Diet, Physical Activity and Cancer

Joanne Dorgan, PhD, MPH

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Overview

- Diet, Physical Activity and High Burden Cancers
  - Breast
  - Prostate
  - Colorectal
  - Lung
- Obesity and Cancer

BMI – Body Mass Index

- Measure of adiposity or fatness
- BMI=kg/m^2

BMI (kg/m^2)	Class
<18.5	Thin
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
30.0 – 39.9	Obese
≥40	Morbidly Obese

WHO Expert Committee 1995

Breast Cancer

Most common cause of cancer among US women after skin cancer.

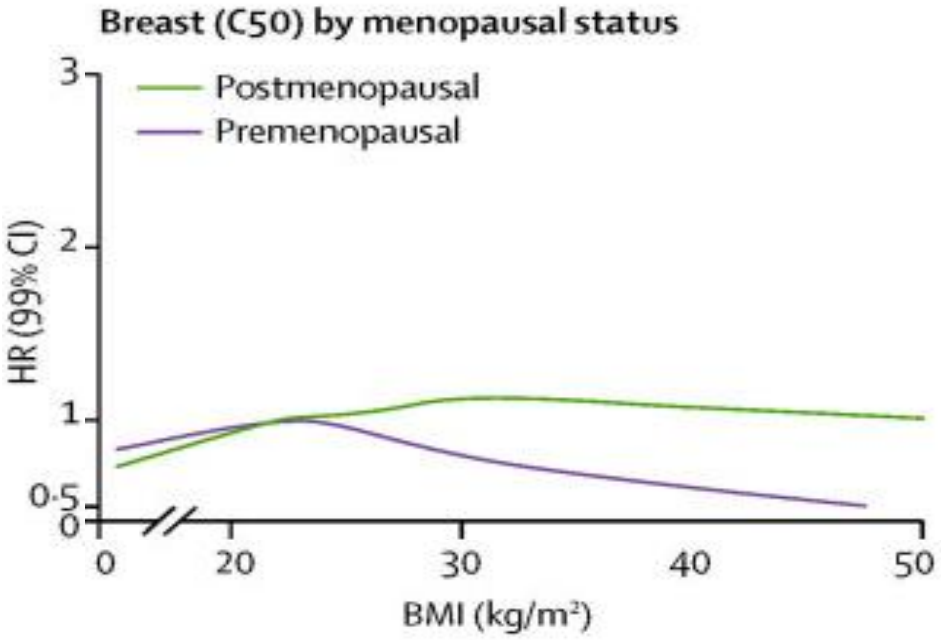
Second most common cause of cancer death.

Breast Cancer: Role of Diet and Energy Balance

- Adiposity
- Physical activity
- Dietary fat
- Alcohol
- Soy
- Other dietary factors

BMI and Breast Cancer Risk

- Risk varies by menopausal status
  - Premenopausal
    - Higher BMI lower risk
    - Anovulatory menstrual cycles
  - Postmenopausal
    - Higher BMI higher risk
    - Estrogen synthesis in adipose tissue
    - Stronger for ER+/PR+

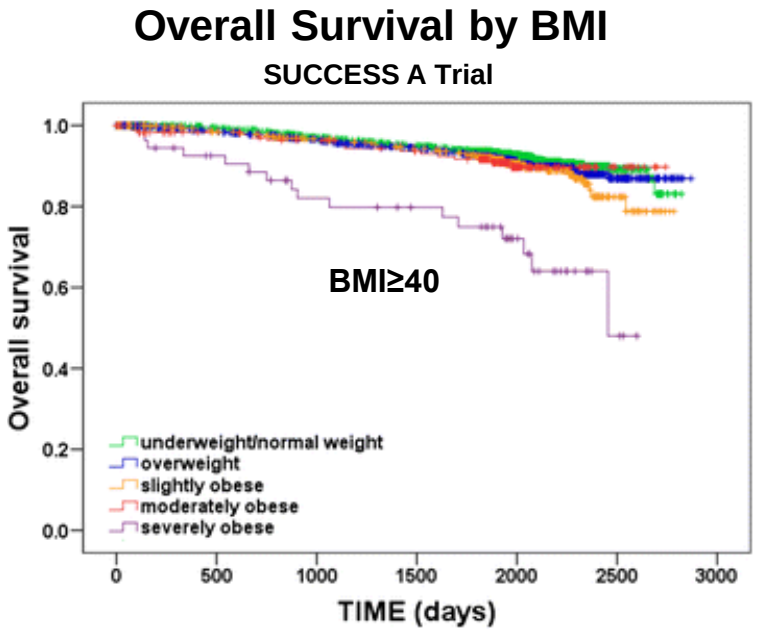


Estimated HR per 5 kg/m² (99% CI)		
Premenopause	<22 kg/m²	1·20 (1·01–1·43)
	>22 kg/m²	0·86 (0·82–0·90)
Postmenopause	<29 kg/m²	1·11 (1·08–1·14)
	>29 kg/m²	0·98 (0·95–1·01)

Bhaskaran 2014

BMI and Breast Cancer Survival

- Obese patients have poorer prognosis
  - Overall survival
  - Breast cancer specific survival
- Association similar in pre- and post-menopausal women
- Conflicting results by tumor subtype

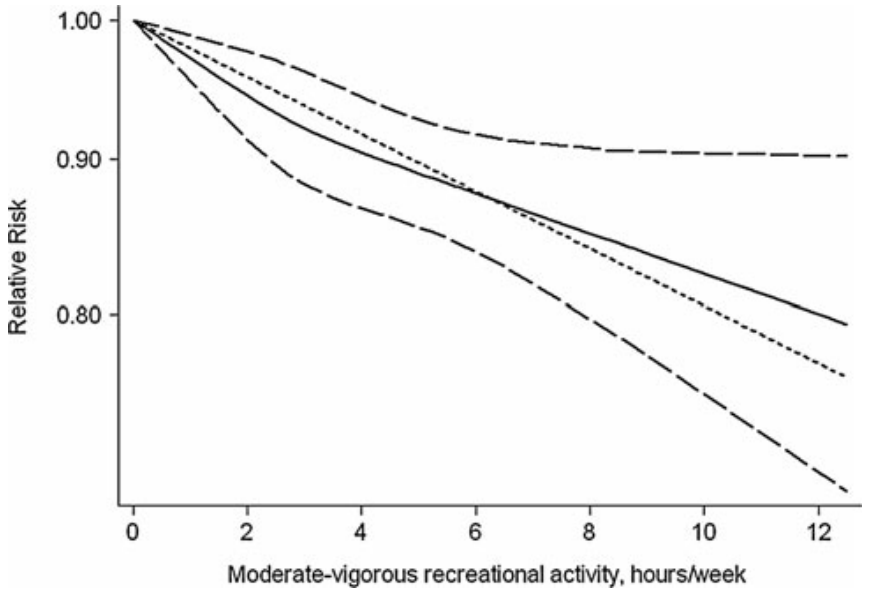


BMI (kg/m2)	Recurrence Rate
<25.0	11.5%
25.0-29.9	14.7%
30.0-34.9	14.4%
35.0-39.9	11.9%
≥ 40	36.8%

Widschwendter 2015

Physical Activity and Breast Cancer Risk

- Physical Activity Reduces Breast Cancer Risk
  - 3% per 10 MET-h/wk (4 hrs leisurely walking or 1 hr running)
  - 5% per 2 hrs moderate to vigorous recreational activity

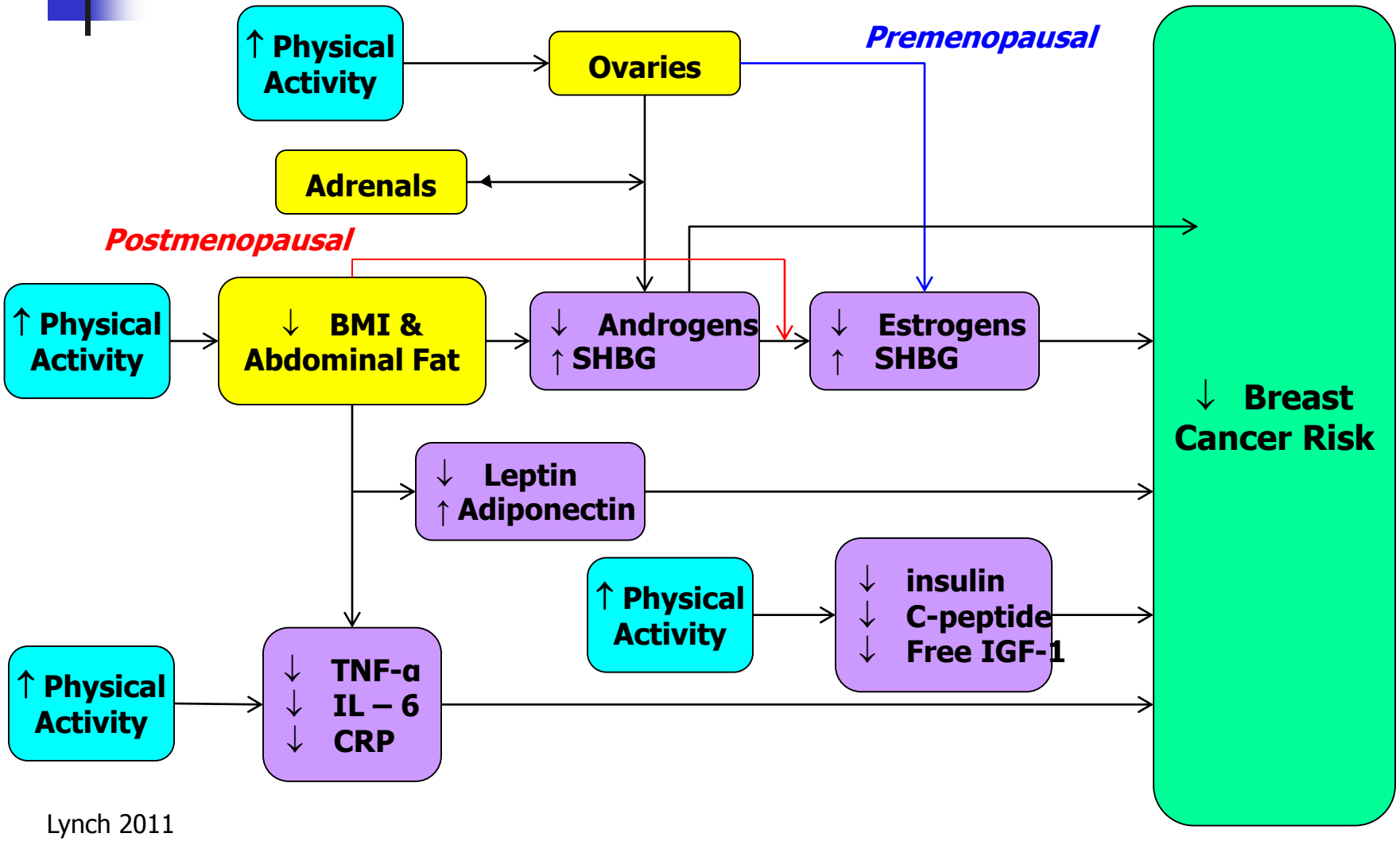


Wu 2013

RR for Women in Highest vs. Lowest Category of Physical Activity

	RR	95% CI
Type Activity		
Recreational	**0.89**	**0.85 – 0.92**
Household	**0.89**	**0.83 – 0.95**
Occupational	**0.90**	**0.83 – 0.97**
BMI Adjustment		
No	**0.89**	**0.85 – 0.93**
Yes	**0.88**	**0.85 – 0.91**
BMI Stratification		
BMI < 25	**0.72**	**0.65 – 0.81**
BMI ≥ 25	**0.93**	**0.83 – 1.05**
Menopausal Status		
Premenopausal	**0.77**	**0.72 – 0.84**
Postmenopausal	**0.88**	**0.84 – 0.92**
Tumor Receptor		
ER-/PR-	**0.80**	**0.73 – 0.87**
ER+/PR+	**0.92**	**0.87 – 0.98**

