Childhood and Adolescence Exposures as Determinants of Lifetime Cancer Risk

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School of Medicine

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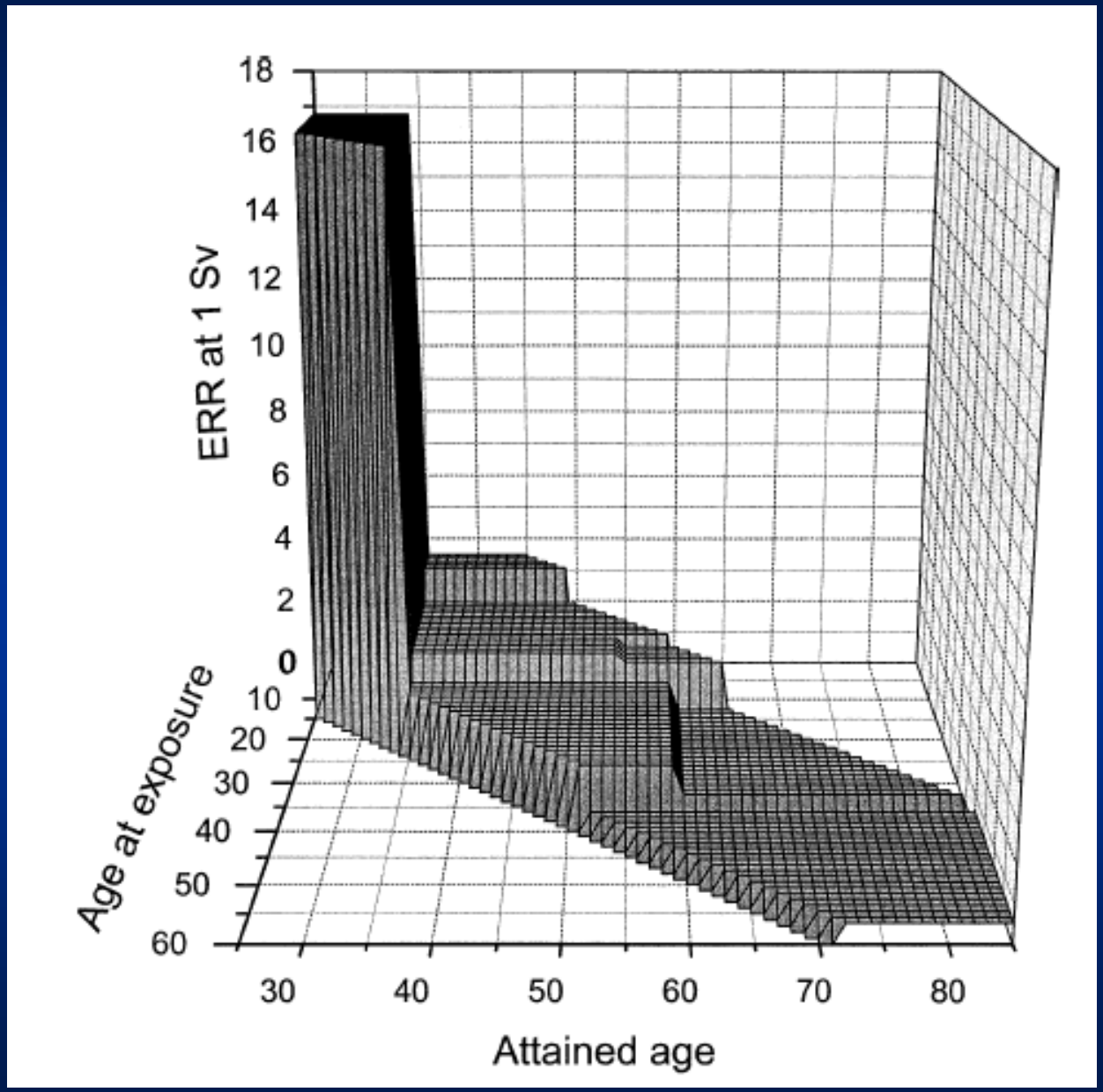
Disclosure information

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

Your Disease Risk
THE SOURCE ON PREVENTION
www.yourdiseaserisk.wustl.edu

Radiation – follow-up study

- Largest study of radiation and breast cancer risk pop 70,165
- Individual dose imputed for each women based on location at time of bomb
- 1059 cases diagnosed 1950 to 1990
- Linear increase in risk with radiation dose
- Early age at exposure (before age 20) conveys substantially greater risk
  - Land et al Radiation Research 2003



Land et al
Radiation
Research
2003

Other evidence

- Birth weight and testicular cancer
- Other birth weight issues – omitted for focus on childhood and adolescent
- Moles, sun exposure, and melanoma
- Tobacco and lung cancer
  - e.g., 5% increase in risk for each year earlier that a woman starts to smoke
    - Kenfield et al, Tobacco Control 2008

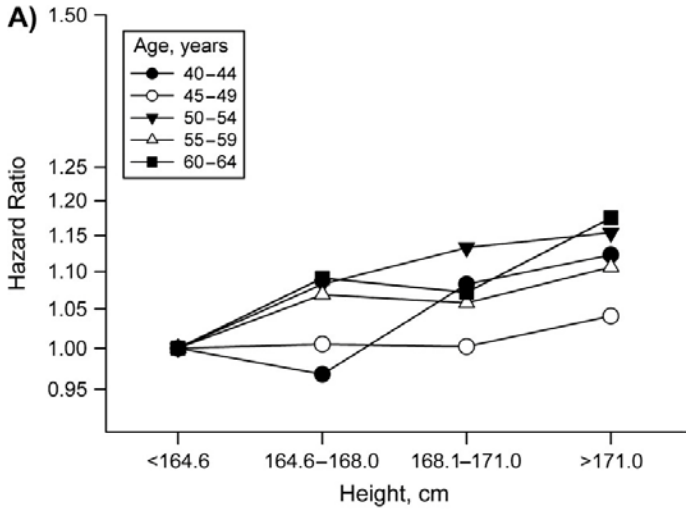
Goals

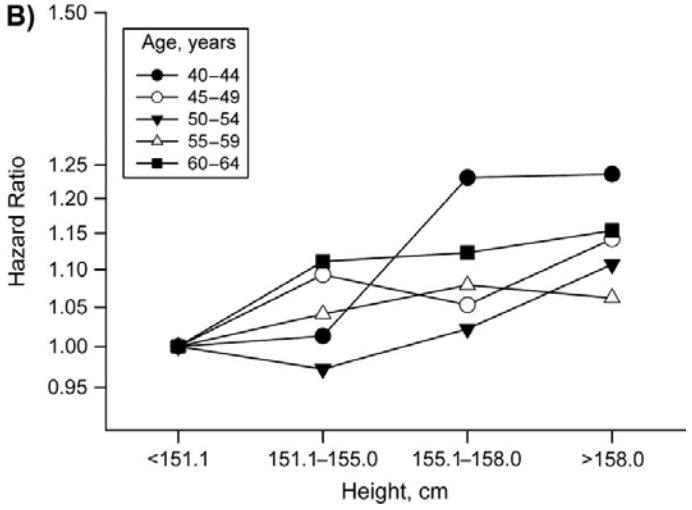
- Review growth, height, and obesity as evidence that childhood and adolescence matter
- Use breast cancer as model for diet and physical activity
- Present recent findings on benign breast disease
- Lessons learned and next steps

Korea health insurance cohort

- 449,414 men, 40 to 64 yrs of age
- 339,575 women
- Measure height and weight as part of insurance exam
- Followed for 10 years (1994-2004)
- 23725 cancers in men, 9443 total cancers in women

Height and combined all-sites cancer by strata for each 5 years of age among men (A) and women (B), Korea, 1994-2003





RR per 5cm increment:
M: 1.05 (1.03-1.06)
W: 1.07 (1.05-1.09)

Sung, J. et al. Am. J. Epidemiol. 2009 170:53-64; doi:10.1093/aje/kwp088

American Journal of EPIDEMIOLOGY

[redacted]

Korea

Height

- Food
- Infection
- SES
- Environment – energy expenditure

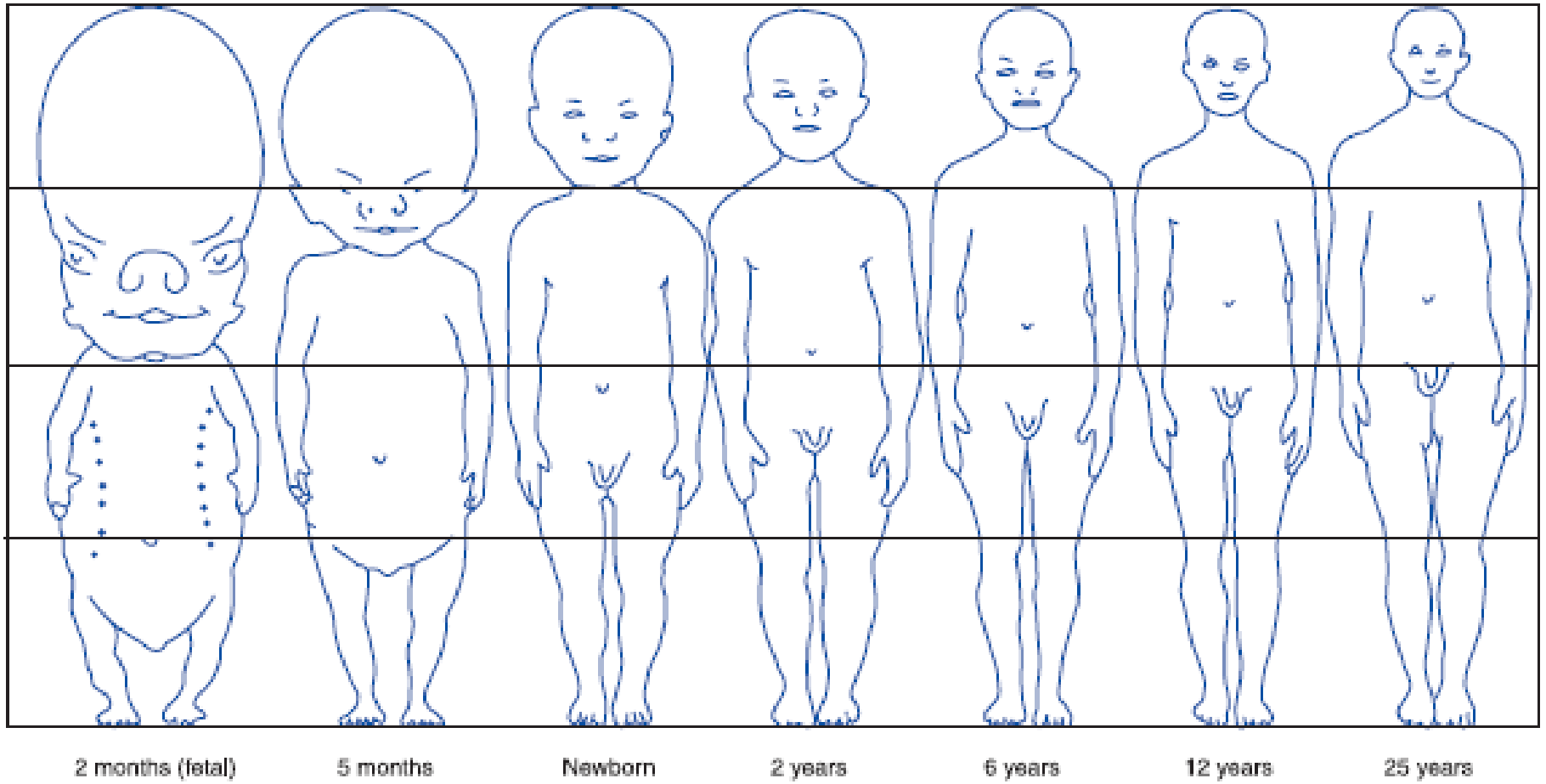
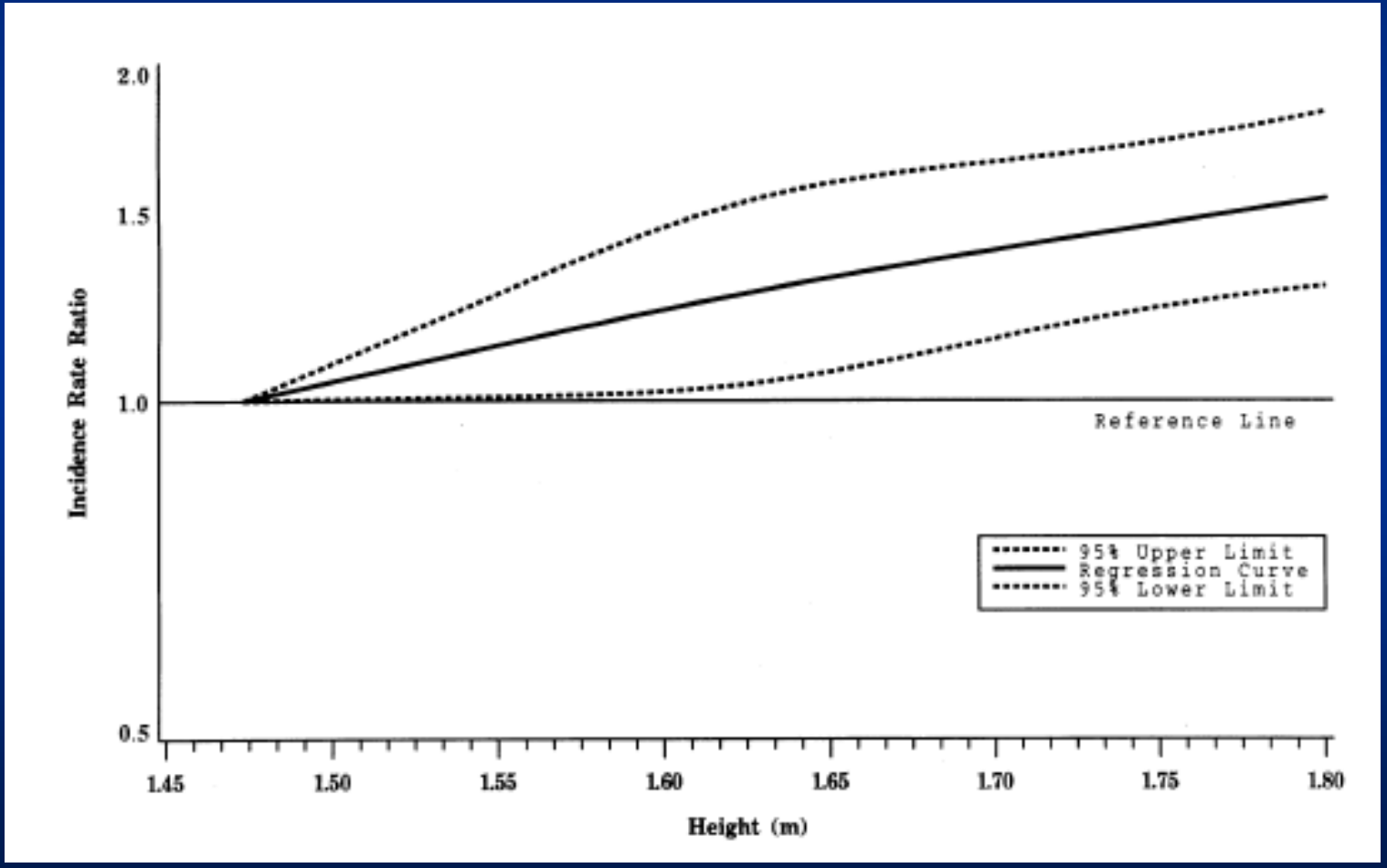


Figure 1. Relative growth of head, trunk and legs at different ages. Reproduced from I Leitch et al (1976, *Progress in Food and Nutrition Research*, vol 2, pp 90–141) with permission from Elsevier Science.

