We can prevent more than half of cancer now: An update on evidence including weight gain and breast cancer

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Goals of talk

Review potential for cancer prevention

Consider time frame and next steps to achieve sustained cancer prevention

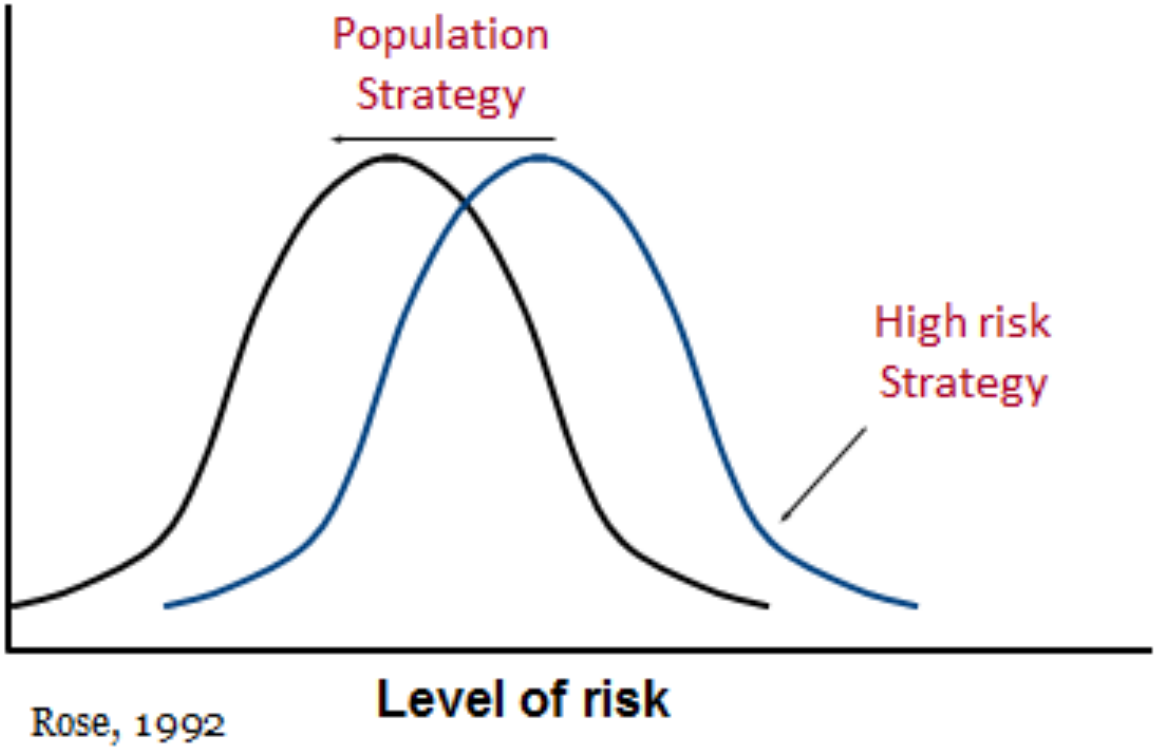
Issues/Lessons:

- Improving cancer prevention,
- Implementing what we know,
- Integrating risk factors across life course, and
- Clarifying our time frame is essential to achieving our goals.

Medical interventions proven to prevent cancer (Colditz et al. Sci Trans Med 2012)

Intervention	Target	Magnitude of reduction	Time (yrs)
Aspirin	Colon mortality	40%	20+
SERMs	Breast incidence	40-50%	5+
Salpingo oophorectomy	Familial breast ca	50%	3+
Screening for colorectal ca	Colon ca mortality	30-40%	10
Vaccination	Cervical ca incidence	50-100%	20+
	Liver ca incidence	70-100%	20+
Mammography	Breast ca mortality	30%	10-20
Serial CT lung	Lung ca mortality	20%	6+

Population approach versus high risk strategy



Rose, 1992

Behavioral, Social and Policy interventions that impact Cancer Prevention

Intervention	Target	Type of Ix	Evidence review
Reduce tobacco use	Children and Adolescents Smokers to quit	Combined Pharmaco/ behavioral Ixs Smoke-free policies Tobacco taxes	Surgeon General, USA
Increase physical activity	Individuals and community norms	Urban design Stairs and workplace	Surgeon General, USA
Reduce Obesity	Population	School & work environment Physical activity Food & beverage	Inst. of Medicine report
Limit alcohol intake	Population	Taxes	WHO

When we implement what we know, we prevent cancer

Tobacco –

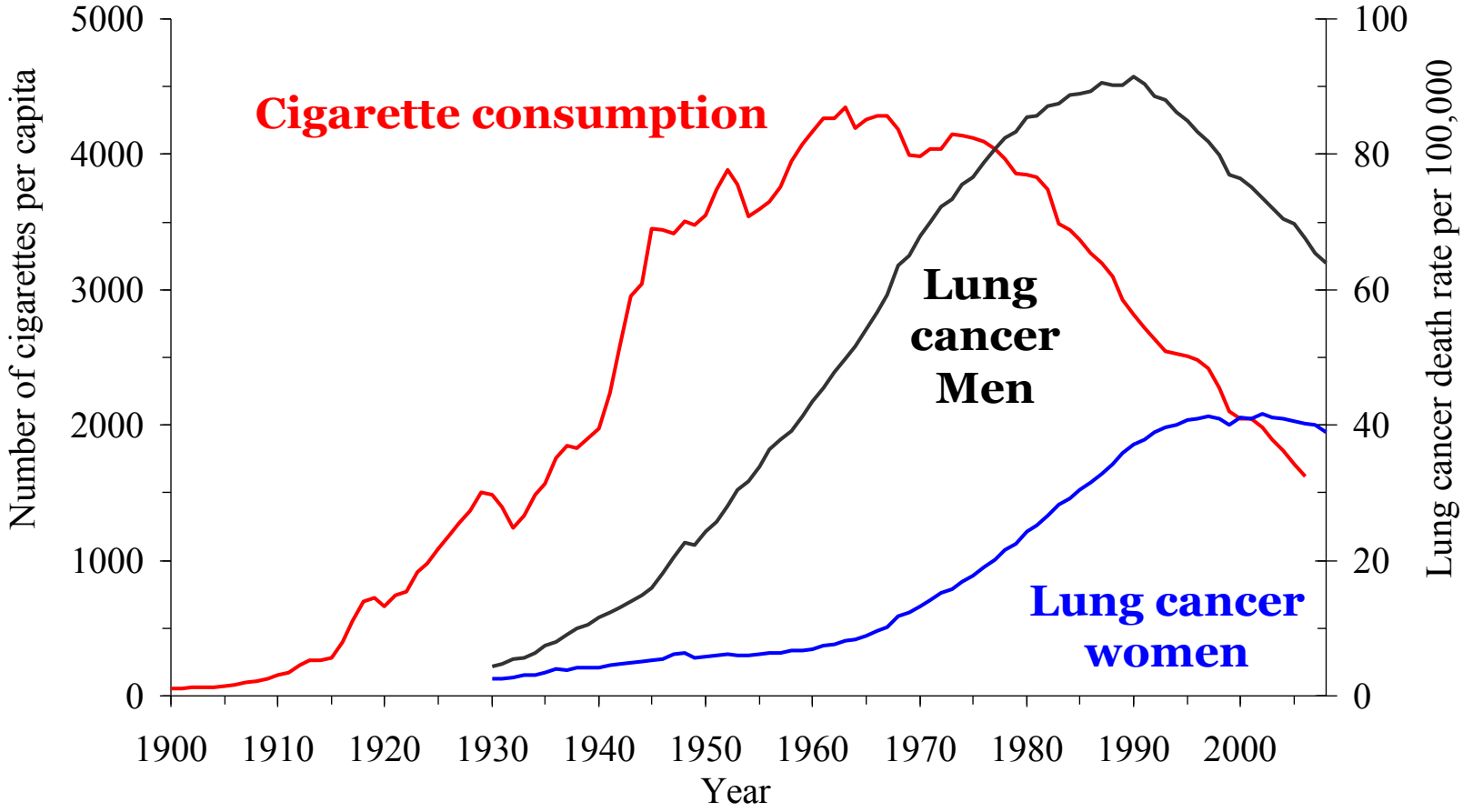
lung cancer mortality decreased by one third