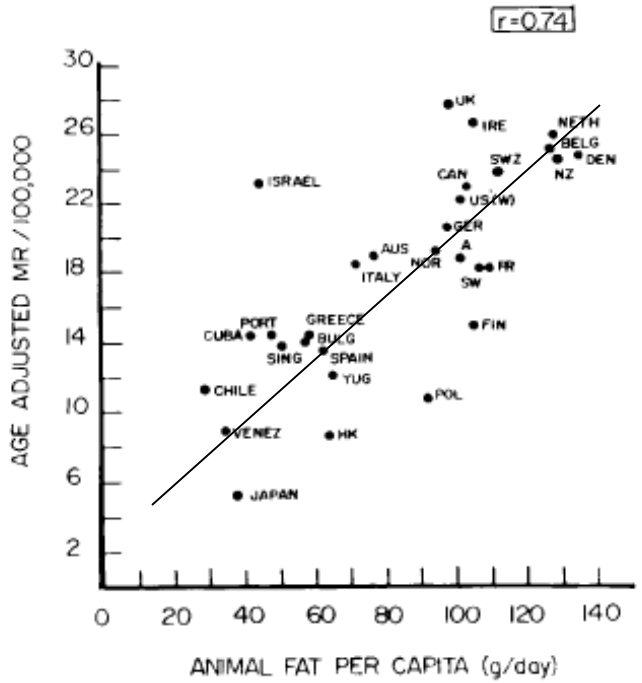
Physical Activity and Breast Cancer – Possible Mechanisms



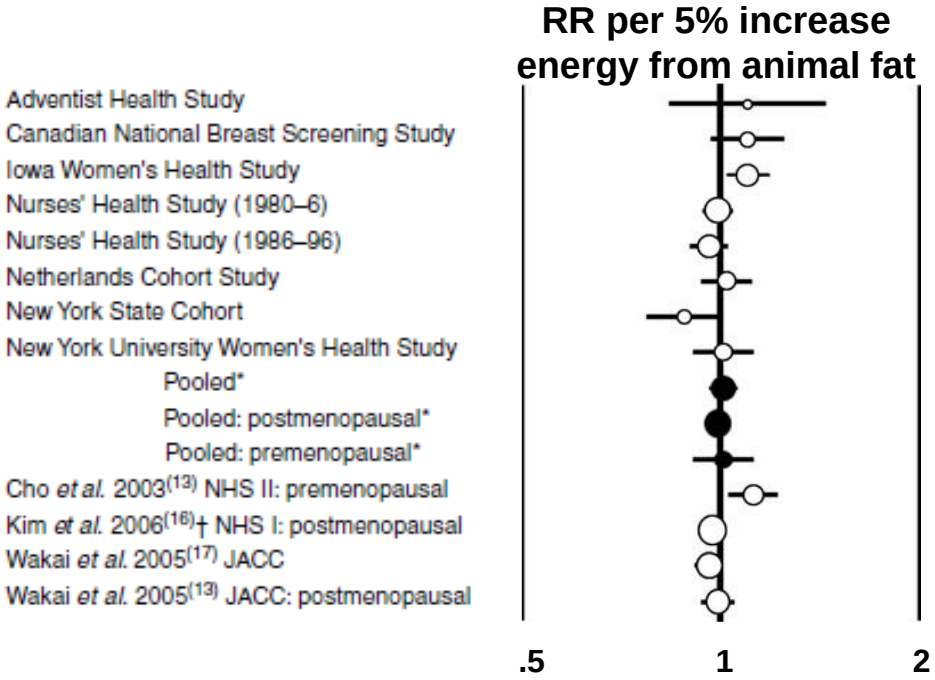
Lynch 2011

Dietary Fat and Breast Cancer

- Animal and ecologic studies suggest positive association of animal or saturated fat intake with breast cancer



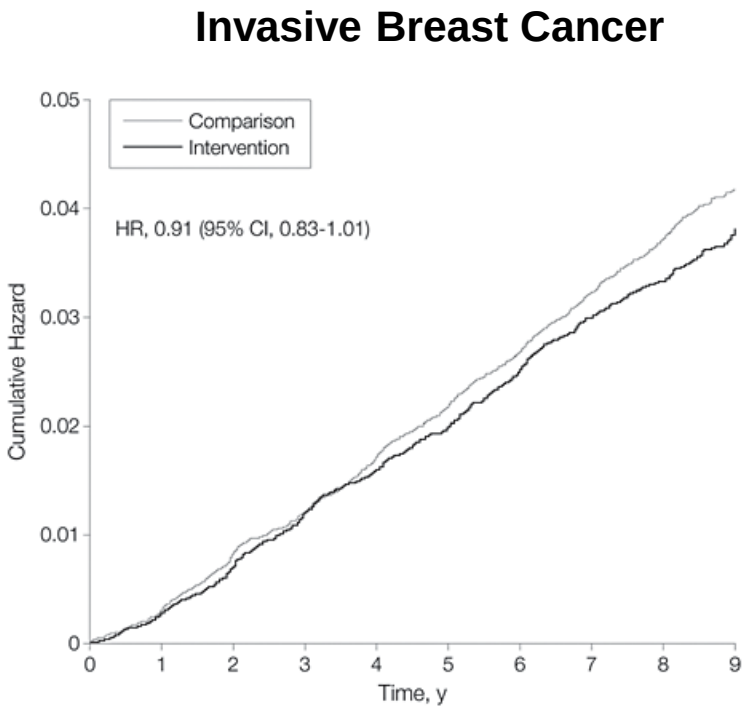
- Prospective epidemiologic studies overall do not support an association



Rose 1986; Alexander 2010

Dietary Fat and Breast Cancer Risk WHI Diet Trial

- **Design**
  - 48,835 postmenopausal women
  - Randomized
    - Low fat diet (≤ 20 %kcal
    - Control group
- **Results**
  - 8 yr - HR=0.91 (0.83 -1.01)
  - 12 yr - HR=0.97 (0.89 -1.05)
- **Conclusion**
  - Evidence does not support role for adult dietary fat in breast cancer risk overall
  - Early life dietary fat may be important



Prentice 2006;Thomson 2014

Alcohol and Breast Cancer Risk

- Breast cancer risk increases by 10% per 10 gm/day ~ 1 drink
- Association similar
  - beer, wine and spirits
  - pre- and post-menopausal women
  - ER+ and ER- tumors
- Possible mechanisms
  - Hormonal
  - Acetaldehyde
  - Oxidative stress
  - DNA methylation

RR ≥ 30 g/day vs. 0 g/day		
	RR	**95% CI**
ER+	**1.35**	**1.23 – 1.48**
ER-	**1.28**	**1.10 – 1.49**

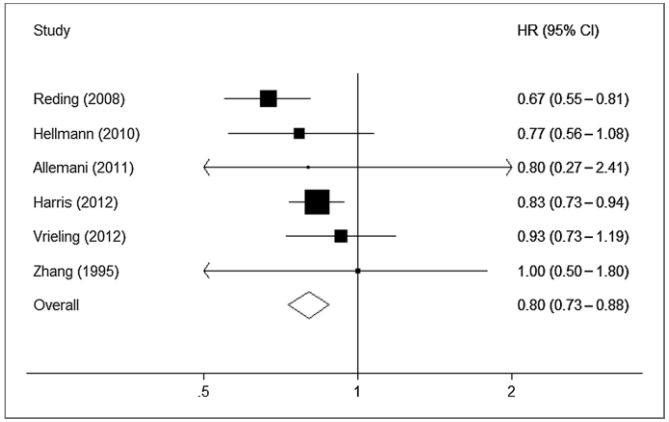
Collaborative Group 2002; Jung 2015

Alcohol and Breast Cancer Survival

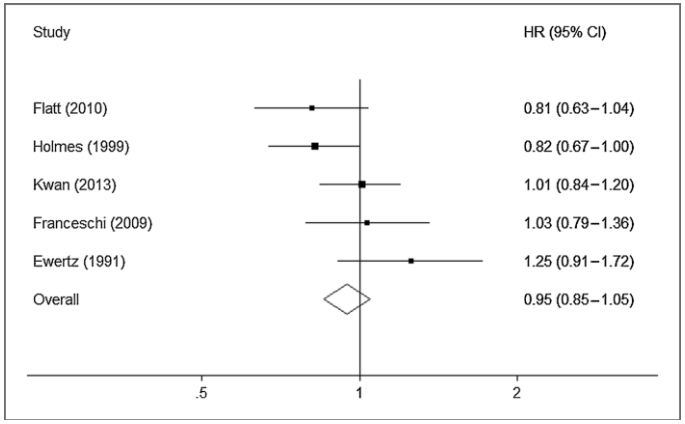
- Overall survival
  - Pre-diagnosis moderate drinkers better overall survival vs. non-drinkers
  - Post-diagnosis alcohol not associated
- Breast cancer specific survival
  - ER+ not associated with moderate pre- or post-diagnosis alcohol
  - ER- possible small benefit associated with post-diagnosis alcohol; no association pre-diagnosis

Overall Mortality – Moderate vs. Non-Drinkers

Pre-diagnosis Alcohol Intake



Post-diagnosis Alcohol Intake



Alaa 2014

Soy Intake and Breast Cancer Risk

- Limited evidence for protective effect in Asian countries
- No association in Western countries

High vs. Low Soy Intake				
	All Studies		Prospective Studies	
	RR	95% CI	RR	95% CI
Asian				
Premenopausal	**0.59**	**0.48 – 0.69**	**0.77**	**0.37 – 1.18**
Postmenopausal	**0.59**	**0.44 – 0.74**	**0.84**	**0.54 – 1.14**
Western				
Premenopausal	**0.90**	**0.77 – 1.04**	**1.03**	**0.84 – 1.22**
Postmenopausal	**0.92**	**0.83 – 1.00**	**0.96**	**0.88 - 1.04**

