Challenges and Opportunities in Cancer Prevention: The Case of Breast Cancer

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Disclosure Information

I have no financial relationships to disclose

I will not discuss off-label use or investigational use of drugs or devices in my presentation

Overview

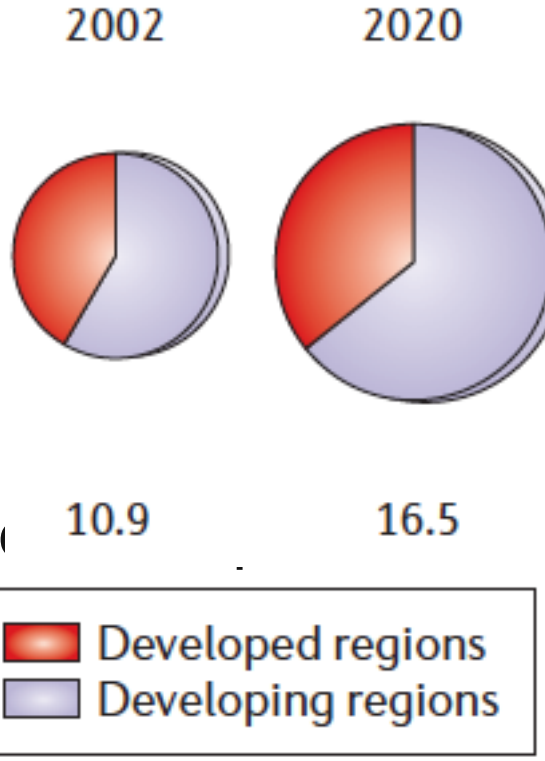
I. Burden – growing

II. Barriers to breast

III. Drivers of breast

IV. Focusing breast cancer prevention

V. Steps we can take *now*



2012 – 14 M cases

1.7 M breast

I. Burden of cancer – e.g., US costs

Total direct cost – billions ($US 125b in 2010)

- Breast cancer: $US 16.6 b, or 13% in 2010

Increasing burden also of indirect costs of cancer

- Lost productivity due to breast cancer $US 10.9b

Hassett & Elkin, 2013

II. Barriers to breast cancer prevention

1. *Skepticism* that cancer can be prevented
2. *Short-term* focus of research
3. *Timing*: Interventions too late in life
4. Research focused on treatment not prevention
5. Debates among scientists
6. Societal factors ignored
7. Lack of transdisciplinary training
8. Complexity of implementation

Colditz et al. Sci Transl Med 2012: March 28

Barrier 1: *Skepticism* of scientists that breast cancer can be prevented

- Marshaling the evidence that breast cancer can be prevented
- Overcoming disagreements about the endpoints for prevention – e.g., benign lesions
- Challenging the premise that we must completely substantiate the biologic pathway before intervening
- Avoiding over-interpreting null studies when they miss the relevant time frame for pathogenesis

Generally accepted breast ca. prevention strategies

Strategy	Risk group	% US pop	Risk reduction
Bilateral oophorectomy	BRCA1/2	<1%	50% ↓
Tamoxifen / Raloxifene	>1.67% 5-yr risk	10-40%	50% ↓
Weight loss (22lb)	Overweight + obese	60%	50%* ↓
Stopping estrogen & progestin Rx	Past vs. current	1-5%	10% ↓

* Loss after menopause based on Eliassen et al. JAMA, 2006; Colditz & Bohlke 2014

Further evidence that breast cancer is preventable

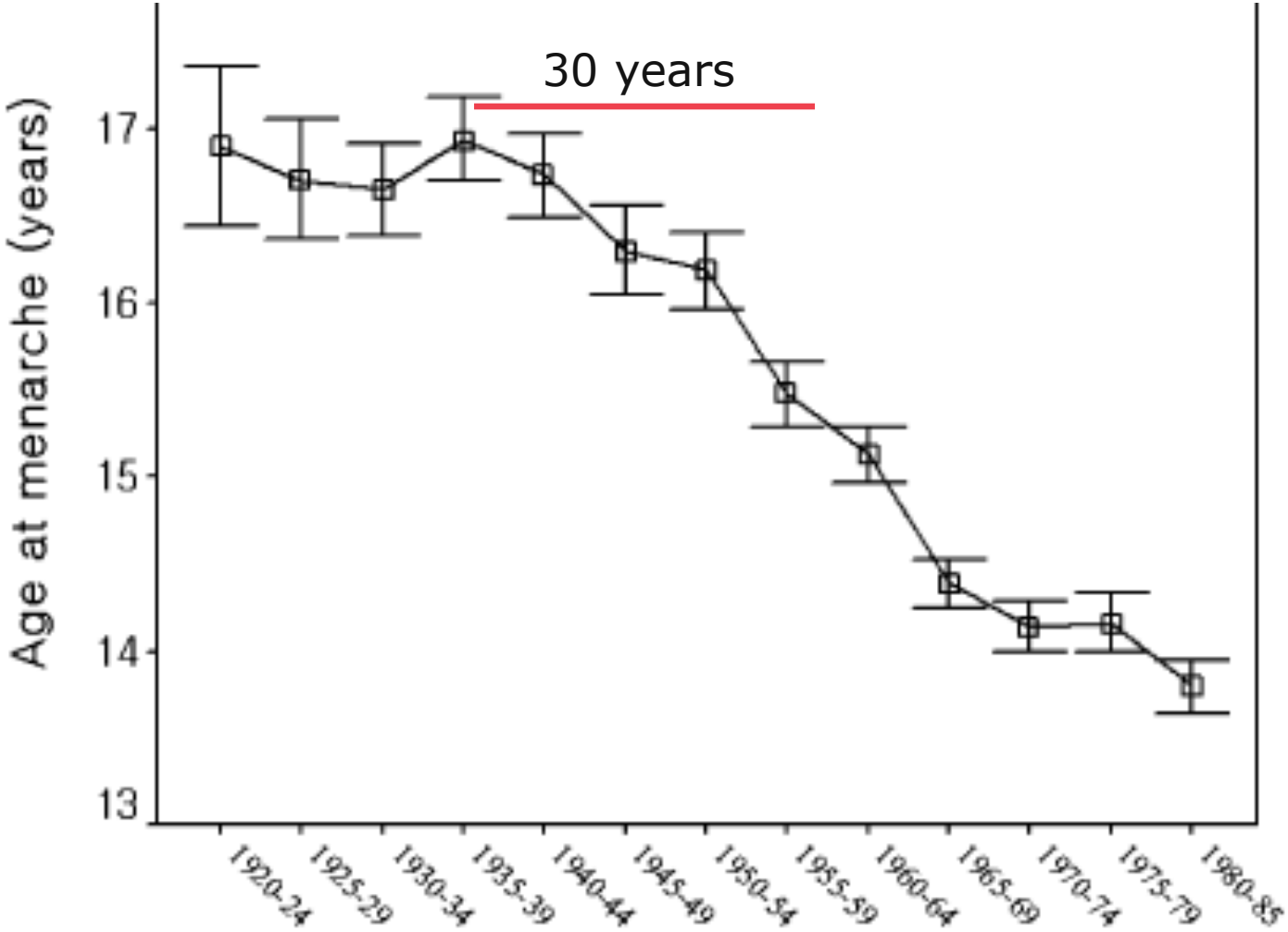
Migrant studies

- No US lifestyle,
- Substantial changes in risk over generations, but disentangling the complexity of lifestyle changes makes interpretation difficult

Within-country changes

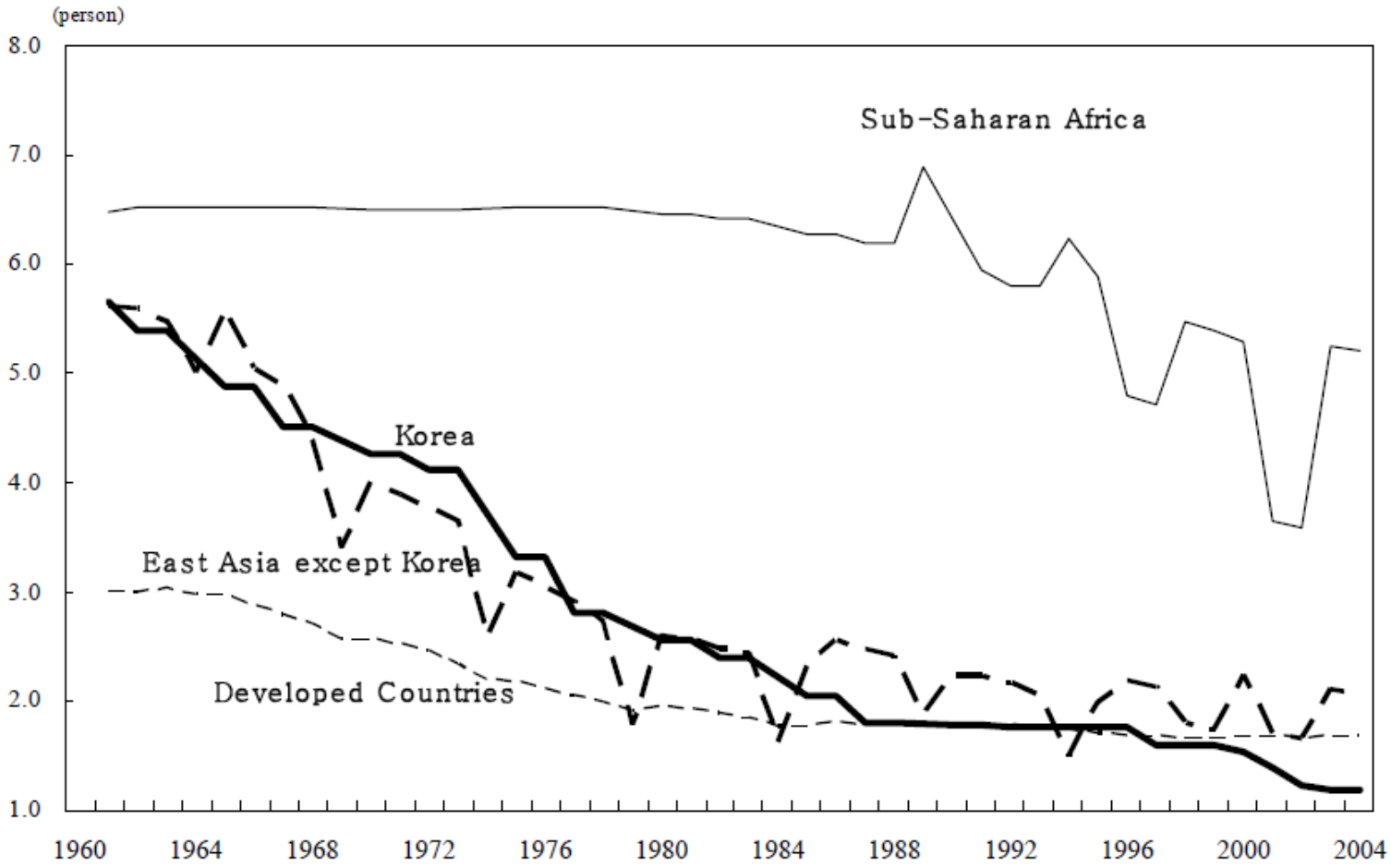
- Remove E&P HT, Korea rapid increase, China, etc.