- Adolescent smoking decrease 35% (1999) to 18% (2011)

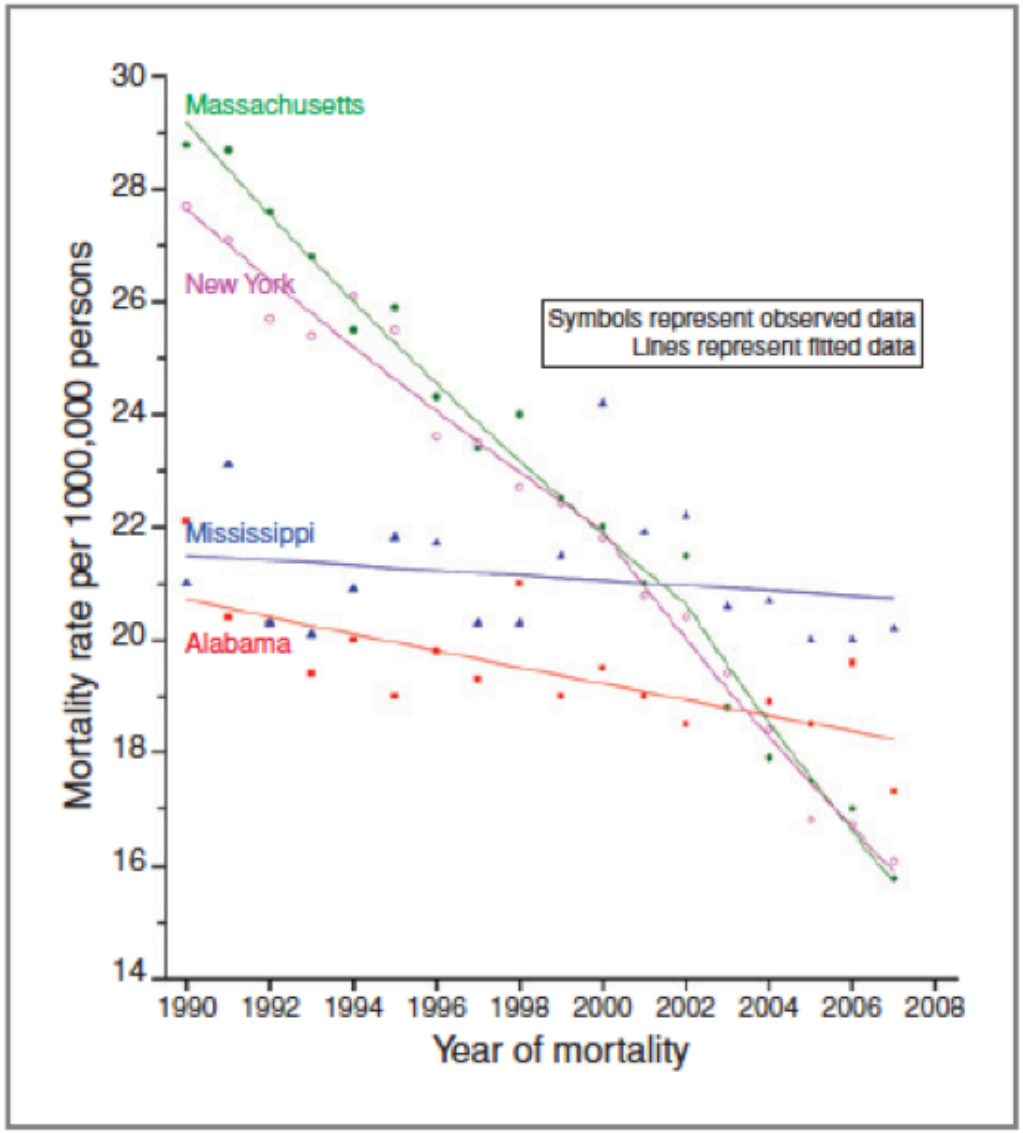
Colorectal cancer screening –

steady increase in use and reduction in CRC mortality over time

Trends in smoking and lung cancer, USA

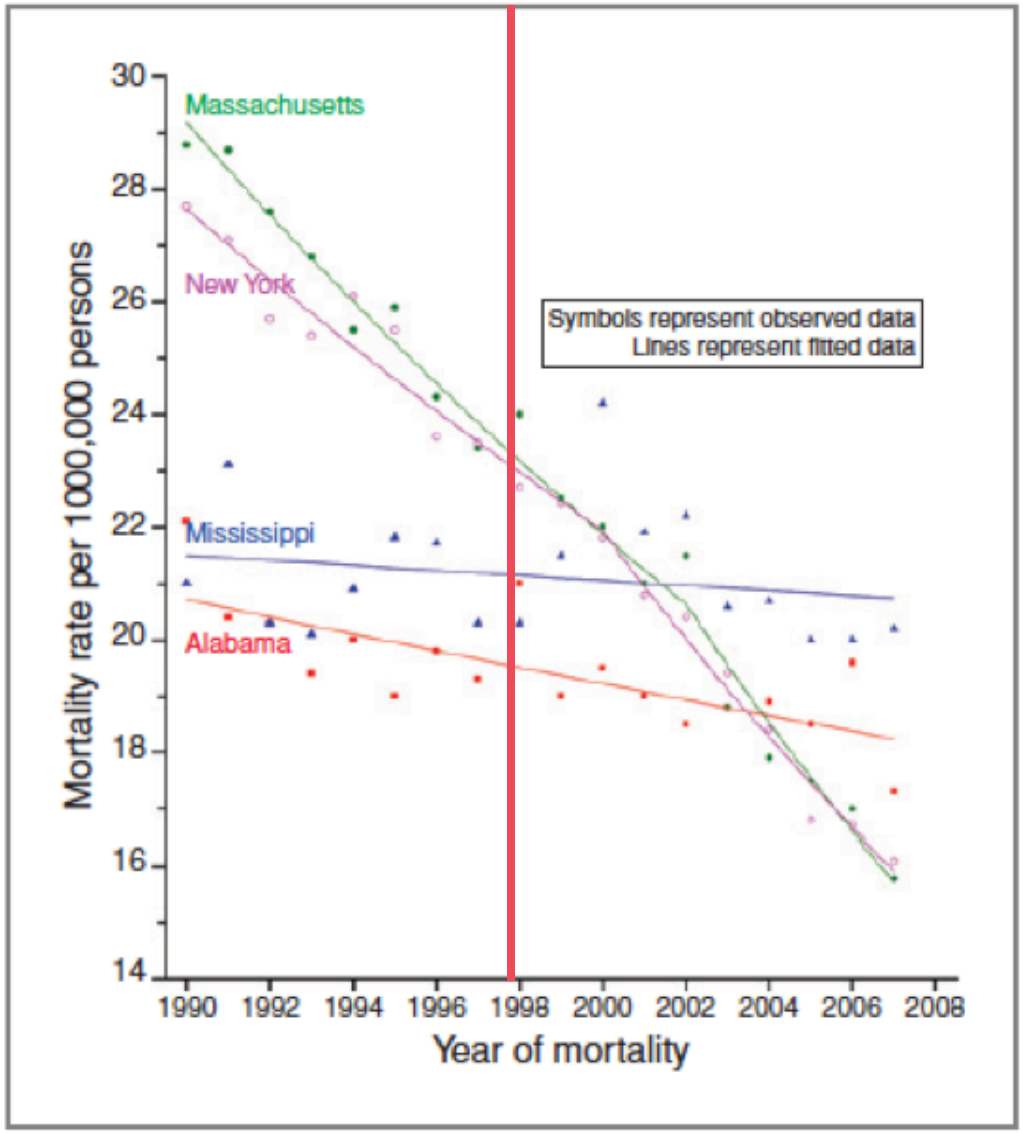


Trends: CRC mortality



Naishadham et al
CEBP 2011

Trends: CRC mortality