Chen 2014

Other Dietary Factors and Breast Cancer Risk

- Dietary carbohydrate and fiber not associated with risk
- Inconsistent results for
  - fruits, vegetables, and meat
  - diet patterns

Mourouti 2014

Advice to Reduce Breast Cancer Risk

- Maintain a healthy weight throughout life
- Engage in regular physical activity
- Limit alcohol consumption

Prostate Cancer

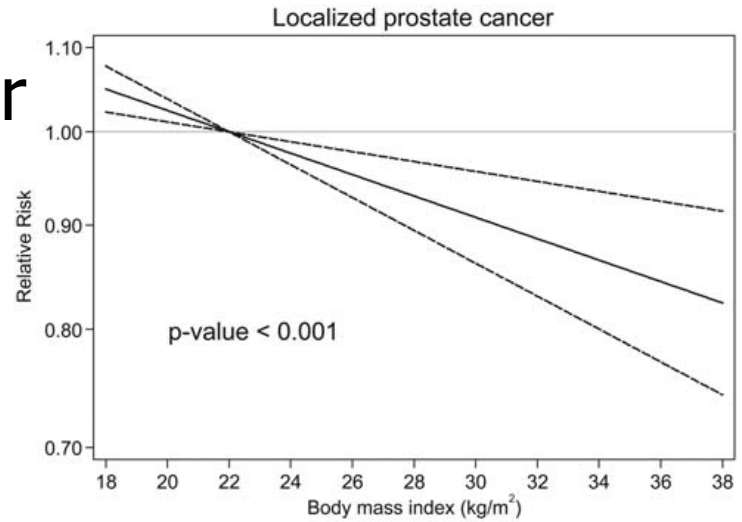
Most common cause of cancer among US men after skin cancer

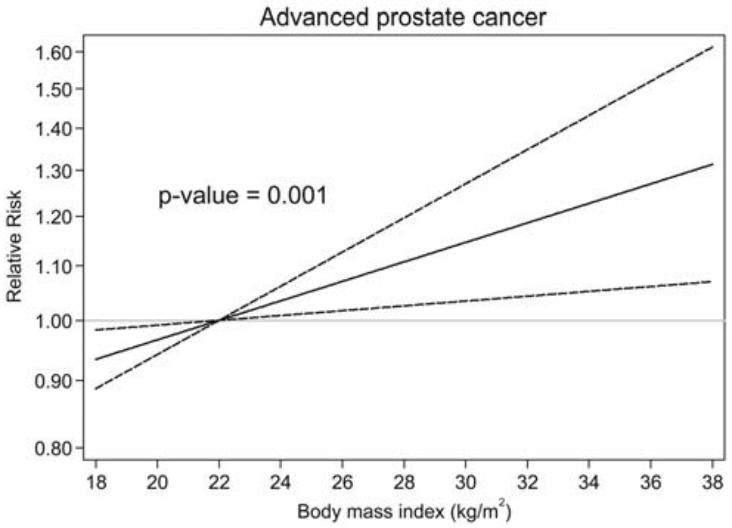
Prostate Cancer: Role of Diet and Energy Balance

- Adiposity
- Physical activity
- Fruits and vegetables
- Antioxidant micronutrients
- Dairy

BMI and Prostate Cancer

- Risk of incident cancer differs for localized and advanced disease
  - RR per 5 kg/m^2 increase in BMI
    - Localized RR = 0.94 (0.91 – 0.97)
    - Advanced RR = 1.09 (1.02 – 1.16)
- Risk of fatal cancer increases with BMI
  - RR = 1.15 (1.05 – 1.25) per 5 kg/m^2
- Mechanism
  - Unclear, possibly testosterone related

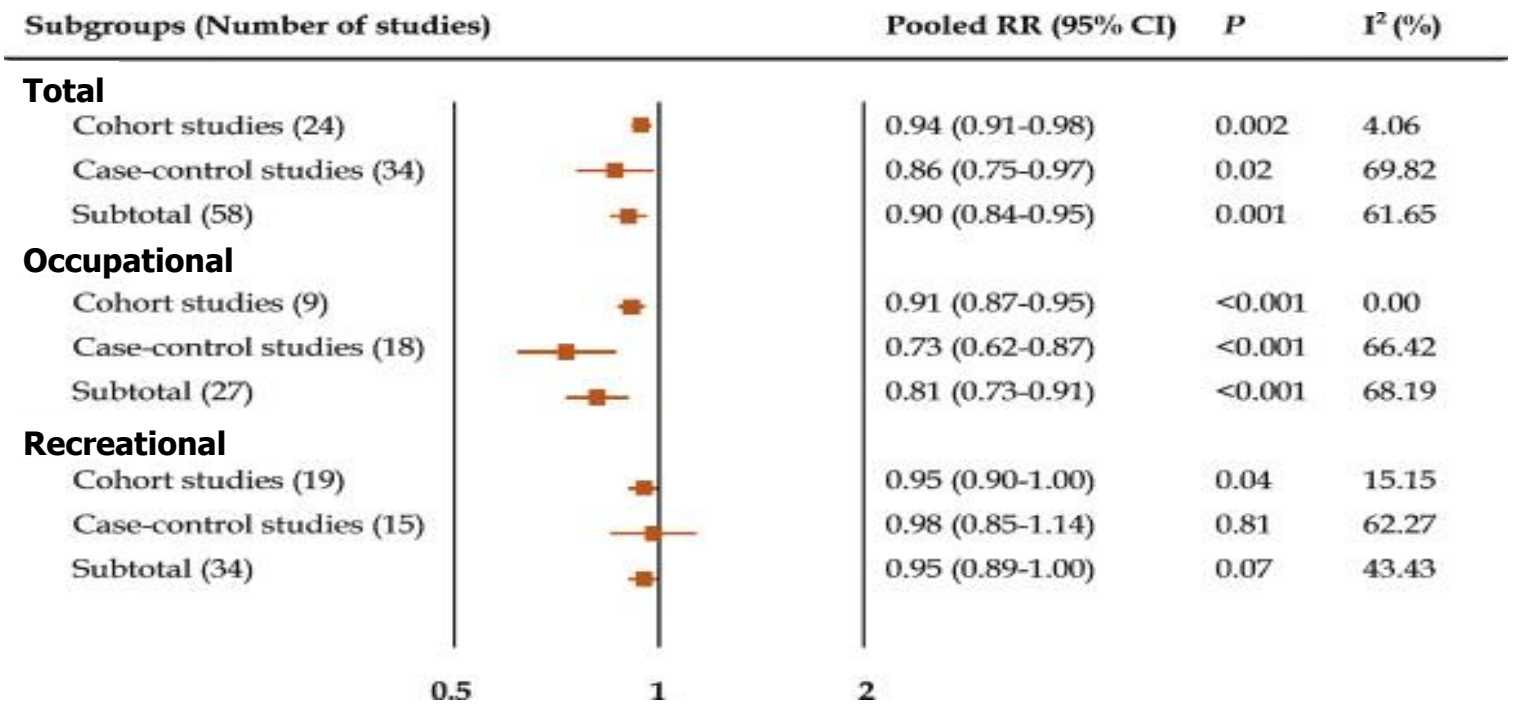




Discacciati 2012; Cao 2011

Physical Activity and Prostate Cancer Risk

- More physically active men at lower risk for prostate cancer
  - Association stronger for occupational activity from case-control studies, but not cohort studies
  - Vigorous activity may reduce risk of advanced disease



Liu 2011

Fruits and Vegetables and Prostate Cancer Risk

- Tomatoes & tomato products

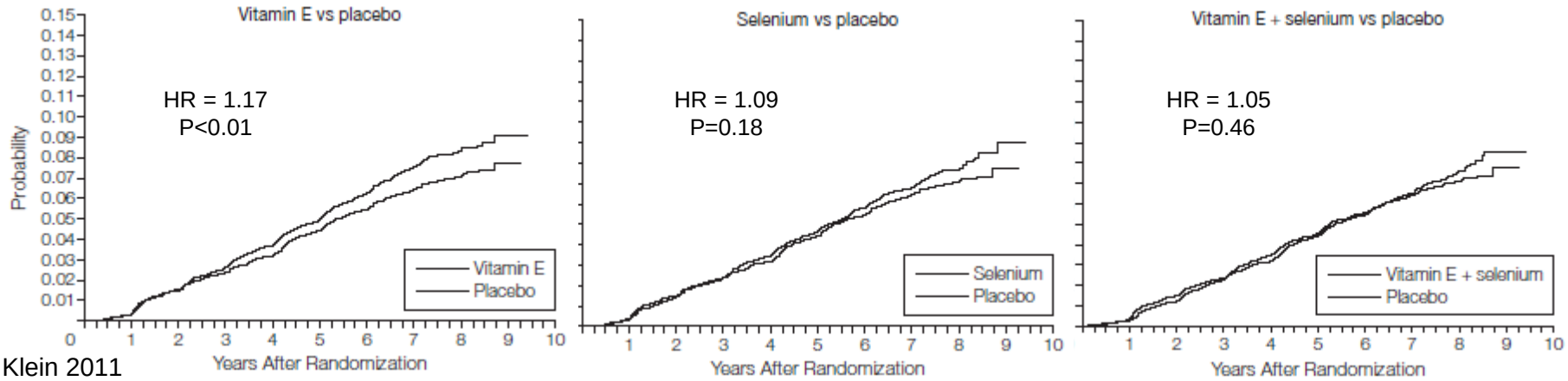
RR of Prostate Cancer for High vs. Low Levels				
	Total Prosate Cancer		Advanced Prostate Cancer	
	RR	95% CI	RR	95% CI
Raw tomato	0.81	0.59 – 1.10	0.65	0.55 – 0.95
Cooked tomato	0.85	0.69 – 1.06		
Dietary lycopene	0.93	0.86 – 1.01	1.03	0.83 – 1.26
Blood lycopene	0.97	0.88 – 1.08	0.77	0.49 – 1.20

- Other fruits not associated with risk
- Findings for vegetables mixed

Chen 2013

SELECT

- Selenium and Vitamin E Cancer Prevention Trial
  - 35,533 men 50+ years old and free of prostate cancer randomized
  - 200 µg/day selenium and/or 400 IU/day vitamin E vs placebo
  - Planned follow-up 7 - 12 years
  - Early discontinuation of intervention for lack of efficacy
  - Results after 7 years follow-up:



Klein 2011

Dairy and Prostate Cancer Risk

- Total prostate cancer risk
  - Increased – total dairy, milk (lowfat), cheese, total dietary calcium
  - No association – calcium from non-dairy foods or supplements
- No association advanced prostate cancer risk

RR of Prostate Cancer for High vs. Low Levels Intake

	Total Prostate Cancer		Advanced Prostate Cancer	
	RR	95% CI	RR	95% CI
Dairy	1.09	1.02 – 1.17	0.92	0.79 – 1.08
Milk	1.11	1.03 – 1.21	1.09	0.86 – 1.38
Cheese	1.07	1.01 – 1.13	1.18	1.00 – 1.41
Dietary Calcium	1.18	1.08 – 1.30	1.00	0.77 – 1.31
Supplements	1.00	0.95 – 1.05	0.99	0.88 – 1.11