Within-country change: Menarche in Korea, 1920-85



Cho Eur J Pediatr 2009

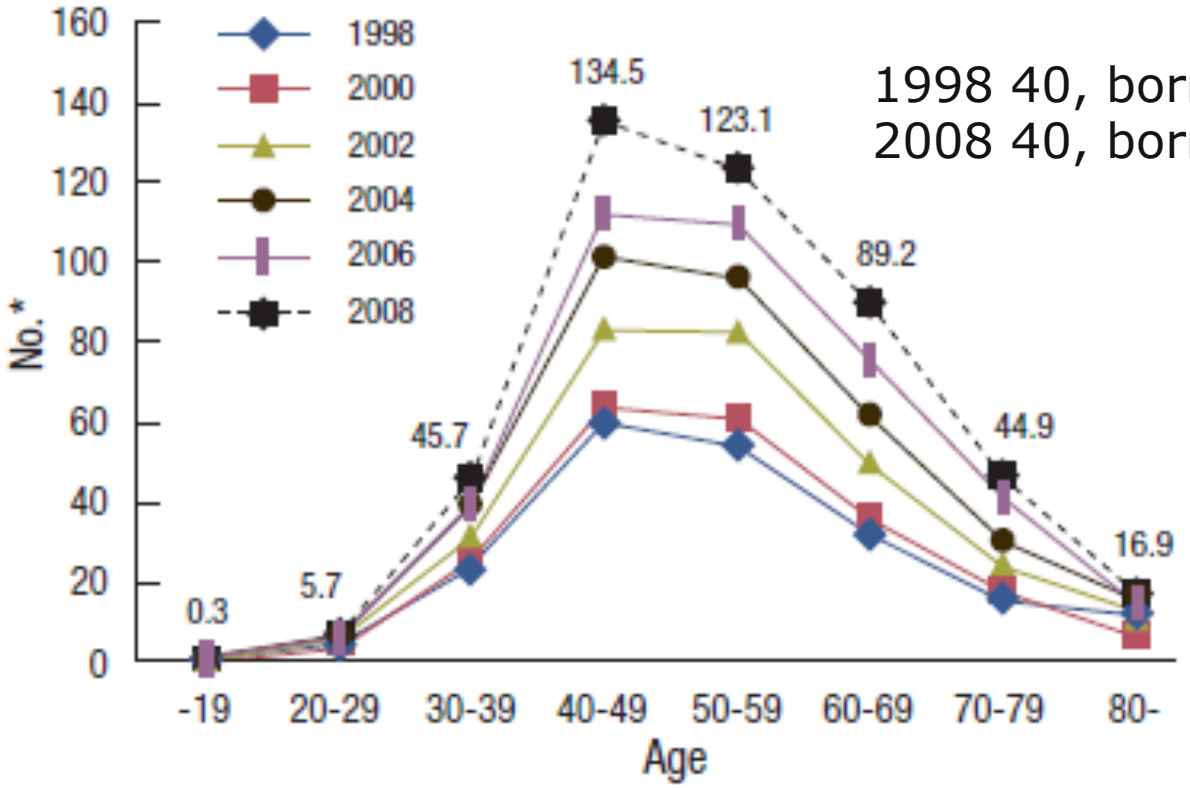
Within-country change: Fertility, 1960-2004



Calendar year

Ito et al. NEBR, 2008

Within-country change: Breast cancer incidence, Korea



1998 40, born 1958
2008 40, born 1968

Jung et al. J Breast Ca, 2011

Barrier 2: *Short-term* focus

- Time required for disease prevention does not match funding periods
- Long-term benefits, e.g., smoking cessation takes decades to show at population level
- Funded studies focus too late in disease development process
- In contrast, the natural history or time-course of cancer shows development over decades

Colditz et al. Sci Transl Med 2012: March 28

Barrier 3: *Timing* – focusing research and current prevention on the period around diagnosis when breast cancer develops over decades

Majority of etiologic studies focus on lifestyle and drugs months before diagnosis

- Epidemiology of breast cancer focuses predominantly on postmenopausal women
- Prevention trials in women at high risk of developing breast cancer within 5 years

This focus distracts us from understanding when risk accumulates and what drives risk

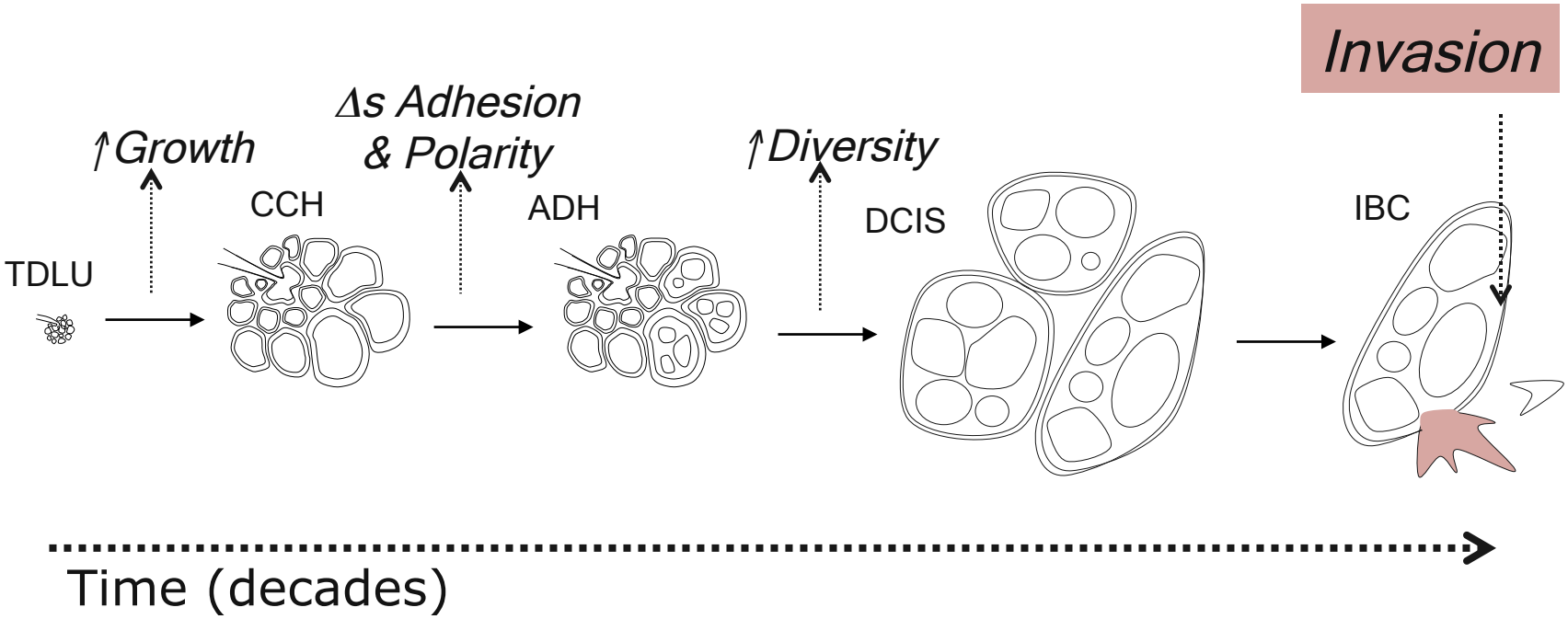
See Colditz, Bohlke, Berkey Br Ca Res Tr 2014

Life-course development of risk accumulation

- Long-term effects of early radiation
- Menopause – cessation of menstrual cycles leads to slower risk accumulation
- Menopause tells us hormones or accumulation through premenopausal years must be important
- Menarche and height point to early life as important

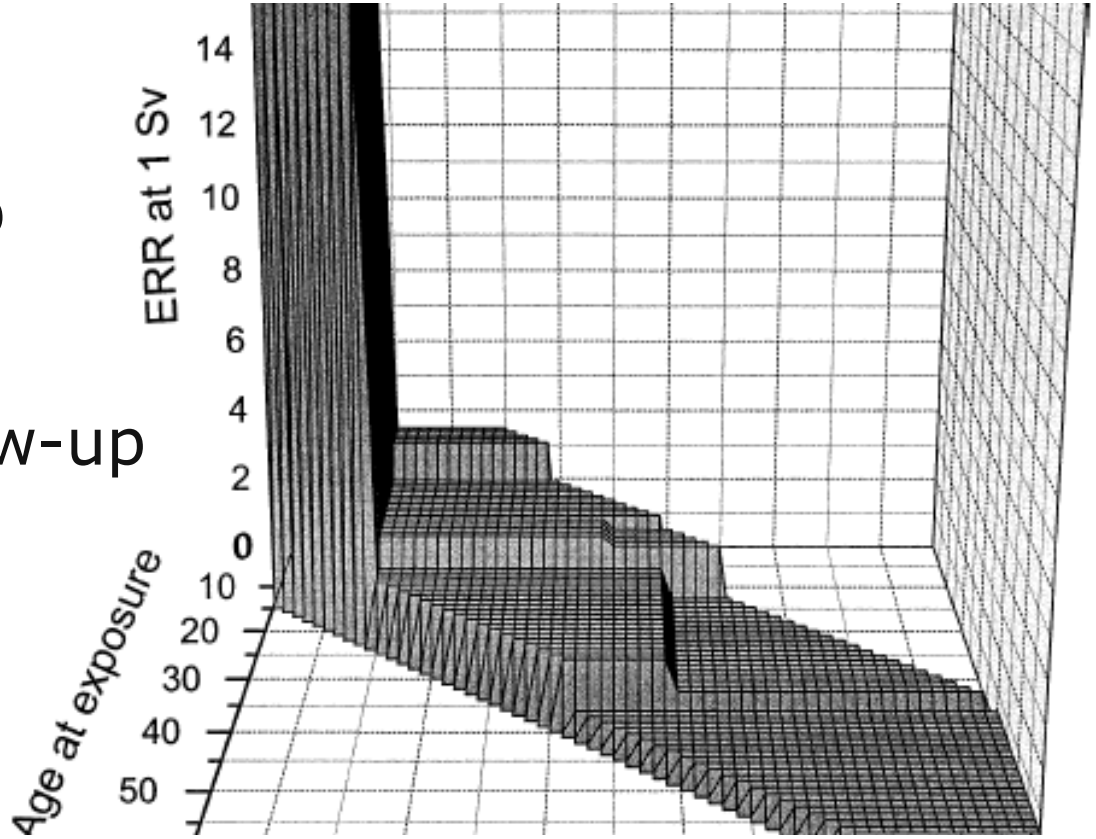
Model of breast cancer development

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



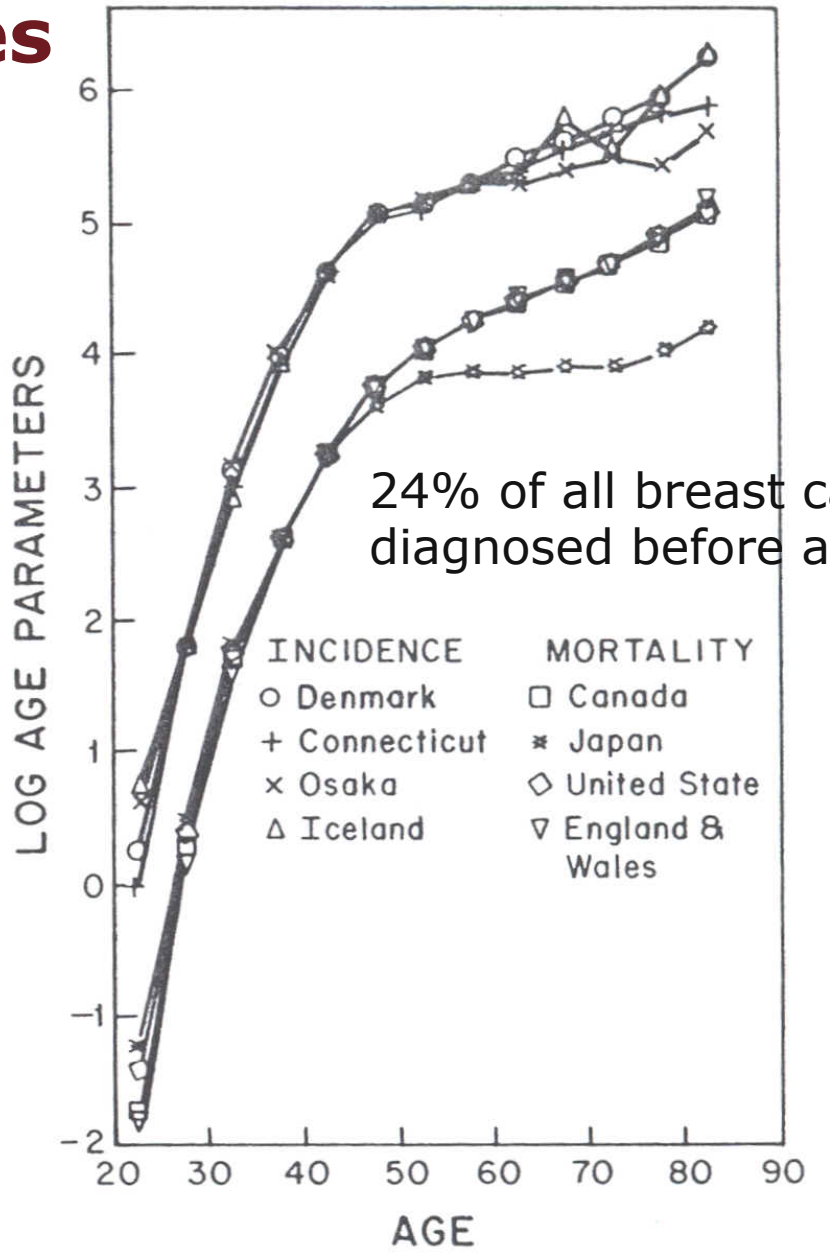
Long-term effects of radiation in early life

