Integrating risk across the lifespan: the case of breast cancer prevention

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Conflict of interest

- I have no financial relationships to disclose
- I will not discuss off-label use and or investigational use in my presentation

Why are we not preventing breast cancer now?

Multiple barriers:

- Skepticism that cancer can be prevented
- Short term focus of cancer research
- Interventions deployed too late in life
- Research focused on treatment not prevention
- Debates among scientists
- Societal factors ignored
- Lack of transdisciplinary training
- Complexity of implementation

Colditz et al Sci Transl Med 2012: March 28

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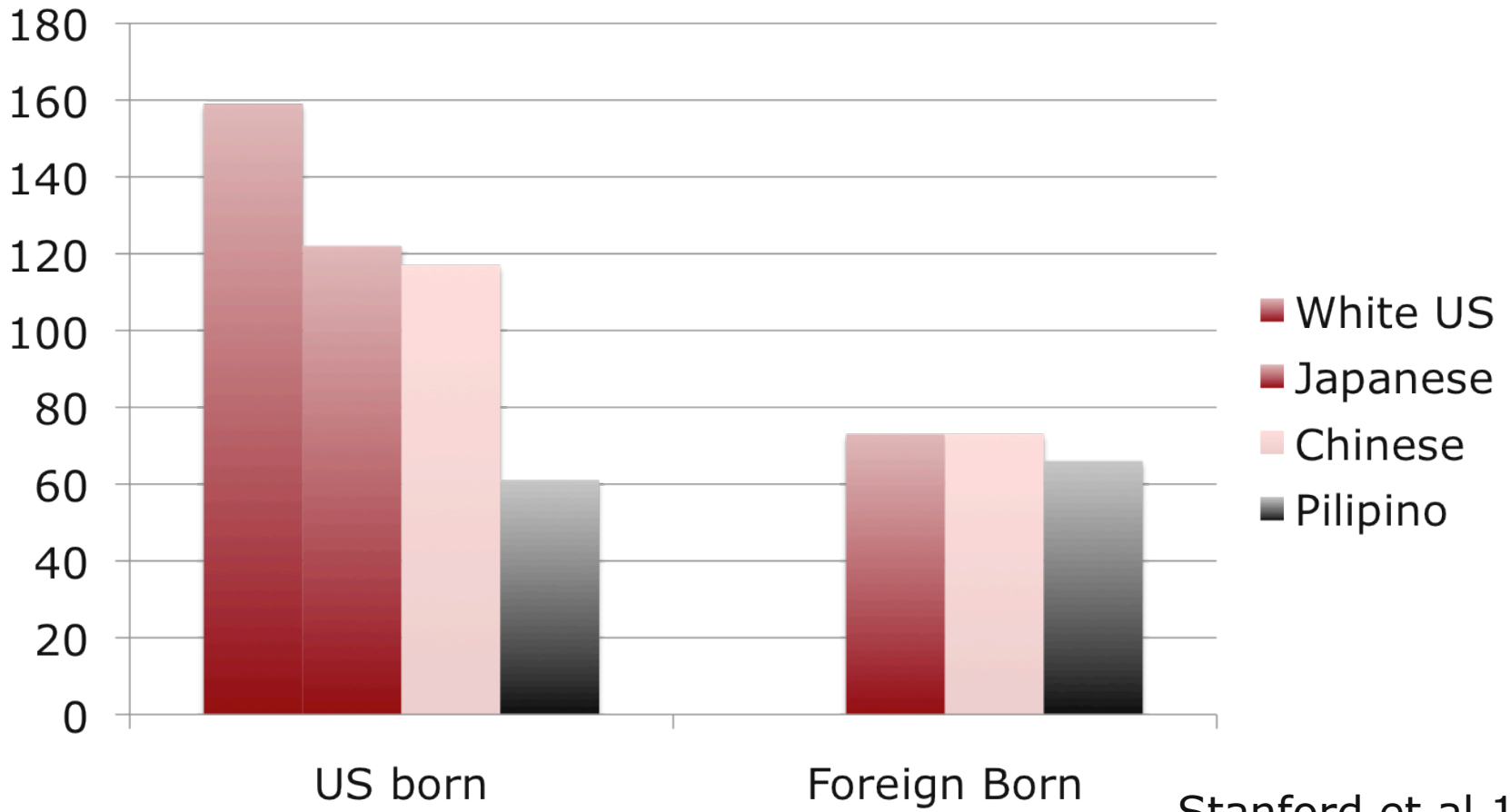
Overcoming obstacles of skepticism and time frame

- Must counter skepticism that cancer can be prevented
  - Goals of prevention: risk marker, premalignant lesion, invasive disease, death
  - Avoid exposure vs. remove later in life
  - Can we intervene if we don't have the pathway defined?
- Take into account time frame of cancer development

Evidence that breast cancer is preventable

- Migrant studies
  - No US lifestyle
- Within country changes
  - Remove HRT, Korea rapid increase, etc
- RCTs of SERMs,
  - Tamoxifen, Raloxifene
- Bilateral oophorectomy for women with BRCA1/BRCA2

Birthplace and breast cancer incidence, SEER registry 1973-86



Stanford et al 1995

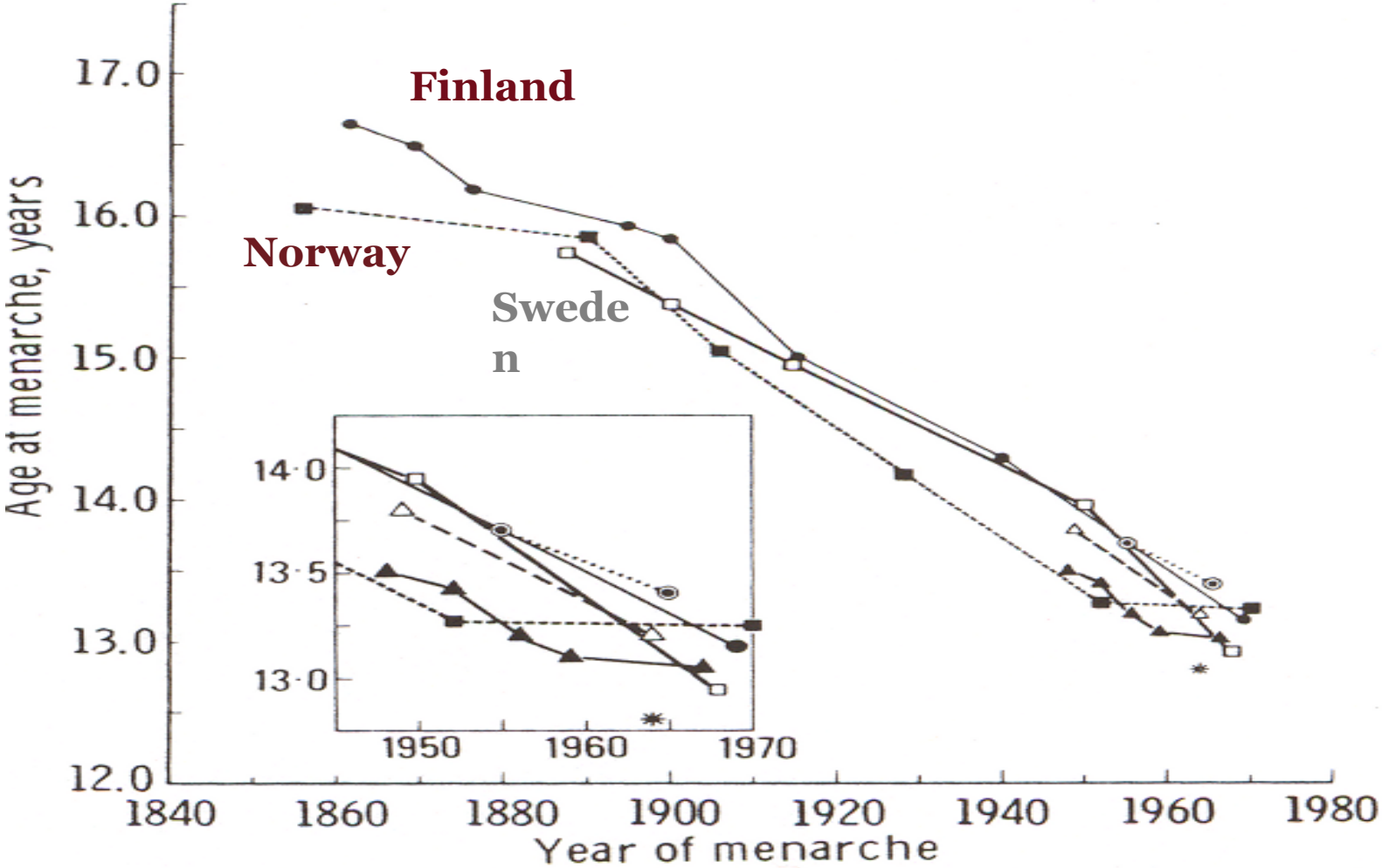
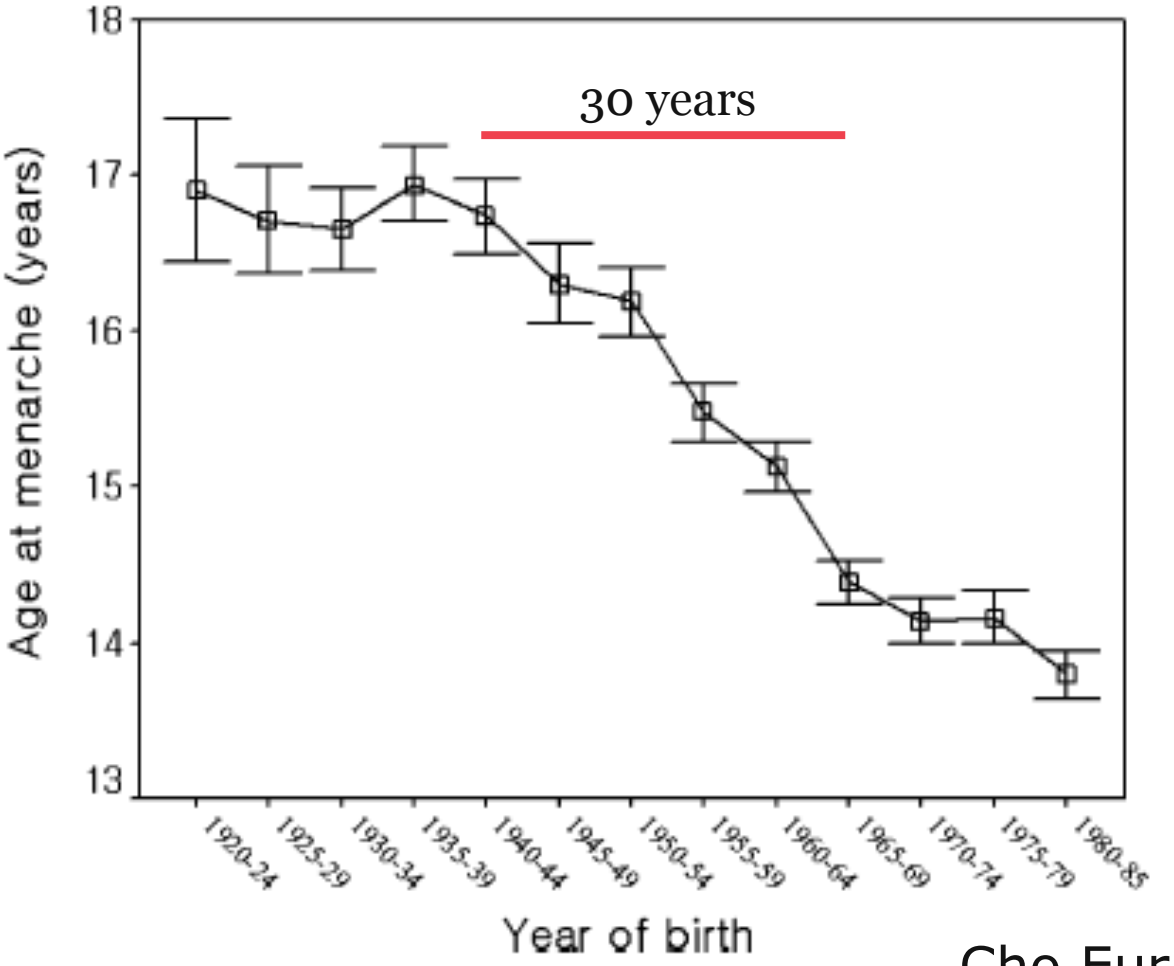