Growth

- Infancy up to age 4
  - Controls similar pre and post natal
- Childhood
  - Majority of growth due to increase in leg length
  - Long bones sensitive to growth hormone
  - Pubertal growth: growth hormone and sex hormones

Height and breast Ca. Cohort pooling project



van den Brandt et al., AJE 2000

Attained height and cancer

- More than 300 studies
- Clearest association with breast
- Also seen for prostate, endometrium, colorectal, hematologic malignancies
- Not associated with stomach cancer and esophageal cancer though number of studies far fewer

Okasha et al 2002; Gunnell et al 2001

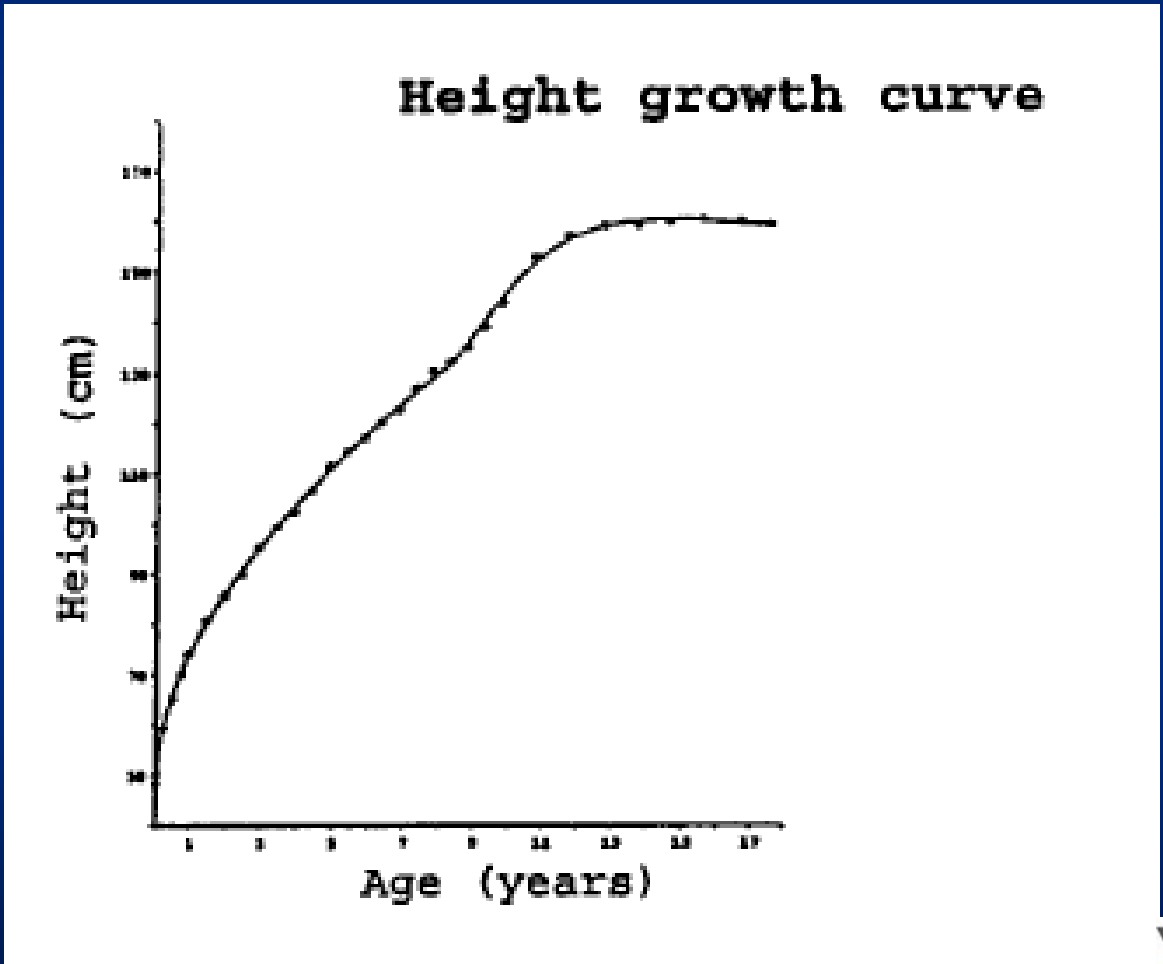
Growth, height and breast cancer

- Height consistently related to risk across prospective studies
- What does height reflect?
- Childhood energy balance?
- Growth spurt
- Compression over time as growth becomes earlier

Harvard Longitudinal Studies of Child Health

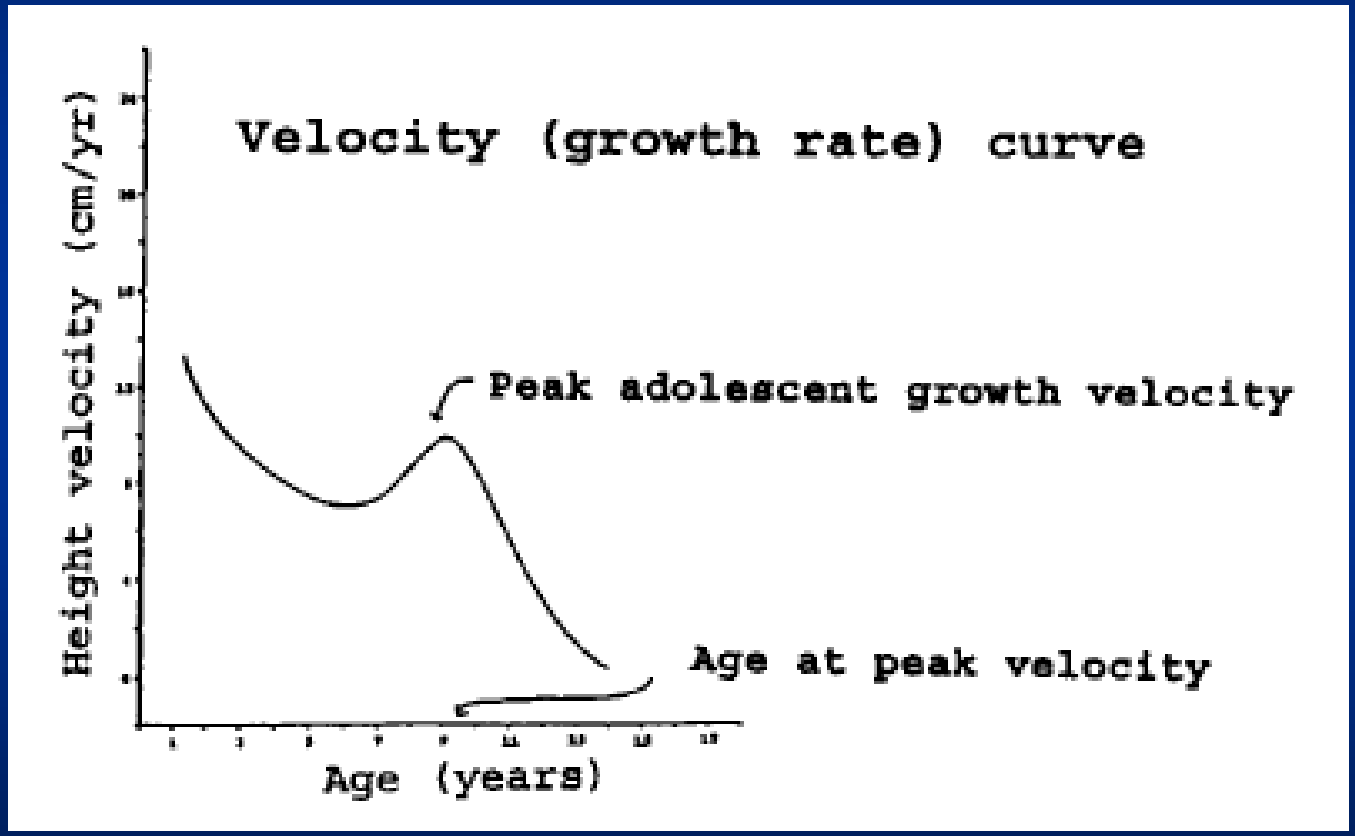
- HLS studied girls from 1929 onwards
- Used to derive model for growth velocity and Peak Height Velocity
  - The greatest growth attained during any single year
    - Berkey ,…Colditz Cancer 1999

Growth curve of girl, HLS



Berkey et al, Cancer 1999

Peak growth velocity



Berkey et al, Cancer 1999

Application in NHS data

- 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. ≤7.6 cm/yr;
  - RR=1.31 premenopausal breast cancer
  - RR=1.40 postmenopausal breast cancer

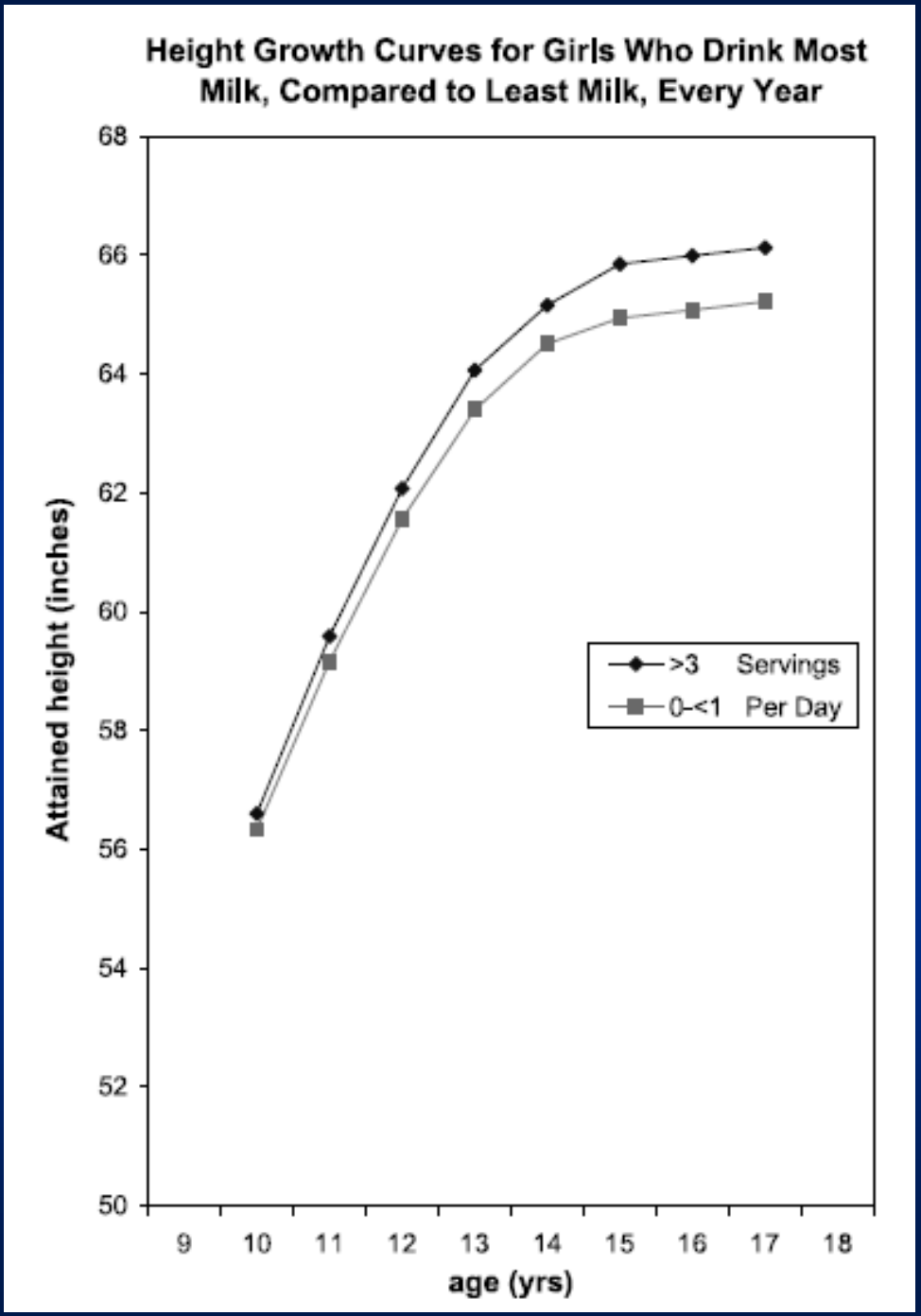
Berkey et al., Cancer 1999

GUTS

- Founded in 1996 after many iterations through study section (G Colditz PI)
- Validated diet, explored measures of physical activity
  - (Rockett et al Preventive Med 1997)
- Aim to relate adolescent diet to long term cancer risk, for funding purposes focused on adolescent weight gain

GUTS Dairy consumption and growth

- Female study participants
- 5101 premenarchal
- Completed annual surveys 1996 to 2001 and 2003
- Reported height, weight, and past year diet
- From serial heights we computed annualized height growth increments