Atomic bomb survivors,
70,165
40 year follow-up
1059 cases



Land et al. Radiation Research 2003

Early life clues



24% of all breast cancer diagnosed before age 50

Moolgavkar et al JNCI 1979

III. Drivers of breast cancer

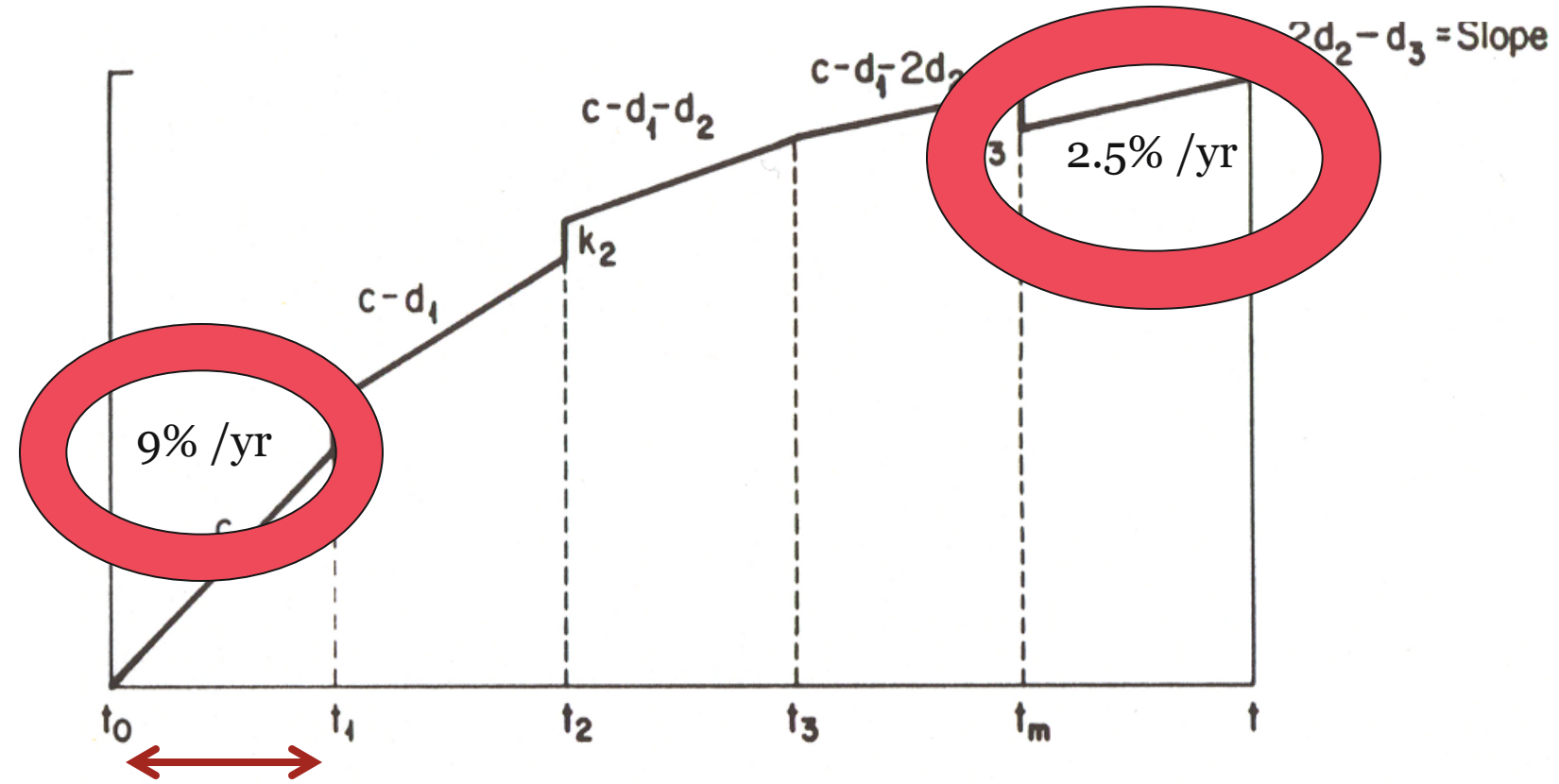
- Progression through premalignant lesions as risk accumulates
- Faster rise in risk before menopause than after
- Hormonal cycling during premenopausal years
- Peak height growth velocity
- Diet and physical activity

Using attained age as a marker of risk is a poor proxy

Attained age as marker of risk masks the underlying risk accumulation

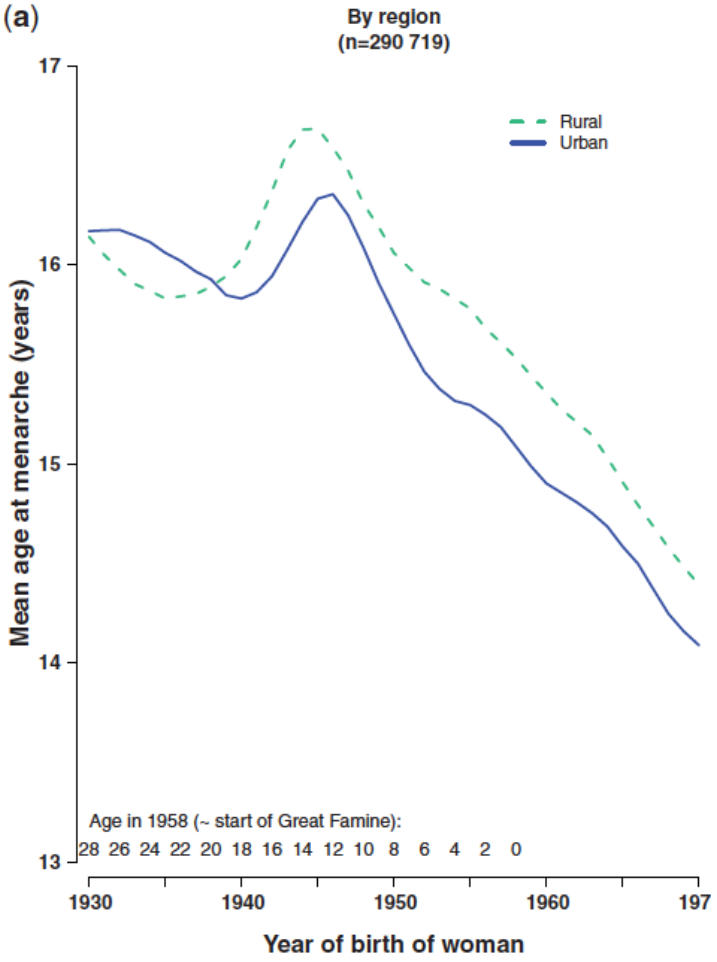
- Accumulated exposure up to an age
- DNA damage
- Some other function of age, e.g., time between menarche and first birth
- One attained year of age may not be the same at age 10 as at age 60
- Look within age across life course to better understand drivers

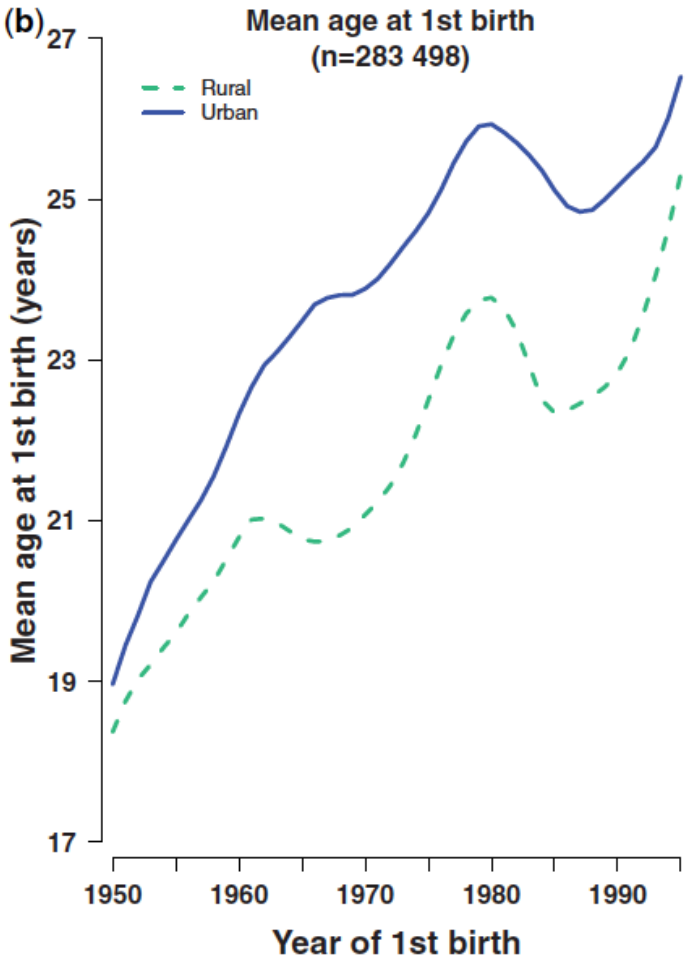
Accumulating risk, multiple birth model



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

300,000 women in the China Kadoorie Study





Lewington IJE 2014

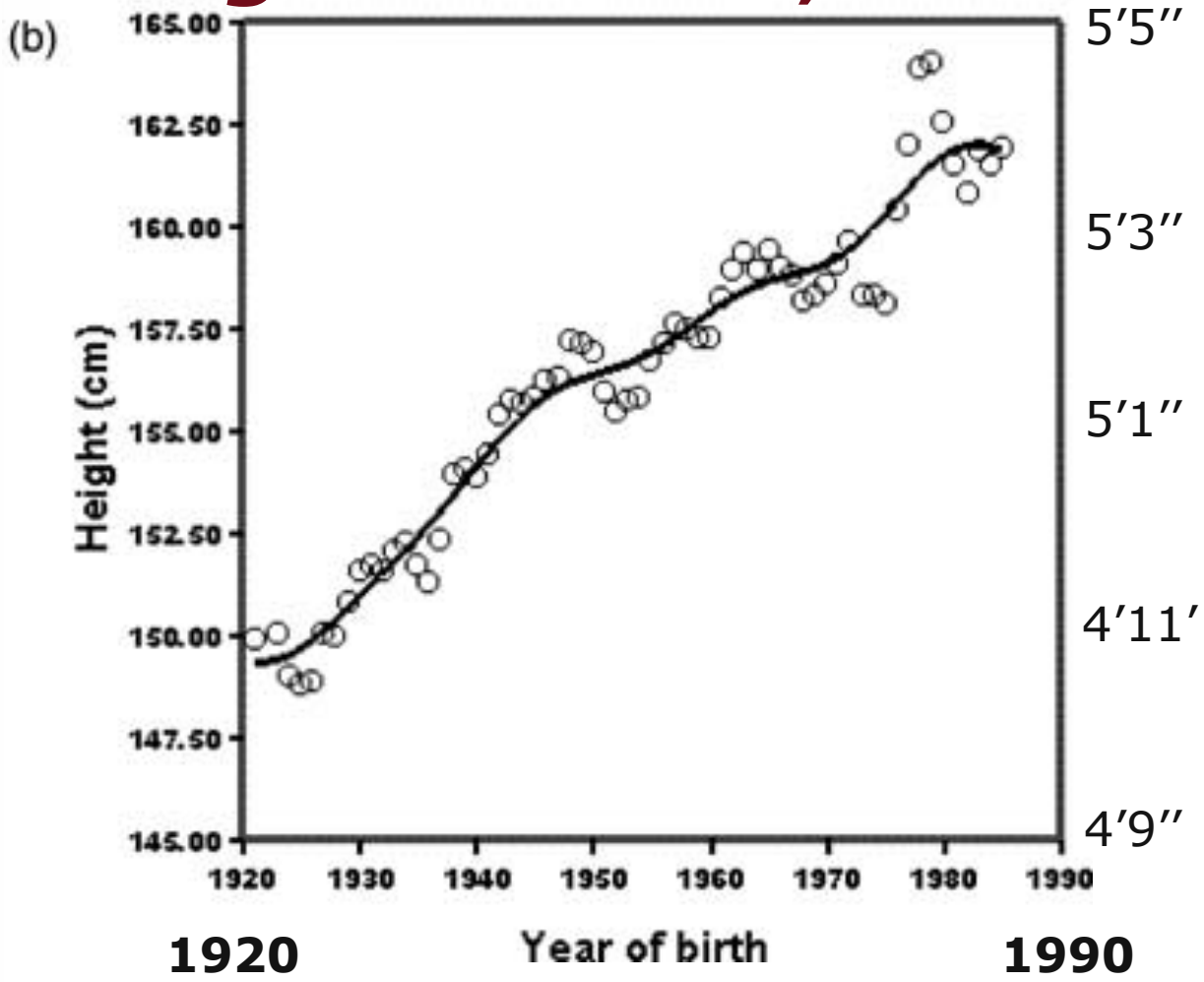
Risk factors account for 76% discrepancy China vs. US