Aune 2015

Advice to Reduce Prostate Cancer Risk

- Maintain a healthy body weight
- Be physically activity
- Eat a variety of fruits and vegetables

Colorectal Cancer

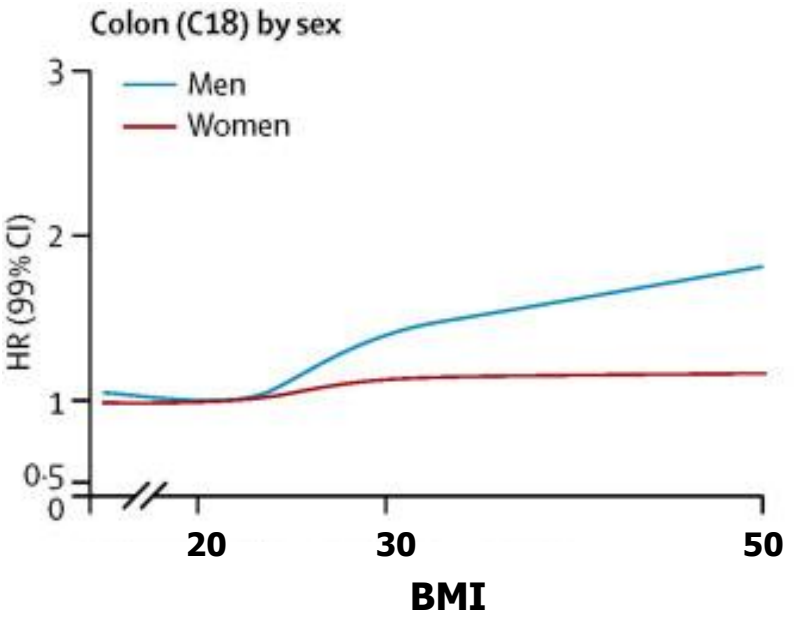
Third most common cause of cancer among US men and women

Colorectal Cancer: Role of Diet and Energy Balance

- Adiposity
- Physical activity
- Red and processed meat
- Dietary fiber
- Calcium and vitamin D
- Alcohol
- Other dietary factors

BMI and Colorectal Cancer

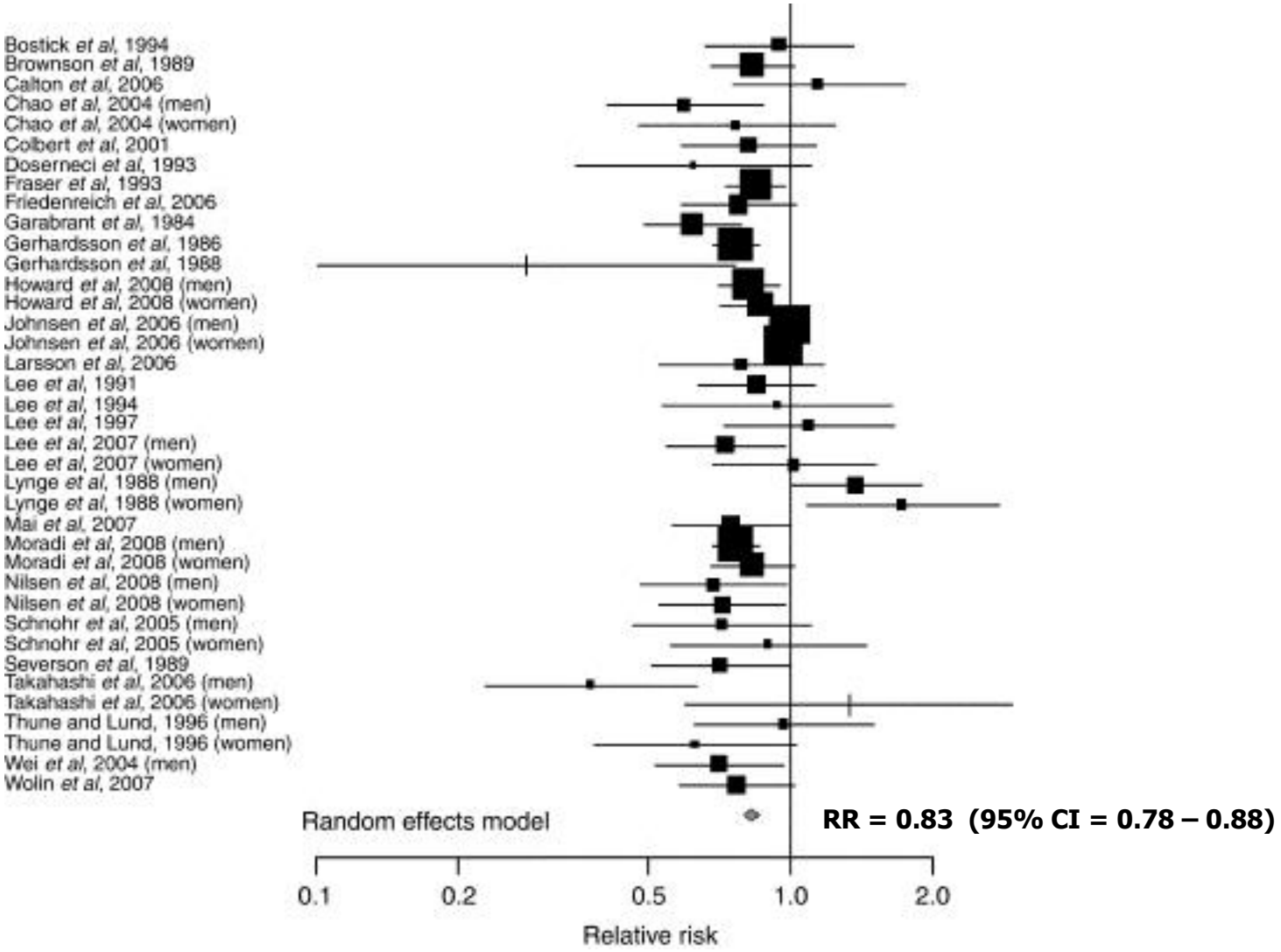
- BMI positively associated with colon cancer risk
  - Overall 10% increase risk per 5kg/m^2 increase BMI
  - Association stronger in men
- BMI weak positive association with rectal cancer risk
  - Overall 4% increase risk per 5kg/m^2 increase BMI
- Higher BMI poorer prognosis following colorectal cancer diagnosis



Estimated HR per 5 kg/m^2 (99% CI)		
Men	<22 kg/m^2	0·92 (0·69–1·23)
	22–34 kg/m^2	1·23 (1·17–1·30)
	>34 kg/m^2	0·97 (0·81–1·15)
Women (overall)		1·05 (1·01–1·08)

Bhaskaran 2014; Campbell 2015

Physical Activity and Colorectal Cancer Risk – Cohort Studies



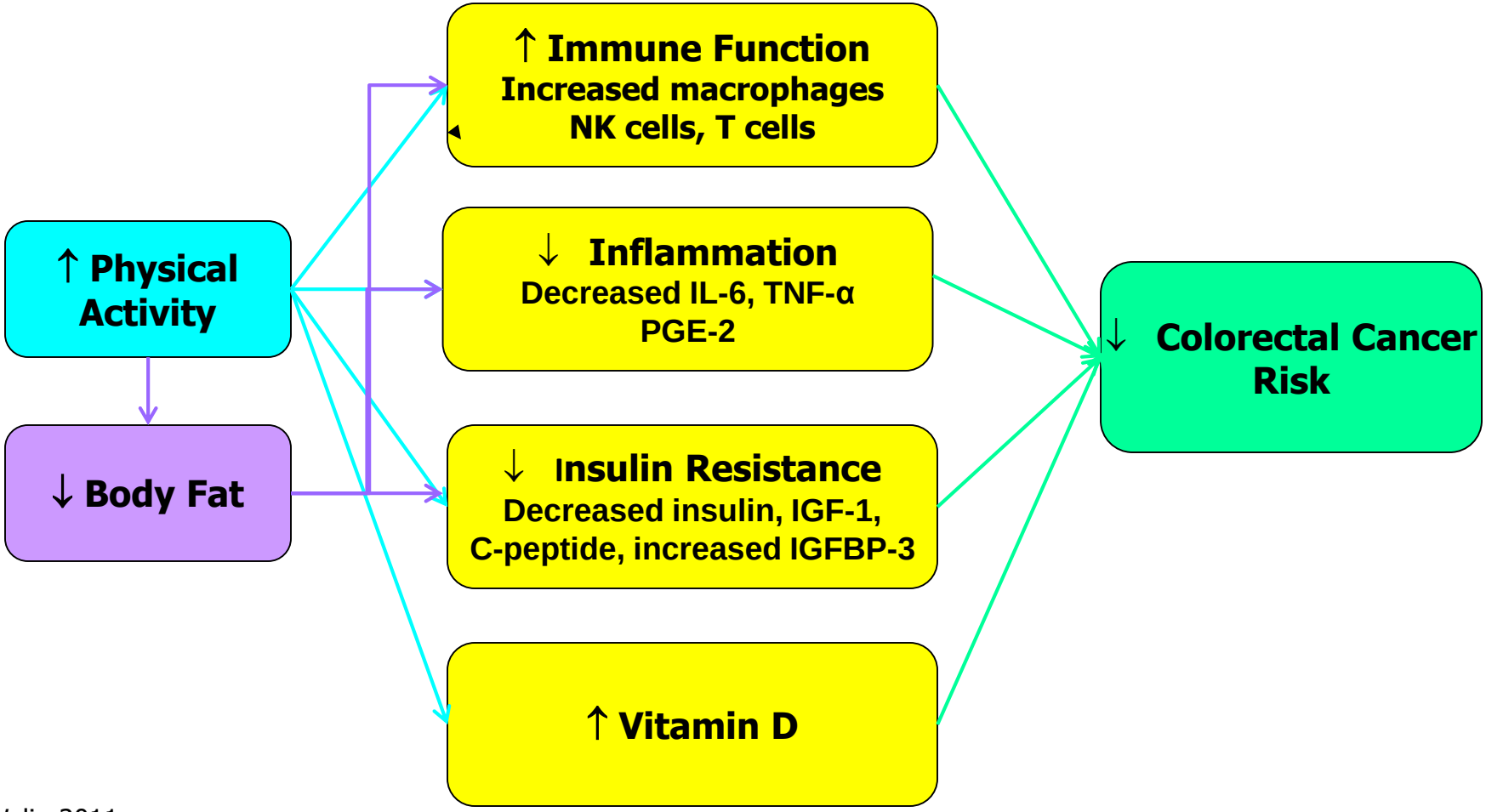
Wolin 2009

Physical Activity and Colorectal Cancer Risk

- **Significant dose response in 24 of 35 studies**
  - High vs. low intensity activity RR = 0.8
  - 1 hr/day vs. <1 hr/day moderate activity RR = 0.6
- **Type of activity**
  - Risk reduction similar for recreational and occupational physical activity
  - Inconsistent associations with walking
- **Timing of activity**
  - Consistent associations for lifetime and adult only physical activity
- **Family history**
  - Association only if no family history
- **Location**
  - Risk similar for distal and proximal colon