Berkey, Colditz et al, CEBP 2009

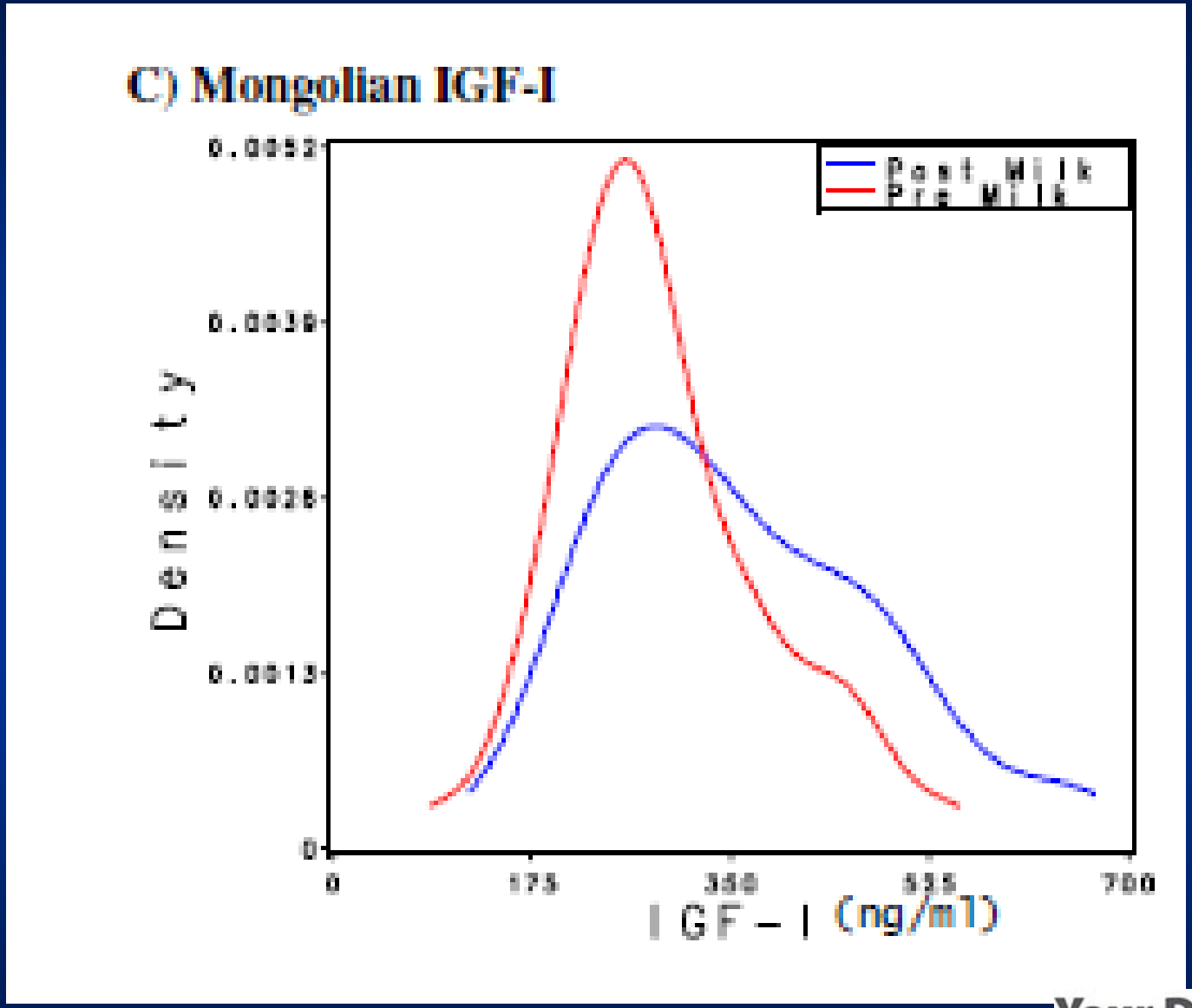
Dairy and growth…

- Drinking >3 servings of milk per day grew more the following year (0.11 in, p=0.02), compared with girls drinking less than 1 serving per day
- Yogurt but not cheese or total calories was also related to height growth

Berkey, Colditz et al, CEBP 2009

Likely mechanism

- Insulin-like growth factor (IGF-1) levels higher in several studies of milk consumption
- Trial of US UHT pasturized vitamin D fortified milk 710 ml per day added to diet of Mongolian children for one month
- After the month, mean plasma levels of IGF-1 significantly increased

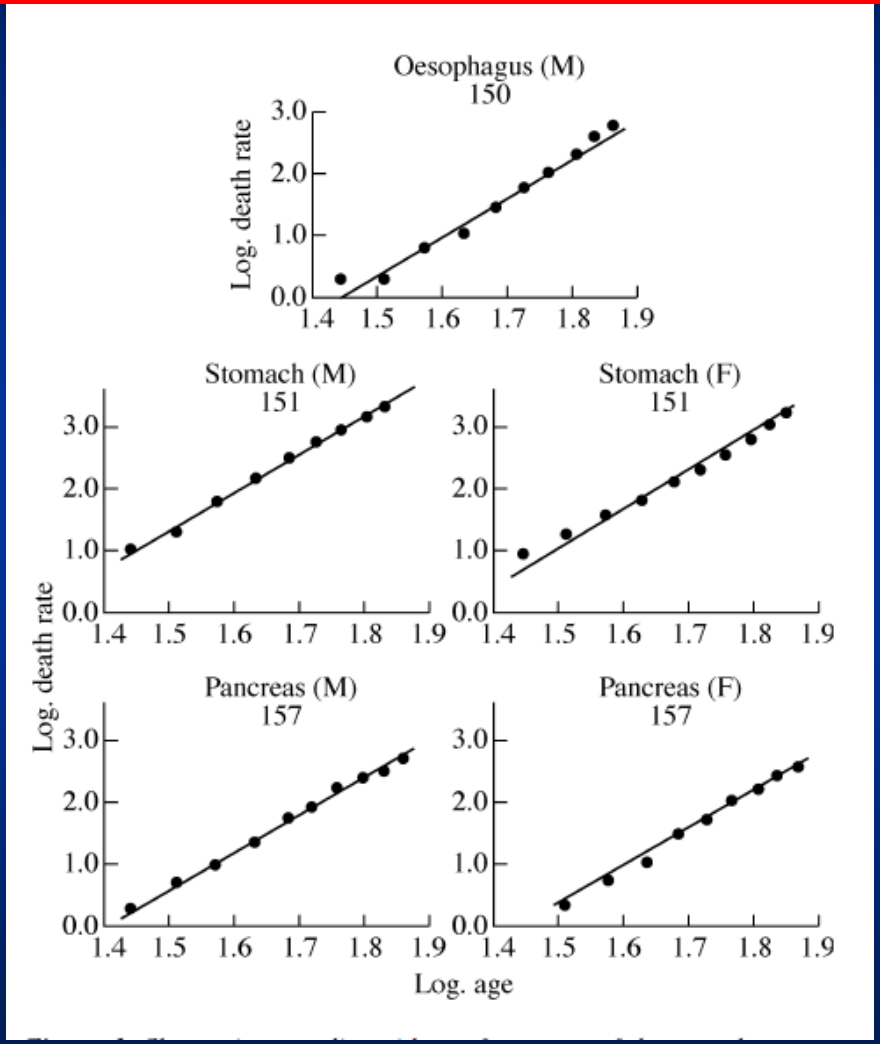


Rich-Edwards et al Nutrition J 2007

Conclusion to date

- Height related to numerous cancers, best studied is breast
- Both attained height and the environmental exposures related to growth may impact cancer risk
- Adolescent exposures, after growth is completed, may be key to early lesions in progression to breast cancer

Cancer Mortality and Age



Armitage and Doll, Br J Cancer 1954

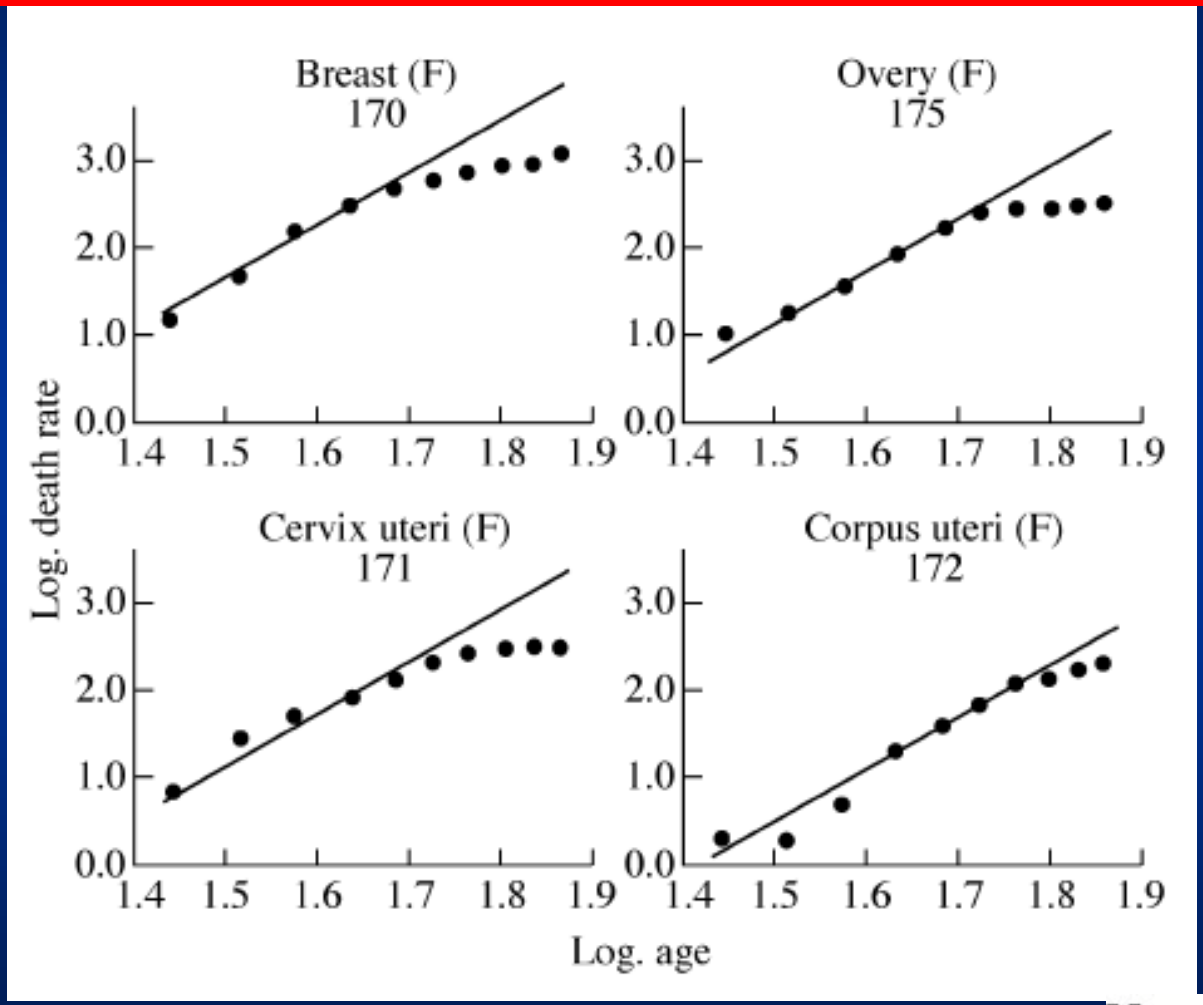
Cancer mortality England and Wales 1950 and 1951

Table 1 Regression of the logarithm of the death rate from cancer of selected sites on the logarithm of the age

Sex	Site of cancer	Regression coefficient of logarithm of death rate on logarithm of age
M	Oesophagus	6.26
	Stomach	5.91
	Colon	5.18
	Rectum	5.62
	Pancreas	5.76
F	Stomach	5.27
	Colon	4.97
	Rectum	5.03
	Pancreas	6.48

Armitage and Doll, Br J Cancer 1954

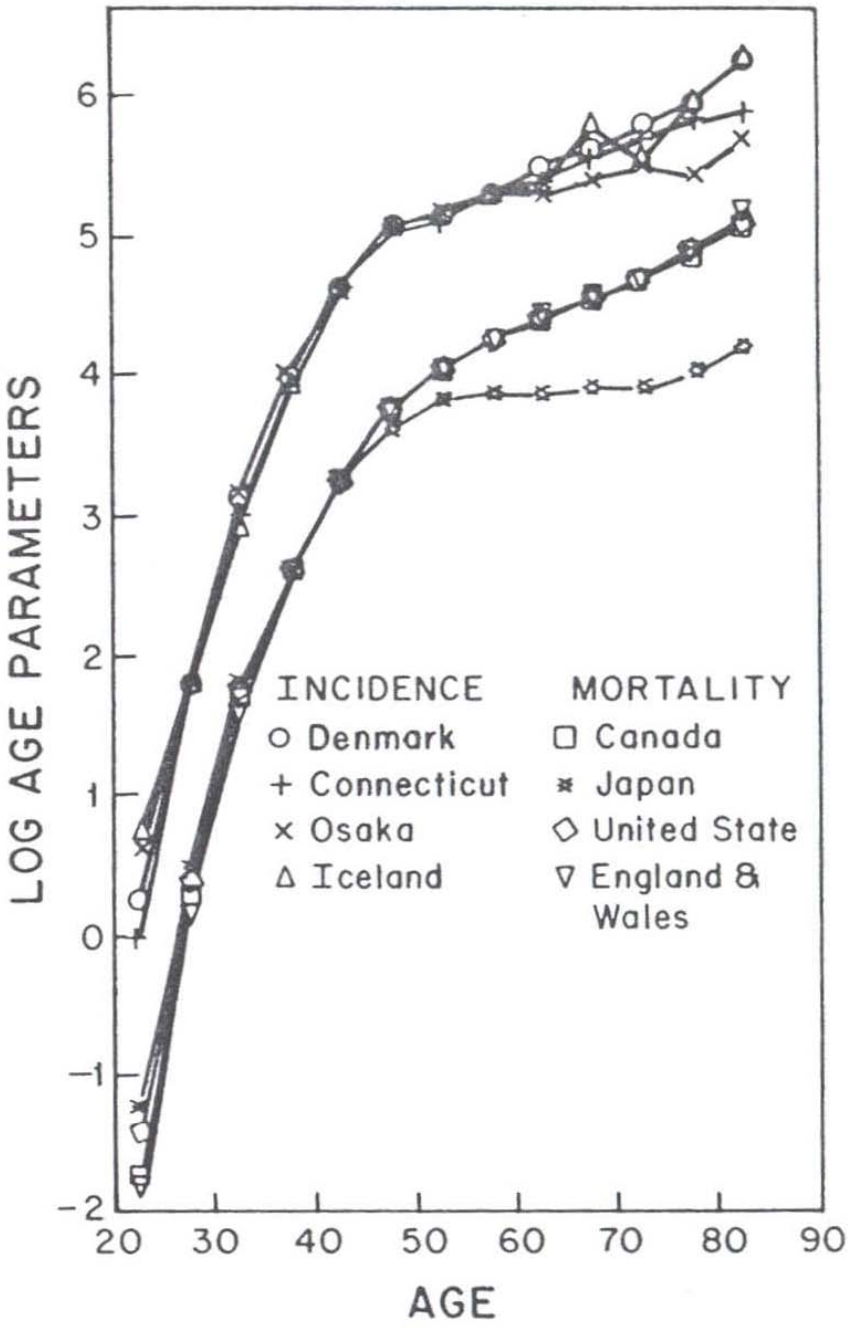
Cancer Mortality and Age



Armitage and Doll, Br J Cancer 1954

Biology – age effect

- 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 et al. JNCI 1979:62:493-501