- Compared age-specific incidence in Shanghai prospective cohort vs. SEER.
- Then fit Rosner-Colditz model to account for risk factors:

  Age at menarche, age at first and subsequent births, height, weight at 18 and through adult life, alcohol, menopause, type of menopause (natural, surgical), use of postmenopausal hormone therapy (E alone, E+P), benign breast disease, family history breast ca.
- 76% of the US excess incidence controlled away with the established risk factors.
- Leaves open the dynamics of growth, childhood and adolescence

Linos,…,Colditz JNCI 2008;100:1352-60

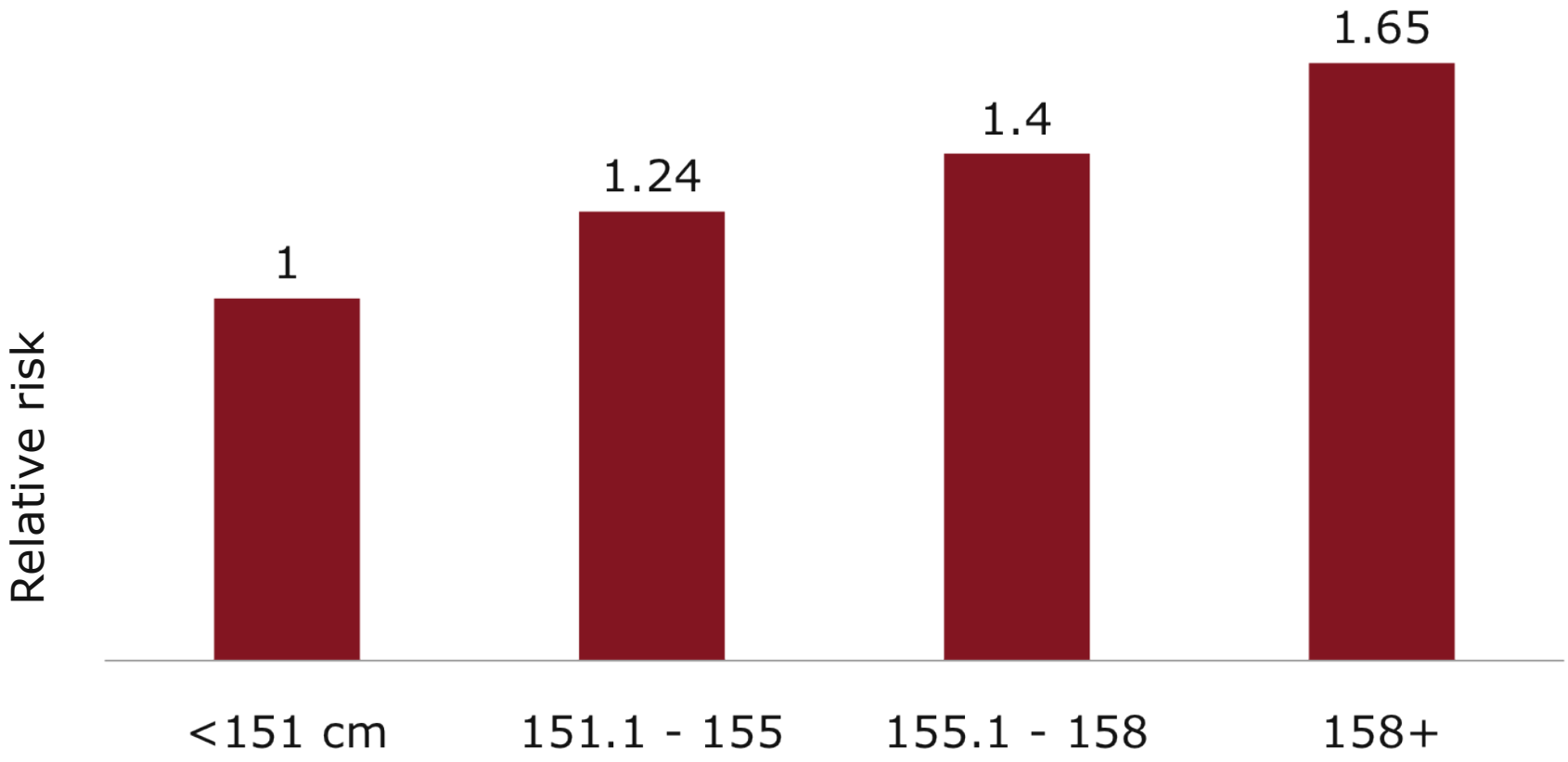
Within-country change: Height in Korea, 1920-90



1920 **1990**

Hwang Ann Hum Biol 2003

Height and relative risk of breast cancer incidence in Korea – 339,000 women, 1994-2004



Sung J, et al. AJE 2009

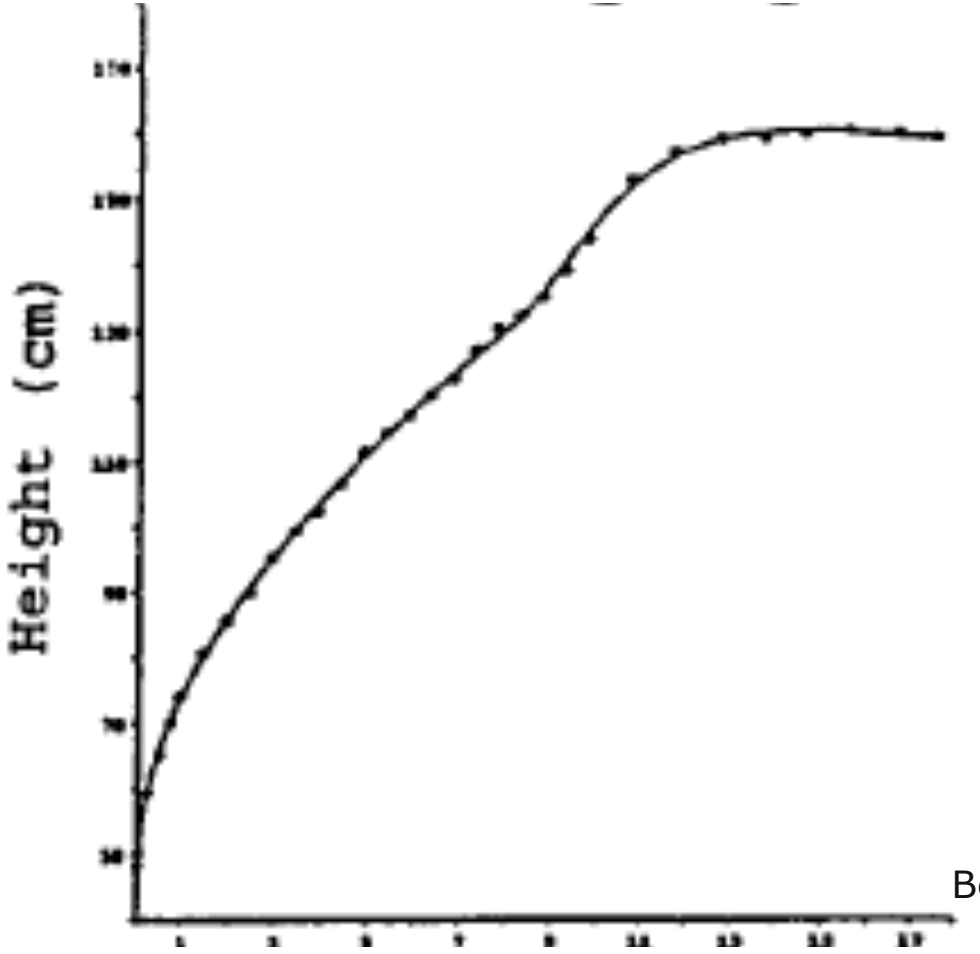
Understanding growth velocity (Stuart study)

Harvard Growth Study (HGS)

Females born in 1930s and 1940s, followed to age 18

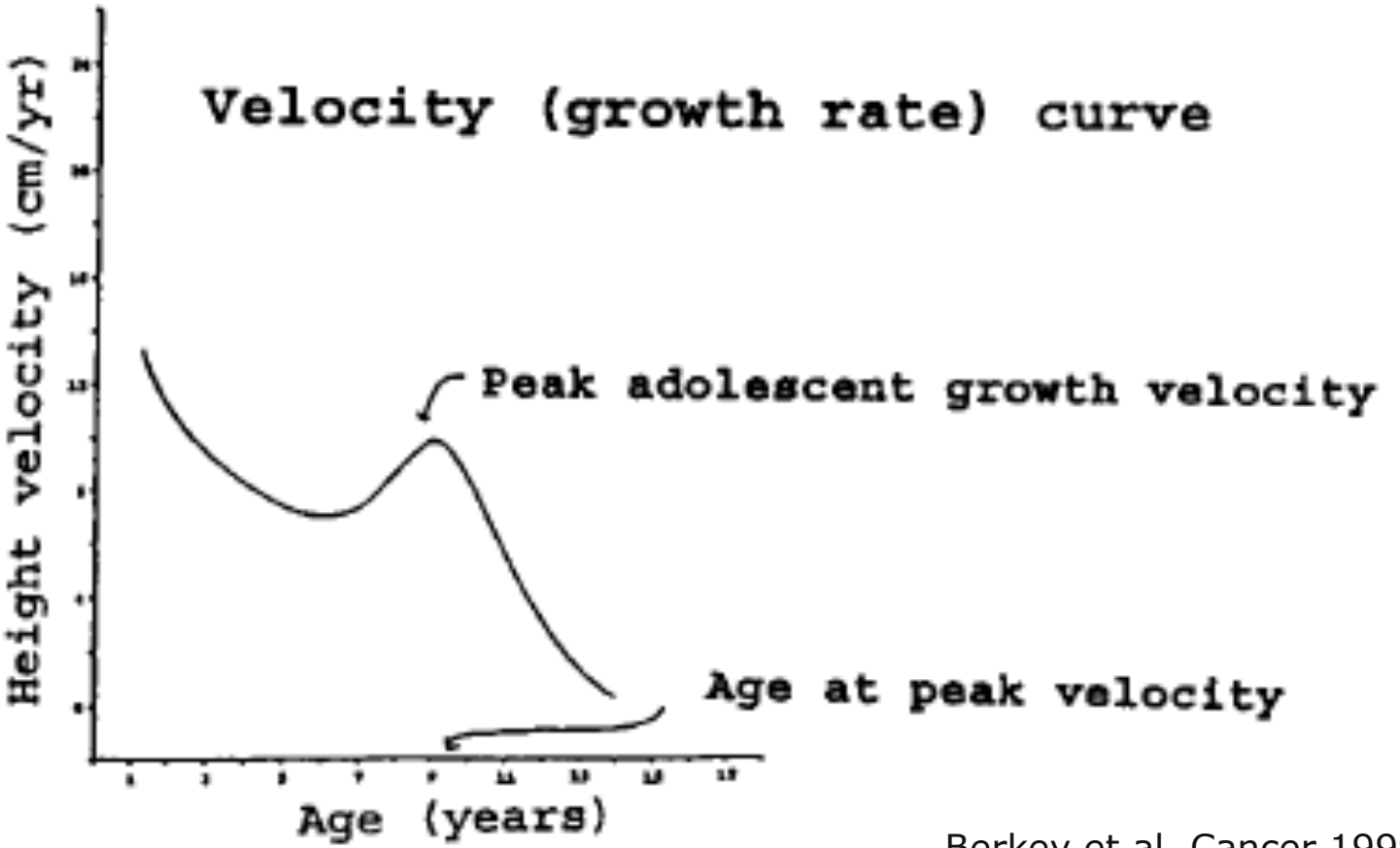
- Age at menarche recorded to month
- Annual height measurements (identify year in which girl experienced most rapid adolescent height growth)
- Mother interviewed annually on dietary intake over past 6 months while child being examined/ measured, etc.