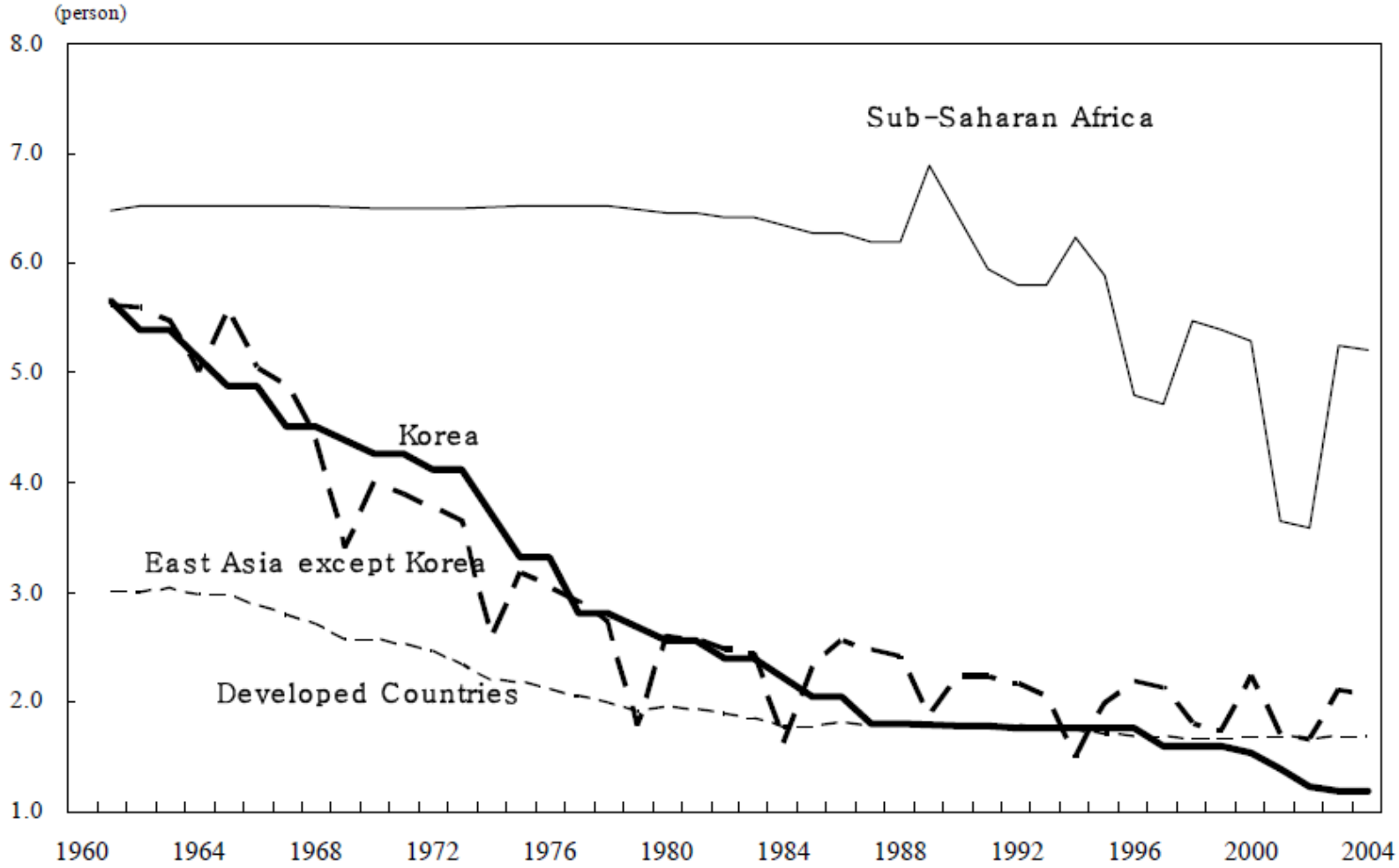
Fig. 1. Trend toward earlier menarche in some European countries. (Sweden (□—□); Norway (■---■); Finland (●—●); Denmark (△---△); Holland (⊙ · · · ⊙); United Kingdom (▲—▲); United States (∗). (From Tanner, 1978.)