Naishadham et al
CEBP 2011

Lifestyle: high income countries

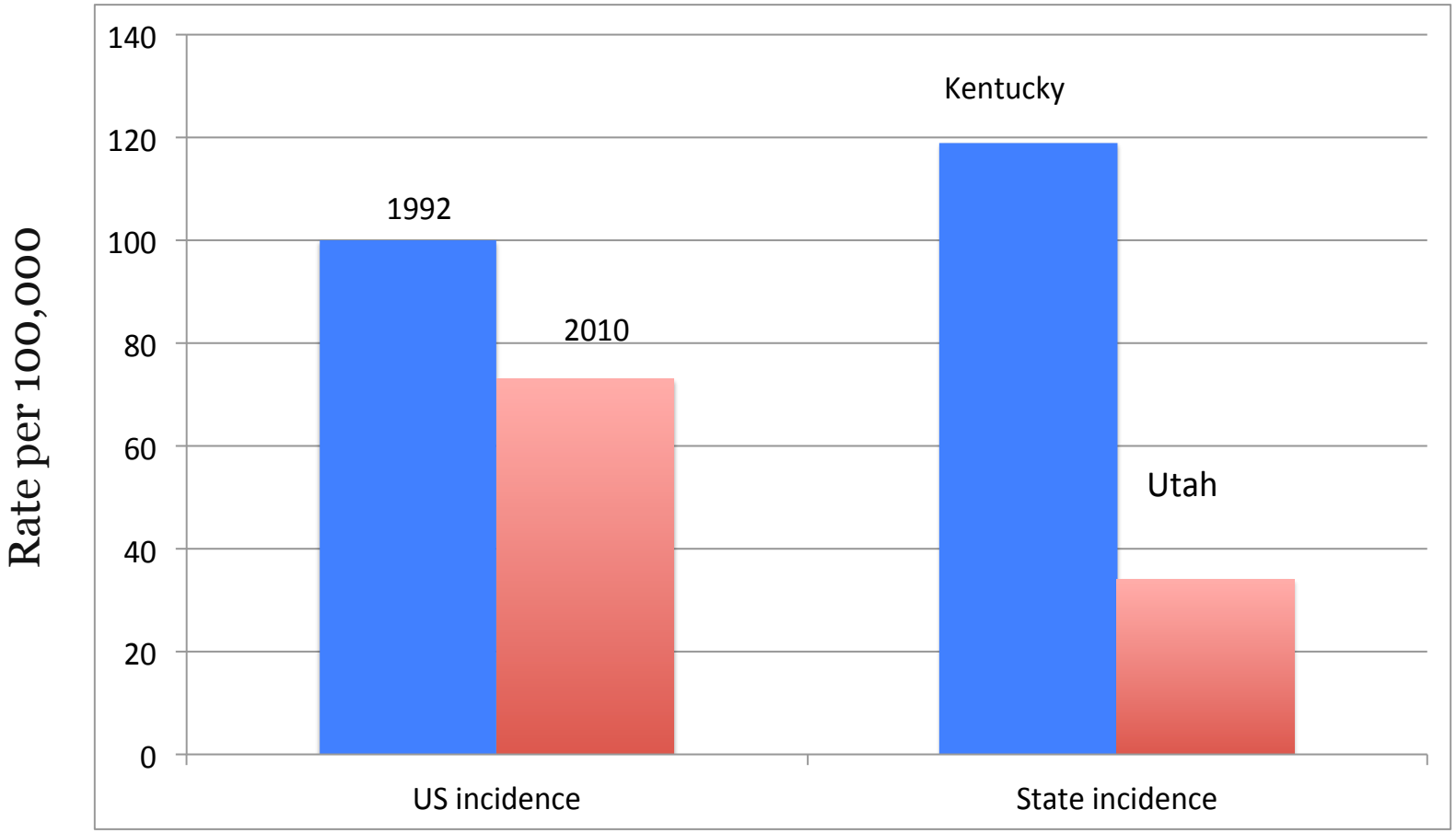
Cause	% cancer caused	Magnitude possible reduction	Time (yrs)
Smoking	33		
Overweight/ obesity	20		
Diet	5		
Lack of exercise	5		
Occupation	5		
Viruses	5-7		
Family history	5		
Alcohol	3		
UV/ionizing radiation	2		
Reproductive	3		
Pollution	2		