Growth curve of one girl, HGS Peak height velocity = amount of greatest height gain in a single year



Berkey et al. Cancer 1999

Peak height velocity



Berkey et al. Cancer 1999

Predictors measured from birth through age 5, HGS

Age at menarche =

12.8 (0.12) – 0.38 (0.12)height at age 3 to 5yr

+ 2.19 (0.91) vegetable protein ages 3 to 5 yr.

Peak height growth velocity =

14.2 + 4.25 (1.07) calories – 0.39 BMI ages 3 to 5yr + 2.08 (0.95) animal protein ages 3 to 5yr

Results consistent when repeated for exposures at age 10

Berkey, …, Colditz AJE 2000; 152:446-52

Milk and growth velocity

Previously published from GUTS

- Higher growth velocity increased risk of BBD (Berkey)
- Also, increased risk of pre and postmenopausal breast cancer
- Milk intake positively related to increase in peak height growth velocity (Berkey CEBP 2009)

Now, meta-analysis of 12 controlled trials

- 0.4cm per year additional height growth for each 8oz (cup) of milk consumed

De Beer. Dairy products and physical stature. Economics and human biology 2012;10:299-309

Applying peak height growth velocity: Nurses' Health Study and 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

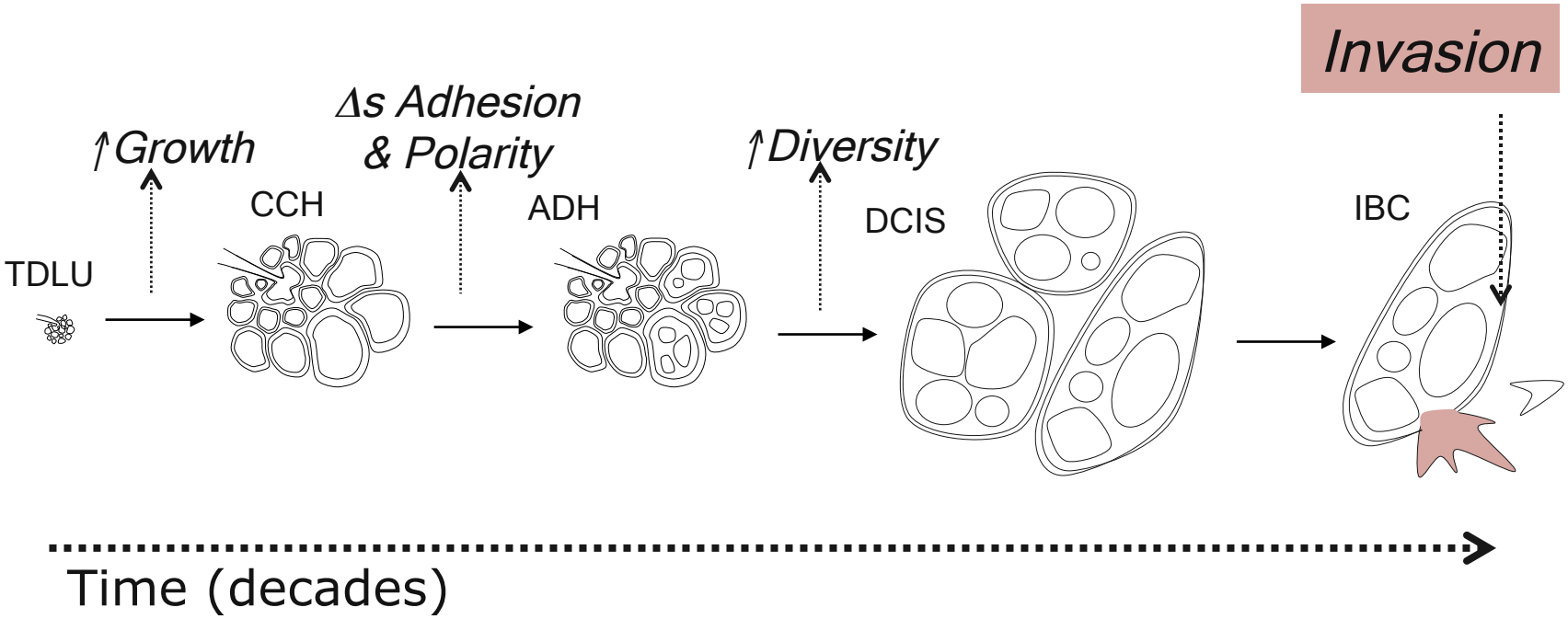
Danish Cohort confirms growth velocity finding

- 141,393 girls, measured height annually in school
- Linked to cancer registry
- 3340 cases of breast cancer
- Height increase age 8 to 14 positively related to risk of breast cancer before age 50 and after
  - RR per 5 cm = 1.15 (1.05, 1.27): age <50 yr
  - RR per 5 cm = 1.18 (1.07, 1.30): age 50+ yr

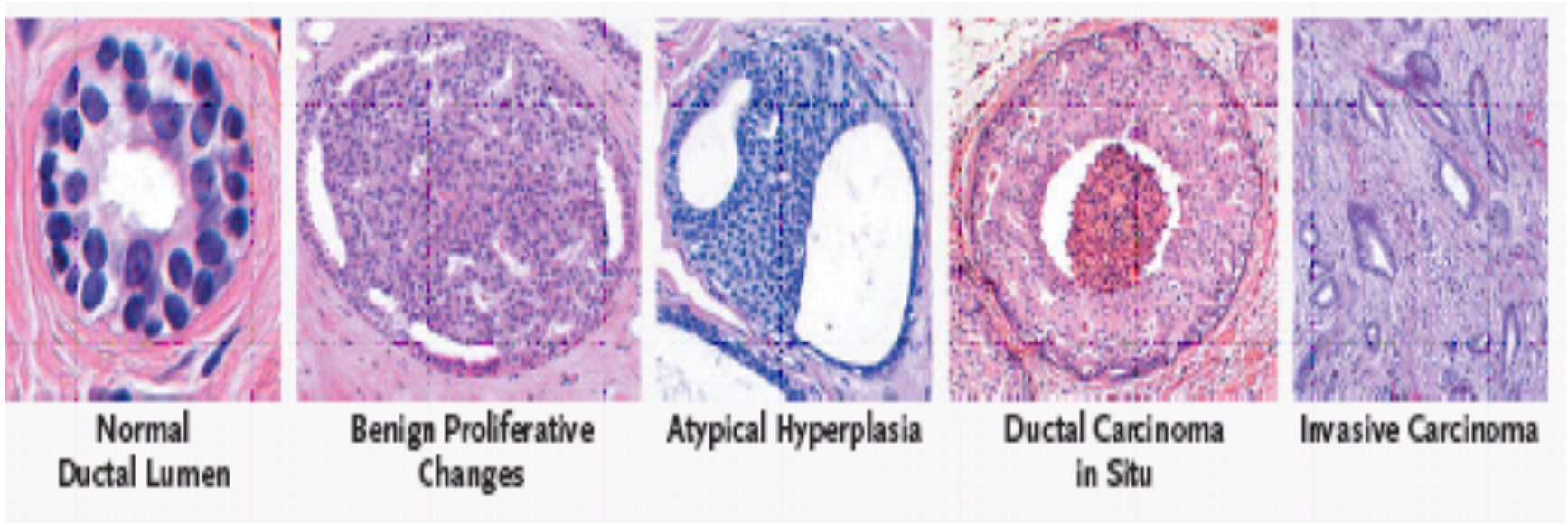
Ahlgren et al. NEJM 2004; 351:1619-26

Model of breast cancer development

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



Intermediate markers: benign breast disease (BBD)



RR = 1.8 = 3 to 5

London et al. JAMA et al 1989

IV. Focusing breast cancer prevention

Understanding what predicts incidence of benign breast disease

NHSII – incident BBD (RO1-CA50385)

- Central pathology review
- Components of adolescent lifestyle:
  - Diet including alcohol
  - Physical activity

GUTS, Growing Up Today Study

- Prospective data collected
- Self-report benign breast disease confirmed by breast biopsy

Alcohol

A known breast carcinogen

IARC 2007

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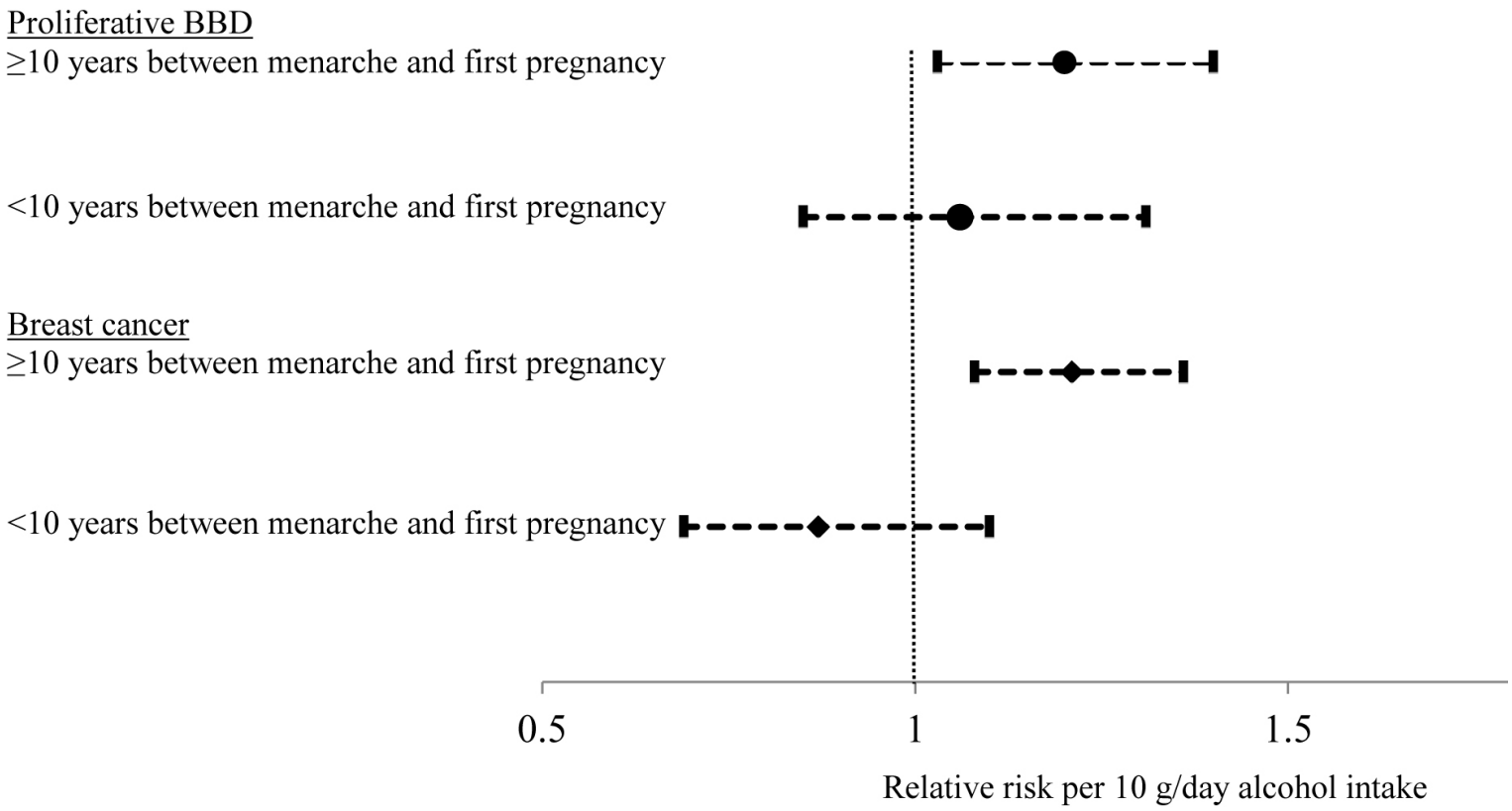
Alcohol intake, ages 18-22, incident proliferative BBD, NHSII