Wolin 2011

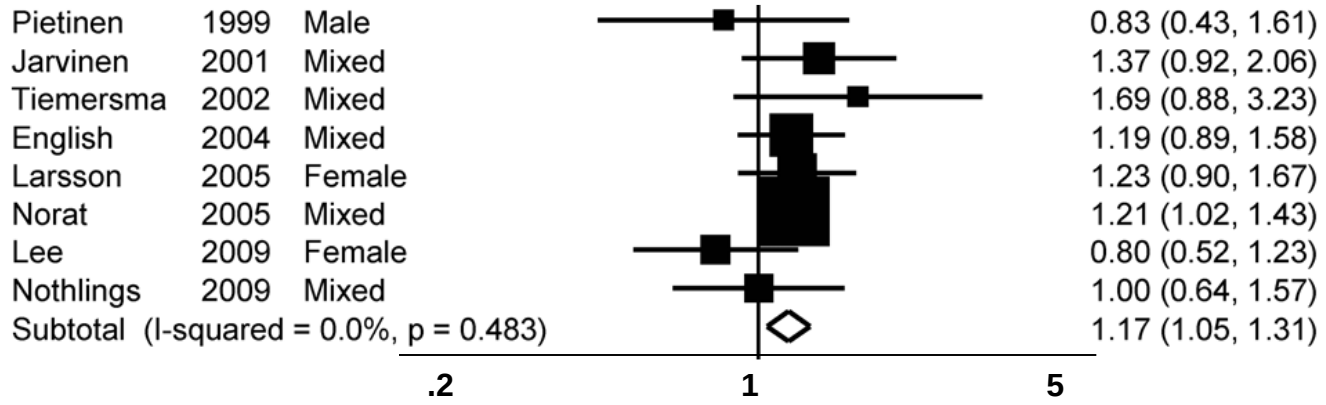
Physical Activity and Colorectal Cancer – Possible Mechanisms



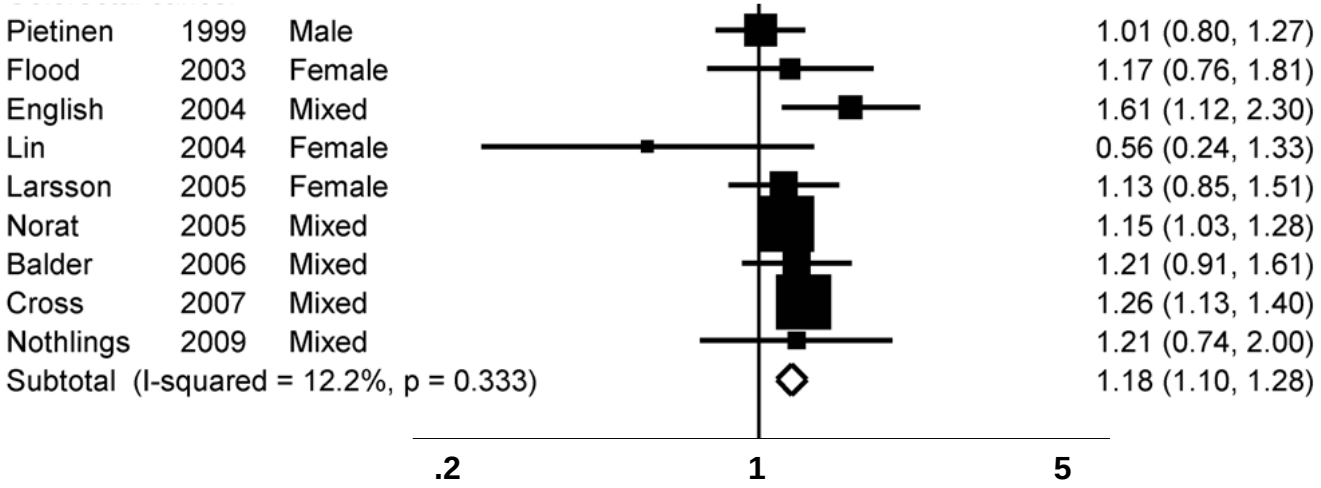
Wolin 2011

Red and Processed Meat and Colorectal Cancer Risk

Relative Risk Colorectal Cancer - Red Meat (100 gm/day ~ 1 serving)



Relative Risk Colorectal Cancer - Processed Meat (50 gm/day ~ 1 hot dog)



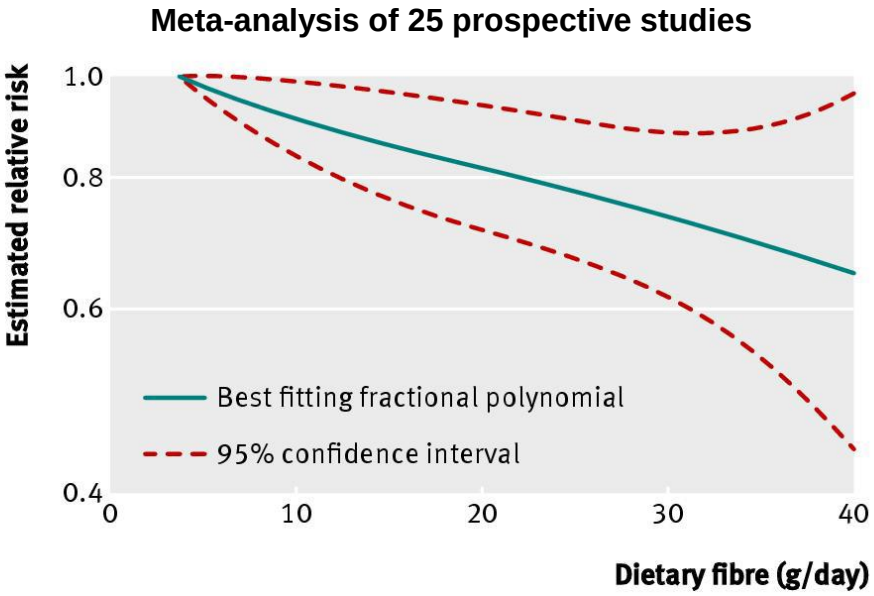
Chan 2011

Red and Processed Meat and Colorectal Cancer Risk - Mechanisms

- Sulfur containing amino acids ⇨ hydrogen sulfide
  - inflammation, DNA damage, epithelial hyperproliferation
- Heme iron
  - Oxidative stress
  - Colonocyte proliferation
  - N-nitroso compounds – potent GI carcinogens
- Cooking at high temperature ⇨ mutagens
  - Heterocyclic amines
  - Polycyclic aromatic hydrocarbons
- Preservatives
  - Inorganic sulfur ⇨ hydrogen sulfide
  - Nitrates and nitrites ⇨ N-nitroso compounds

Dietary Fiber and Colorectal Cancer Risk

- **Epidemiologic studies**
  - Observatinal studies show overall protective effect but heterogenous
  - 6 RCTs of fiber supplements in patients with colorectal polyps showed no benefit
- **Mechanisms**
  - Decreased stool transit time, carcinogen dilution
  - Decreased adiposity
  - Anticancer properties of bacterial fementation products

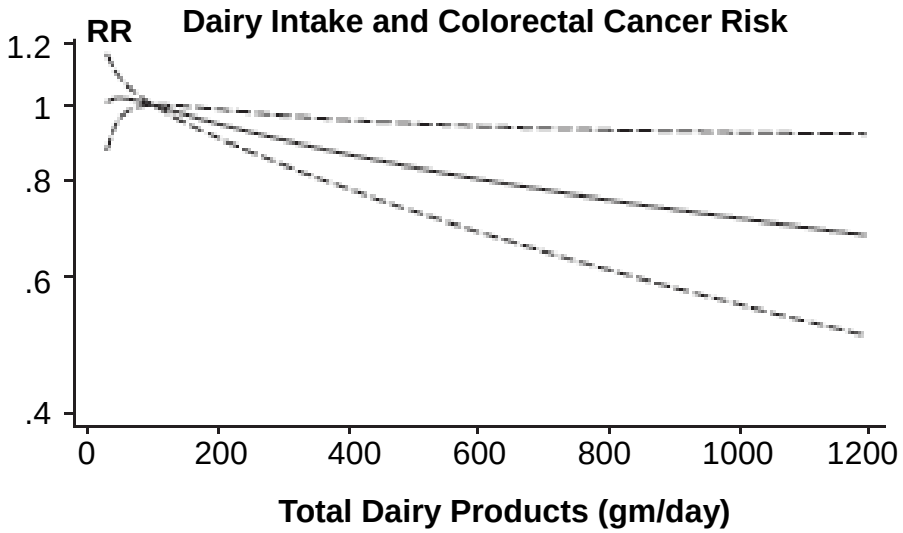


Summary RR per 10 gm fiber/day		
Source	**RR**	**95% CI**
All sources	**0.90**	**0.86 – 0.94**
Legumes	**0.62**	**0.27 – 1.42**
Cereal	**0.90**	**0.83 – 0.97**
Fruit	**0.93**	**0.82 – 1.05**
Vegetables	**0.98**	**0.91 – 1.06**

Aune 2011

Dairy and Colorectal Cancer Risk

- Dairy associated with lower risk of colorectal cancer
  - RR = 0.83 per 400 g/day
- Specific foods
  - High fat dairy
  - Milk
- Possible mechanisms
  - Fatty acids linoleic and butyric acid protective in animals
  - Lactoferrin
  - Calcium
  - Vitamin D