Colditz et al. Sci Transl Med 2012: March 28

Lifestyle: high income countries

Cause	% cancer caused	Magnitude possible reduction	Time (yrs)
Smoking	33	75%	
Overweight/ obesity	20	50%	
Diet	5	50%	
Lack of exercise	5	85%	
Occupation	5	50%	
Viruses	5-7	100%	
Family history	5	50%	
Alcohol	3	50%	
UV/ionizing radiation	2	50%	
Reproductive	3	0	
Pollution	2	0	

Burden Cigarette Smoking, USA



Lifestyle: high income countries

Cause	% cancer caused	Magnitude possible reduction	Time (yrs)
Smoking	33	75%	10-20
Overweight/ obesity	20	50%	2-20
Diet	5	50%	5-20
Lack of exercise	5	85%	5-20
Occupation	5	50%	20-40
Viruses	5-7	100%	20-40
Family history	5	50%	2-10
Alcohol	3	50%	5-20
UV/ionizing radiation	2	50%	2-10
Reproductive	3	0	N/A
Pollution	2	0	N/A

Risk of Cancer with Increased BMI

Cancer	Sample Size	Follow-up (yrs)	RR Men	RR Women
Breast (premenopausal)	2.5 mil	11.0	-	0.92**
Breast (postmenopausal)	2.5 mil	11.0	-	1.12***
Colon	4.8 mil	11.0	1.24*	1.09*
Endometrium	3.0 mil	10.6	-	1.59*
Gallbladder	3.3 mil	12.7	1.09	1.59***
Gastric	4.7 mil	10.8	0.97	1.04
Leukemia	4.7 mil	13.7	1.08**	1.17***
Liver	3.3 mil	12.7	1.24	1.07
Lung	2.6 mil	11.9	0.76*	0.80***
Multiple myeloma	5.2 mil	14.6	1.11*	-
Non-Hodgkin lymphoma	5.0 mil	12.4	1.06*	1.07
Oesophageal adenocarcinoma	4.7 ml	10.8	1.52*	1.51*

Relative risk for a 5 point increase in BMI. For example, the relative risk linked to a BMI of 28 compared to a BMI of 23; or a BMI of 32 compared to 27.
*p < .0001; **p < .01; ***p < .05

Adapted from Renehan et al, 2008; Fig 3

1 Maintain a healthy weight

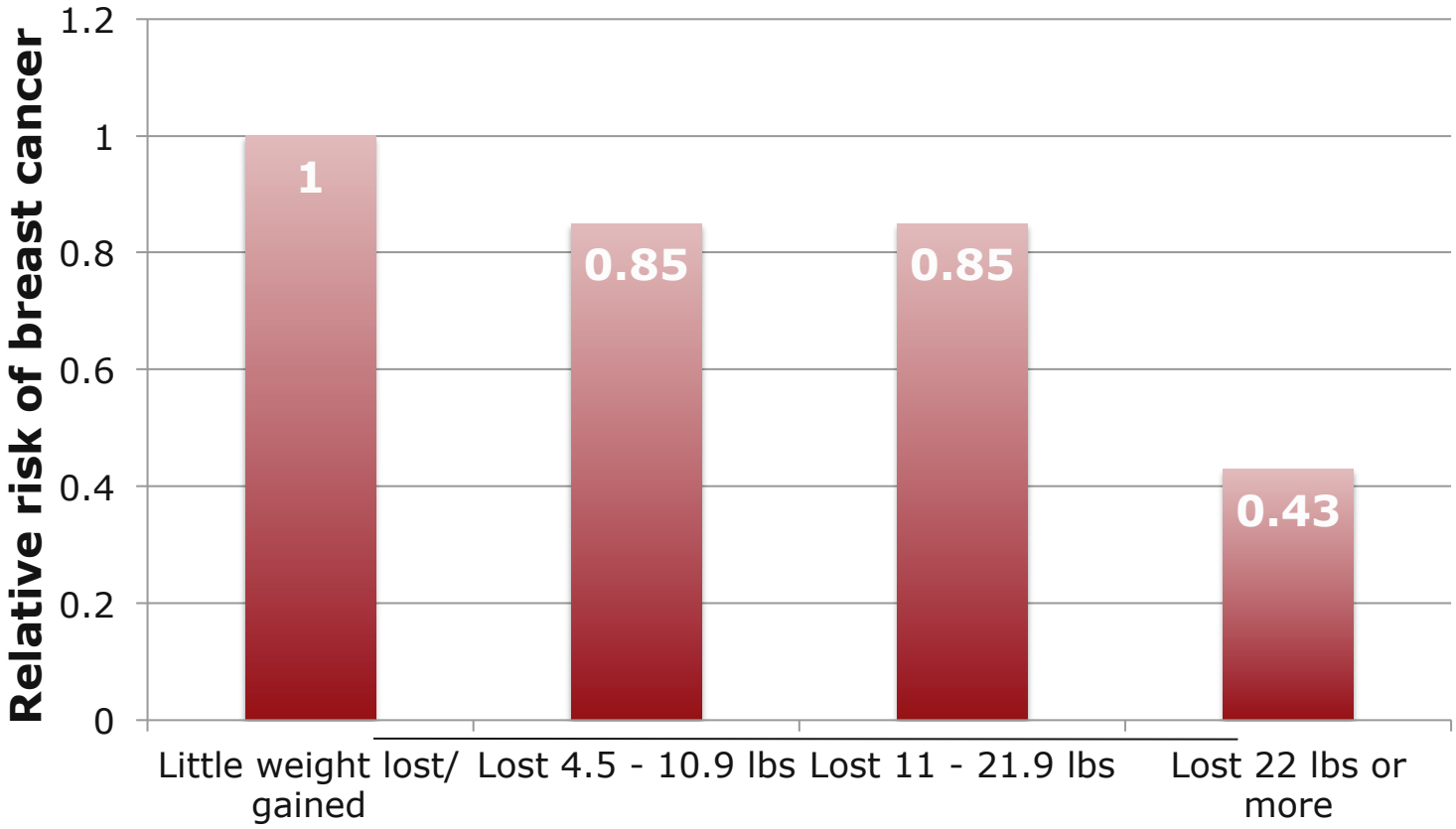
Weight loss lowers risk

Risk of breast cancer dropped by 60% in women who lost more than 10 kg (22 pounds) after menopause

Loss of just 5 pounds lowered risk by 15%

Eliassen et al JAMA 2006

Sustained Weight Loss and Risk of Breast Cancer in Postmenopausal Women Who Never Used Postmenopausal Hormones