Moolgavkar et al

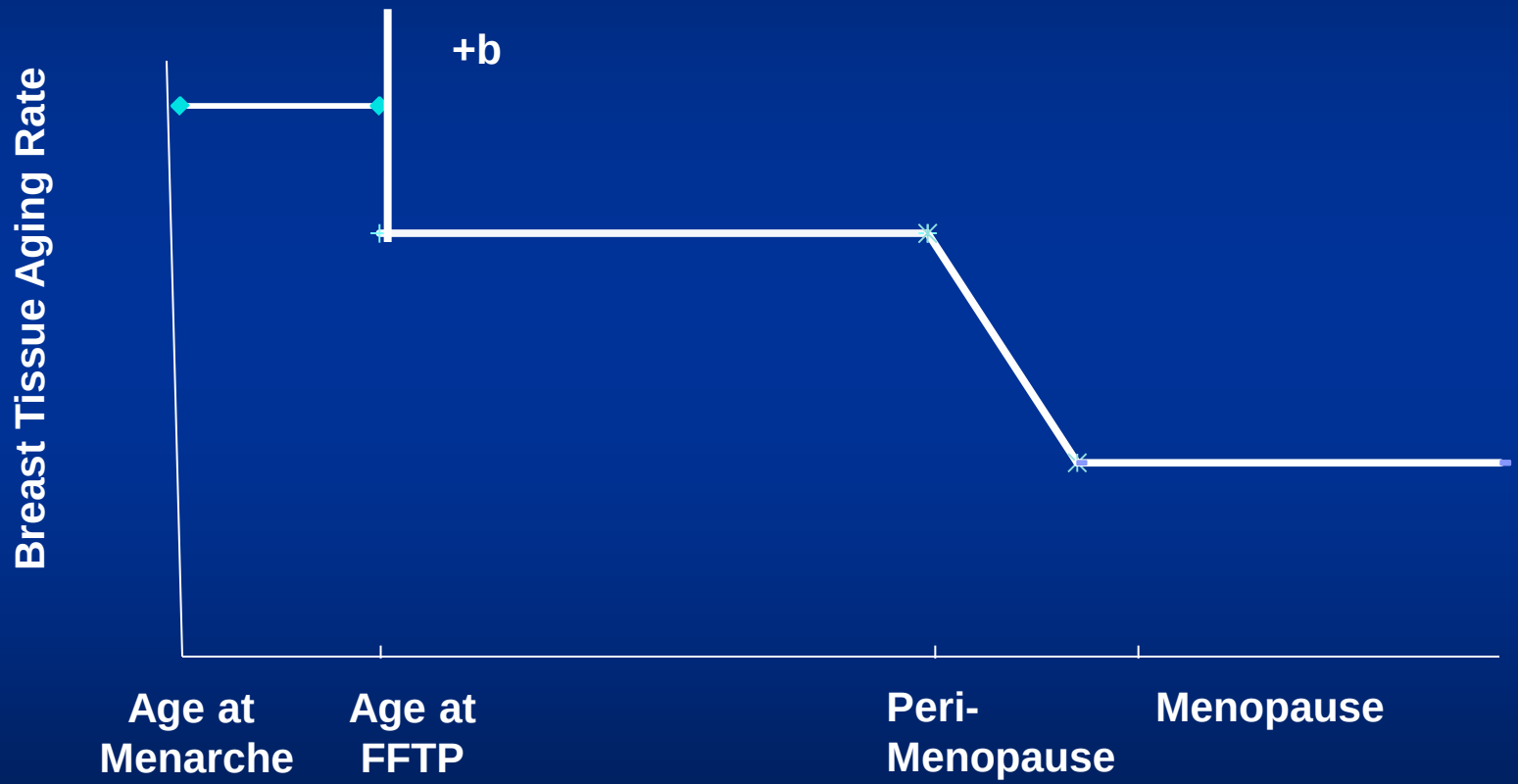
JNCI 1979

Models of disease incidence

- Can summarize risk factors and take account of temporal relations between risk factors and disease
- Temporal relations often ignored in standard risk estimation and interpretation
- Give added insight to potentially important mechanistic features

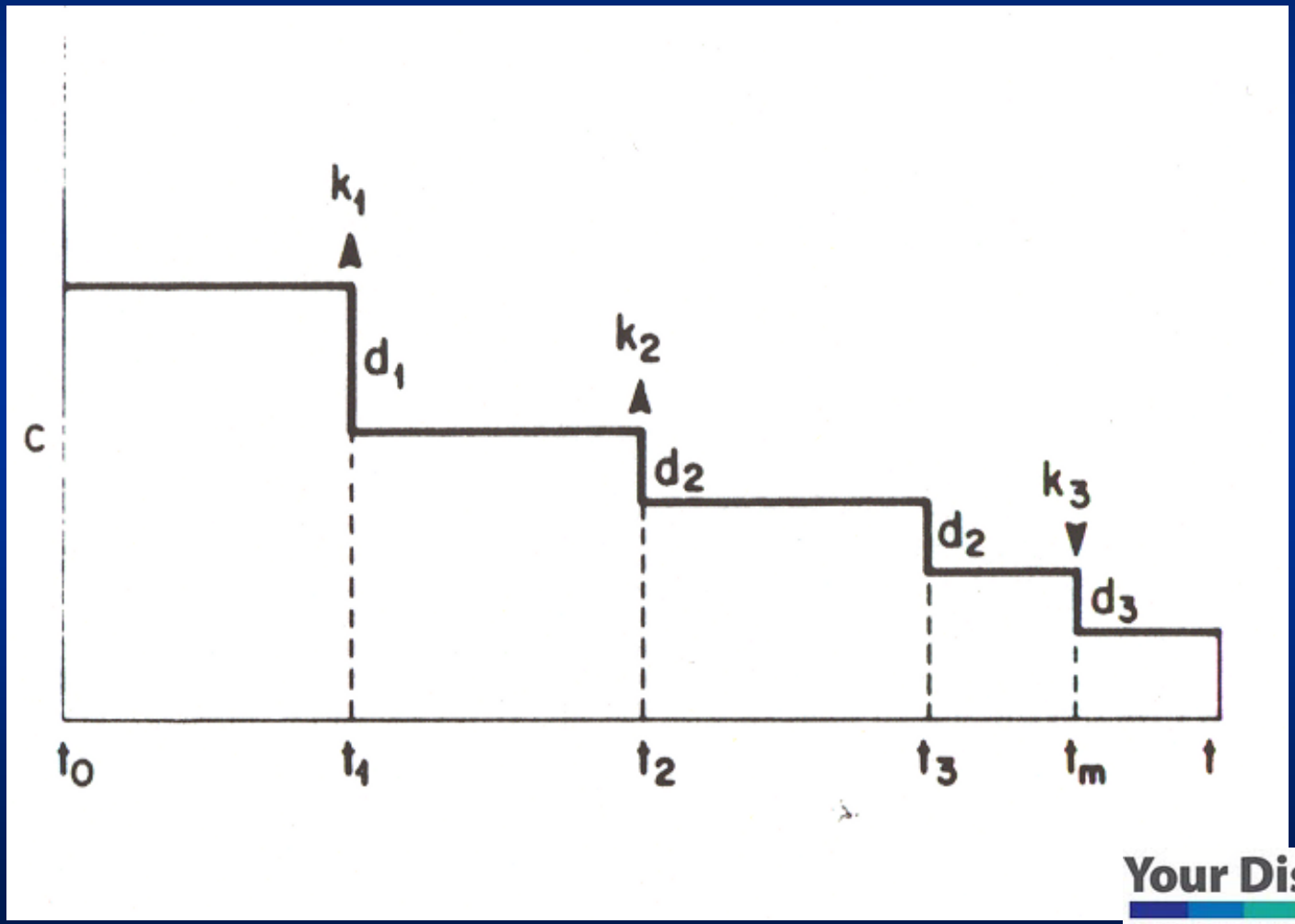
Colditz and Rosner.
Breast Ca Research, 2006

Pike's Model of Rate of Breast Tissue Ageing



Pike et al, Nature 1983

Multiple Birth Model



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

Application of models to NHS

- Spacing of births is significantly related to reduced risk of **breast** cancer – closer births, lower risk
- A transient increase in risk with first birth, but not subsequent births
- Risk increases ~8.5% per year from menarche to first birth
- Risk increases ~2.5% after menopause

Rosner et al AJE 1994; Colditz and Rosner AJE 2000

Why is childhood and adolescence important?

- Risk accumulation from menarche to first birth and then to menopause
- Age at menarche, strong history of relation with breast cancer
- Dramatic changes with industrialization
- Growth and height are related to risk
  - Colditz and Frazier CEBP 1995

Age at menarche

- Later age - lower risk
- Age 15 vs age 11 gives 30% lower risk to age 70
- Clear trend over time in earlier menarche with industrialization

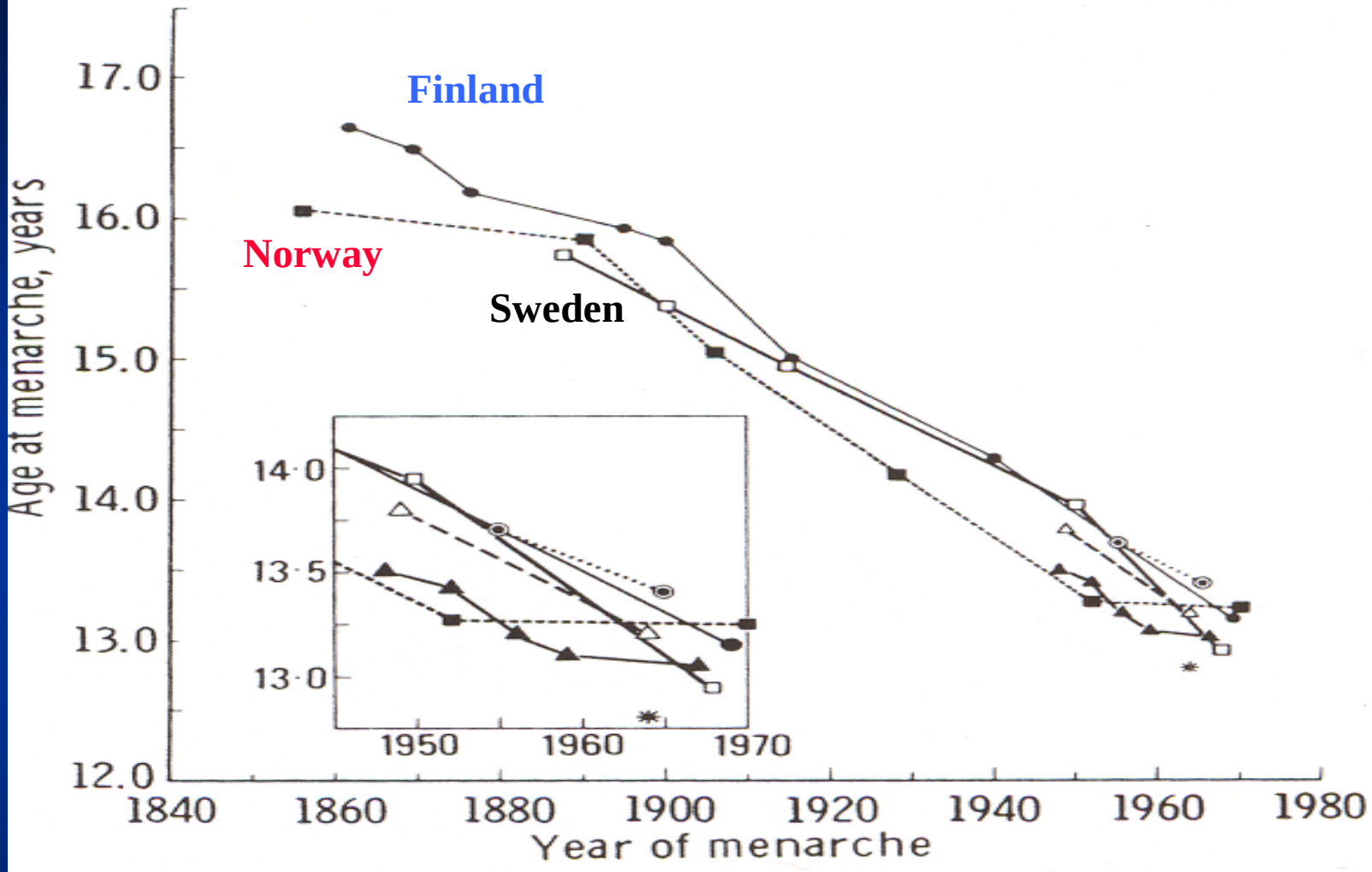
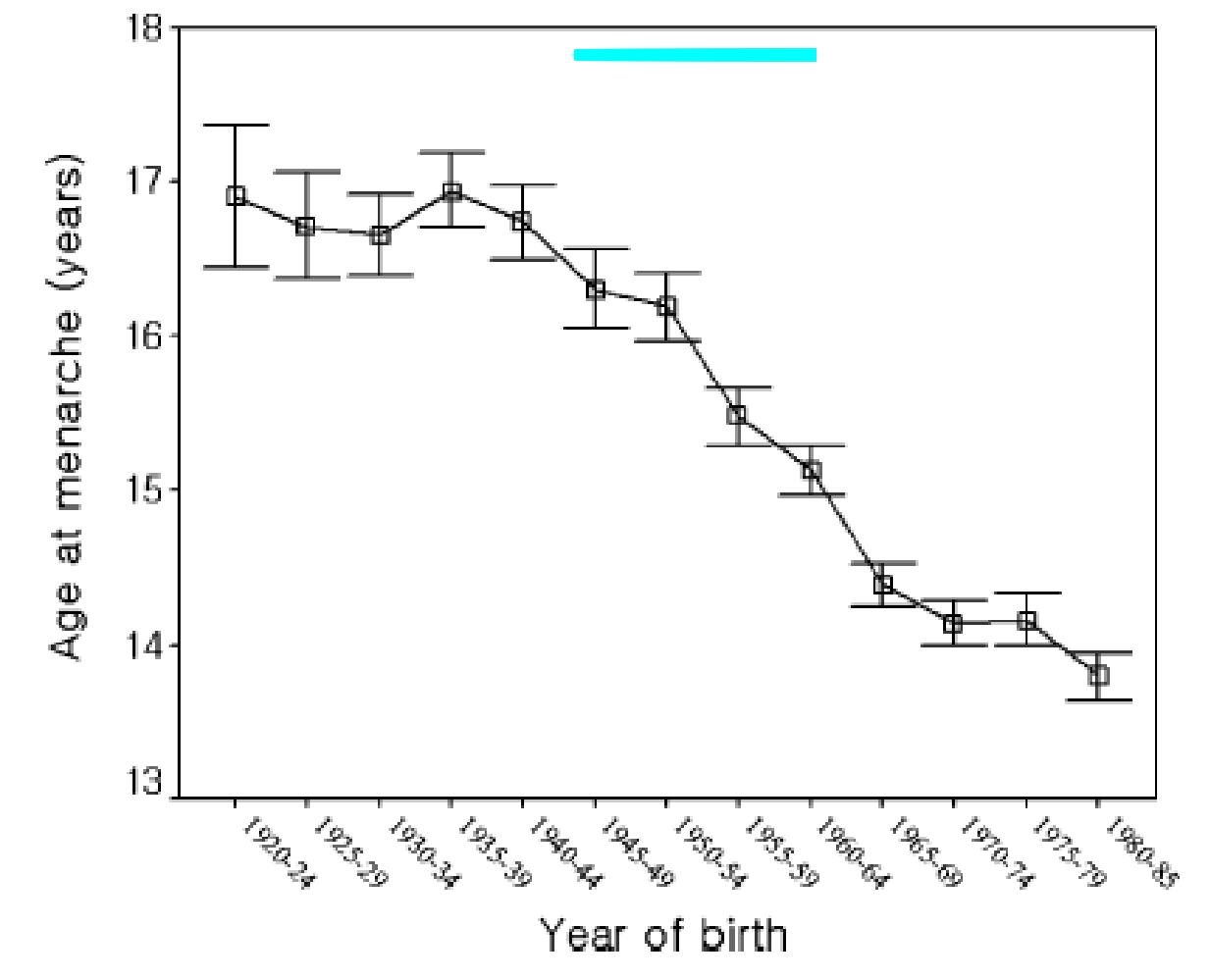