Change in menarche, Korea



Cho Eur J Pediatr 2009

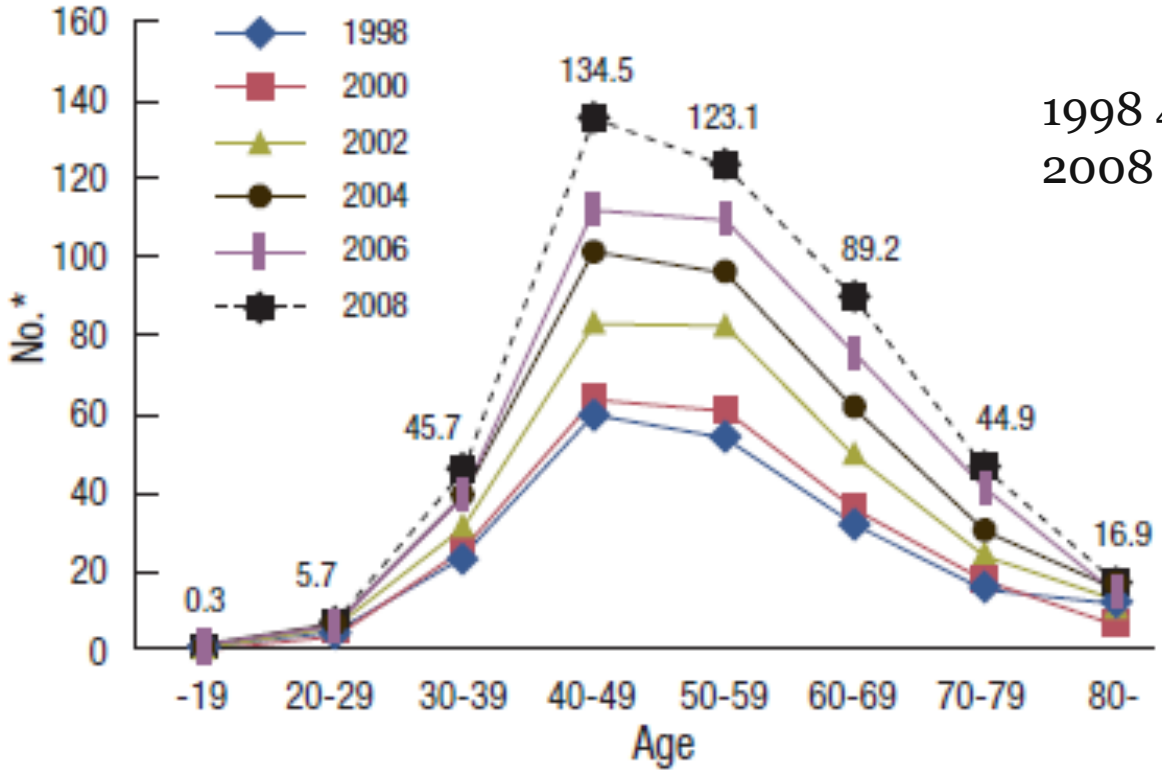
Trends in Fertility



Calendar year

Ito et al NEBR, 2008

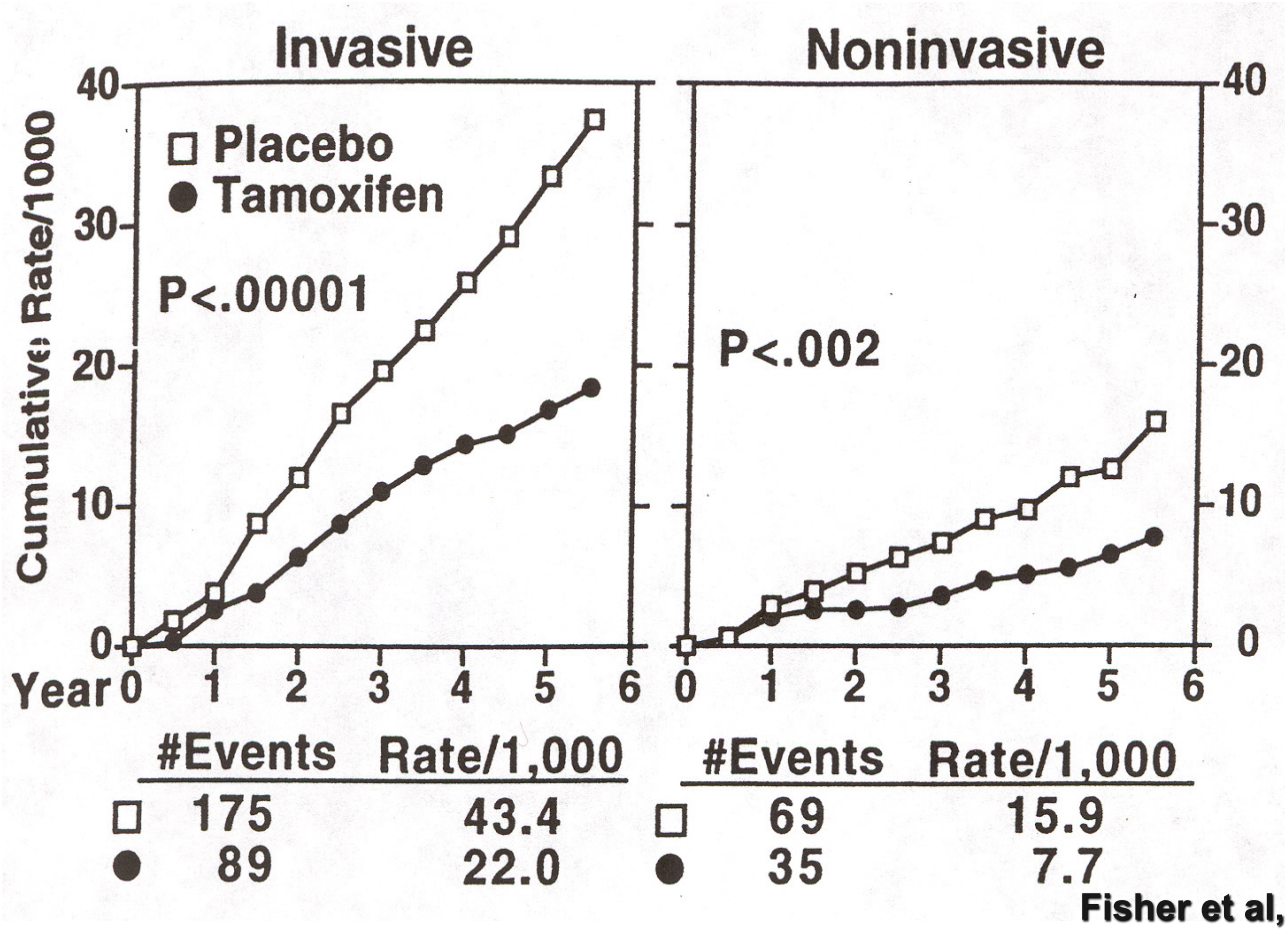
Breast Cancer Incidence, Korea



1998 40, born 1958
2008 40, born 1968

Jung et al, J Breast Ca, 2011

RCT: Rates breast cancer P1 trial



Fisher et al, 1998; 90:1371-88

Evidence that breast cancer is preventable

- Migrant studies
  - No US lifestyle
- Within country changes
  - Remove HRT, Korea rapid increase, etc
- RCTs of SERMs,
  - Tamoxifen, Raloxifene
- Bilateral oophorectomy for women with BRCA1/BRCA2
  - 10 studies, HR 0.49 (0.35, 0.64)
    Rebbeck JNCI 2009;101:80-7

Summary of breast cancer prevention strategies

Strategy	Risk group	% US pop	Risk reduction
Bilateral oophorect-y	BRCA1/2	<1%	50% ↓
Tamoxifen / Raloxifene	>1.67% 5-yr risk	10-40%	50% ↓
Weight loss (22lb)	Overweight + obese	60%	50%*
Increase exercise	<30 min/d	>60%	Timing matters

* Loss after menopause based on Eliassen JAMA, 2006

Huge potential for cancer prevention

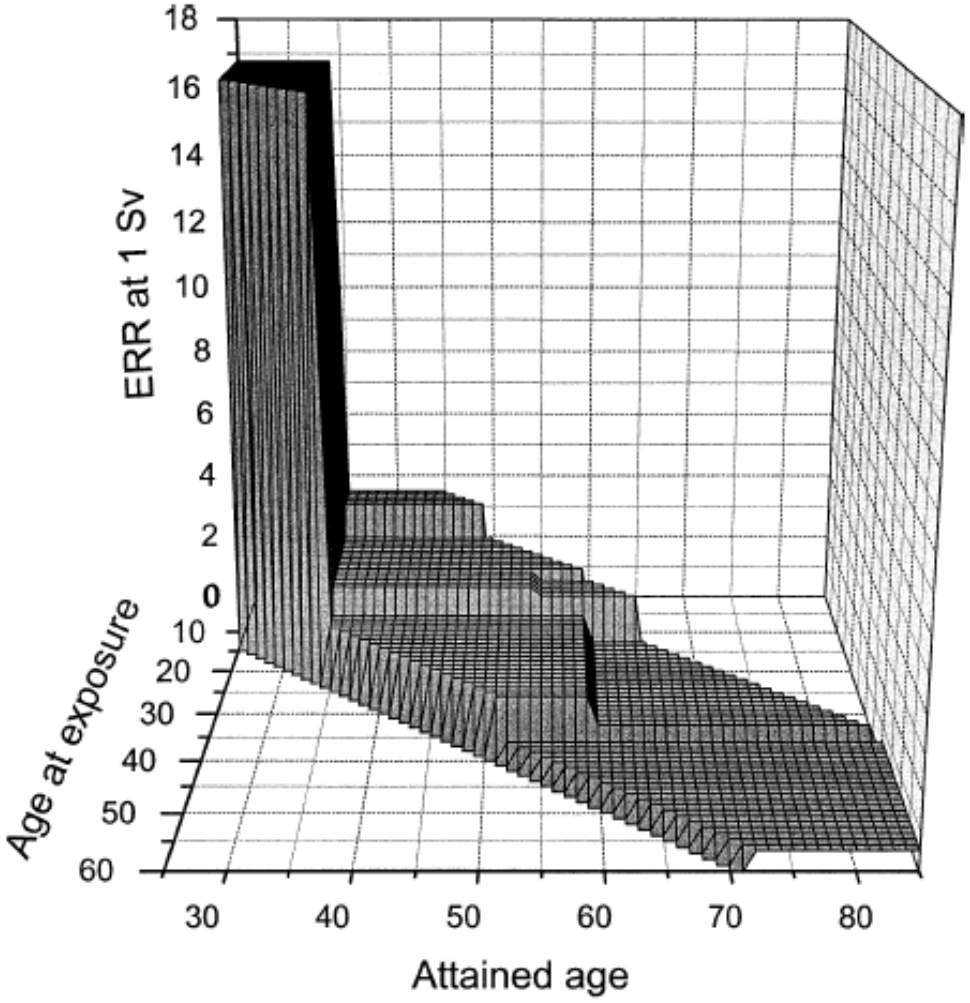
- More than half of cancer incidence and mortality could be prevented with what we know now.
- This applies to breast cancer as it does to other major malignancies

Time frame: Where is evidence for prevention in the development sequence of cancer?

- Majority of etiologic studies focus on lifestyle and drugs in proximate time before diagnosis
  - Epidemiology predominantly in postmenopausal women
  - Trials in high-risk women

Radiation

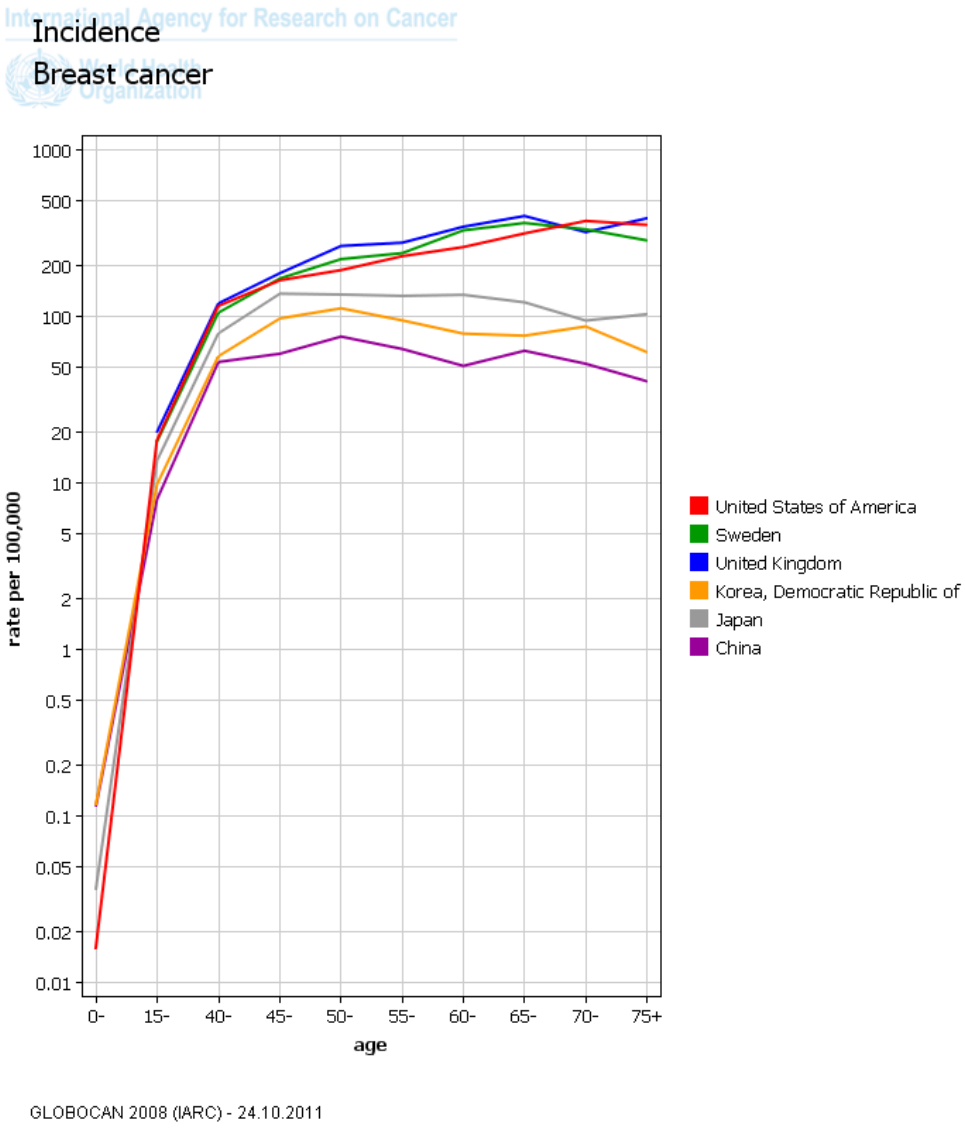
- Atomic bomb survivors, 70,165
- 40 year follow-up
- 1059 cases
- Linear increase with radiation dose
- Early age at exposure conveys substantially greater risk