Alcohol intake (grams/ day)	Cases (678)	Person-year	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, 2012

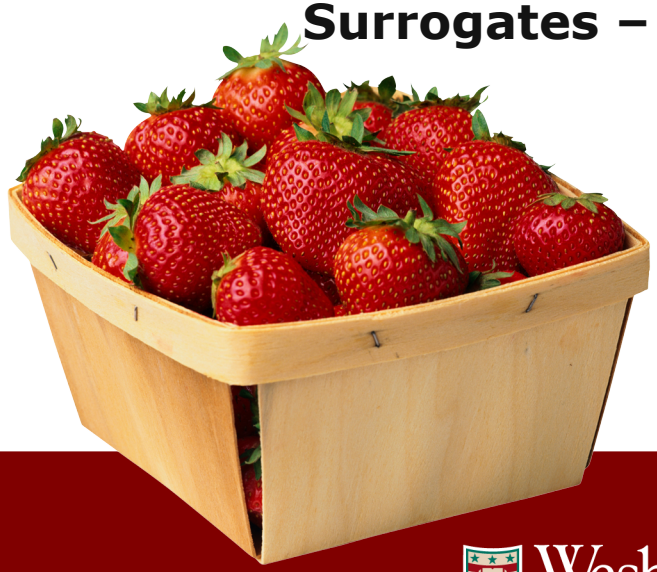
Alcohol before first pregnancy, NHSII



Liu, Colditz, Tamimi JNCI 2013

Vegetable protein intake

Surrogates – soy, fiber, fruit and vegetables



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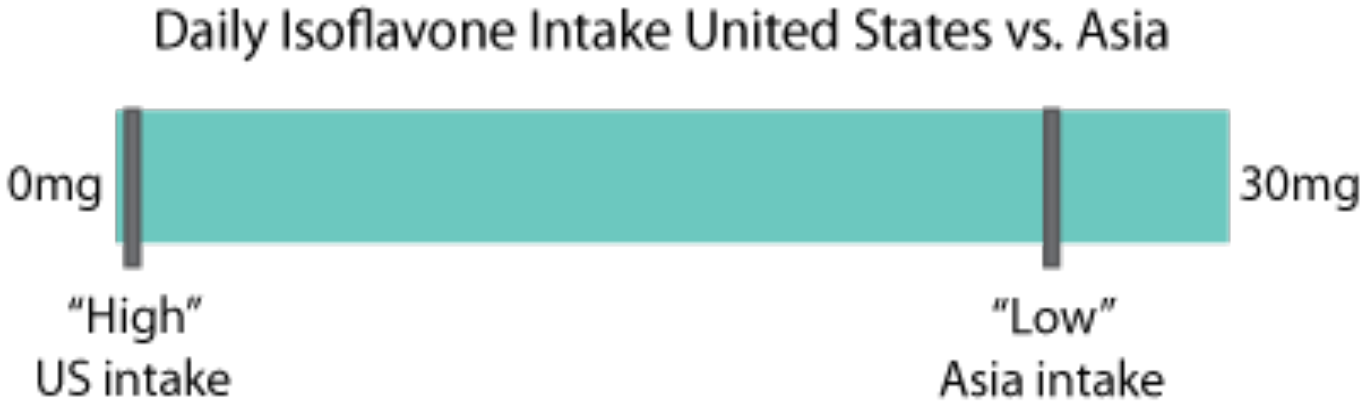
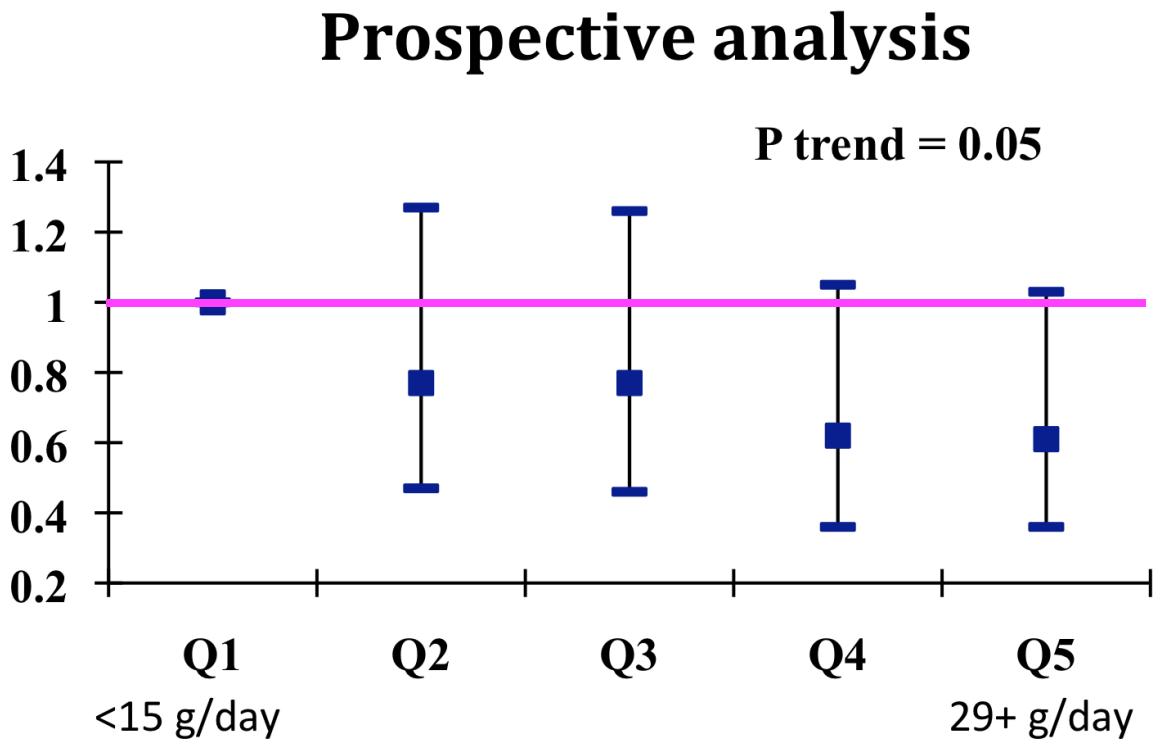
Soy Asia vs. USA



The highest soy intake in the United States (measured by isoflavone intake) is well below the lowest intake in Asia

Wu et al. 2008

Adolescent fiber & proliferative BBD: NHSII



Su et al. Cancer Causes Control 2010

BBD, GUTS cohort

112 women confirmed biopsy for benign breast lesion

6950 free from biopsy

FFQ at entry 1996, then 1997, and 1998

- Peanut consumption (peanut butter and bags of peanuts) significantly inverse
- Total servings of vegetable per day inversely related to risk of BBD

Cumulative dietary intake 1996 to 1998 and risk of BBD

Dietary intake	Mean intake	OR	95% Confidence Interval
Vegetable protein (10gm/d)	24 g	0.86	0.55-1.34
Vegetable fat (10gm/d)	33 g	0.72	0.52-0.98
Peanut butter and bags of peanuts (servings/3d)	0.52	0.56	0.35-0.87
Beans, lentils, soybeans (servings/3d)	0.24	0.95	0.55-1.62
Corn (servings/3d)	0.40	0.73	0.37-1.43
Total servings per day of peanut butter, bags of nuts, beans, lentils, soybeans, and corn	0.38	0.33	0.13-0.82

Multivariable adjusted models include childhood adiposity, age at menarche, adolescent alcohol intake, and pregnancy (ever). Berkey et al. Breast Ca Res Treat, 2013

Ontario, Canada: Population-based case-control study

Recall of adolescent diet

- (55 food items)

High participation

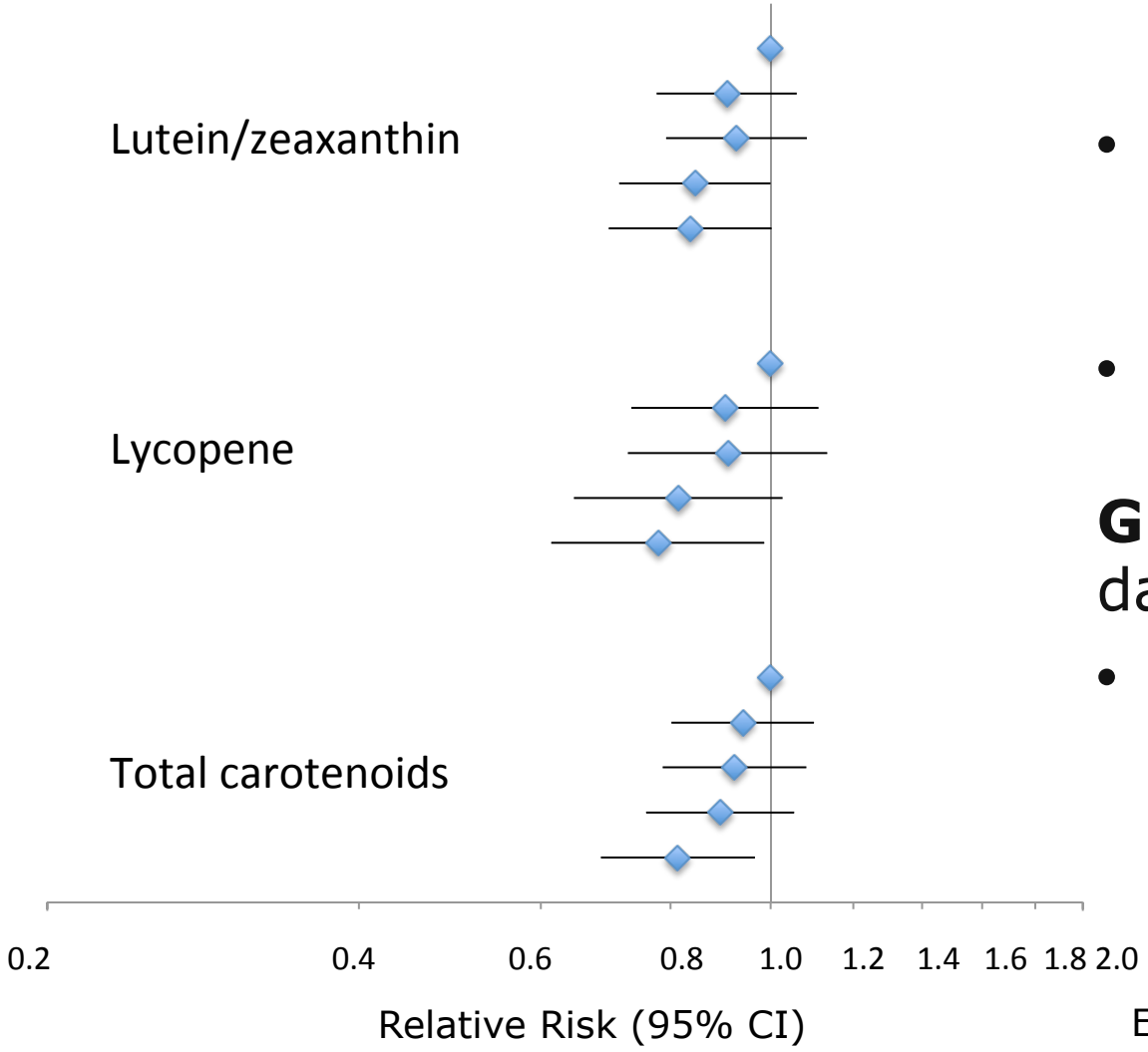
- (2865 cases, 3299 controls)

Top vs. bottom quintile of intake

- Fiber — mvOR = 0.66 (0.55 - 0.78)
- Vegetable protein — mvOR = 0.80 (0.68 – 0.95)
- Nuts — mvOR = 0.76 (0.61 - 0.95)

Liu, Y., Colditz, et al. Breast Cancer Res Treat 2014.