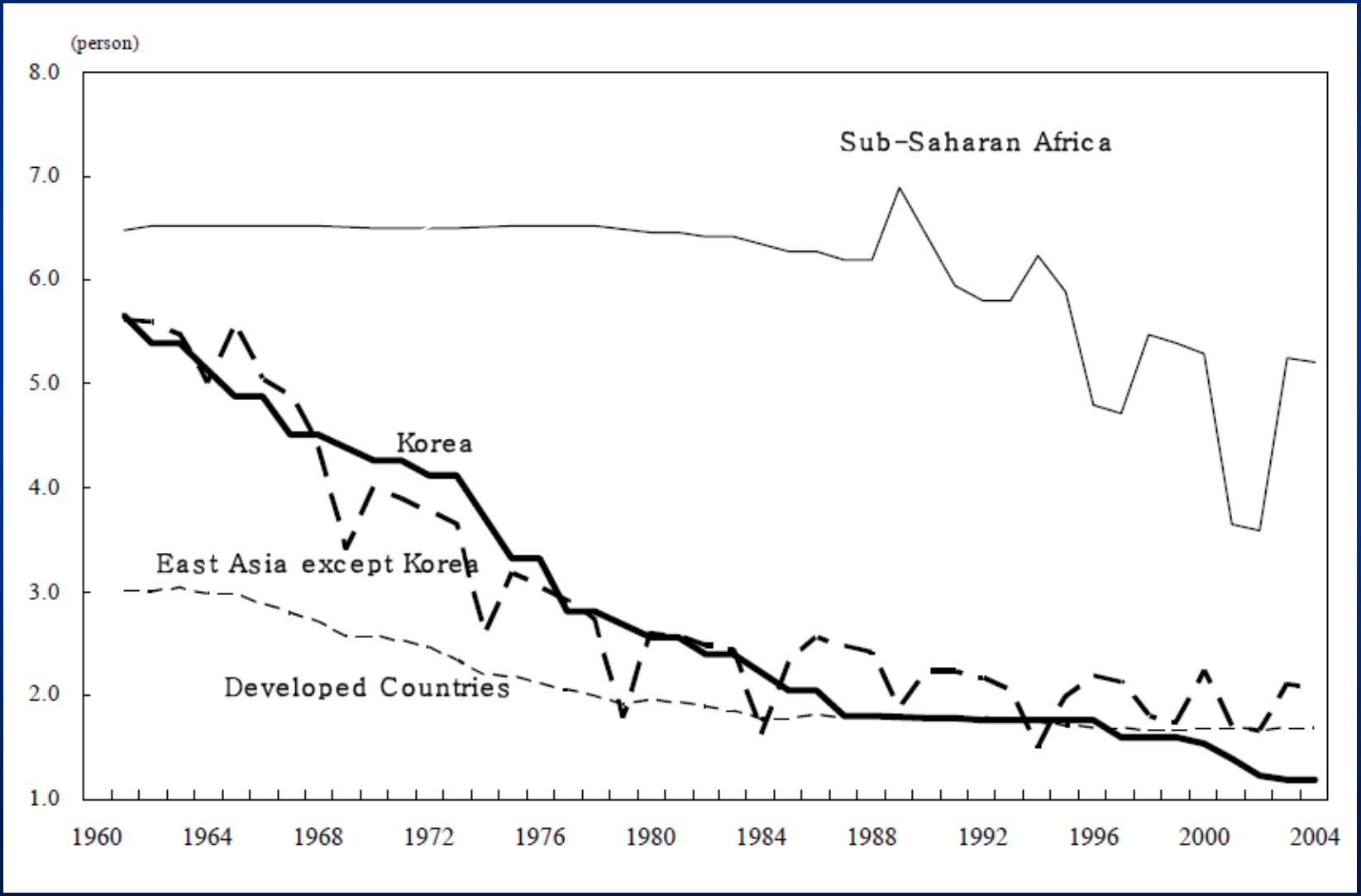
Fig. 1. Trend toward earlier menarche in some European countries. (Sweden (□—□); Norway (■---■); Finland (●—●); Denmark (△---△); Holland (⊙ · · · ⊙); United Kingdom (▲—▲); United States (∗). (From Tanner, 1978.)

Change in menarche, Korea

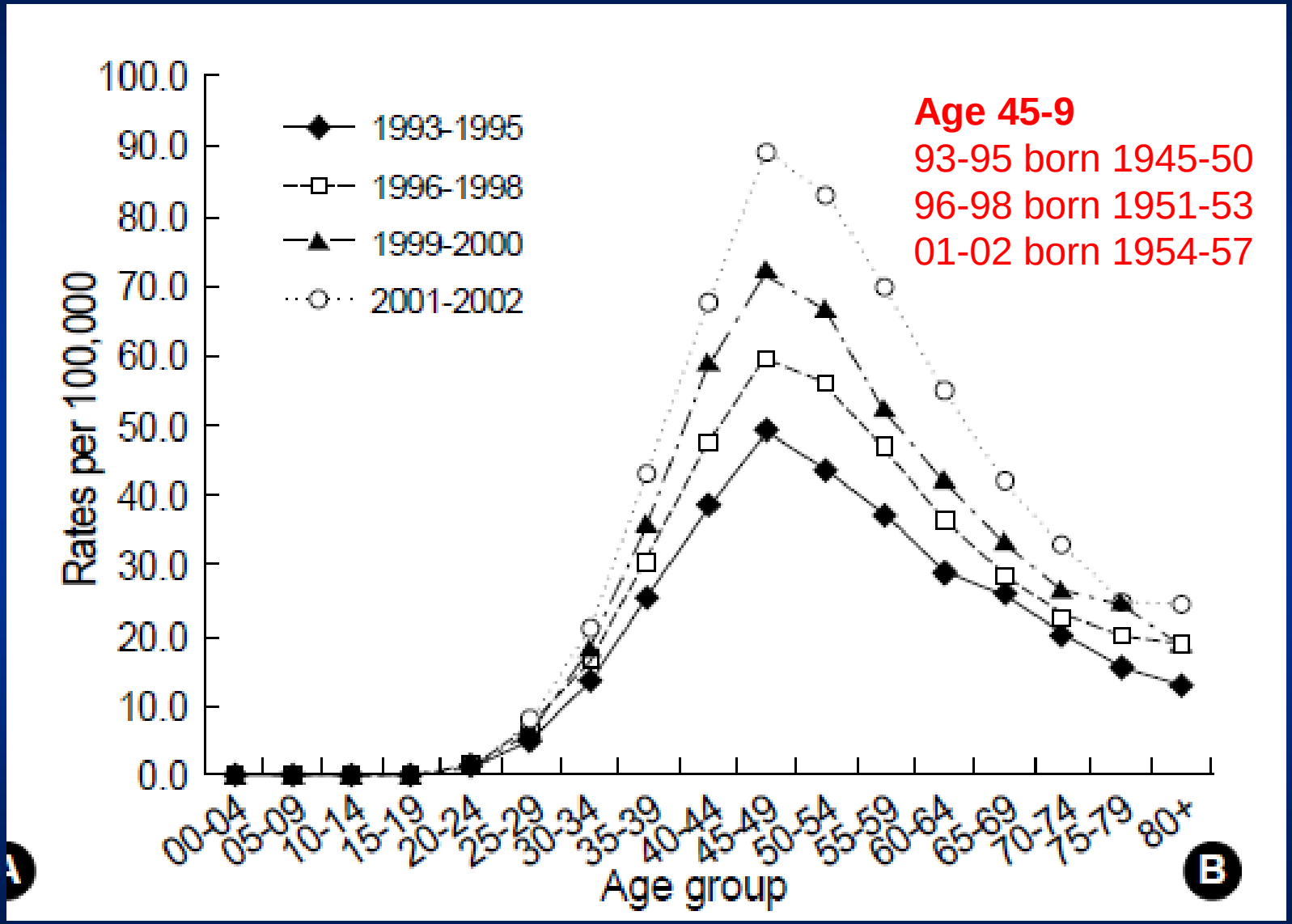


Cho
Eur J
Pediatr
2009

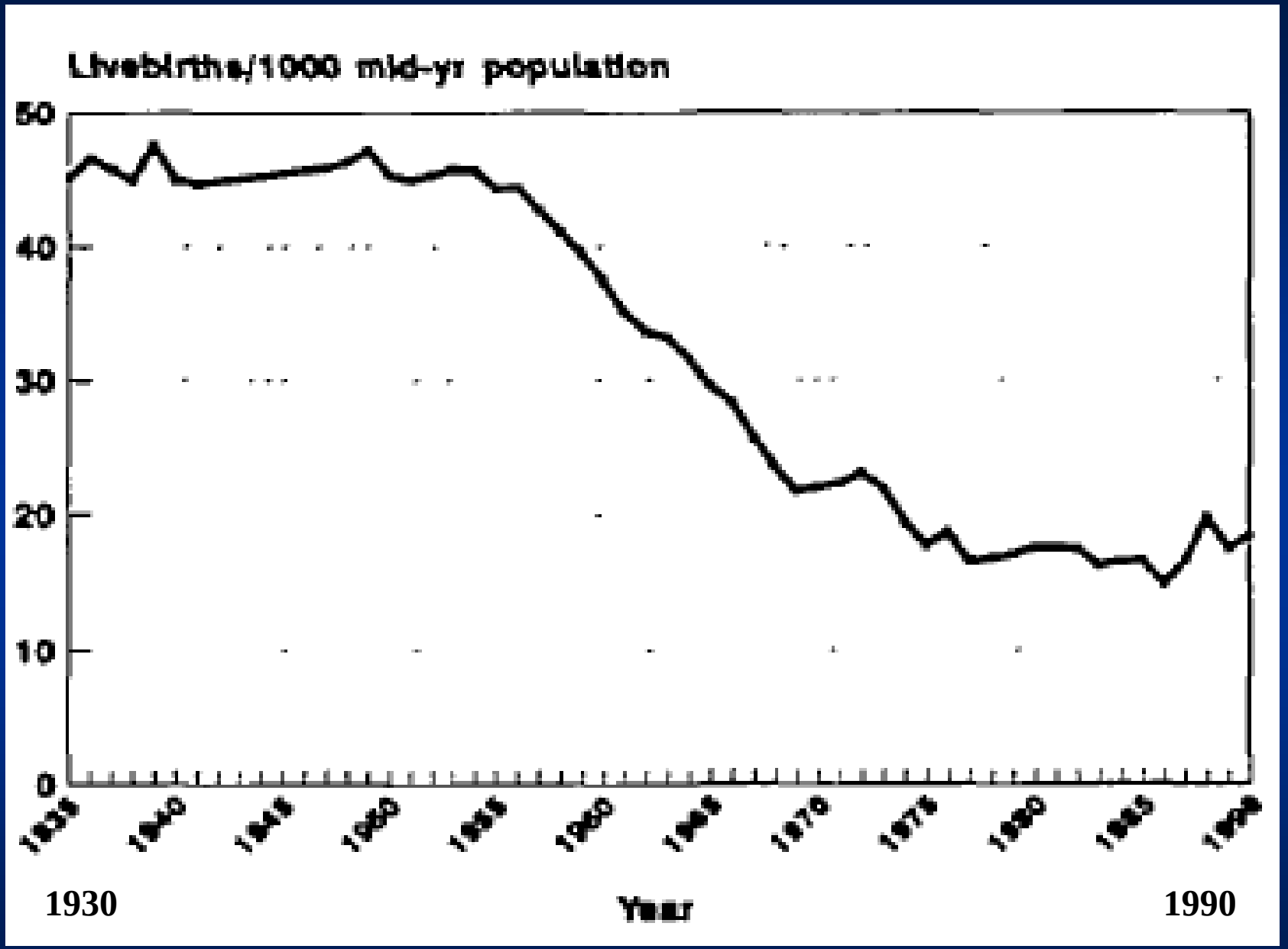
Trends in Fertility, Ito et al NBER, 2008