Land et al Radiation Research 2003

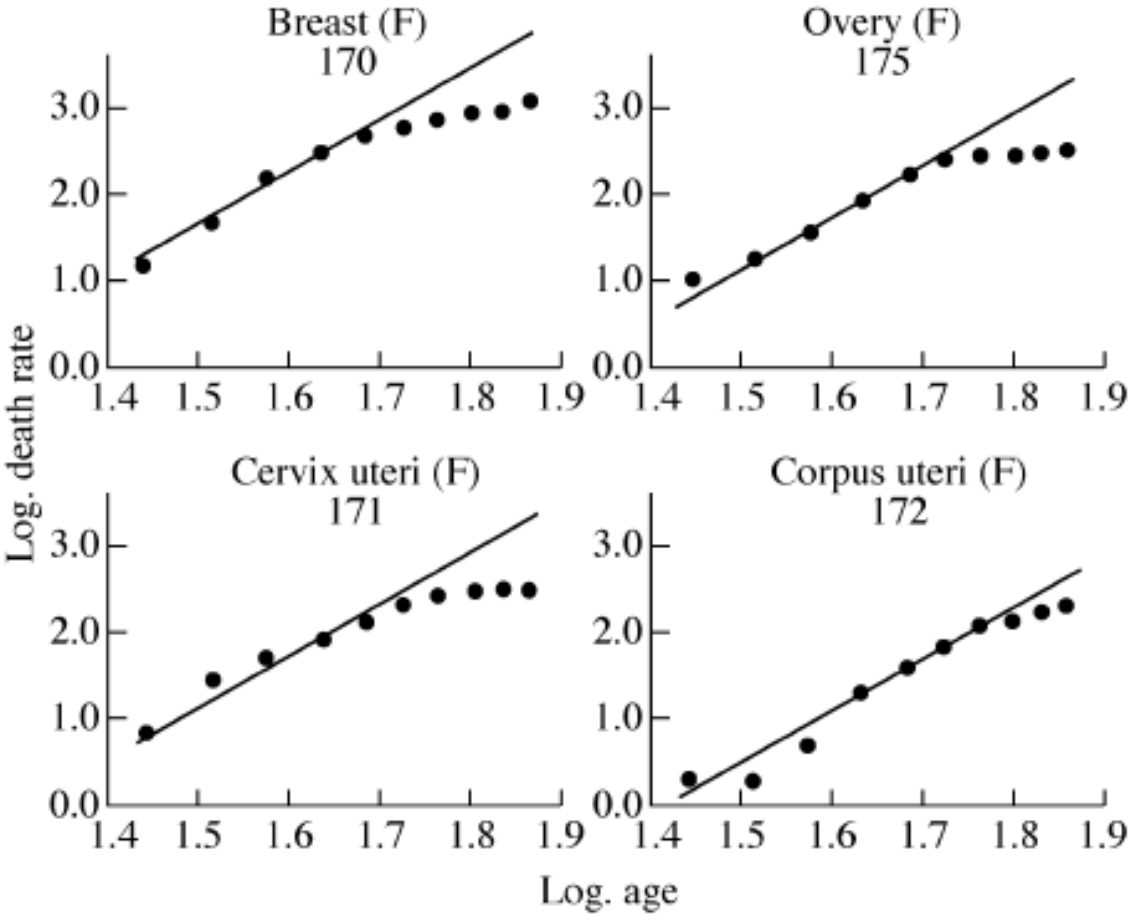
Breast cancer incidence

Globalcan 2008 incidence



Female cancer mortality by age

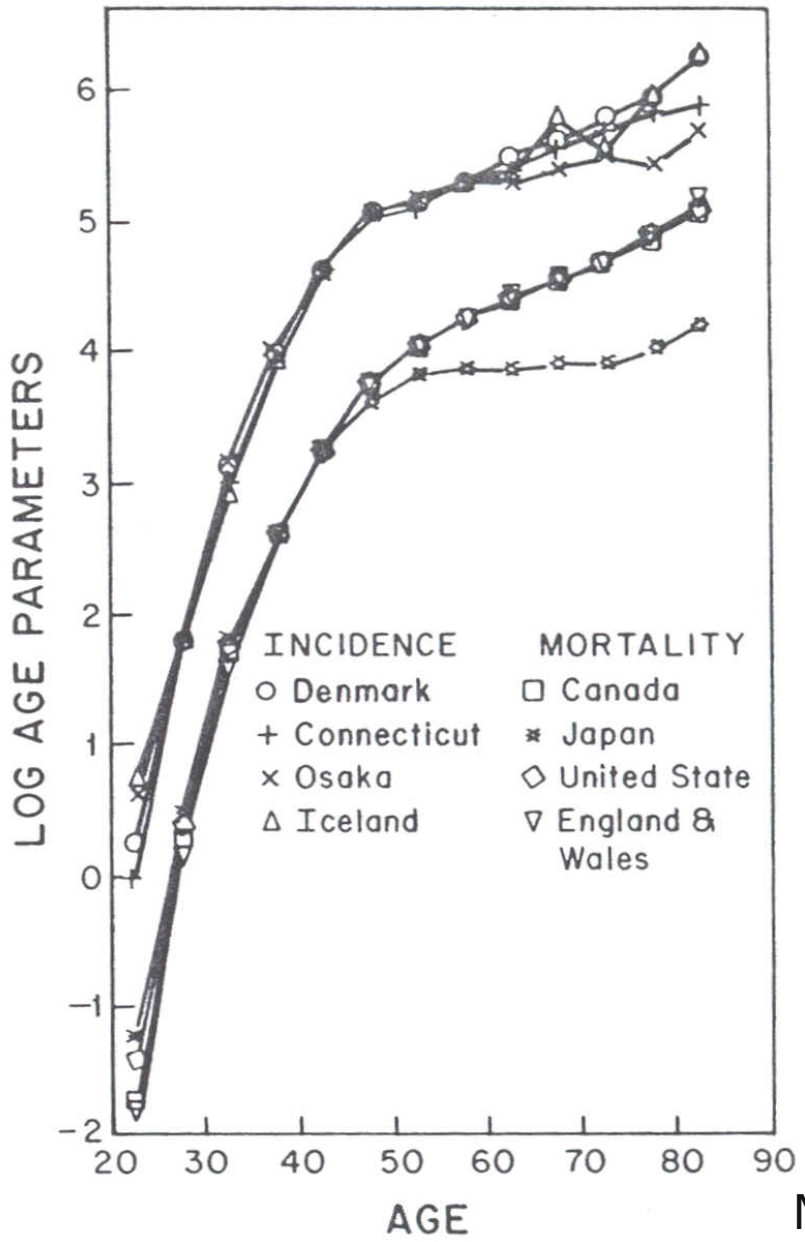
Cancer mortality England and Wales 1950 and 1951



Armitage and Doll, Br J Cancer 1954

Biology – association with age

- Armitage & Doll – increase with age – multistage model, BJC 1954
- Moolgavkar et al.,1981 JNCI evaluated data from Denmark, Japan, Iceland and the USA.
- The underlying effect of age is modulated by birth cohort
- Normalized incidence curves to age 40-44 in Connecticut
  - Moolgavkar JNCI 1979:62:493-501



Moolgavkar et al JNCI 1979

If we conclude that attained age is marker of risk, then:

What does attained age mean?

- Accumulated exposure up to an age?
- Some other function of age?
- Menopause tells us “hormones” or accumulation through premenopausal years must be important

Attained age finding generates other key questions:

- Which lifestyle component to change?
- At what age?
- By how much?
- For how long?
- When will benefit be observed, and how long will benefit last?