Eliassen et al, JAMA 2006

TREC – Cross TREC project

DISENTANGLING WEIGHT WEIGHT GAIN AND TIMING

U54 CA155496

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

Pike model – Nature 1983

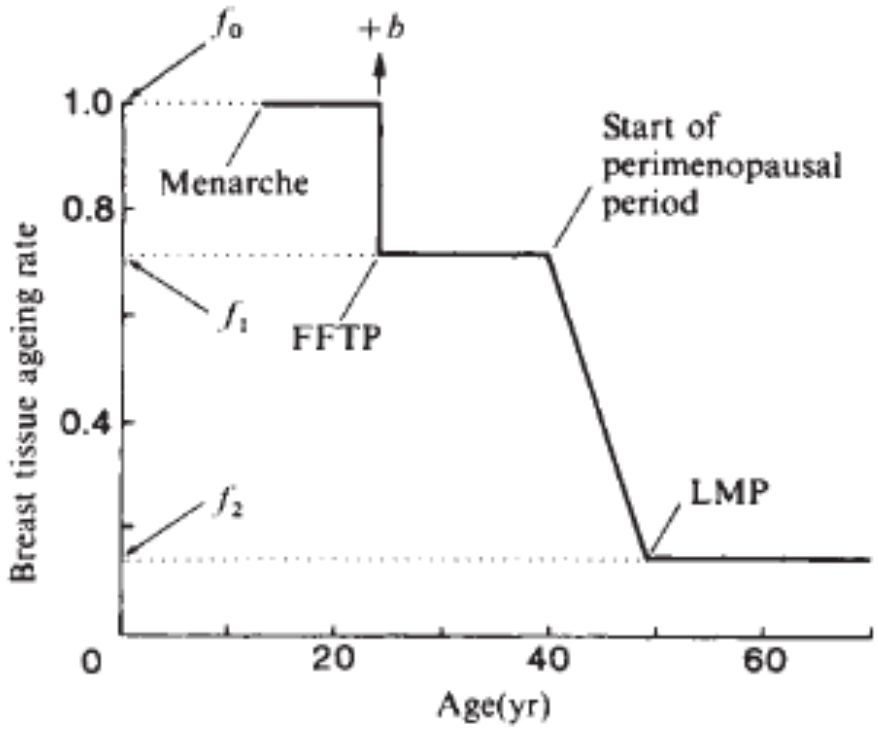


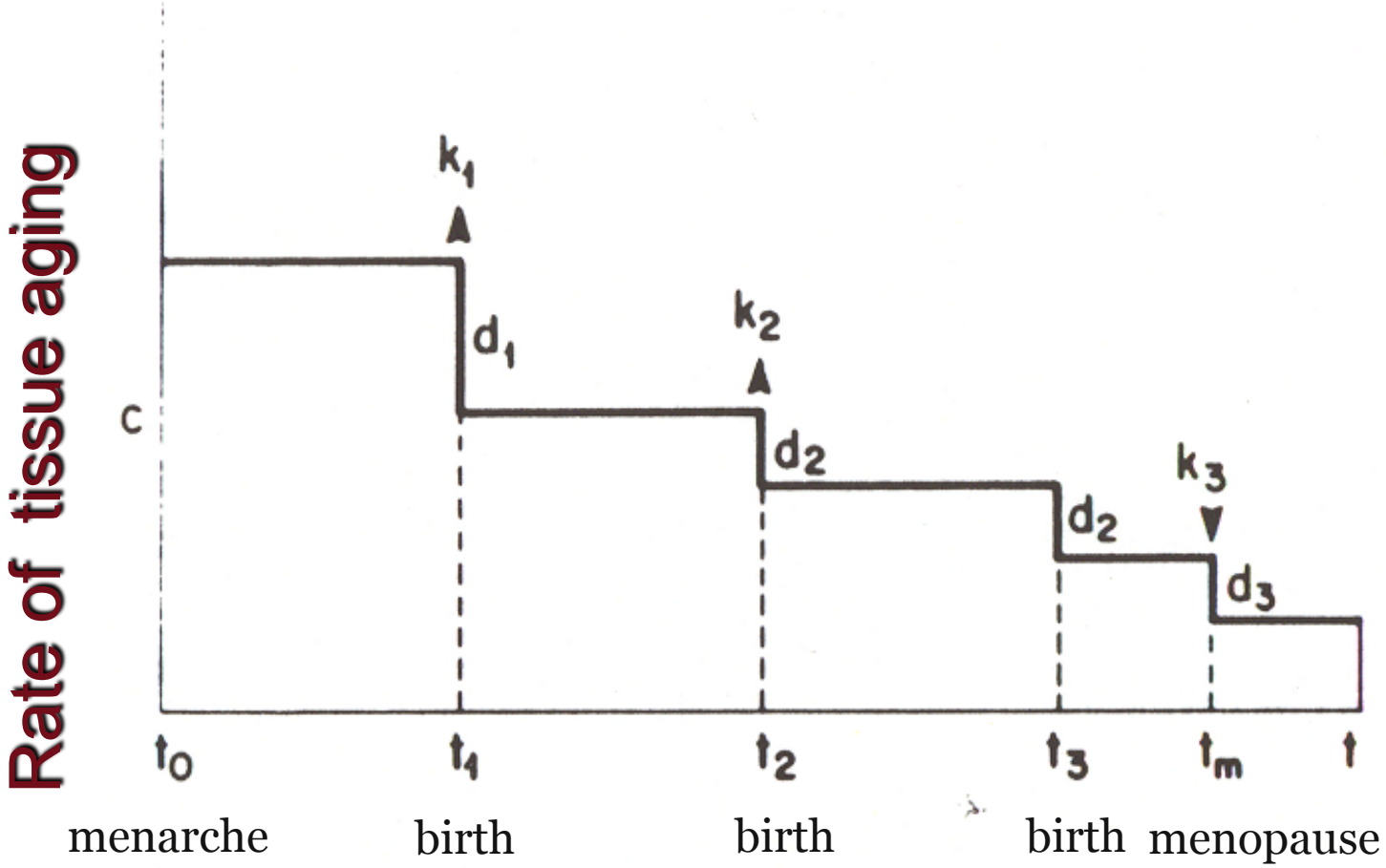
Fig. 2 Model of rate of breast tissue ageing (see text). LMP, last menstrual period.

To accommodate the higher incidence with late first birth, we add a constant representing an increase in risk with FFTP