Breast cancer incidence, Korea, by year

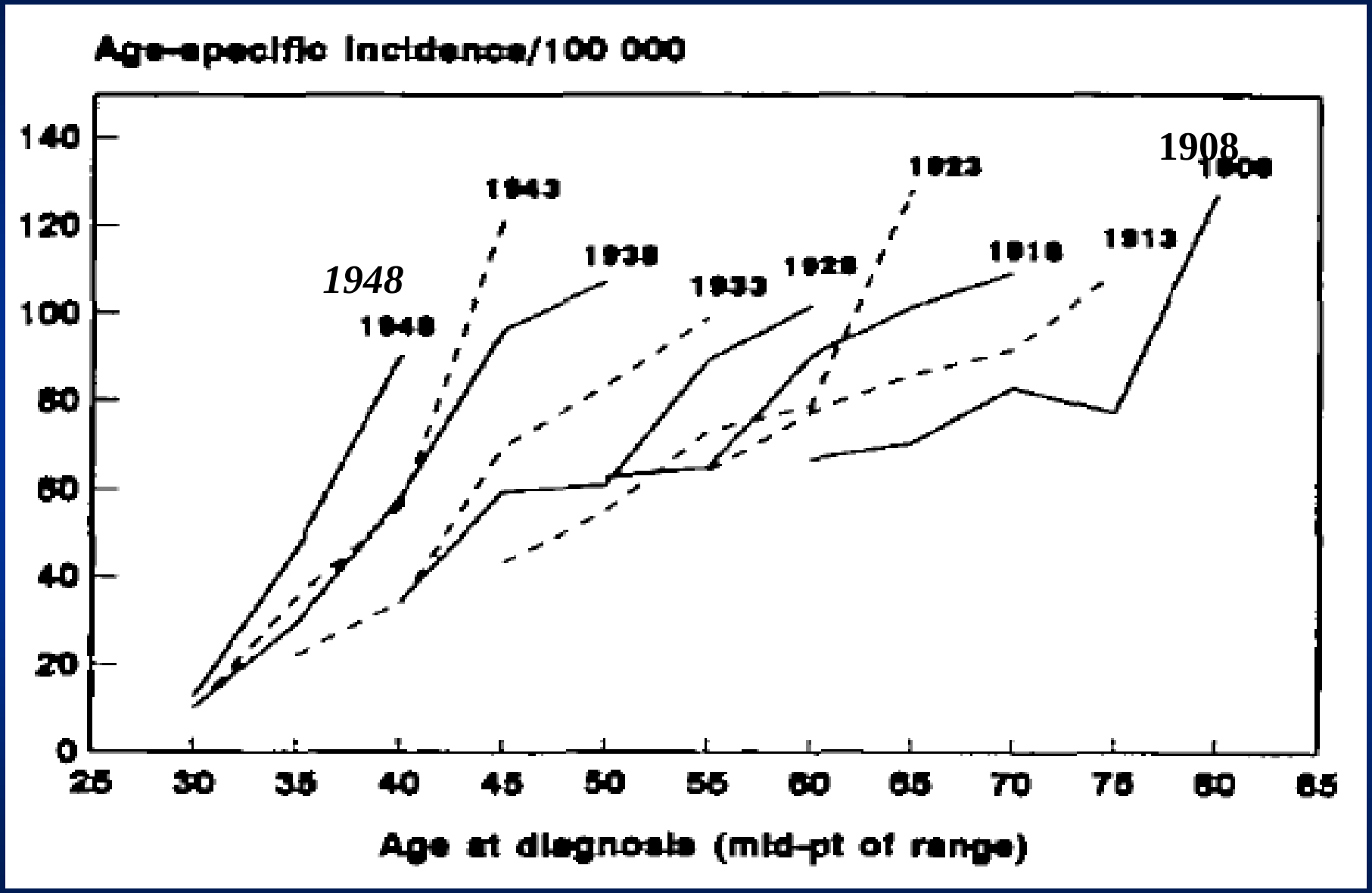


Lee J-H et al, J Korean Med Sci 2007



Seow A, et al Int J Epi 1996

Singapore breast cancer incidence by age and birth cohort

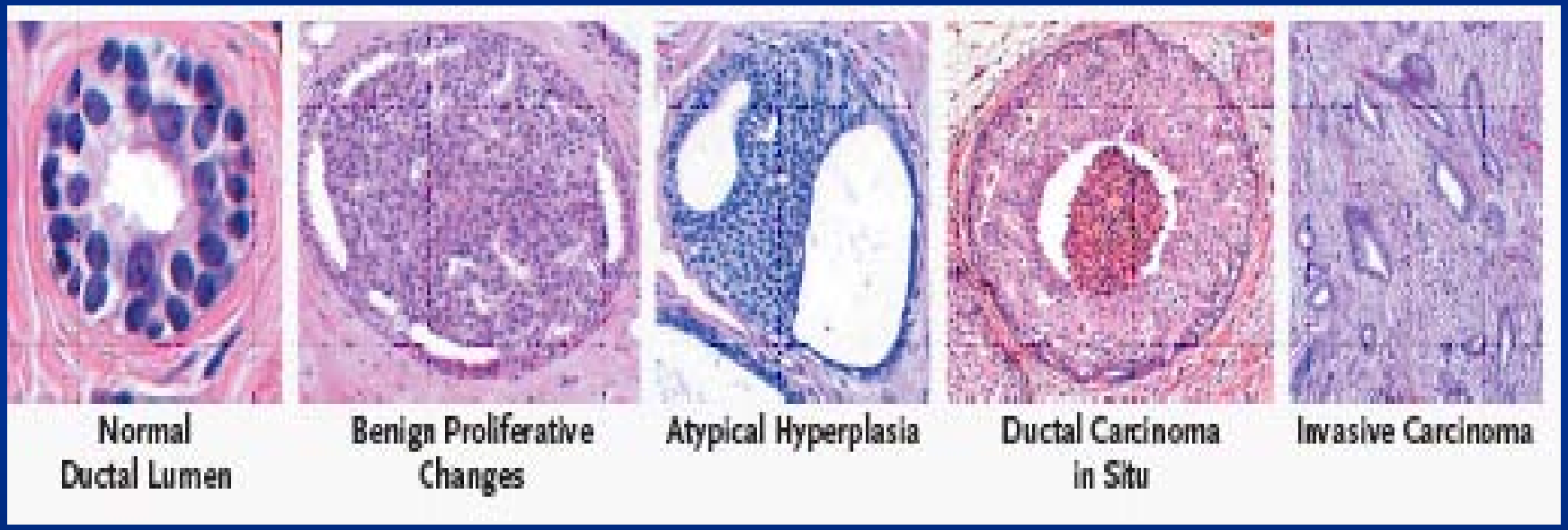


Seow 1996

Impact of Menarche on Hormone levels

- Singapore data
- Breast cancer rates doubled
- 144 post menopausal women
- Late menarche (after 17) 24% lower estradiol (circulating female hormone) than women with menarche before 17
  - Wu et al CEBP 2002

Precursor lesions: intermediate endpoints



RR = 1.8 = 3 to 5

London JAMA et seq

Benign breast disease (yes / no) in model

- Modeled as 4 components
  - Intercept-impact at birth
  - Birth to menarche
  - Menarche to first birth/menopause
  - Postmenopause

Annual increase in risk

- Nulliparous no BBD +8%/yr
- BBD
  - Birth to menarche +7%
  - Menarche to first birth -1.5%

Colditz & Rosner, AJE 2000

Implications

- BBD negative woman
  - Strong effect of menarche
  - RR = 0.71 for age 15 vs. 11
- BBD-positive woman, virtually no effect of menarche
  - RR=0.98 p = nonsignificant

Colditz & Rosner AJE 2000

What predicts BBD

- NHSII – incident BBD (RO1-CA50385)
- Central pathology review
- Study adolescent
  - diet
  - physical activity
  - body shape at ages 5 and 10
- GUTS, Growing Up Today Study

High school diet and risk

- **NHSII**
  - In 1998, 45,948 women responded to a HS-FFQ asking about their usual dietary intake during adolescence, further defined as ages 13–18 years
- **HS-FFQ**
  - Semi-quantitative 131-item FFQ
  - Used food composition data from the relevant time period (1960s and 1970s)
  - Reproducibility: ICC for dietary fiber: 0.67
  - Correlation with current adult diet in 1995: 0.38
  - Correlation with the Nurses' mothers' reports: 0.35

Maruti et al, AJE 2005

Maruti et al.

HS FFQ: Validity

- Compared against 3 24-hour recalls completed 10 years earlier
- 153 participants from prior GUTS diet validation (Rockett et al., 1995)
- Average corrected correlation = 0.45

Maruti et al Epidemiology 2006

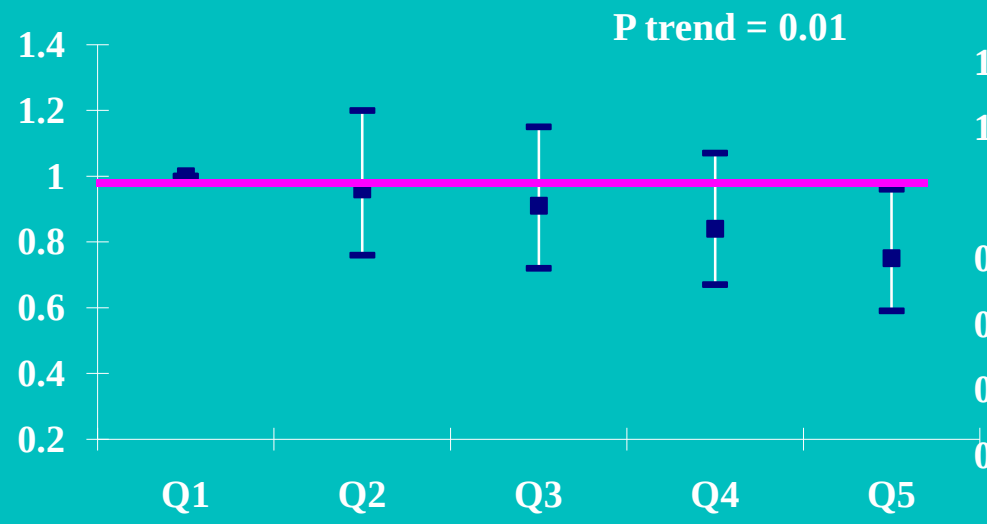
Adolescent Diet and Benign Breast Disease

- 29,494 women free from benign breast disease and participating in the NHSII completed a 131 item FFQ in 1998
- 470 incident cases of proliferative BBD confirmed by central pathology review
- Animal fat positively related to risk, ns
- Vegetable fat inversely related to risk, ns
- Vitamin E and fiber inverse, (RR .75; p=0.05)
- Vitamin A, retinol, carotenoids, and folate, null