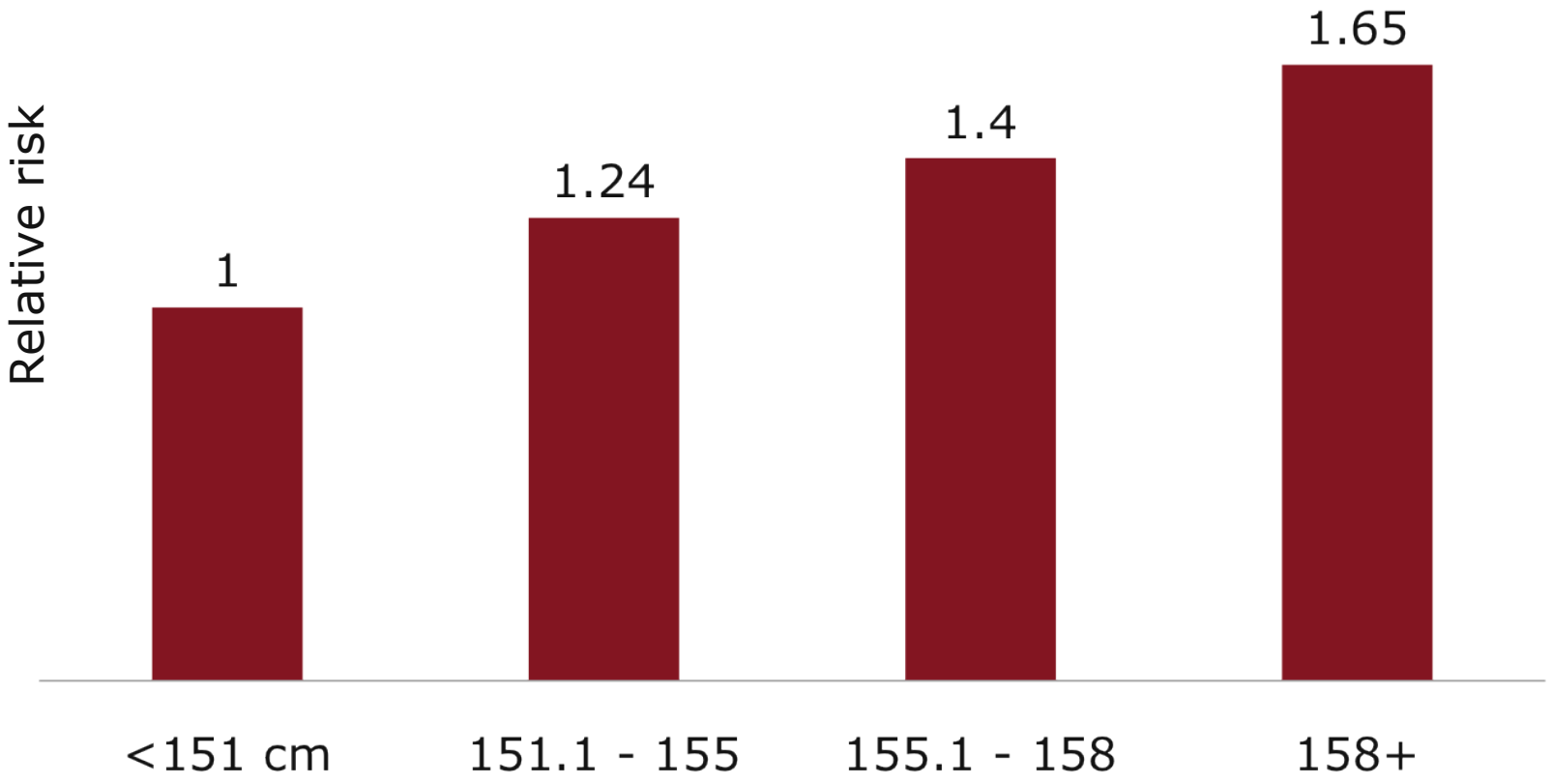
See Colditz, Cancer Causes and Control 2010
Colditz and Taylor, Ann Rev Public Health 2010

Why are childhood and adolescence important?

- Risk accumulation from menarche to first birth and then to menopause
- Age at menarche has strong history of relation with breast cancer
- Dramatic changes with industrialization
  - Menarche reduced from 17 or 18 to 12 eliminating one third of growth and development period
- Growth and height are related to risk

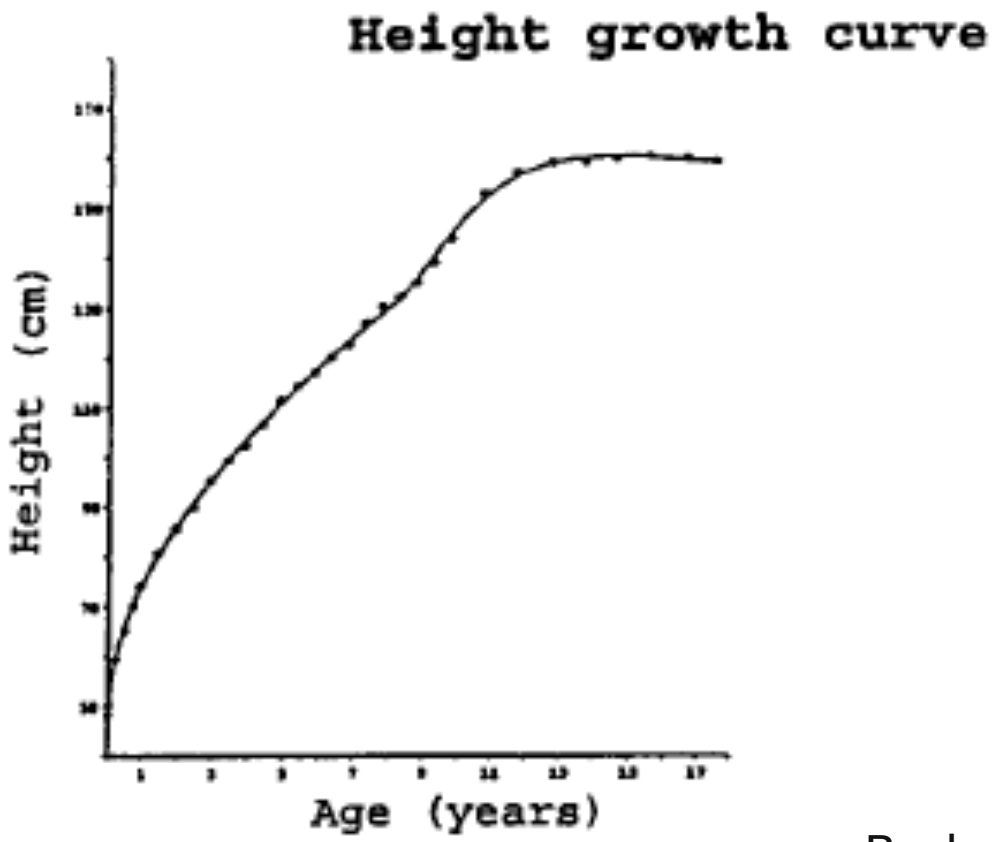
Colditz and Frazier CEBP 1995

Height and relative risk of breast cancer incidence, Korea. 339,000 women, 10 yr



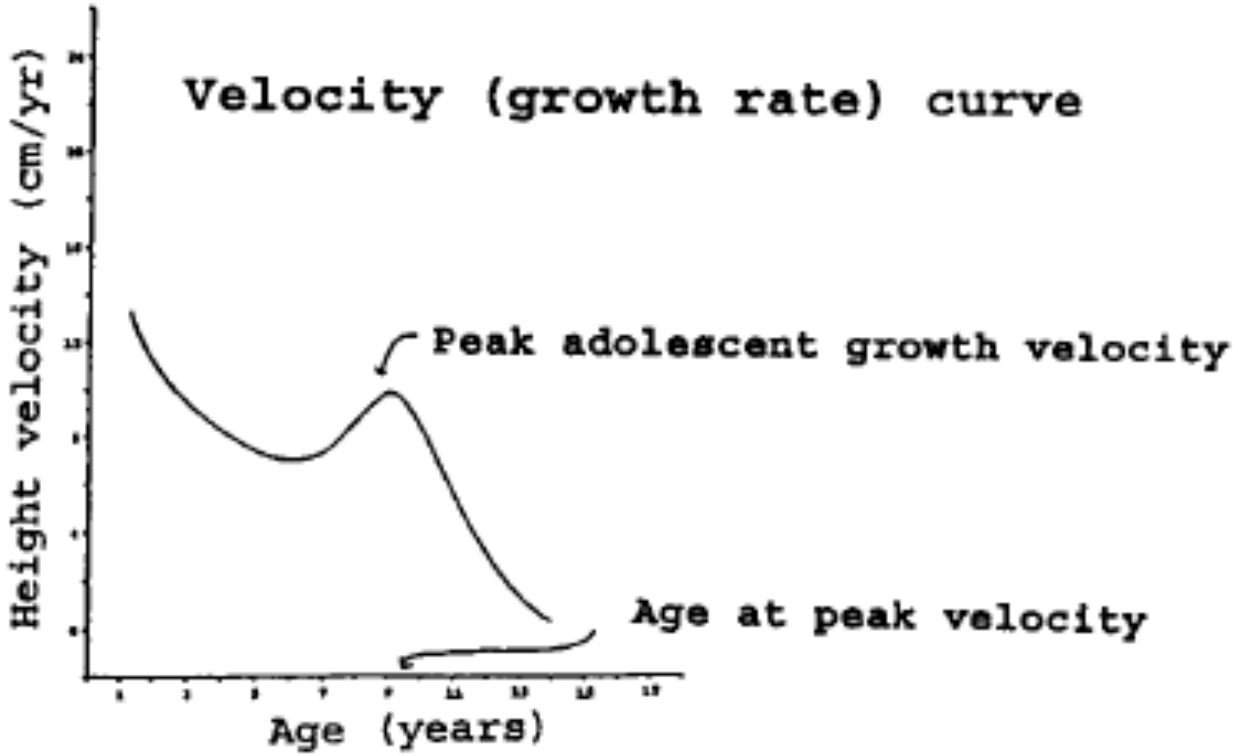
Sung J, et al AJE 2009

Growth curve of a girl, HLS
Peak height velocity
= greatest growth in single year