(+b) in figure

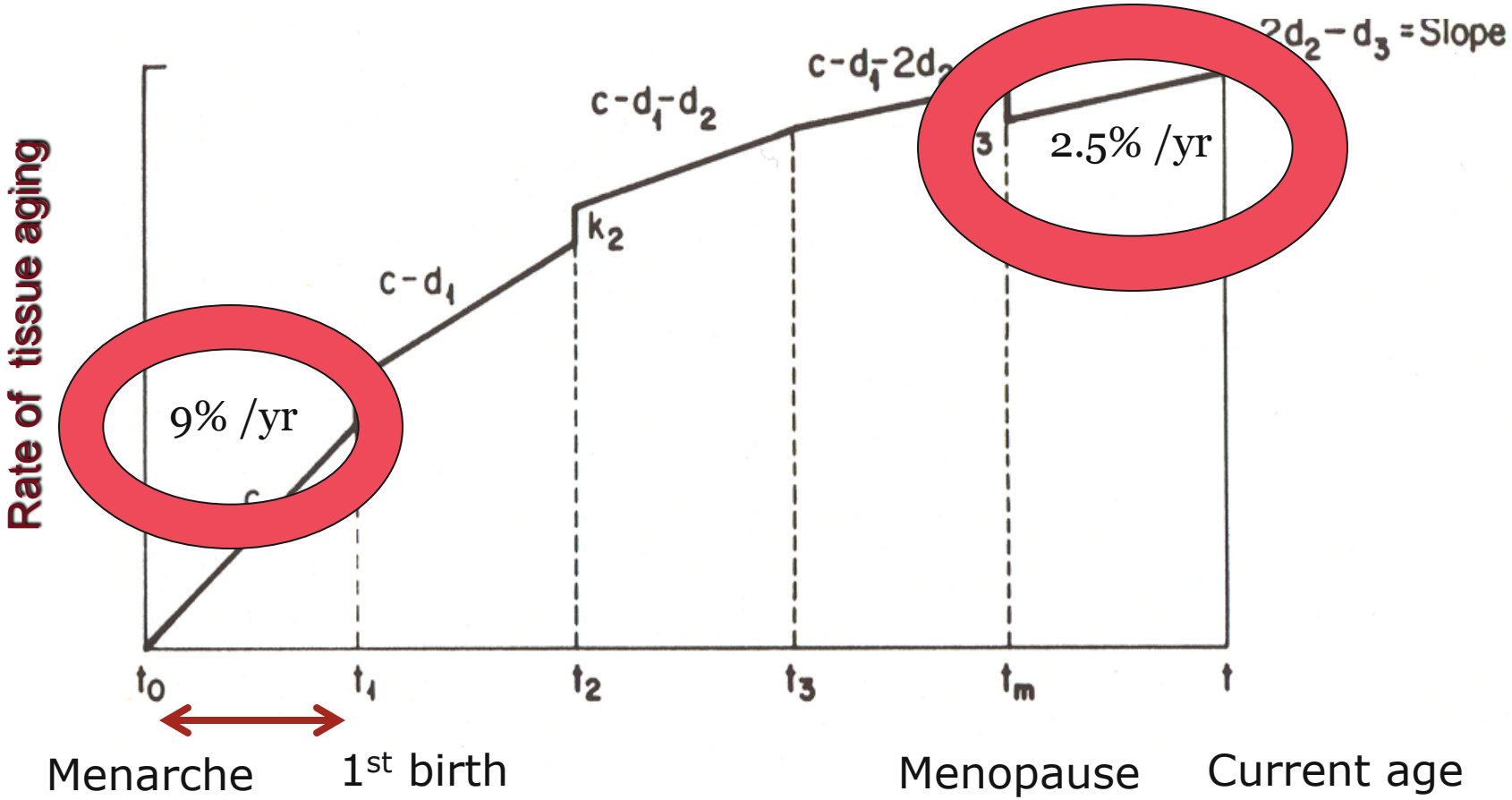
Pike, et al. Nature 1983

Accumulating risk, multiple birth model



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

Accumulating risk, multiple birth model



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

Effects of obesity on breast cancer

- Obesity is well-established as a risk factor for post-menopausal breast cancer.
- Obesity is protective for pre-menopausal breast cancer

Short-term effects of weight gain on breast cancer incidence

- Short-term effects of weight change on breast cancer risk are largely unknown

- We investigated short-term effects of obesity on breast cancer using NHS data

Study Population – Nurses' Health Study

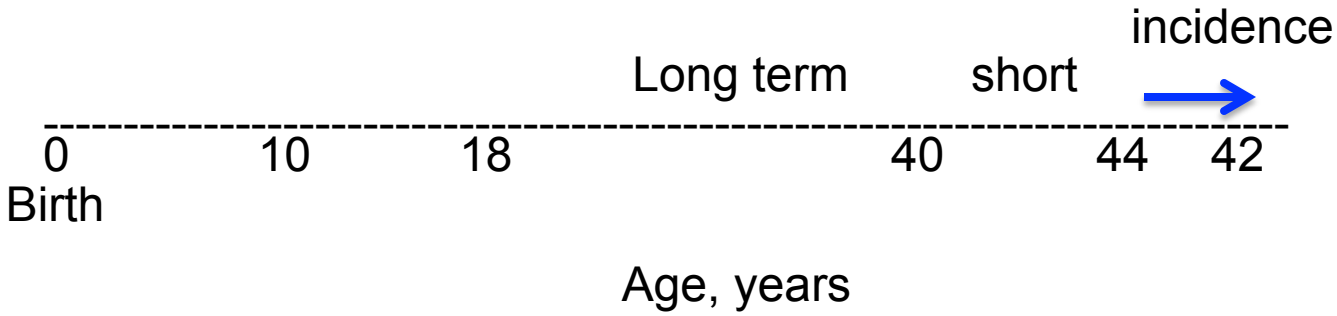
- 77, 232 women followed over 1,445,578 person-years from 1980-2008
- 4,196 incident cases of invasive breast cancer

Rosner et al Breast Cancer Res Treat 2015

Analytical approach

- Log incidence model of breast cancer (Colditz, et al AJE 2000) used to predict incident breast cancer as a function of
  1) Average BMI before menopause
  2) Average BMI after menopause
  3) Other breast cancer risk factors

- Short-term weight gain ≡ weight gain over previous 2 cycles (≈ 4 years) added as an additional risk factor



Association between 4-year weight change (1990-1994) and selected breast cancer risk factors in 1994, NHS, 45,009 women

Variable		Wt loss of > 5lbs	No change	Wt gain of 5.1-9.9lbs	Wt gain of 10.0-14.9lbs	Wt gain of ≥ 15.0lbs
	N	**5,610**	**22,202**	**5,207**	**5,732**	**6,258**
Age	Mean	**61.8**	**60.8**	**59.6**	**58.8**	**57.9**
Pre-menopausal	(%)	**9**	**12**	**14**	**17**	**18**
Weight at age 18	Mean	**130.7**	**124.1**	**123.3**	**126.2**	**131.8**
Current weight	Mean	**153.2**	**147.1**	**152.4**	**164.5**	**185.4**
Current HT use	(%)	**35.9**	**43.6**	**45.5**	**44.2**	**44.1**
Age at 1st birth	Mean	**25.5**	**25.3**	**25.1**	**25.0**	**24.9**
Parity	Mean	**3.0**	**3.0**	**2.9**	**2.9**	**2.9**