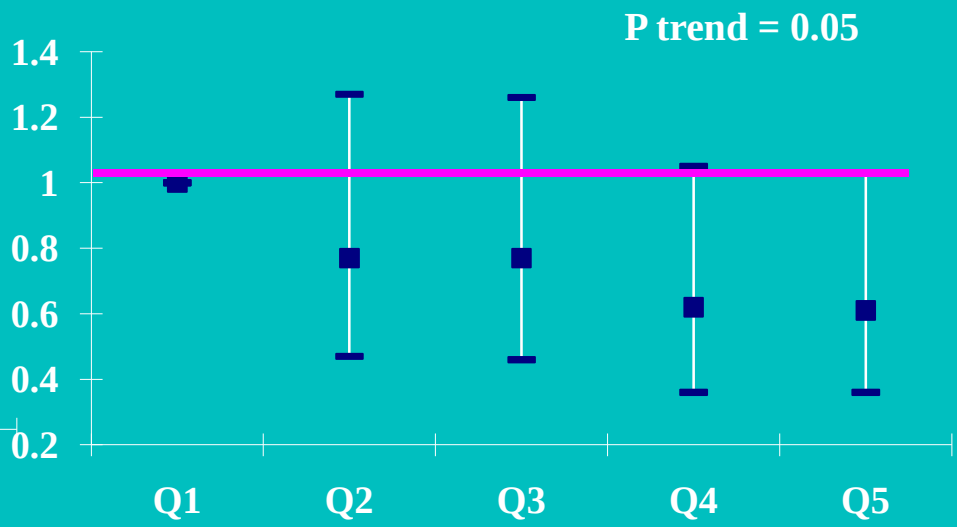
Baer et al, CEBP , 2003

Adolescent fiber & BBD

Combined analysis



Prospective Analysis

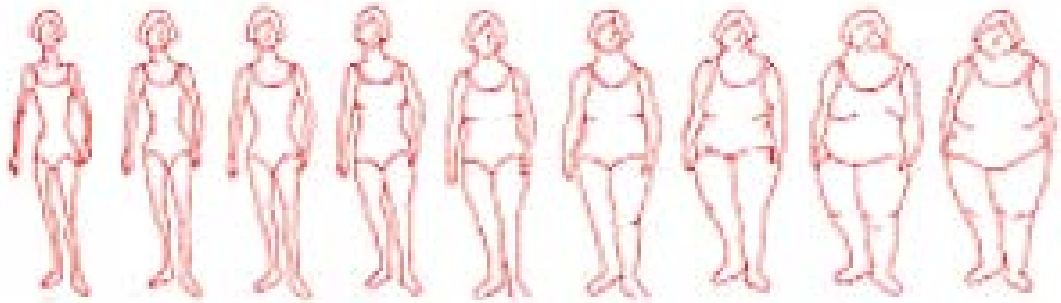


Su et al Cancer Causes Control 2010

Sources of fiber intake

Validate measure of adiposity

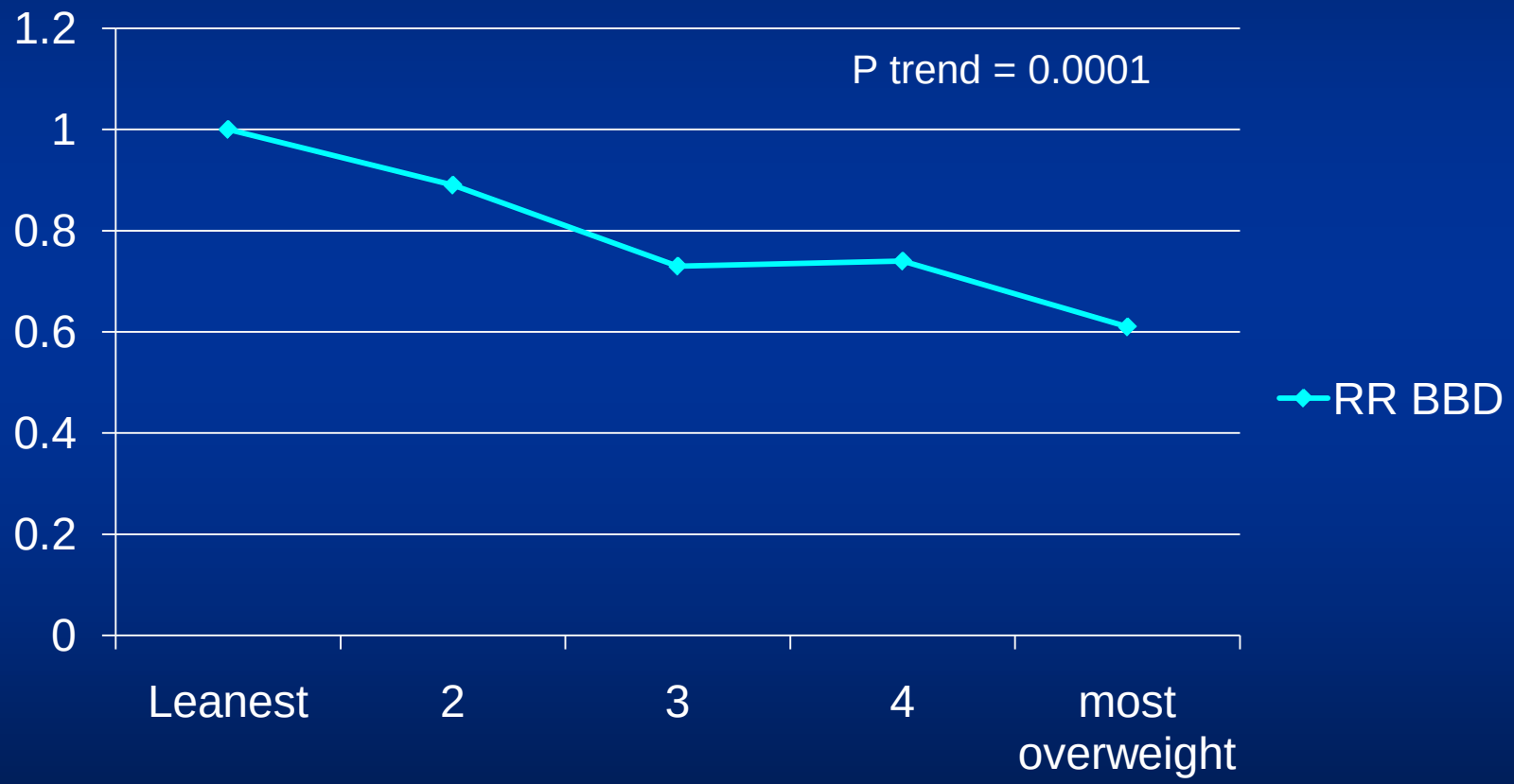
44. Which diagram best depicts your outline at each age?



	1	2	3	4	5	6	7	8	9
Currently	○	○	○	○	○	○	○	○	○
Age 5	○	○	○	○	○	○	○	○	○
Age 10	○	○	○	○	○	○	○	○	○
Age 20	○	○	○	○	○	○	○	○	○
Age 30	○	○	○	○	○	○	○	○	○
Age 40	○	○	○	○	○	○	○	○	○

Validated; Must et al AJE 1993, r=0.7 adult vs measured weight age 10

Childhood adiposity and proliferative BBD

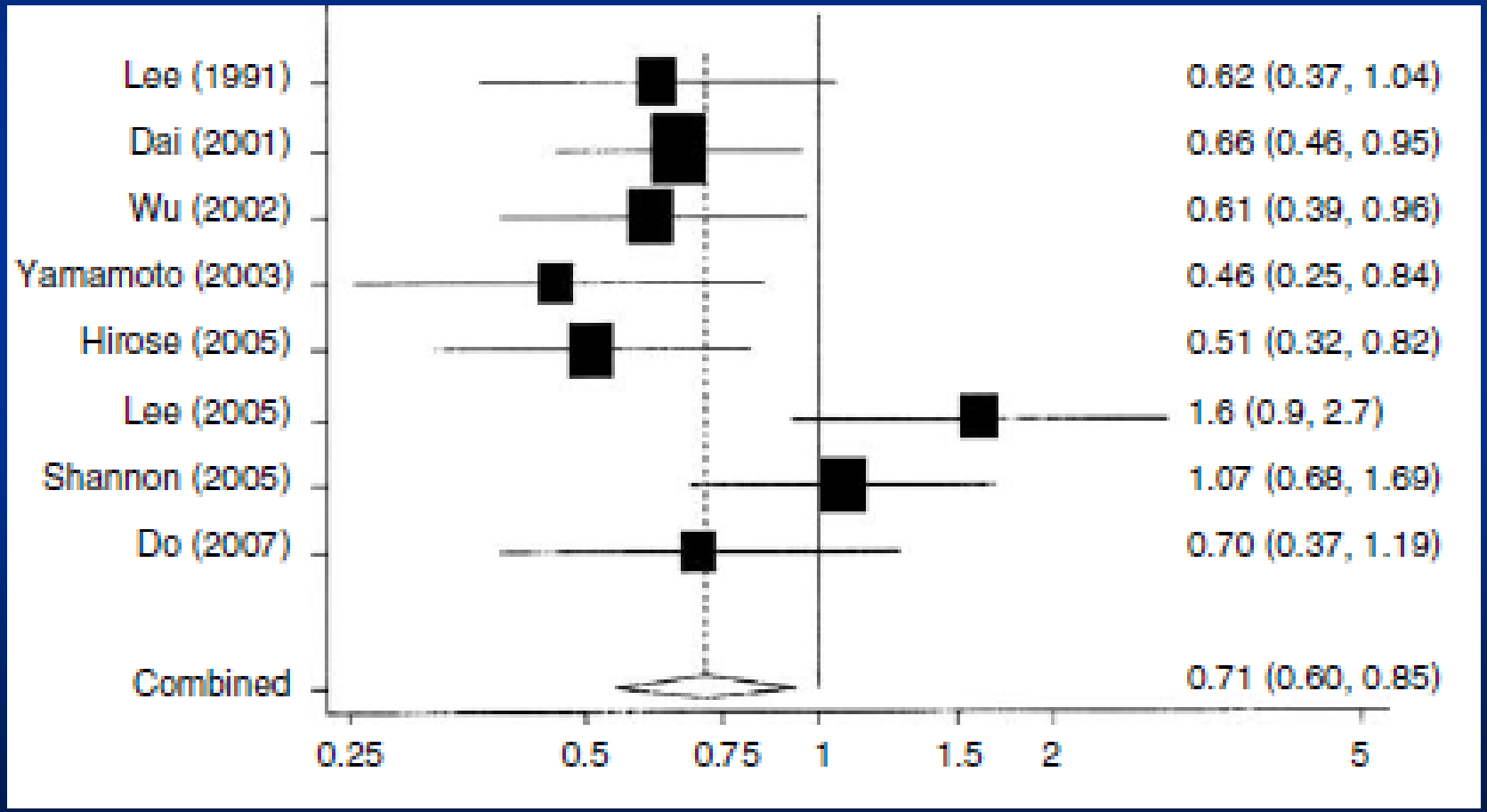


Baer et al CEBP 2005

Adolescent diet exposures

- Soy: Hi vs low intake (Korde CEBP2009)
  - Childhood RR=0.42
  - Adolescent RR=0.77
  - Adult RR = 0.71
- Prospective data from Shanghai cohort support this protective effect, (Lee AJCN 2009)
- US based studies of recent consumption of soy based products show no protection
  - US intake ~0.8mg isoflavone per day
  - Asian intake ~20 mg/d vs <5mg/d

8 Asian studies adult intake: >20 mg /d vs. <5mg/d isoflavone



Wu et al BJC 2007

GUTS

- Founded in 1996 after many iterations through study section (G Colditz PI DK46834)
- Validated diet, explored measures of physical activity
  - (Rockett et al Preventive Med 1997)
- Aim to relate adolescent diet to long term cancer risk, for funding purposes focused on adolescent weight gain

Adolescent measures: GUTS

- Higher adolescent BMI – lower risk BBD
- Later menarche associated with increased risk of BBD
- More rapid growth positively related
- Height positively related
- Adolescent physical activity reduces risk comparable magnitude to risk reduction for premenopausal breast cancer

Alcohol and BBD - GUTS

- 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)
  - Berkey et al , Pediatrics 2010

Adolescent and early adult physical activity

- Retrospective data – Bernstein suggests sustained high activity from menarche reduces risk premenopausal breast cancer (RR = 0.42; 3.8 hr per week vs inactive)
  - Bernstein et al., JNCI 1994
- NHSII – prospective data show similar results
  - Maruti et al., JNCI 2008

Physical Activity: Life Periods

12. Following are questions about your physical activity at various times in your life and at various intensity levels. For each age range below, please estimate the ***average*** amount of time that you spent in these activities. We recognize that this is a difficult task, but we ask that you ***average*** your activity over seasons and years during the given age categories.

a) Walking to and from School or Work

	Average hours per WEEK						
	None	0.5	1–2	3–4	5–6	7–10	11+
Grades 7–8	○	○	○	○	○	○	○
Grades 9–12	○	○	○	○	○	○	○
Ages 18–22	○	○	○	○	○	○	○
Ages 23–29	○	○	○	○	○	○	○
Ages 30–34	○	○	○	○	○	○	○

b) TV Watching

	Average hours per WEEK								
	None	1	2–5	6–10	11–20	21–40	41–60	61–90	91+
Grades 7–8	○	○	○	○	○	○	○	○	○
Grades 9–12	○	○	○	○	○	○	○	○	○
Ages 18–22	○	○	○	○	○	○	○	○	○
Ages 23–29	○	○	○	○	○	○	○	○	○
Ages 30–34	○	○	○	○	○	○	○	○	○

c) Strenuous Recreational Activity
Causing increased breathing, heart-rate, or sweating
(e.g., running, aerobics, lap swimming)

	Average hours per WEEK						
	None	0.5	1–2	3–4	5–6	7–10	11+
Grades 7–8	○	○	○	○	○	○	○
Grades 9–12	○	○	○	○	○	○	○
Ages 18–22	○	○	○	○	○	○	○
Ages 23–29	○	○	○	○	○	○	○
Ages 30–34	○	○	○	○	○	○	○

d) Moderate Recreational Activity
e.g., hiking, walking for exercise, casual cycling, yard work
(do not count activities already reported)

	Average hours per WEEK						
	None	0.5	1–2	3–4	5–6	7–10	11+
Grades 7–8	○	○	○	○	○	○	○
Grades 9–12	○	○	○	○	○	○	○
Ages 18–22	○	○	○	○	○	○	○
Ages 23–29	○	○	○	○	○	○	○
Ages 30–34	○	○	○	○	○	○	○

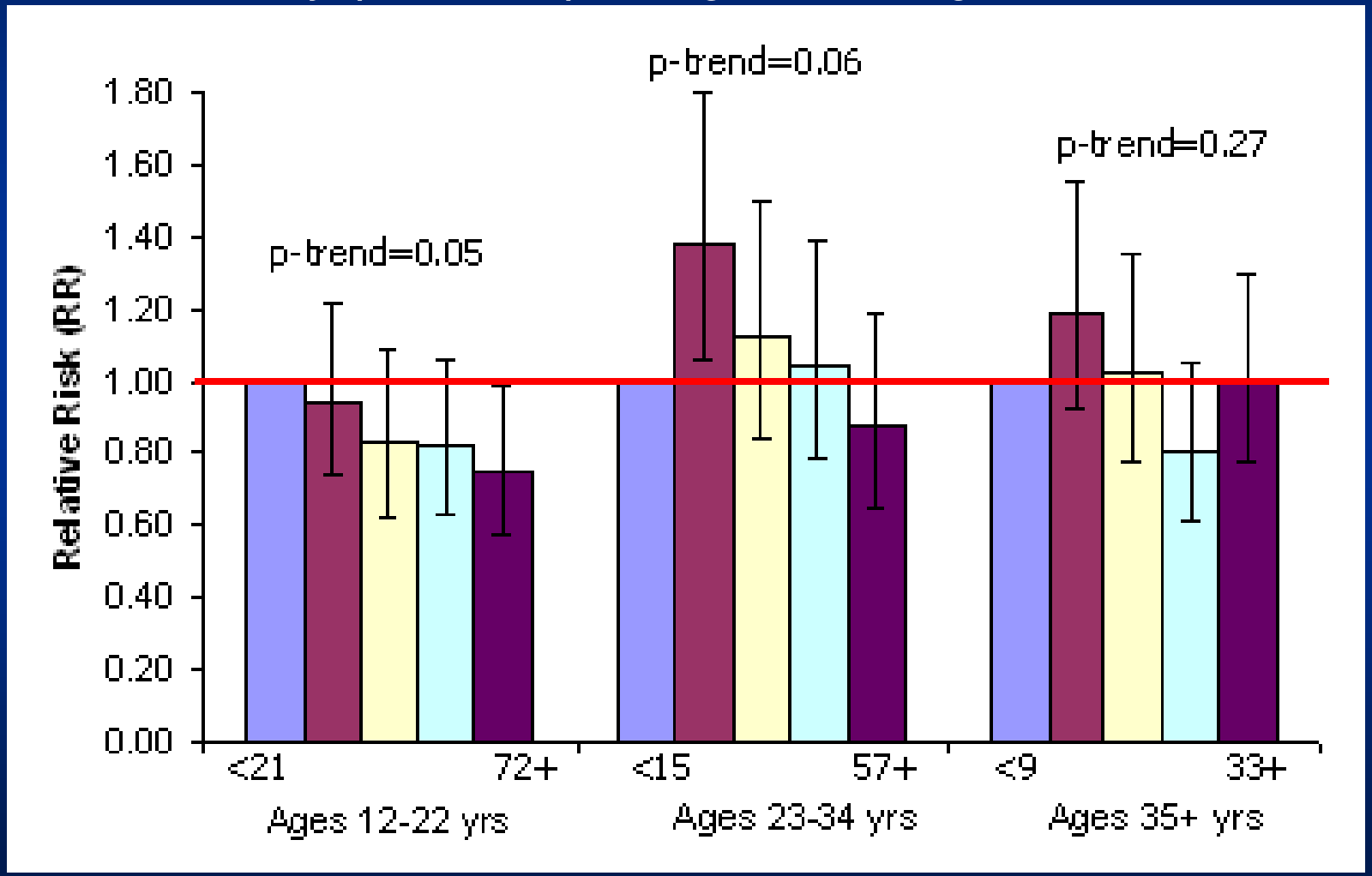
NHS II 1997 questionnaire

Reproducibility & Validity

- Life periods
  - 4-year reproducibility
    - r=0.64 for total activity during adolescence
- Past-year total adult activity
  - Validity
    - r=0.79 questionnaire vs. past-week recalls
    - r=0.56 questionnaire vs. four 7-day dairies
    - Also, measures are also associated with lower resting pulse (r=-0.45) and increased maximal oxygen consumption (r=0.54) in a separate study group

What Time Period is Important for breast cancer?