Berkey et al, Cancer 1999

Peak height velocity



Berkey et al, Cancer 1999

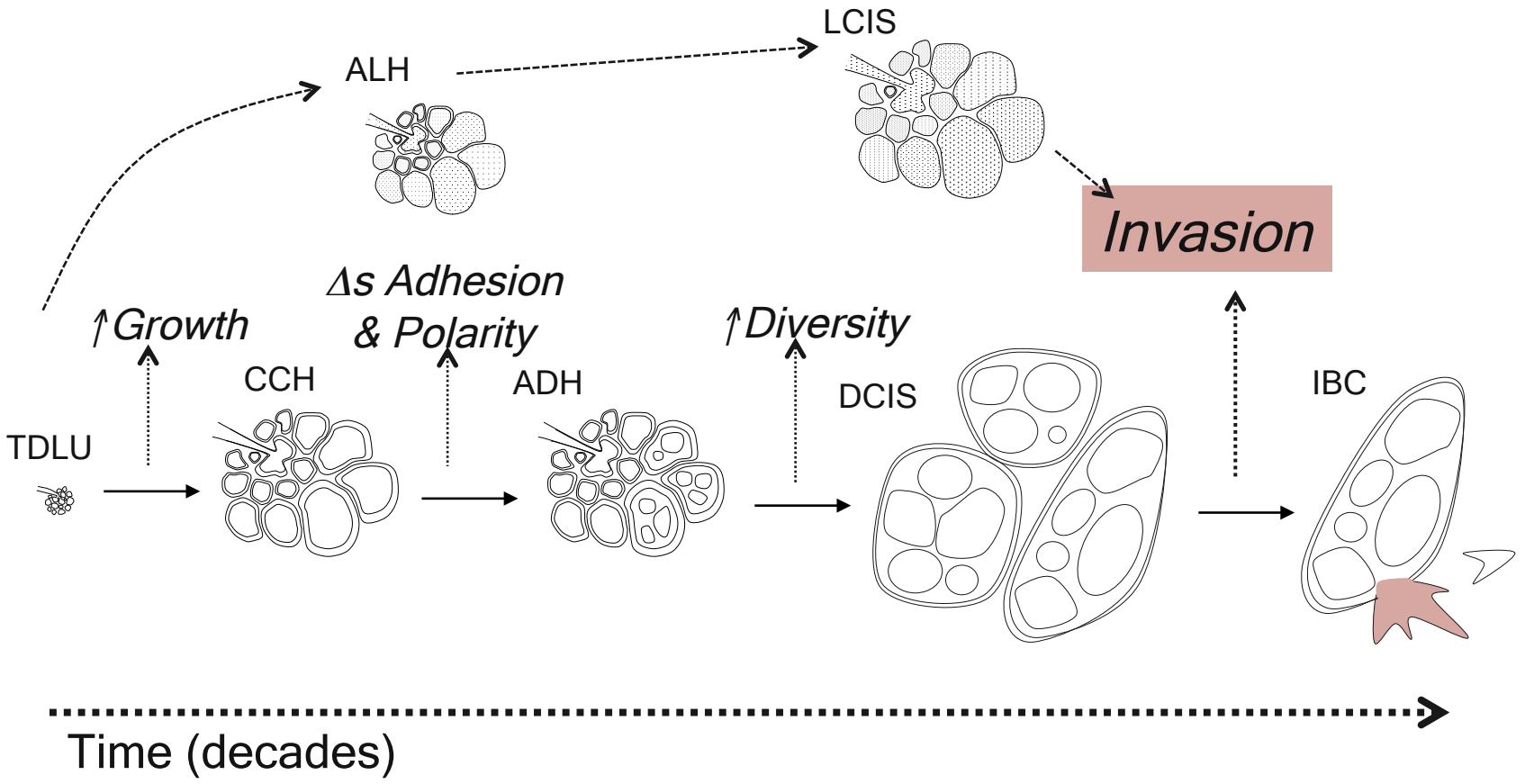
Application: Nurses' Health Study, then in adolescent cohort (GUTS)

- Higher peak height growth velocity (PHGV) associated with increased risk of pre and post menopausal breast cancer
- Highest vs. lowest quintile of PHGV; 8.9cm/yr vs. $\leq$7.6 cm/yr;
  - RR=1.31 premenopausal breast cancer
  - RR=1.40 postmenopausal breast cancer
- For Benign Breast Disease same range in PHGV gave RR = 2.10

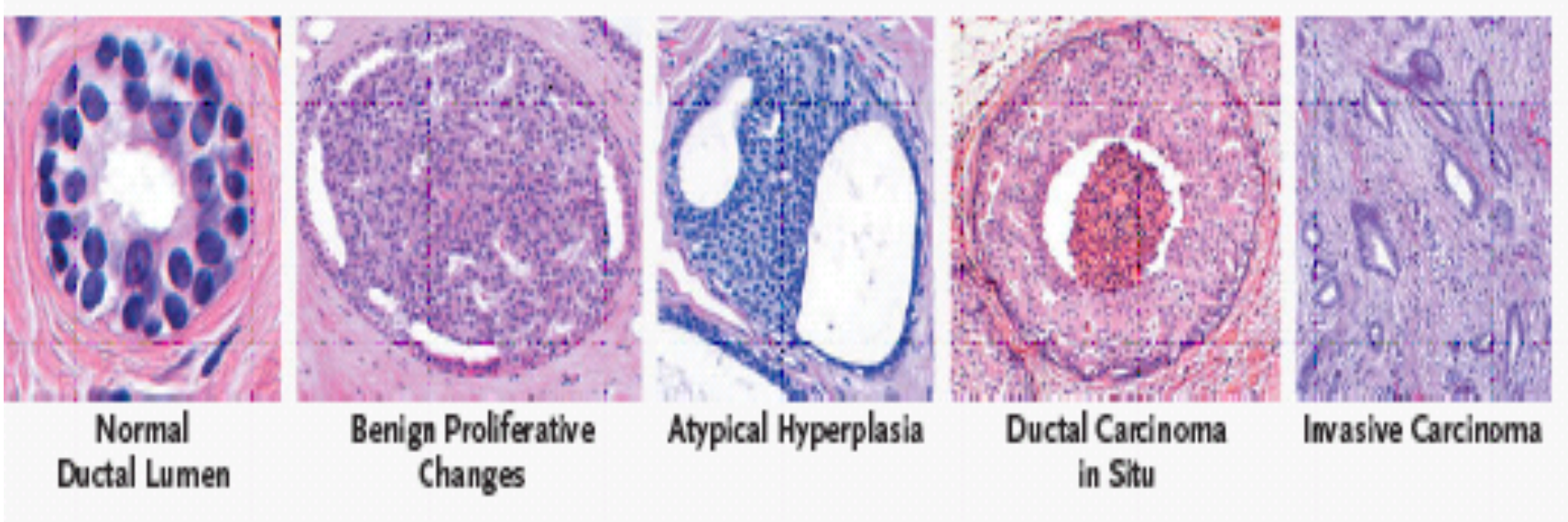
Berkey et al. Cancer 1999 & 2011

Model of breast cancer evolution

Wellings-Jensen Model (JNCI 55:231, 1975)



Precursor lesions: benign breast disease (BBD)



RR = 1.8 = 3 to 5

London JAMA et al 1989

What predicts incidence of BBD?

NHSII – incident BBD (RO1-CA50385)

- Central pathology review
- Study of adolescent:
  - diet
  - physical activity
  - body shape at ages 5 and 10
- GUTS, Growing Up Today Study
  - Self-report benign breast disease confirmed by breast biopsy

Alcohol and BBD – GUTS data

- 6899 females, 9-15 in 1996
- 2000, 2001, 2003 assessed alcohol
- 147 confirmed physician diagnosed benign breast disease
- Those who drank typically 3 to 5 days per week at increased risk (RR 2.99, 1.26-7.09)

The Breast Cancer Research Foundation

Berkey et al, Pediatrics, 2010

Alcohol and incident proliferative BBD, NHSII

- Adolescent recall of high school diet
- Incident BBD – proliferative lesions on central pathology review
- 678 cases of proliferative BBD among 29,329 women followed over 10 years
- Alcohol intake directly related to subsequent risk of proliferative BBD

The Breast Cancer Research Foundation

Liu et al – Pediatrics, in press, April 2012

Alcohol intake, ages 18-22, incident proliferative BBD

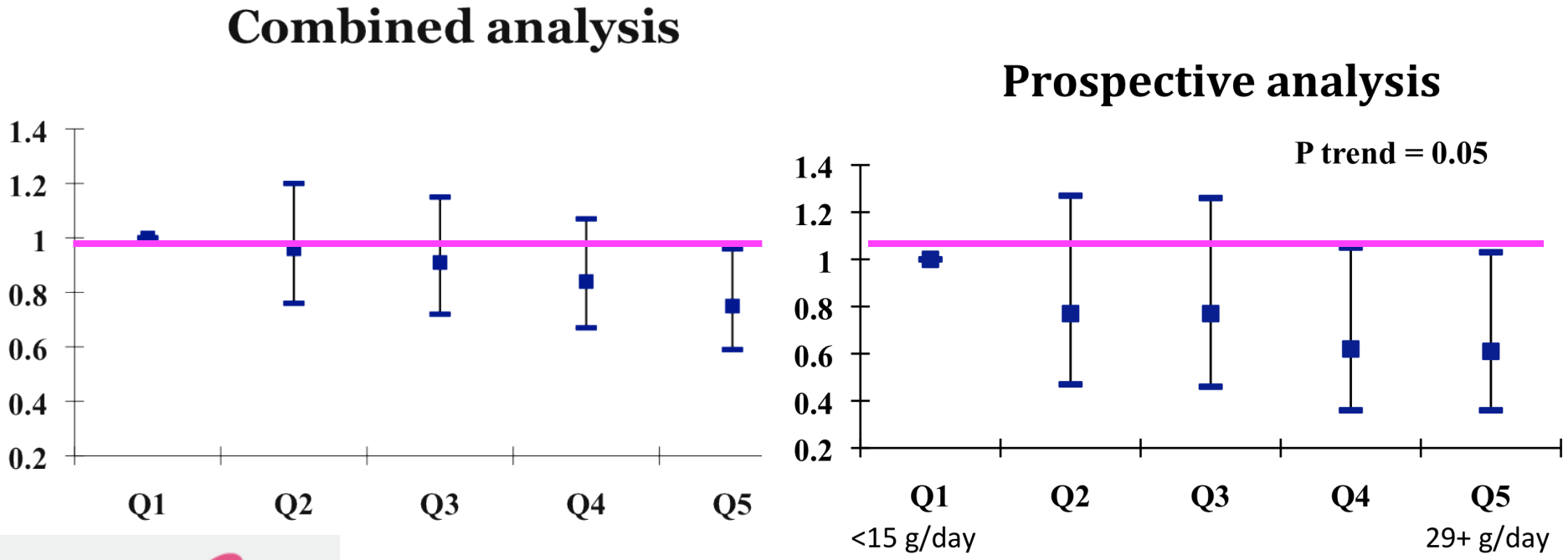
Alcohol intake (grams/ day)	Cases	Person-yr	RR (95% CI)
None	155	64,827	1.0 reference
0.1-4.9	193	78,365	1.11 (0.89, 1.38)
5.0-14.9	236	88,310	1.36 (1.09, 1.69)
≥15	30	9519	1.35 (1.01, 1.81)
			p_{trend} <0.01

Liu et al – Pediatrics, April 2012

Protein, fiber, and risk of BBD

- Previous retrospective evidence suggests vegetable fat inversely related to risk of proliferative BBD (Webb et al 2004)
  - Not confirmed in prospective analysis
- Evaluating sources of protein intake, we observe significant inverse relation for vegetable protein intake after onset of menses
- This finding significant among those with and without maternal history of breast cancer