4-year weight change, breast ca. incidence

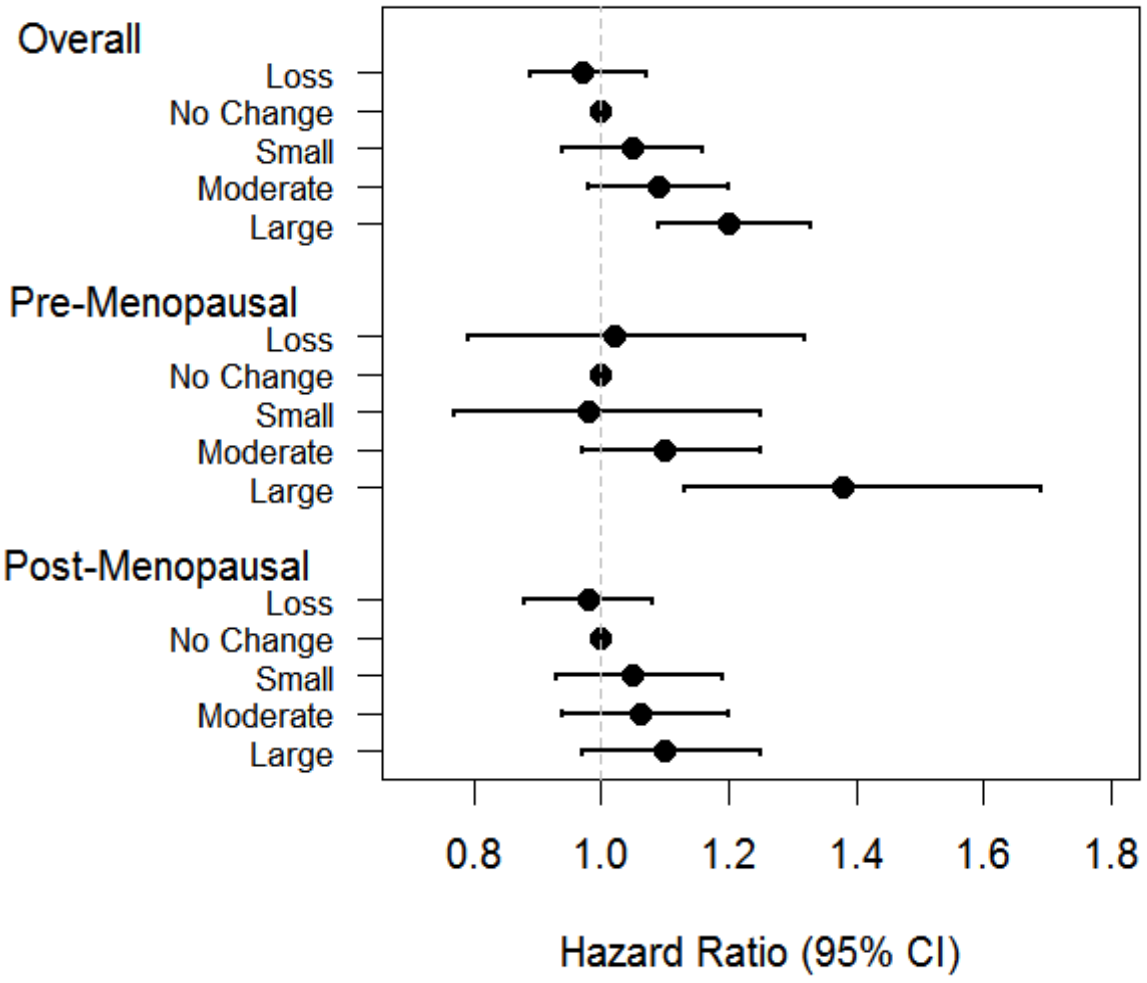
Group	Number of Cases	Loss of > 5lbs	No change (ref)++	Gain of 5.1-9.9lbs	Gain of 10.0-14.9lbs	Gain of ≥ 15.0lbs	RR**	P_trend
overall	**4196**	**0.97* (0.89-1.07)**	**1.0**	**1.05 (0.94-1.16)**	**1.09 (0.98-1.20)**	**1.20 (1.09-1.33)**	**1.13 (1.06-1.21)**	**<0.001**
Pre-menopausal +	**736**	**1.02 (0.79-1.32)**	**1.0**	**0.98 (0.77-1.25)**	**1.10 (0.88-1.38)**	**1.38 (1.13-1.69)**	**1.26 (1.08-1.48)**	**0.004**
Post-menopausal +	**3443**	**0.98 (0.88-1.08)**	**1.0**	**1.05 (0.93-1.19)**	**1.06 (0.94-1.20)**	**1.10 (0.97-1.25)**	**1.08 (1.00-1.16)**	**0.063**

*HR (95% CI)
** per 25 lbs.
+ at both time points
++ weight change of ≤ 5lbs.

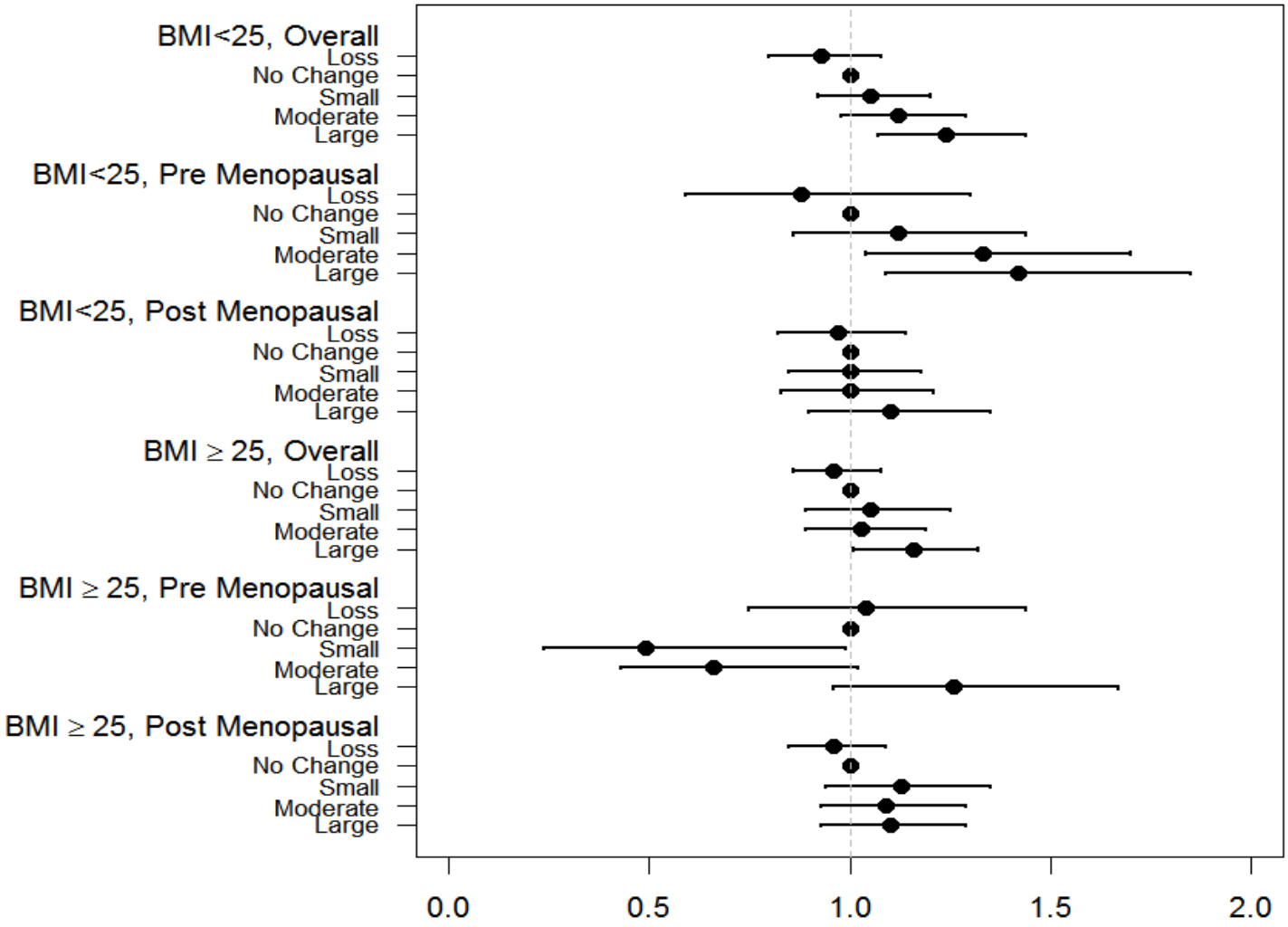
Rosner et al Breast Cancer Res Treat 2015