Carotenoids Breast Ca. & BBD



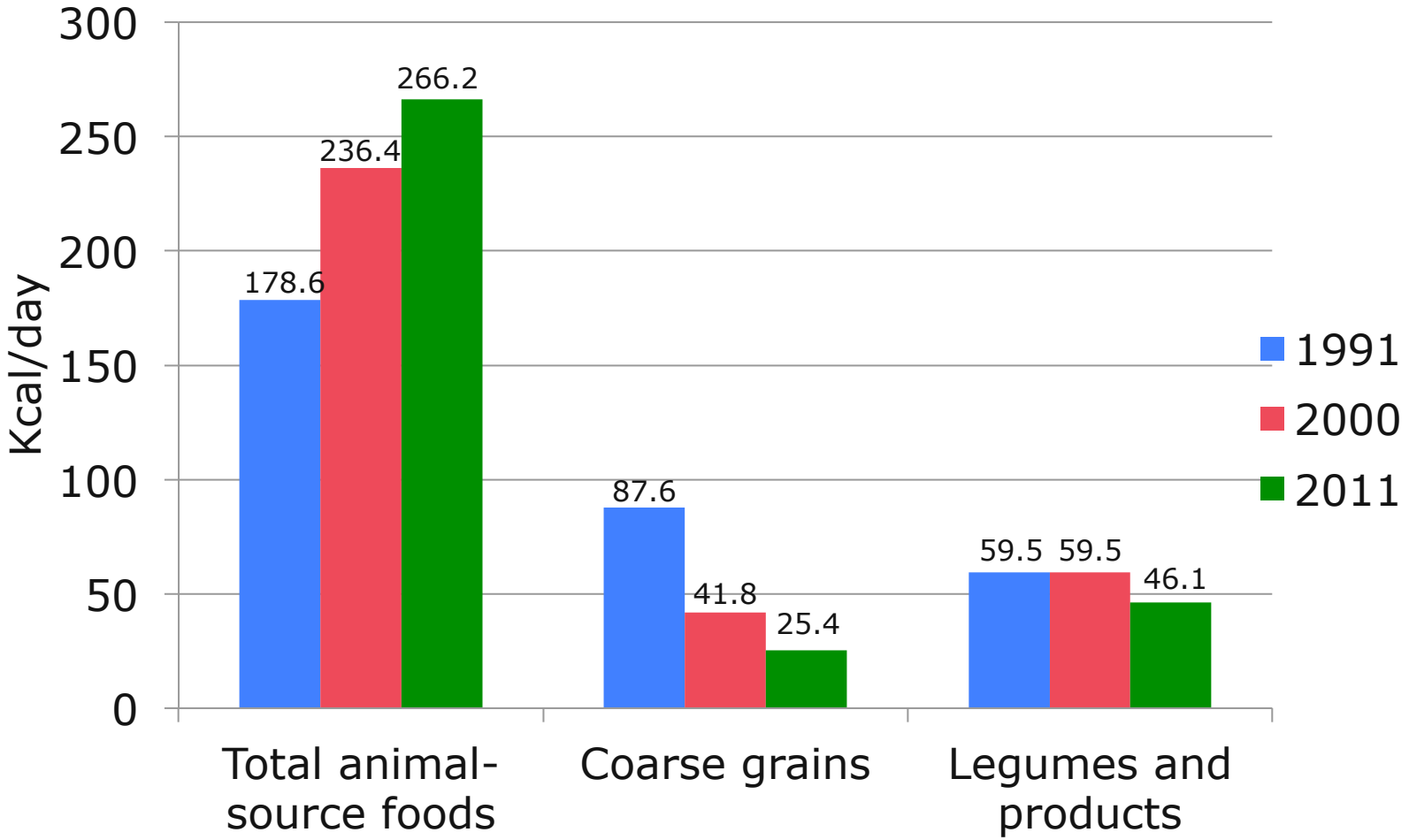
- 3055 prospective cases breast and controls with bloods stored
- Total carotenoids: 19% lower risk

GUTS Prospective diet data (Boeke Peds 2014)

- Beta-carotene, Alpha-carotene, Lutein all inversely related to risk of incident BBD

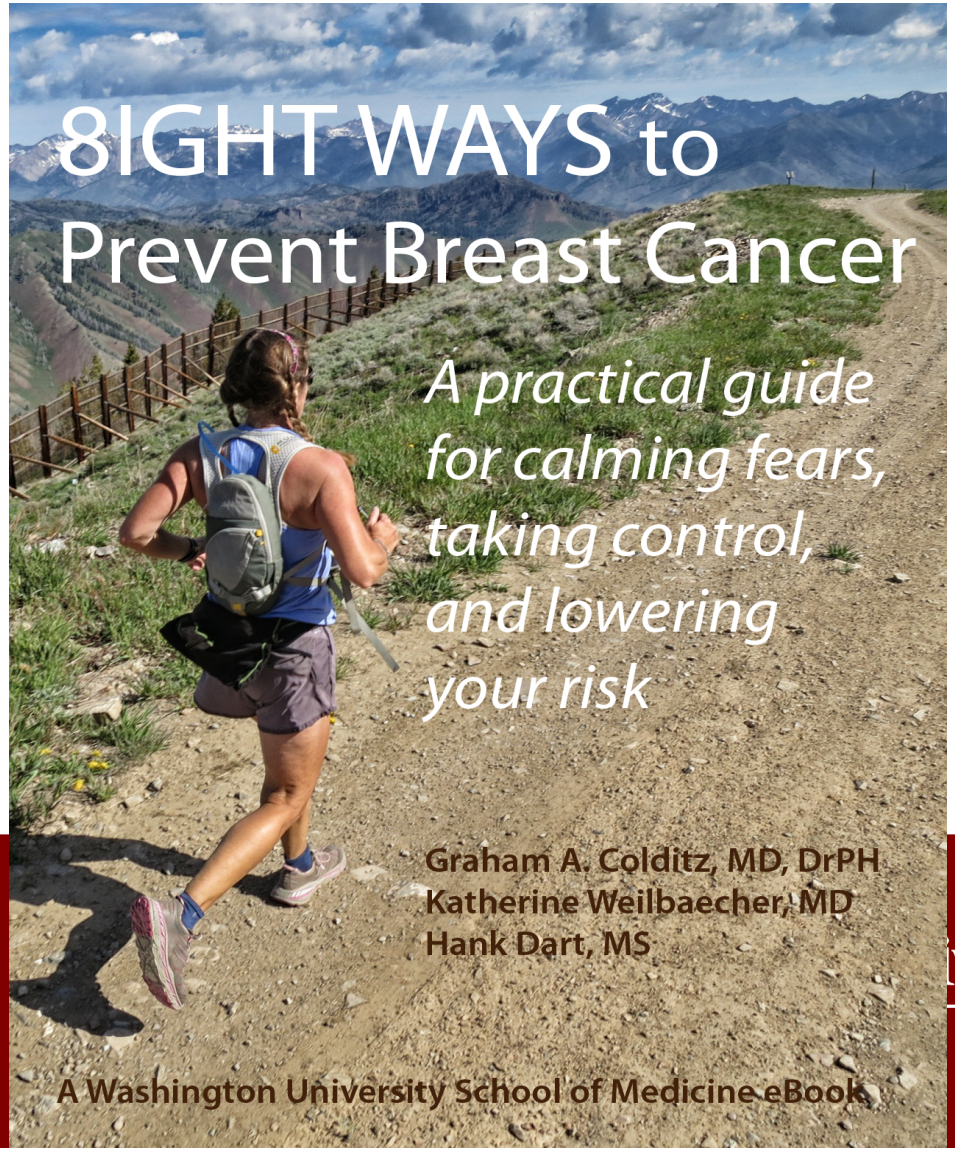
Eliassen, et al. *J Natl Cancer Inst* 2012

Food consumption trends in China (ages 2-18), 1991 to 2011



F. Y. Zhai *et al.*, Dynamics of the Chinese diet and the role of urbanicity, 1991-2011. *Obes Rev* **15 Suppl 1**, 16 (Jan, 2014).

Physical activity



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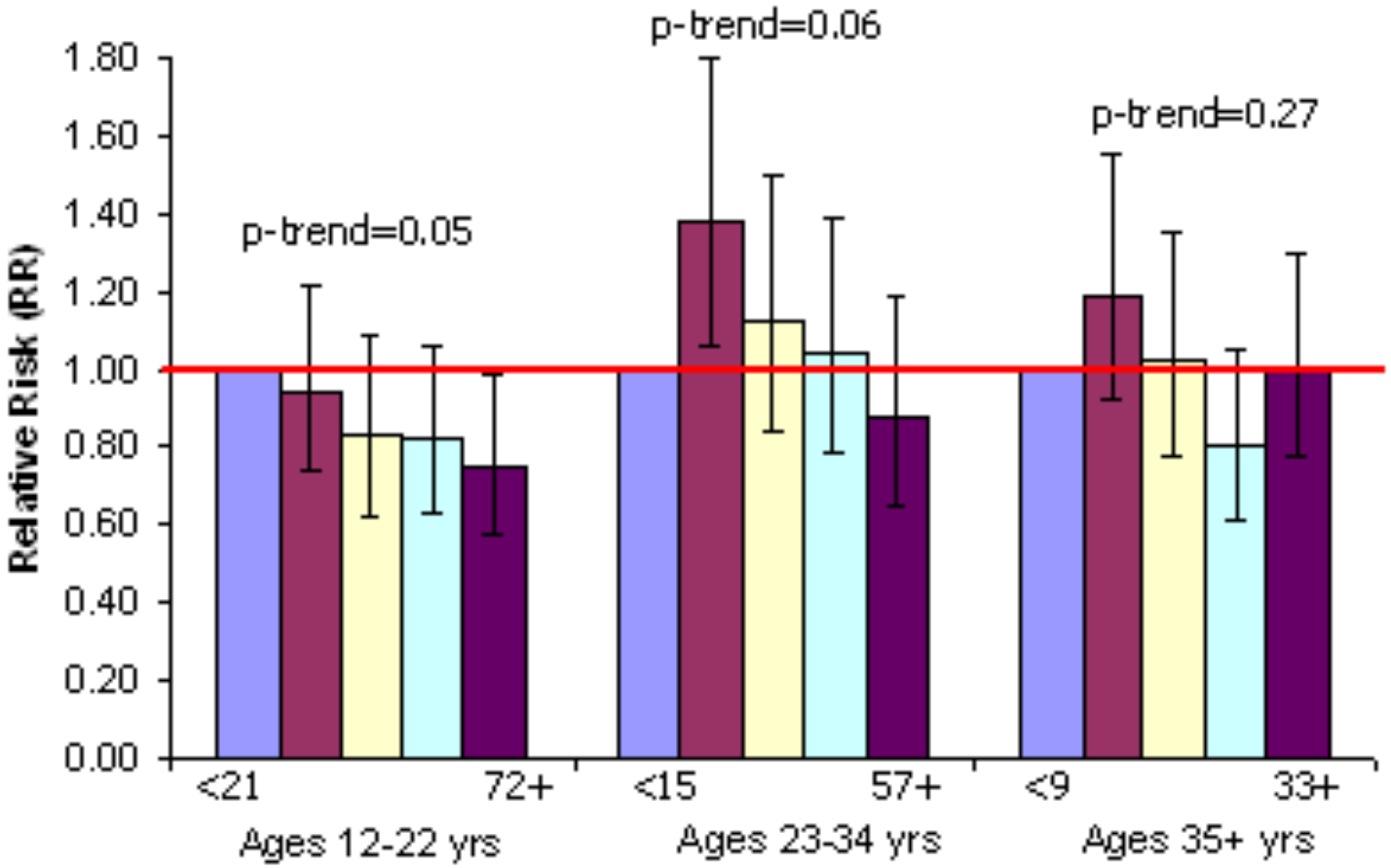
Physical activity