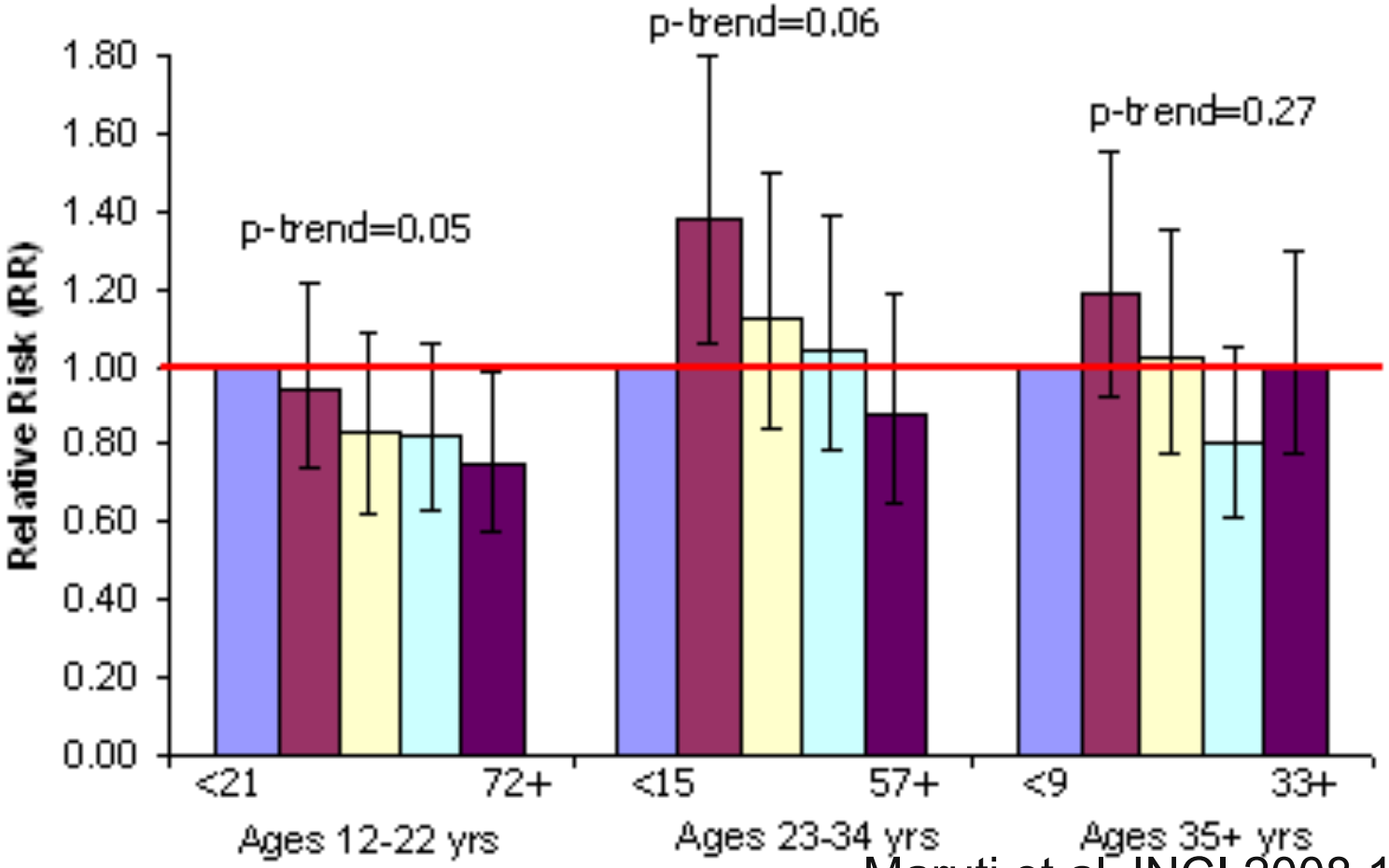
Adolescent fiber & BBD: NHSII



Su et al Cancer Causes Control 2010

Physical activity: What time period is important?

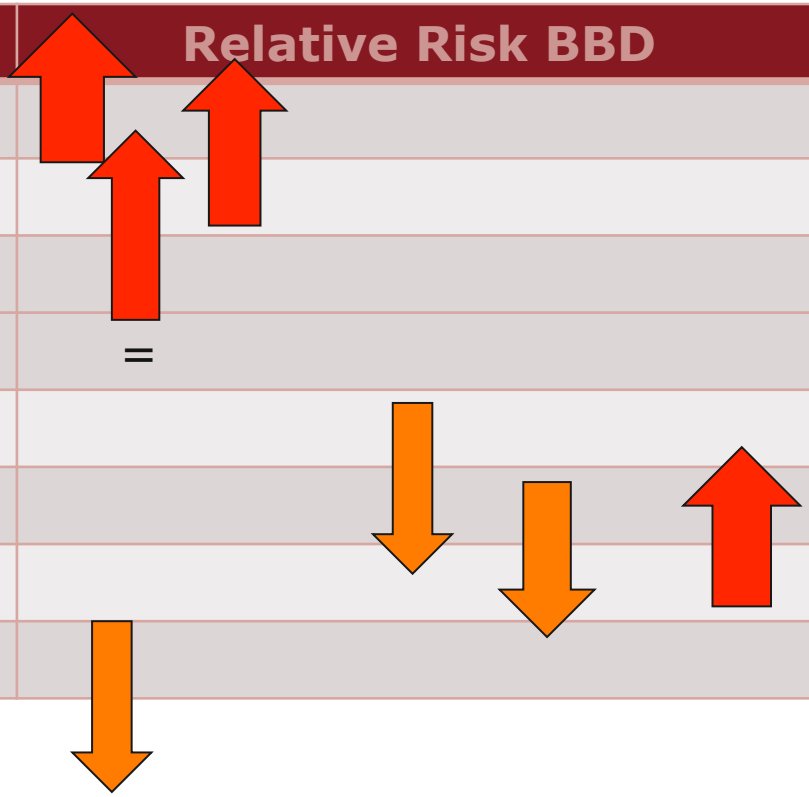
Total activity (MET-h/wk) during different ages and breast cancer



Maruti et al JNCI 2008 100:728-737

Summary of evidence: Adolescent exposures and BBD

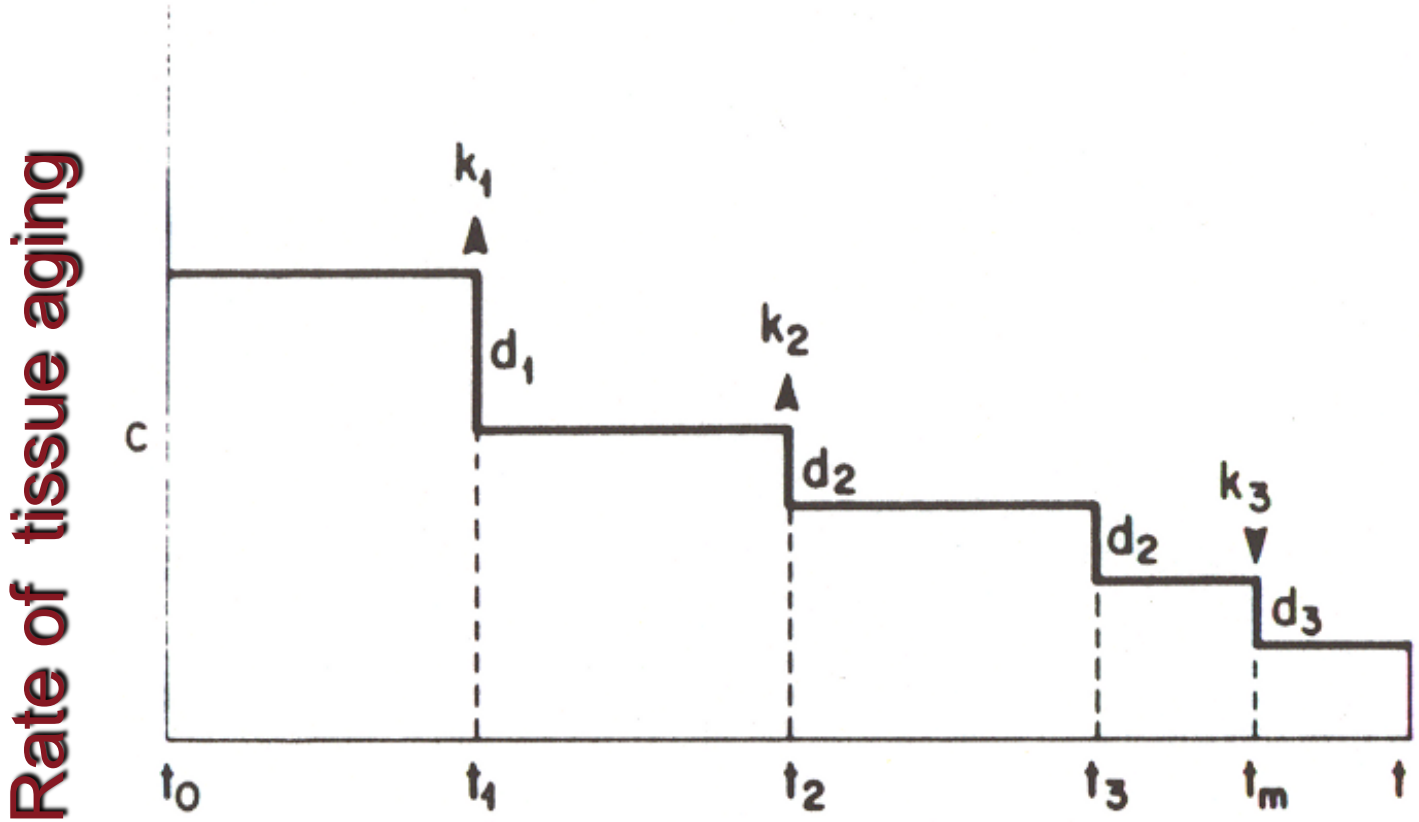
Lifestyle	Relative Risk BBD
Alcohol	
Peak Growth Velocity	
height	
Dairy	=
Fiber	
Vegetable protein	
Family history	
Physical activity	



Understanding the accumulation of breast cancer risk: Pike model

- Factors associated with reduced risk of breast cancer were considered to lower the rate of breast tissue aging
  - Pike et. al., Nature 1983;303:767-70
- We translated this to mean the rate of cell division and accumulation of molecular damage on the pathway to breast cancer