Overall there is a significant association of short-term weight gain with breast cancer incidence, particularly during pre-menopause.

Short term weight change, risk of breast ca



Weight gain and risk according to starting BMI



Rosner et al Breast Cancer Res Treat 2015

Associations of short-term weight gain by tumor subtype, pre-menopausal women

Group	Number of cases	Loss of > 5lbs	No change	gain of 5.1-9.9lbs	gain of 10.0-14.9lbs	gain of ≥ 15.0lbs	RR **	P_trend	P_het+
ER+/PR+	316	0.94* (0.63-1.40)	1.0	0.92 (0.63-1.34)	1.16 (0.83-1.61)	1.2 (0.93-.73)	1.13 (0.89-1.42)	0.32	---
ER+/PR-	42	1.34 (0.50-3.58)	1.0	1.11 (0.41-2.95)	0.60 (0.18-1.99)	1.7 (0.80-.89)	2.19 (1.33-3.61)	0.002	0.019
ER-/PR-	100	1.07 (0.50-2.29)	1.0	1.13 (0.57-2.26)	2.10 (1.23-3.56)	2.0 (1.21-3..1)	1.61 (1.09-2.38)	0.01	0.12

*HR (95% CI)
**per 25lbs
+vs ER+/PR+

Associations of pre-menopausal weight gain are stronger for ER+/PR- and ER-/PR- breast cancer, although case counts are small

Association of short-term weight gain by tumor subtype, post-menopausal women

Group	Number of cases	Loss of > 5lbs	No change	gain of 5.1-9.9lbs	gain of 10.0-14.9lbs	gain of ≥ 15.0lbs	RR **	P_trend	P_het+
ER+/PR+	**1518**	**0.96* (0.84-1.10)**	**1.0**	**1.03 (0.87-1.23)**	**1.01 (0.84-1.21)**	**1.06 (0.88-1.27)**	**1.05 (0.94-1.16)**	**0.40**	**---**
ER+/PR-	**419**	**0.73 (0.54-0.97)**	**1.0**	**1.21 (0.90-1.64)**	**0.80 (0.55-1.14)**	**0.91 (0.63-1.30)**	**1.25 (1.01-1.54)**	**0.043**	**0.15**
ER-/PR-	**419**	**1.36 (1.06-1.75)**	**1.0**	**1.00 (0.70-1.41)**	**1.39 (1.02-1.90)**	**1.01 (0.70-1.46)**	**0.99 (0.80-1.23)**	**0.93**	**0.65**

*HR (95% CI)
**per 25lbs
+vs ER+/PR+

No significant heterogeneity by tumor type for post-menopausal women

Summary – short-term weight gain

- Overall, there is a significant positive association of short-term weight gain on breast cancer incidence
- Associations are stronger among pre-menopausal women and women with BMI < 25
- Results are consistent with EPIC /PANACEA study (Emaus, et al., Int. J. Cancer 2014: 10.1002/ ijc28926)

Summary – long-term weight change

- Overall, there is a protective effect of weight at age 10 on breast cancer incidence, which is present for all breast cancer subtypes.

- Premenopausal weight change since age 18 positively related to breast cancer incidence for ER+/PR+ tumors.

Possible Mechanisms

- Adiposity at age 10 is related to lower peak height growth which is related to lower risk of pre and post menopausal breast cancer
- Short-term weight gain leads to increase in glucose, a likely pathway for short-term weight gain and breast cancer incidence
- Long-term weight gain and ER+ breast cancer largely attributed to higher circulating estrogen levels, particularly after menopause
- Other pathways cannot be ruled out (inflammation)

8 WAYS to Stay Healthy & Prevent Cancer

1. Maintain a healthy weight
2. Exercise regularly
3. Don't smoke
4. Eat a healthy diet
5. Drink alcohol only in moderation
6. Protect yourself from the sun
7. Avoid sexually transmitted infections
8. Get screening tests

Possible Mechanisms

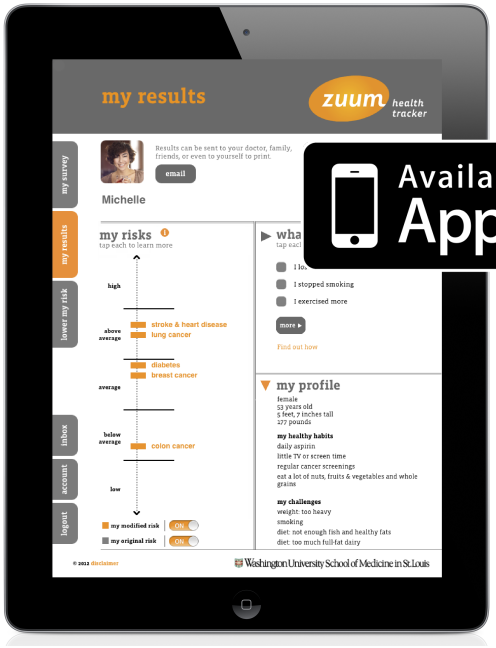
Short-term:

- Short-term weight gain leads to increase in glucose a likely pathway for short-term weight gain and breast cancer incidence
- Evidence stronger among leaner women where change in glucose may be more marked with short term weight gain

Possible Mechanisms

Long-term weight gain

- Adiposity at age 10 is related to lower peak height growth velocity, which is related to lower risk of pre and post menopausal breast cancer
- Long-term weight gain and ER+ breast cancer largely attributed to higher circulating estrogen levels, particularly after menopause



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