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



Maruti et al JNCI 2008 100:728-737

Lessons learned

- Breast clearest example
- Multiple cancer relations for height and growth
- Diet and physical activity in adolescence validly measured
- Pictogram validated
- Adolescent and early adult exposures drive subsequent cancer risk

Given cancer is preventable: Key questions

- What 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

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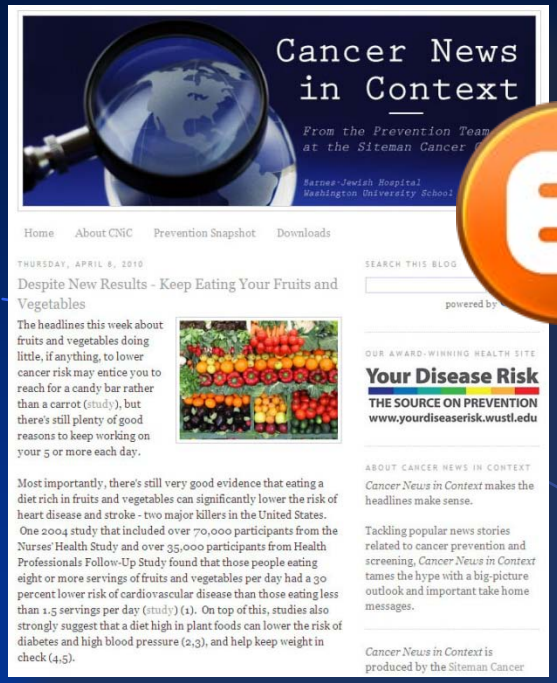
Conclusion

- Focus more attention on childhood and adolescence as key periods in development of lifetime cancer risk
- Diet, physical activity, and adiposity serve as model
- Improve our use of intermediate end points to speed our understanding


Cancer News in Context
From the Prevention Team at the Siteman Cancer
Barnes-Jewish Hospital
Washington University School
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THURSDAY, APRIL 8, 2010
Despite New Results - Keep Eating Your Fruits and Vegetables
The headlines this week about fruits and vegetables doing little, if anything, to lower cancer risk may entice you to reach for a candy bar rather than a carrot (study), but there's still plenty of good reasons to keep working on your 5 or more each day.
Most importantly, there's still very good evidence that eating a diet rich in fruits and vegetables can significantly lower the risk of heart disease and stroke - two major killers in the United States.
One 2004 study that included over 70,000 participants from the Nurses' Health Study and over 35,000 participants from Health Professionals Follow-Up Study found that those people eating eight or more servings of fruits and vegetables per day had a 30 percent lower risk of cardiovascular disease than those eating less than 1.5 servings per day (study) (1). On top of this, studies also strongly suggest that a diet high in plant foods can lower the risk of diabetes and high blood pressure (2,3), and help keep weight in check (4,5).
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Cancer News in Context makes the headlines make sense.
Tackling popular news stories related to cancer prevention and screening, Cancer News in Context tames the hype with a big-picture outlook and important take home messages.
Cancer News in Context is produced by the Siteman Cancer


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Cancer News in Context: Adolescent & Young Adult Drinking, Benign Breast Disease, and Cancer Risk
12:20pm Apr 15
Adolescent drinking adds to risk of breast disease, breast cancer | Newsroom | Washington
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Cancer News in Context: Adolescent & Young Adult Drinking, Benign Breast Disease, and Cancer Risk
www.cancernewsincontext.org
In results widely reported this week, a new study has found strong links between the drinking behavior of young women and adolescent girls and their later risk of developing benign breast disease, a marker ...
Yesterday at 12:20pm · Comment · Like · Share
Your Disease Risk New research from YDR's Dr. Graham Colditz, showing that early life can have an important impact on later cancer risk.
Adolescent drinking adds to risk of breast disease, breast cancer | Newsroom | Washington Universit.
news.wustl.edu
Girls and young women who drink alcohol increase their risk of benign (noncancerous) breast disease, says a study by researchers at Washington University School of Medicine in St. Louis and Harvard University. Benign breast disease increases the risk for developing breast cancer.
April 12 at 12:54pm · Comment · Like · Share
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Cancer News in Context: Despite New Results - Keep Eating Your Fruits and Vegetables
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The headlines this week about fruits and vegetables doing little, if anything, to lower cancer risk may entice you to reach for a candy bar rather than a carrot(study), but there's still plenty of good ...
April 9 at 1:23pm · Comment · Like · Share
Mary Lee likes this.
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Cancer News in Context: Health care reform and prevention of cancer
www.cancernewsincontext.org
In Sunday's New York Times (story), Robert Pear wrote about the many disease prevention initiatives contained in the new health care law recently passed by congress and signed by the president. It's important to stop and consider the full implications of this.
April 7 at 1:08pm · Comment · Like · Share


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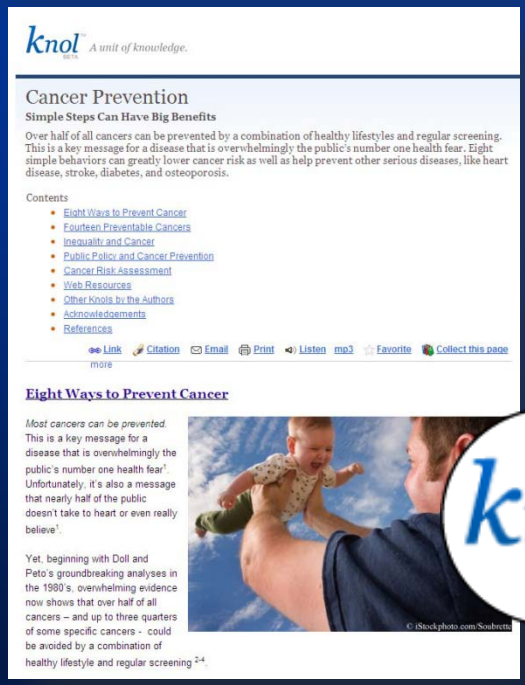
Glossary
Welcome to Your Disease Risk, the source on prevention. Here, you can find out your risk of developing five of the most important diseases in the United States and get personalized tips for preventing them.
Developed over the past ten years by world-renowned experts, Your Disease Risk collects the latest scientific evidence on disease risk factors into one easy-to-use tool.
To get started, choose one of the diseases below.
What is your risk?
Cancer: There's much more to it than just smoking and lung cancer.
What's your cancer risk?
Diabetes: Over 18 million in the U.S. suffer from it. Take steps now to lower your risk.
What's your diabetes risk?
Heart disease: The #1 killer in the U.S. is also one of the most preventable.
What's your heart disease risk?
Osteoporosis: Calcium isn't the only way (or even the best way) to protect yourself.
What's your osteoporosis risk?
Stroke: Most cases of this feared disease can be avoided by lifestyle changes.
What's your stroke risk?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Cancer Prevention
Simple Steps Can Have Big Benefits
Over half of all cancers can be prevented by a combination of healthy lifestyles and regular screening. This is a key message for a disease that is overwhelmingly the public's number one health fear. Eight simple behaviors can greatly lower cancer risk as well as help prevent other serious diseases, like heart disease, stroke, diabetes, and osteoporosis.
Contents
Eight Ways to Prevent Cancer
Fourteen Preventable Cancers
Inequality and Cancer
Public Policy and Cancer Prevention
Cancer Risk Assessment
Web Resources
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Eight Ways to Prevent Cancer
Most cancers can be prevented. This is a key message for a disease that is overwhelmingly the public's number one health fear[1]. Unfortunately, it's also a message that nearly half of the public doesn't take to heart or even really believe[1].
Yet, beginning with Doll and Peto's groundbreaking analyses in the 1980's, overwhelming evidence now shows that over half of all cancers – and up to three quarters of some specific cancers - could be avoided by a combination of healthy lifestyle and regular screening [2-4].
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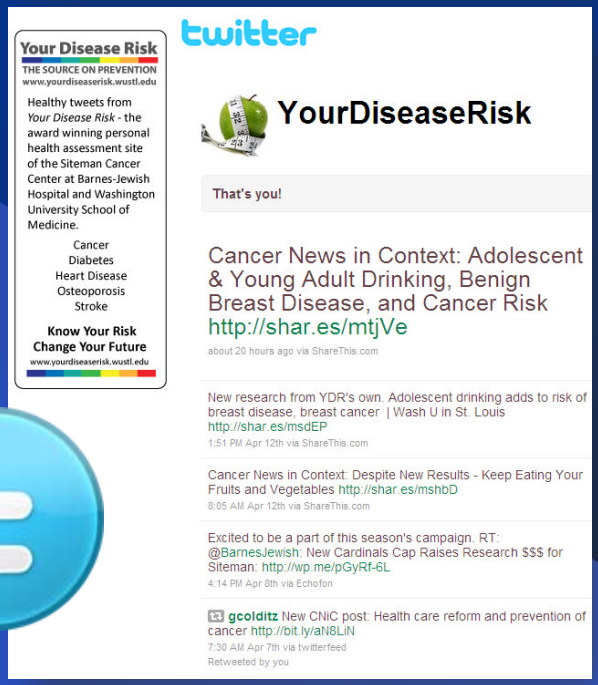
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1:51 PM Apr 12th via ShareThis.com
Cancer News in Context: Despite New Results - Keep Eating Your Fruits and Vegetables http://shar.es/mshbD
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gcolditz New CNiC post: Health care reform and prevention of cancer http://bit.ly/aN8LiN
7:30 AM Apr 7th via twitterfeed
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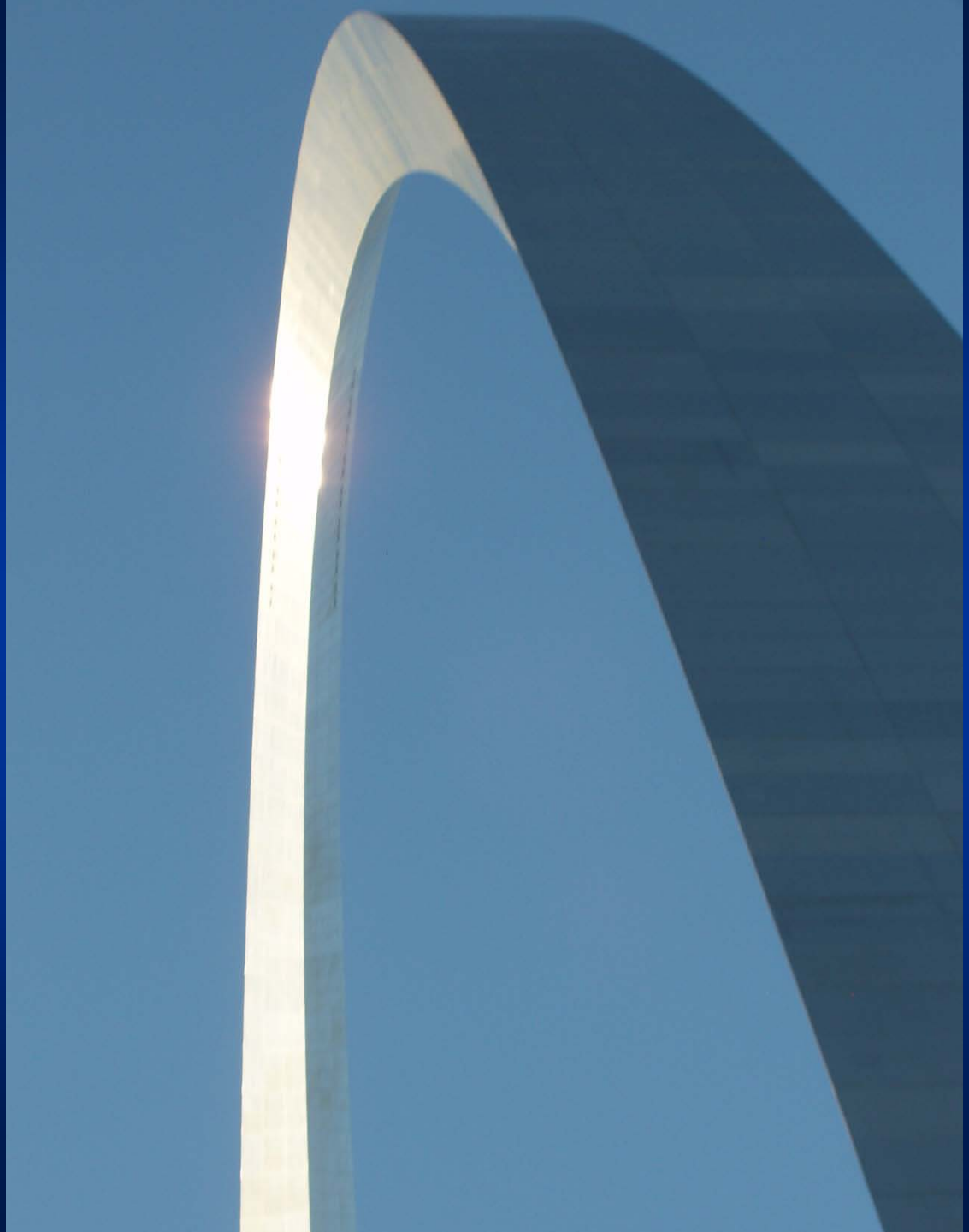

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