC that remains unexplained (stratification by tumor subtype)
- More research on the specific hormonal patterns that increase risk (stratification by tumor subtype)
- Interrelations among dietary factors, physical activity and anthropometric characteristics at specific points during women's life (stratification by tumor subtype)
- Evaluation of many genes suspected of conferring low to moderate risk (stratification by tumor subtype)
- Better models for individual risk assessment (stratification by tumor subtype)



No Clear Association of Diet with Breast Cancer Risk

- Dietary fat intake
 - Hunter 1996
 - Pooled prospective studies
 - 4980 cases in 337,819 women
 - Prentice, JAMA 2006
- Fruits & vegetables
 - Smith-Warner, JAMA, 2001
 - Pooled prospective studies
 - 7377 cases in 351,825 women
- Carotenoids; Vitamins A, C, E
- Selenium

WHEL Study (Women's Healthy Eating and Living Study)

RCT 3088 early stage breast cancer survivors (1995-2000); age 27-74 yrs

Randomised



Diet intervention counselling

5 vegetable servings
16 oz vegetable juice
3 servings fruit
30g fibre
15-20% calories fat

Control (print material, 5 a day)

Primary outcome: breast cancer events, death- no effect on disease free survival

Secondary outcomes

1. Significant diet change
2. Significant change in selected biomarkers (carotenoids, oestradiol (total and bioavailable))
3. No significant weight change (1 year)

WHEL Study (Women's Healthy Eating and Living Study)

- Among survivors of early stage breast cancer, adoption of a diet that was very high in vegetables, fruit, fibre and low in fat did not reduce additional breast cancer events or mortality during a 7.3 year follow up period

Women's Intervention Nutrition Study (WINS) Evaluating Dietary Fat Reduction in Early Stage Breast Cancer

Eligibility Criteria:

- Women 48-79 years
- Early breast cancer
- Primary surgery \pm RTx
- Systemic therapy (ER⁺: tamoxifen/chemotherapy; ER⁻: chemotherapy)
- Dietary fat intake > 20% of calories

(n = 2437)

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Dietary intervention:
reduced fat intake
(n = 975)

Control
(n = 1462)

Primary Endpoint: Relapse-free survival

Randomization 60:40 within a
year from primary surgery

WINS

Risk of Recurrence: Low Fat Diet vs. Control

	RR (95% CI)	p-value
All women	0.76 (0.60-1.00)	0.03
ER+	0.85 (0.63-1.14)	0.28
ER-	0.58 (0.37-0.91)	0.02

WINS

Risk of Recurrence: Low Fat Diet vs. Control

- Lifestyle intervention reducing dietary fat intake (target 20% E), with modest influence on body weight, may improve relapse-free survival of breast cancer
- 24% reduction in risk for recurrence; subset analyses suggest that this effect was even greater among women with oestrogen receptor-negative disease

Conclusions

- Baseline obesity has negative impact on survival for pre-menopausal women with ER positive breast cancer
- No relationship found for post-menopausal women, although clinical trial population may not be representative
- Exact mechanism is unclear but likely multifactorial
- Does losing weight make a difference?