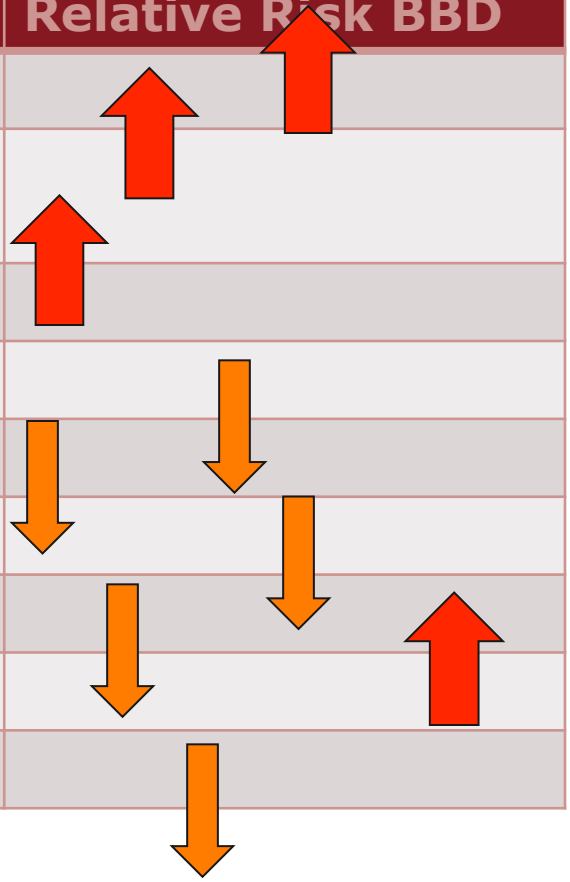
Total activity (MET-h/wk) during different ages and breast cancer



Maruti et al. JNCI 2008 100:728-737

Summary of evidence: Adolescent exposures -- BBD

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



V. Steps we can take *now* to prevent breast cancer

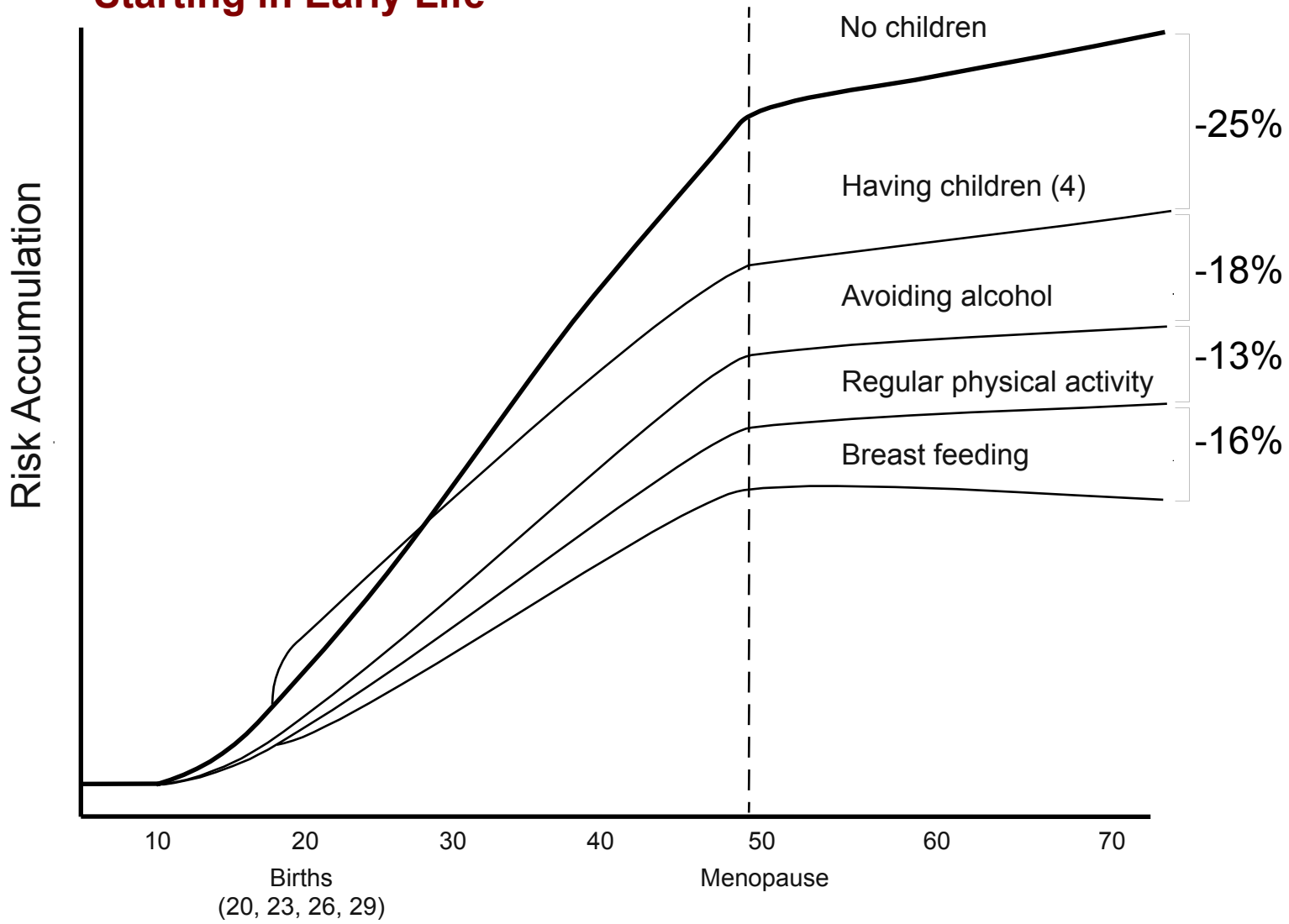
Target prevention early in life

- Eat mostly a plant-based diet
- Limit alcohol before first pregnancy
- Increase and maintain physical activity

Work globally and locally

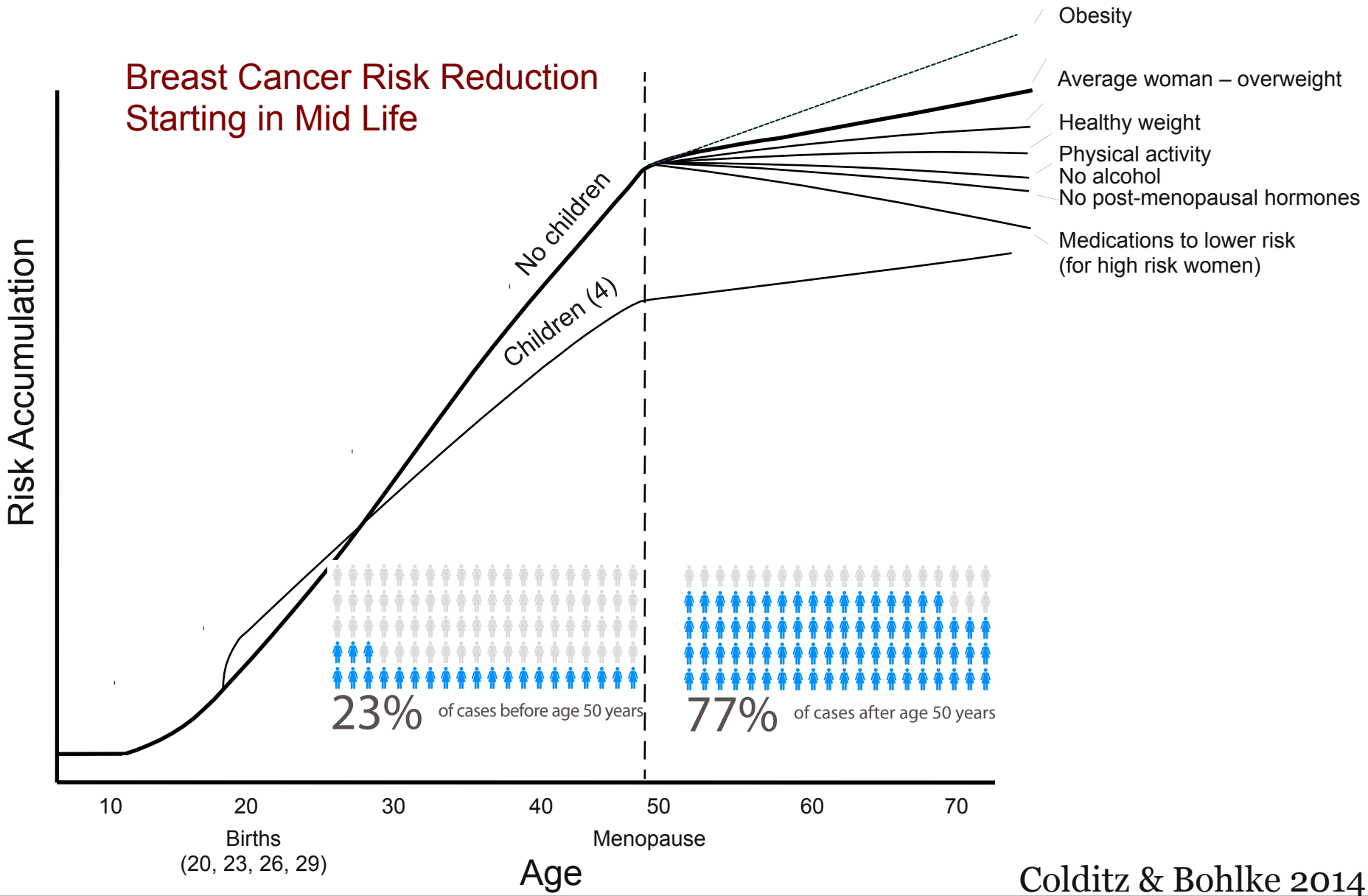
Refine messaging and social strategy

Breast Cancer Risk Reduction Starting in Early Life



Colditz and Bohlke 2014

Breast Cancer Risk Reduction Starting in Mid Life



Colditz & Bohlke 2014

A global prevention imperative

Timing matters

- To maximize benefits we must focus on biologically relevant periods
- Identify lifestyle factors that limit the impact of drivers
- Tap potential benefit from childhood and adolescent plant diet and physical activity
  - What intermediate marker can we measure?

Must identify strategies to counter adverse effect of alcohol

Implement prevention

Develop and refine strategies for delivery of prevention through:

- Health care providers
- Regulatory approaches
- Families and communities

Refine prevention messages and our societal response to improve childhood and adolescent environment

Messages for 16 to 30 year old women and their families and communities

Go big with plant based foods –
fruits, vegetables, nuts, and whole grains

Think before you drink

Put on those Dancing – and Walking and Running and Cycling shoes

Don't obsess – but watch your weight

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/WUSTL/Cancer Care Ontario investigators and trainees and participants
- American Cancer Society Clinical Research Professorship
- NCI & Breast Cancer Research Foundation for funding

Hey, Mom & Dad

It's a good time to help me lower my BREAST CANCER risk

Exercise

The more active I am, the lower my risk of breast cancer when I'm an adult. Really active teens and young adults have a 25% lower risk than those less active.

25% ↓ Risk

Puberty

The earlier I go through puberty the higher my risk of breast cancer later - as much as 25 percent higher. Staying at a good weight and keeping active helps me develop at a healthy age.

Alcohol

Drinking also increases my risk as an adult. A drink a day in my late teen/early adult years, increases my risk of serious types of benign breast disease - an important risk for breast cancer.

35% ↑ Risk

Diet

A healthy diet full of fruits, vegetables, and whole grains and low in red meat, sugar, and fast food can help me stay at a good weight and set the stage for lifelong good health.

Help me with these healthy habits

- Stay active and exercise
- Keep TV/screen time to a minimum
- Eat a diet rich in fruits, vegetables, and whole grains
- Be smart about alcohol; zero is best

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