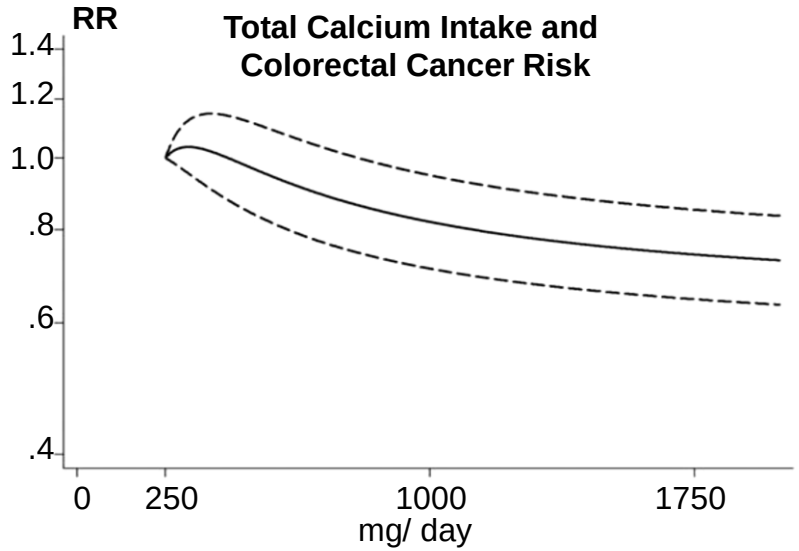


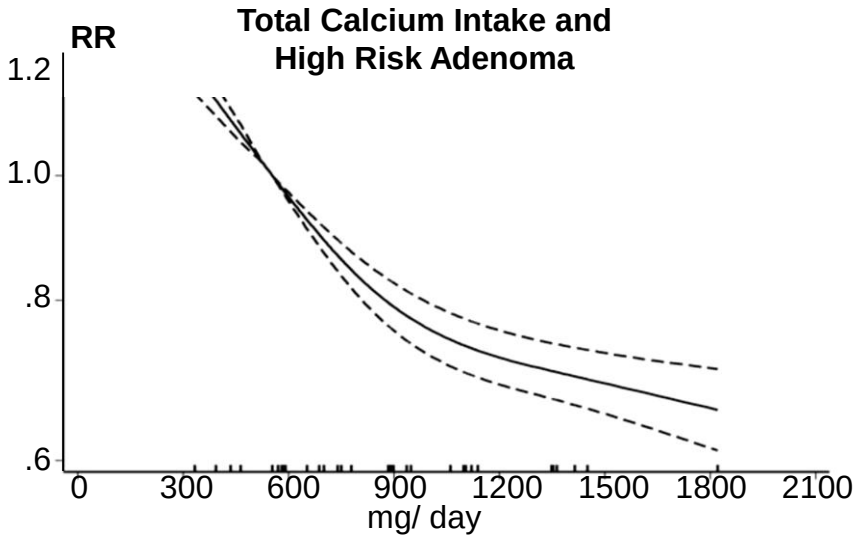
Summary RR for High vs. Low Dairy Intake		
Source	**RR**	**95% CI**
All sources	**0.81**	**0.74 – 0.90**
High fat	**0.74**	**0.53 – 1.02**
Low fat	**0.97**	**0.74 – 1.28**
Milk	**0.83**	**0.74 – 0.93**
Cheese	**0.94**	**0.75 – 1.18**
Yogurt	**1.00**	**0.67 – 1.48**

Aune 2012

Calcium and Colorectal Cancer Risk

- **Observational Studies**
  - Colorectal cancer
    - RR = 0.92 (0.89–0.95) per 300 mg/day
  - High risk adenoma (large, villous histology, dysplasia, multiplicity)
    - Non-linear
    - Compared to 550 mg/day RR = 0.77 (0.74–0.81) at 1000 mg/day
- **Randomized Trials**
  - Reduction adenoma recurrence in most but not all trials
  - Colorectal cancer - WHI
    - Overall no effect
    - 17% reduction in non-supplement users at baseline

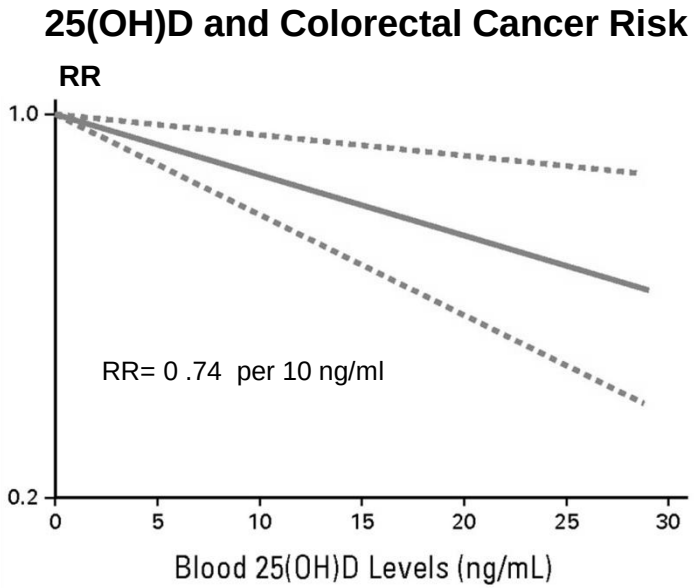




Keum 2014, 2015

Vitamin D and Colorectal Cancer Risk

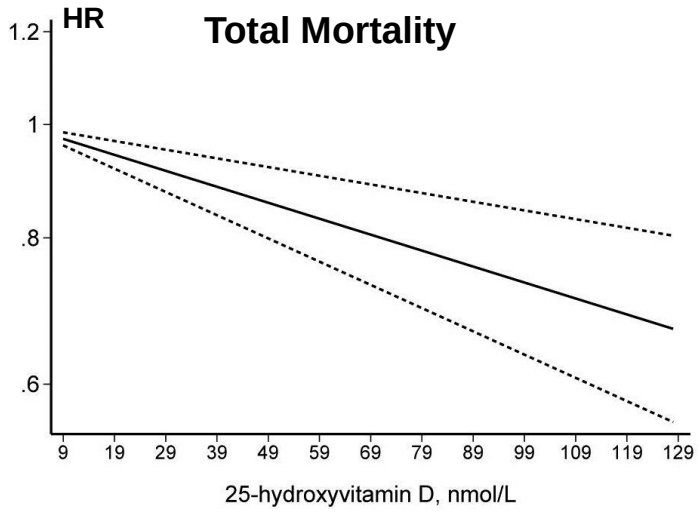
- **Observational Studies**
  - Colorectal cancer
    - Diet - high vs. low vitamin D intake RR = 0.88 (0.80–0.96)
    - Blood – high vs. low 25(OH)D levels RR=0.67 (0.54 – 0.80)
  - Adenoma
    - Diet - high vs. low vitamin D intake RR = 0.89 (0.79–1.01)
    - Blood - RR = 0.84 (0.72 - 0.97) per 20 ng/ml increase in 25(OH)D
- **Randomized Trials**
  - No reduction adenoma recurrence
  - Colorectal cancer - WHI
    - Overall no effect

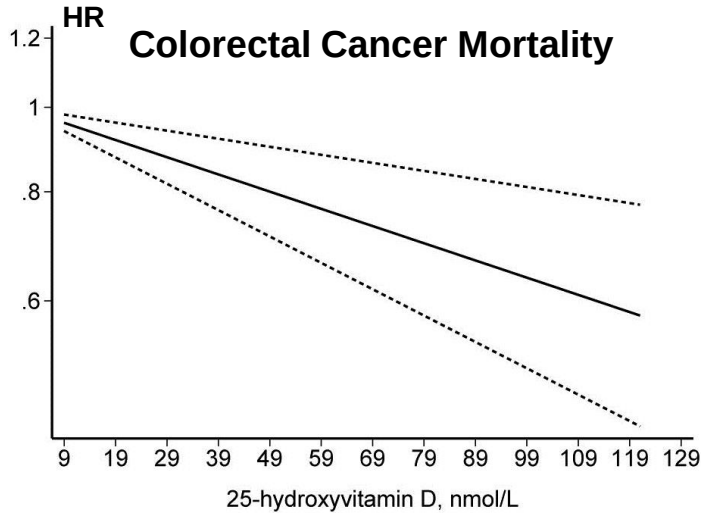


Wei 2008; Ma 2011; Yin 2011; Cauley 2013; Baron 2015

Vitamin D and Colorectal Cancer Mortality

- Higher serum vitamin D associated with improved survival
  - Total mortality
    HR=0.91 (0.81 – 1.01) per 20 nmol/L increase 25(OH)D
  - Disease specific mortality
    HR=0.90 (0.84 – 0.97) per 20 nmol/L increase 25(OH)D





Wang 2014, 2015

Calcium, Vitamin D and Colorectal Cancer - Mechanisms

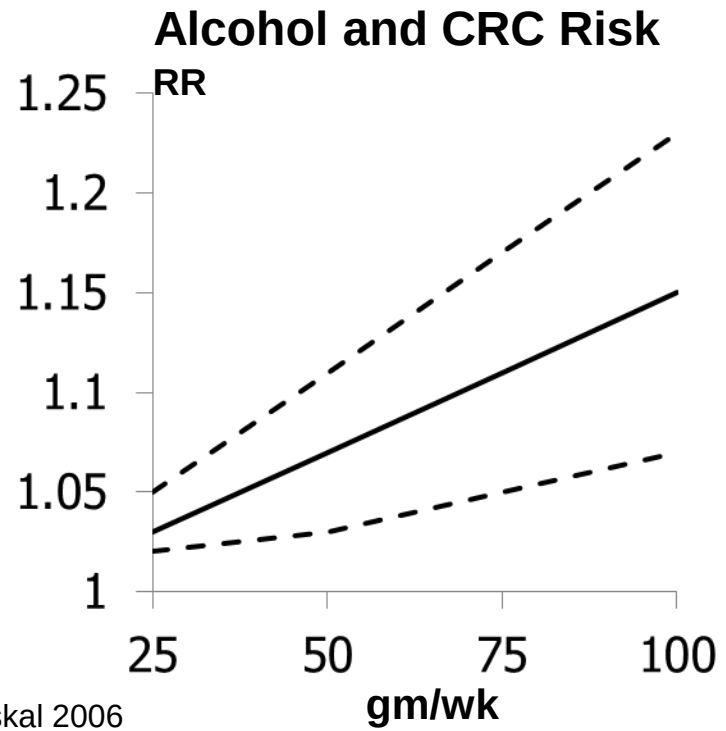
- Calcium
  - Binds to fatty acids and free bile acids
  - Decreases cell proliferation
  - Promotes cell differentiation and apoptosis
  - Inhibits oxidative DNA damage
  - Modulates signaling pathways
- Vitamin D
  - Decreases cell proliferation
  - Promotes cell differentiation and apoptosis
  - Anti-inflammatory
  - Inhibits invasion and metastasis
  - Suppresses angiogenesis

Reasons for Different Findings from Observational Studies and Trials

- Study design
- Threshold effect with high baseline intake
- Poor compliance
- Short duration of treatment or follow-up
- Anatomic site heterogeneity
- Other dietary factors
- Genetic background

Alcohol and Colorectal Cancer Risk

- Alcohol increases colorectal cancer risk 15% per 100 gm/wk ~ 10 drinks
- No difference by type of beverage



Colorectal Cancer Risk		
	RR	95% CI
Site		
Colon	1.50	1.25 – 1.79
Rectum	1.63	1.35 – 1.97
Sex		
Men	1.73	1.00 – 2.98
Women	0.88	0.61 – 1.27
Region		
USA	1.16	0.63 – 2.14
Europe	1.83	1.14 – 2.92
Asia	1.16	0.64 – 2.13

Moskal 2006

Advice to Reduce Colorectal Cancer Risk

- Maintain healthy body weight
- Increase intensity and duration of physical activity
- Limit intake of red and processed meats
- Consume adequate vitamin D and calcium
- Avoid excess alcohol