Multiple birth model



Rosner, Colditz, Willett, Am J Epidemiology 1994;139:826

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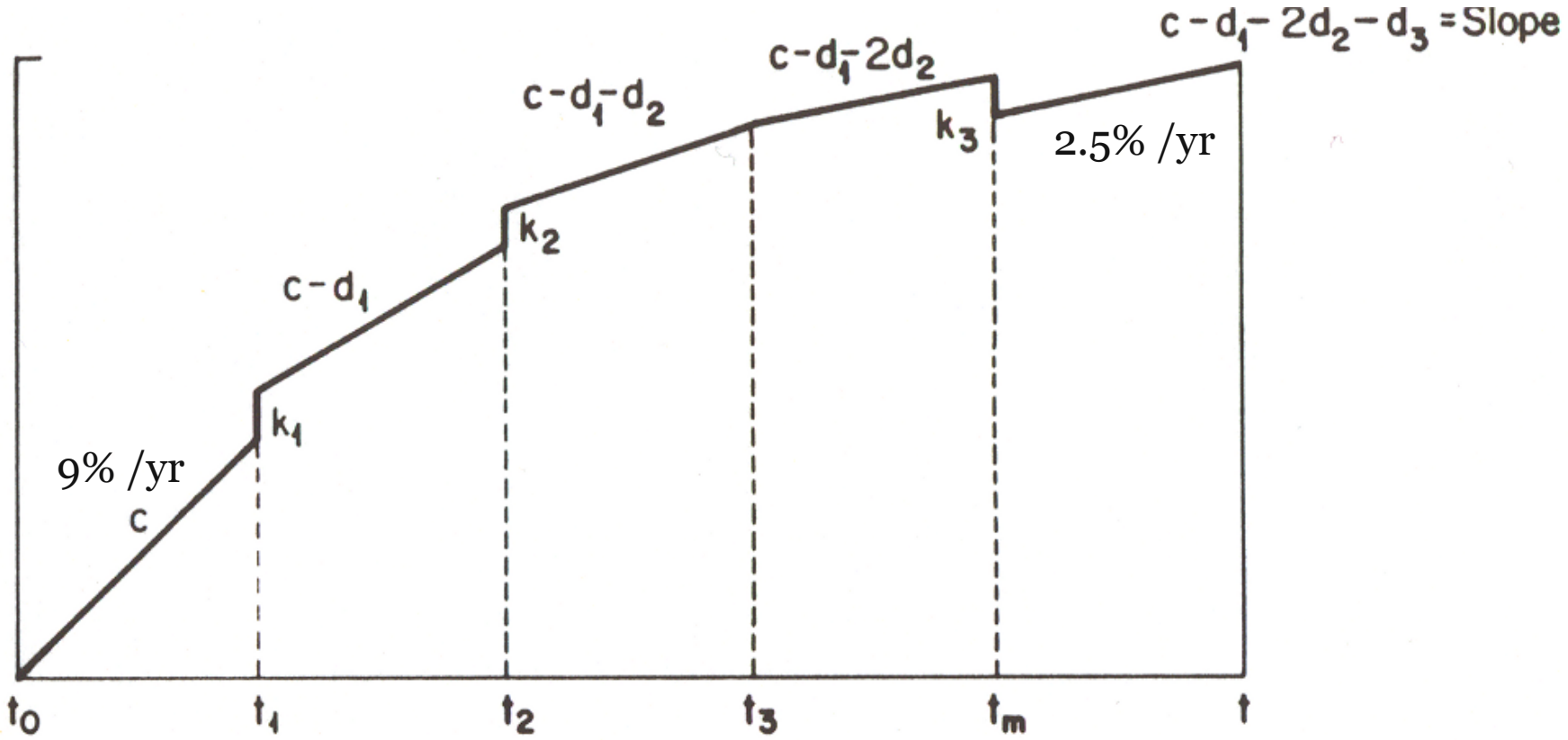

Rosner, Colditz, Willett, Am J Epidemiology 1994;139:826

Extensions to modeling

- Includes time from birth to menarche
- Allows the impact to the first birth to vary with age at first birth
- Fits log incidence (Poisson regression) model giving terms that are interpretable
- Contrast contribution of risk factors for receptor positive and negative breast cancer

Colditz and Rosner AJE 2000

Integrating exposures across lifecourse

- Our approach to incidence modeling is different from standard analytical approaches.

- Risk factors are assumed to have an effect on the rate of increase of breast cell proliferation.

- The cumulative number of breast cell divisions at age *t* is a latent variable that is assumed to be proportional to incidence at age *t*.

Interpretation

- The effect of most risk factors is cumulative over more than one year; although possibly differential in different periods of life
  - e.g., premenopause vs. postmenopause.
- This makes it more difficult to quantify associations of risk factors with disease
- But our approach is more consistent with the evidence that tumors take many years to develop and are affected by risk factors early in life even when very few cases are present.

Breast cancer prevention

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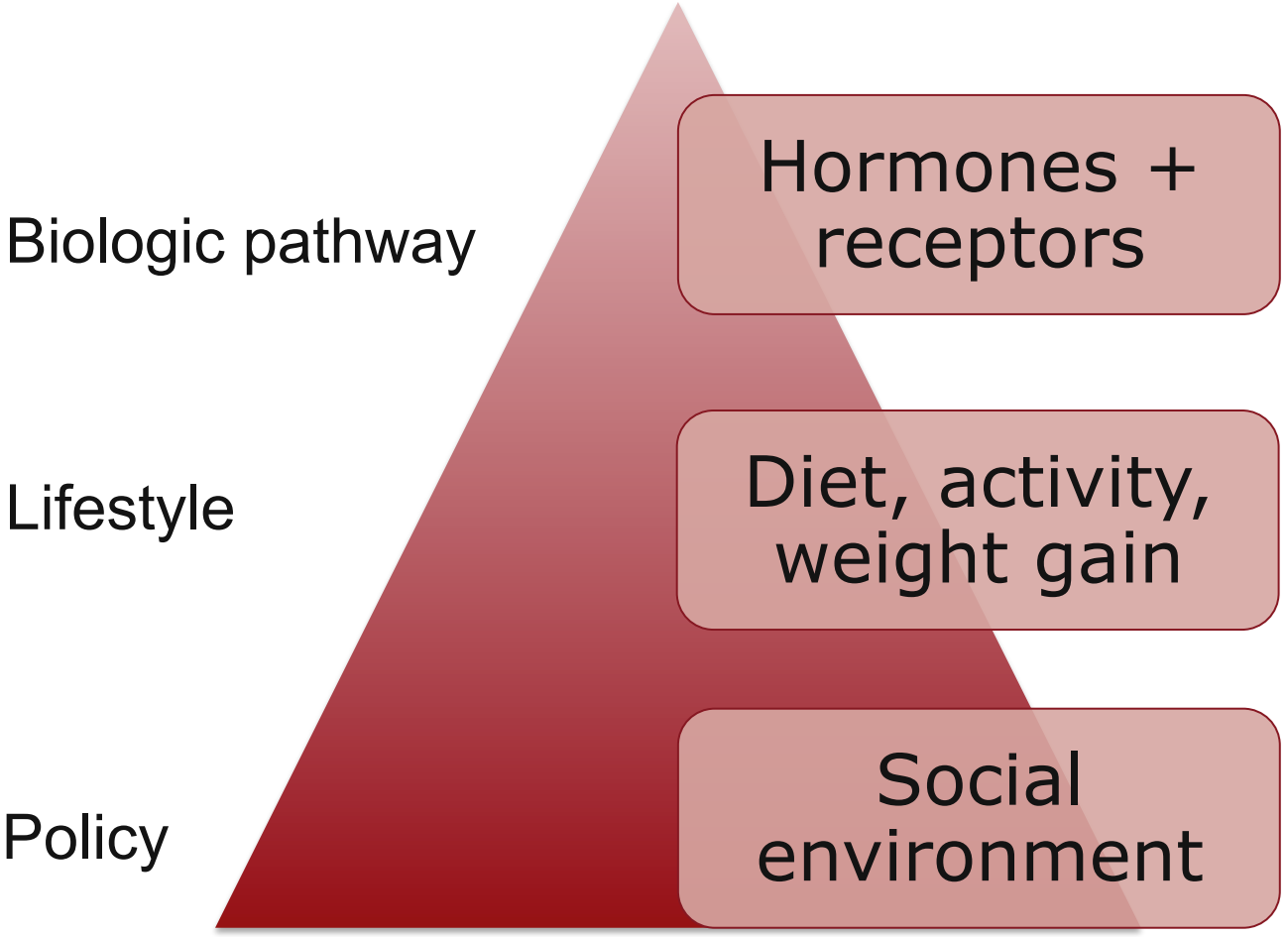
Weight loss (22lb)	Overweight + obese	60%	50%*
Increase exercise	<30 min/d	>60%	Timing matters
Adolescent Increase Activity	1-2 hrs / d	80%	25% ↓
Reduced alcohol	None, <1/wk	?	0 to 40% ↓
Increase fiber/ (veg protein)?	30+ g/day	80%	30-40% ↓

Conclusions: breast cancer prevention

- Timing matters
- To maximize benefits we must focus on biologically relevant periods
- Untapped potential for adolescent diet and perhaps other strategies to counter adverse effect of alcohol
- We already have many tools for prevention that are not fully used

Breast Cancer Prevention



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Colditz et al Sci Transl Med 2012: March 28

How to move forward

- Design and fund research that is not chopped up, siloed
- TREC is one example (NCI U54)
- IOM report advocates for transdisciplinary science to bridge genes and environment among other challenges of integration
- "create incentives to promote transdisciplinary research" (NIH and universities)
  - IOM 2006

Our societal obligation

- As cancer prevention scientists, we must accept responsibility for breast cancer prevention.
- Prioritize studies that will identify key points for intervention to maximize prevention.
- Move beyond obstacles to implement prevention of breast cancer here and throughout the world.

Very long term prevention action:

"In the beginning of every enterprise we should know, as distinctly as possible, what we propose to do, and the means of doing it… We desire to lay the foundation and to mature some parts of the plan. Those who come after us must finish the work."

William Greenleaf Eliot, co-founder
Washington University in St Louis
1854

Thank you

- Bernie Rosner & Cathy Berkey (statisticians)
- Stu Schnitt, Laura Collins, Jim Connolly, Craig Allred (pathologists)
- NHS investigators and trainees and participants
- American Cancer Society Clinical Research Professorship
- NCI & Breast Cancer Research Foundation for funding