Lung Cancer

Second most common cause of cancer among US men and women after skin cancer

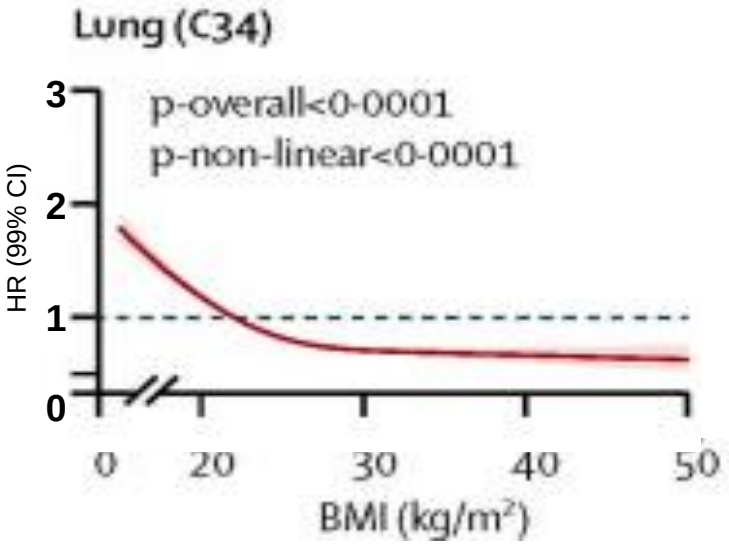
Leading cause of cancer death

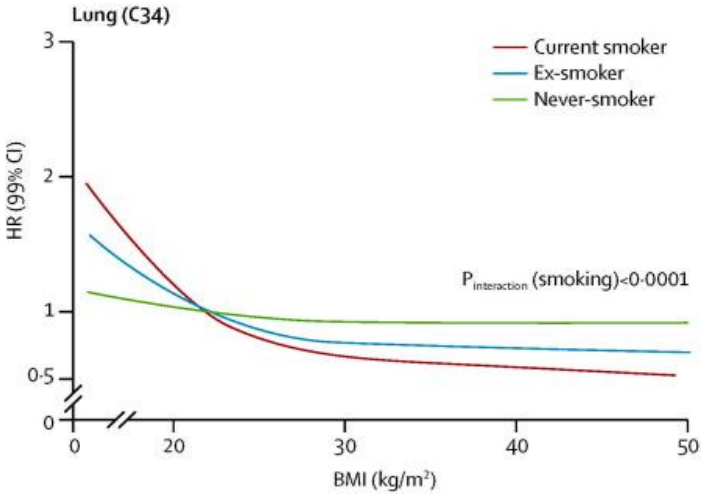
Lung Cancer: Role of Diet and Energy Balance

- Adiposity
- Physical activity
- Fruits and vegetables
- Antioxidant micronutrients

BMI and Lung Cancer Risk

- Overall apparent decreased risk of lung cancer associated with higher BMI
- Smokers are leaner than non-smokers
- Among non-smokers no association of BMI with lung cancer risk
- Apparent decreased risk overall due to uncontrolled confounding by smoking

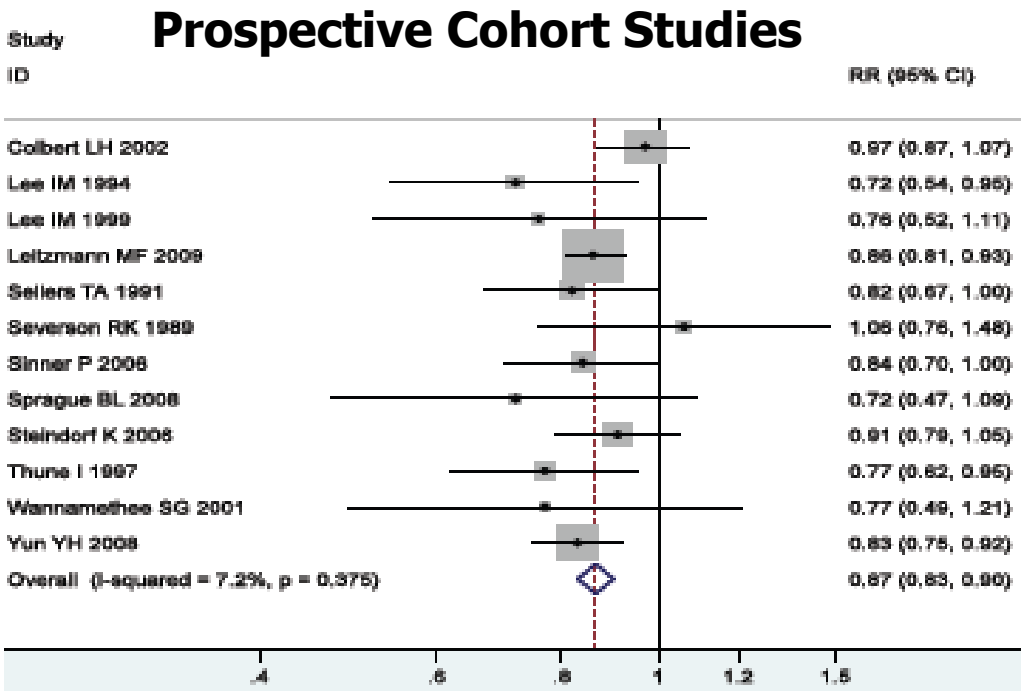




Bhaskaran 2014

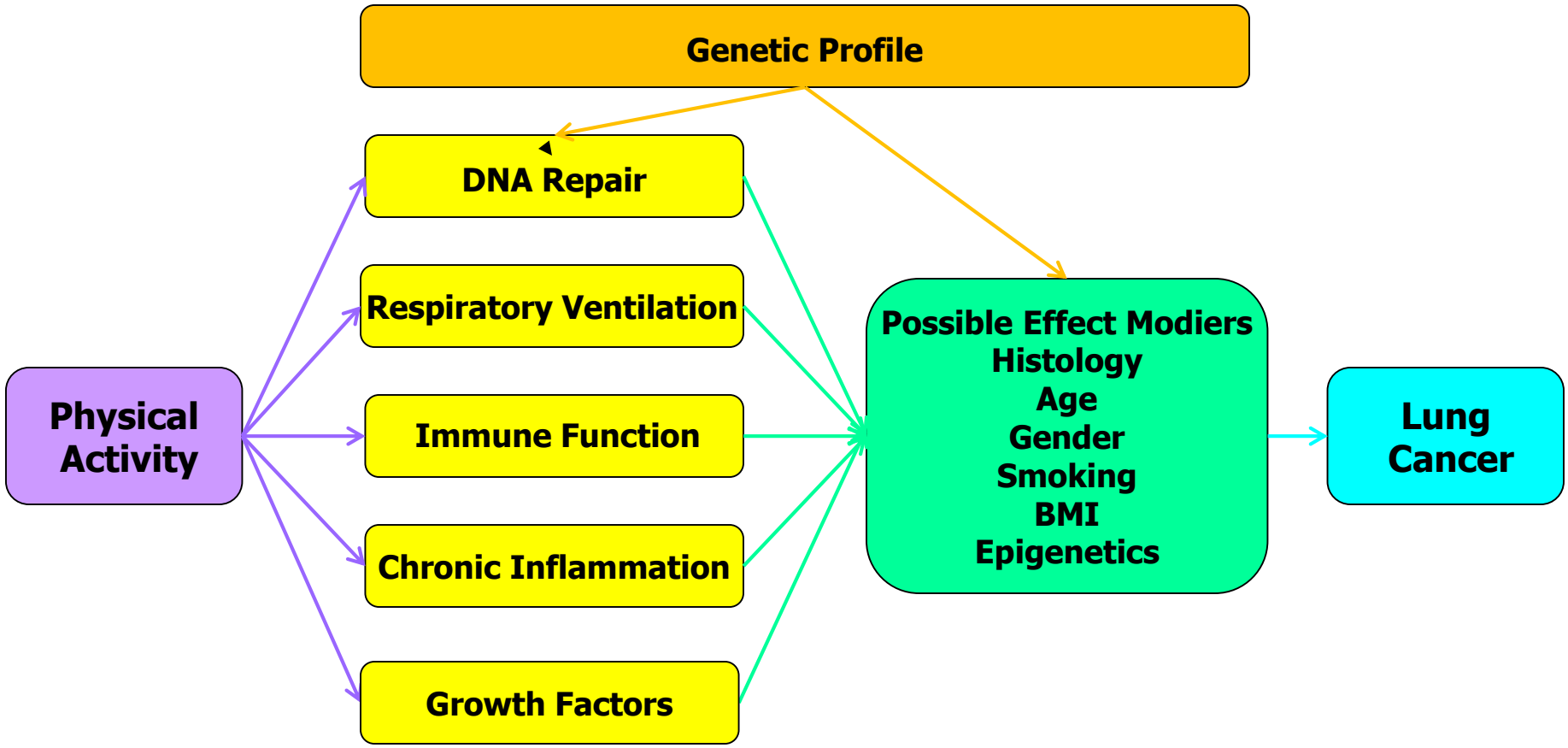
Physical Activity and Lung Cancer Risk

- Physical activity associated with lower lung cancer risk
- Active vs. inactive RR = 0.87 (0.83 – 0.90)



Sun 2012

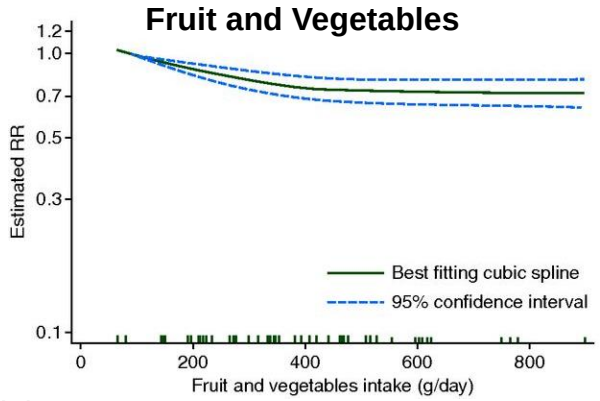
Physical Activity and Lung Cancer – Possible Mechanisms

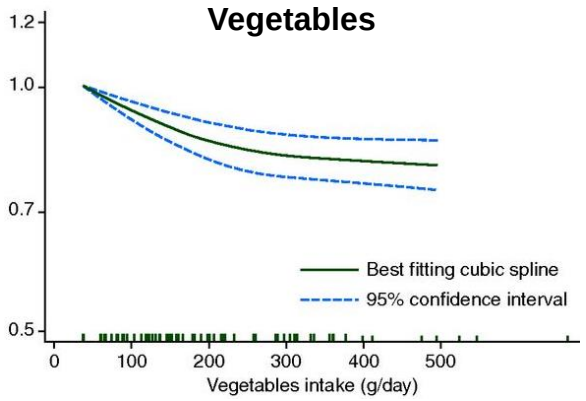


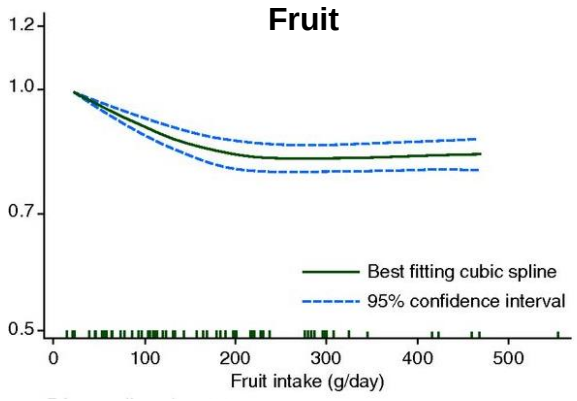
Emaus 2011

Fruits and Vegetables and Lung Cancer Risk

- Lung cancer risk for high vs. low intake
  - Fruits and vegetables: RR = 0.86 (0.78 – 0.94)
  - Vegetables: RR = 0.92 (0.87 – 0.97)
  - Fruits: RR = 0.82 (0.76 – 0.89)
- Results consistent across different types fruits and vegetables
- Association non-linear, no benefit when increase intake above ~400 g/day fruits and vegetables



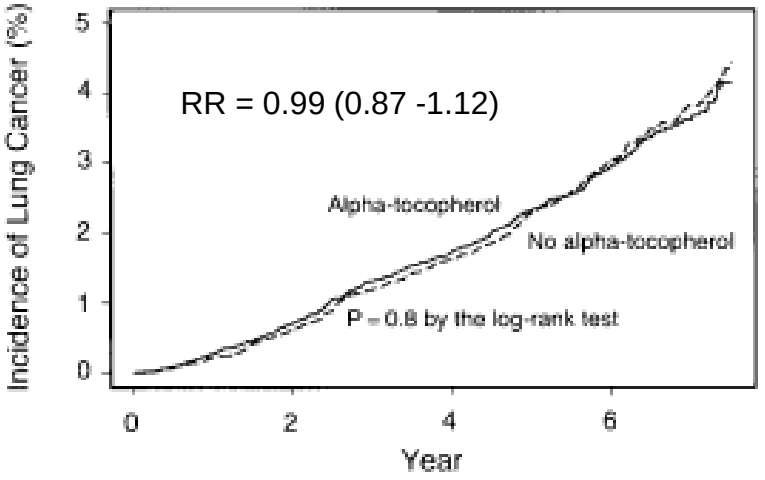


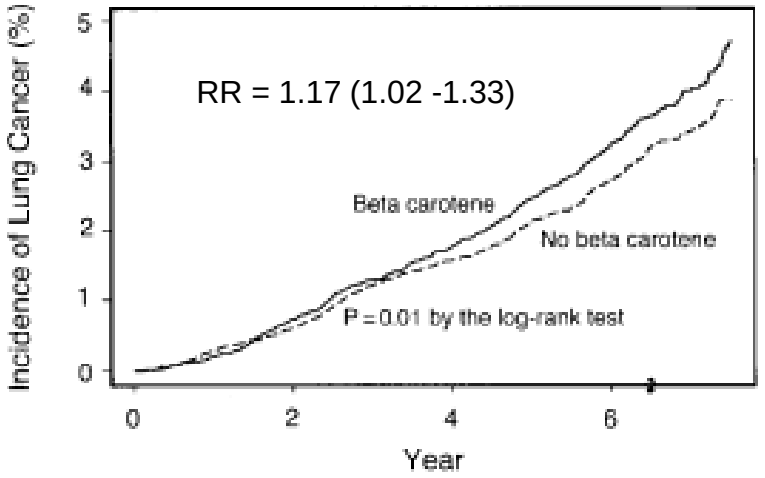


Vieira 2015

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)

- Design
  - 29,133 male smokers 50-69 years old randomized
  - 50 mg/day α-tocopherol, 20 mg/day β-carotene, both or placebo
  - On trial median 6.1 years
- Lung cancer at end of trial
  - α-tocopherol no effect on risk
  - β-carotene increased risk
- Follow-up at 5 yrs post-intervention
  - α-tocopherol: RR = 1.14 (0.96 – 1.35)
  - β-carotene: RR = 0.97 (0.82 – 1.15)





ATBC Study Group 1994, 2003

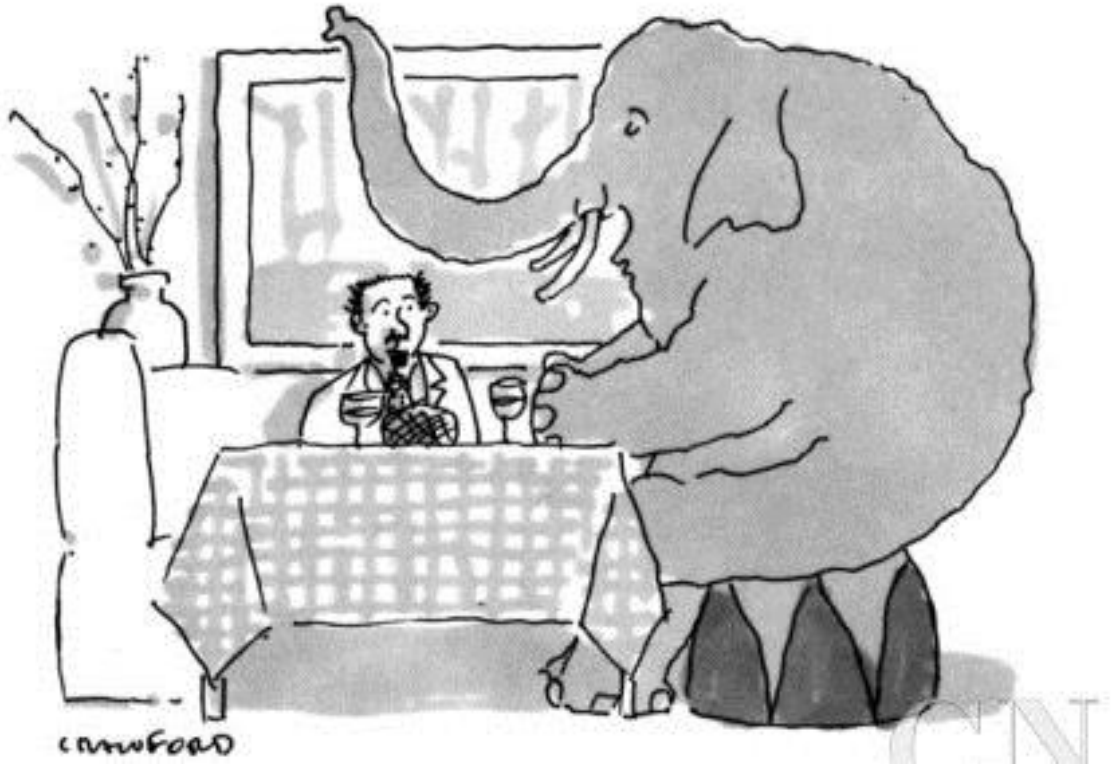
Advice to Reduce Lung Cancer Risk

- Avoid tobacco
- Avoid environmental radon

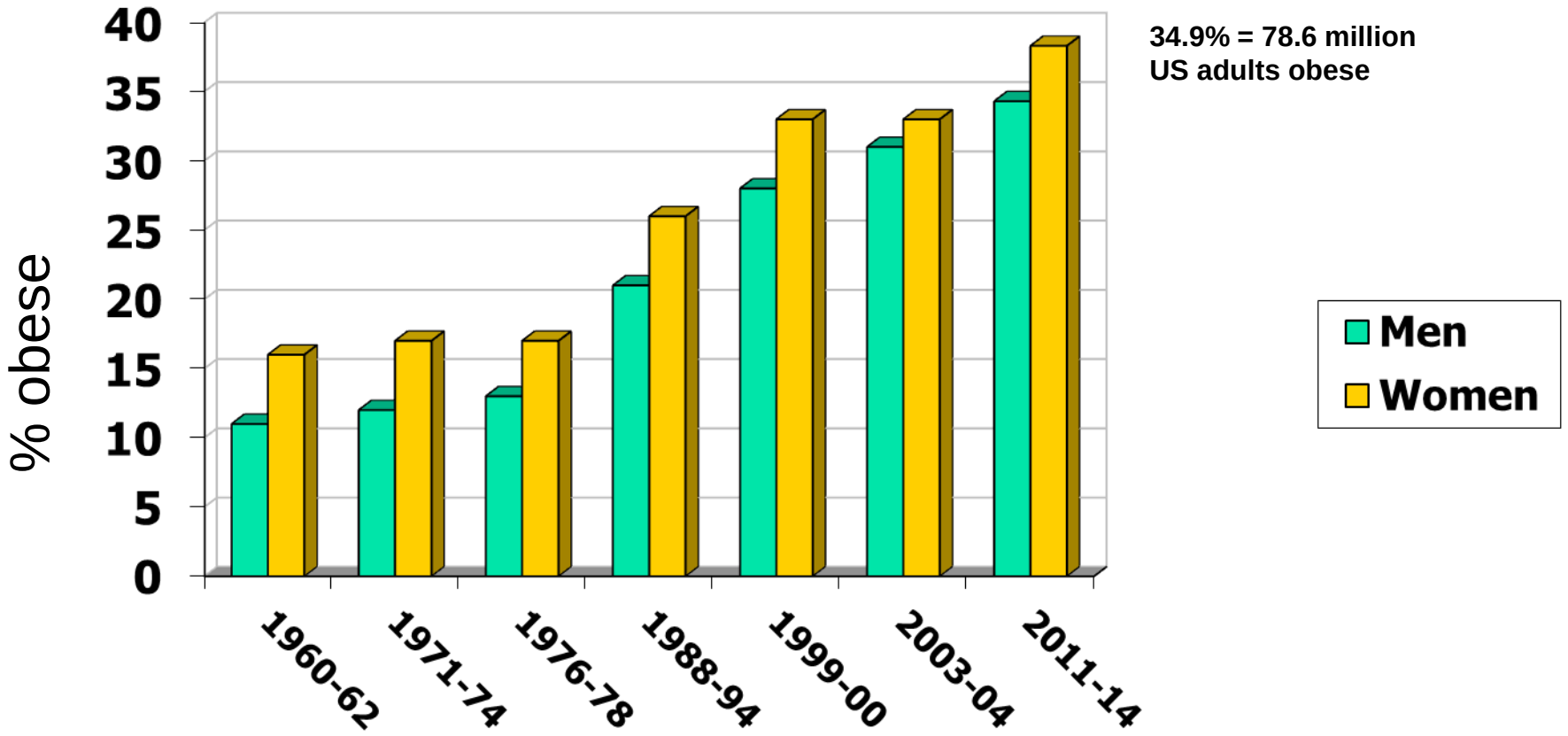
Summary: Ways to Reduce Risk of High Burden Cancers

- Maintain a healthy weight
- Be physically active
- Eat fruits and vegetables
- Choose whole over refined grains
- Limit consumption of red and processed meats
- Limit alcohol intake

Obesity and Cancer



Obesity Prevalence in the US
Adults (20-74 yrs)



CDC 2003; Ogden 2006, 2015

Obesity Prevalence in the US
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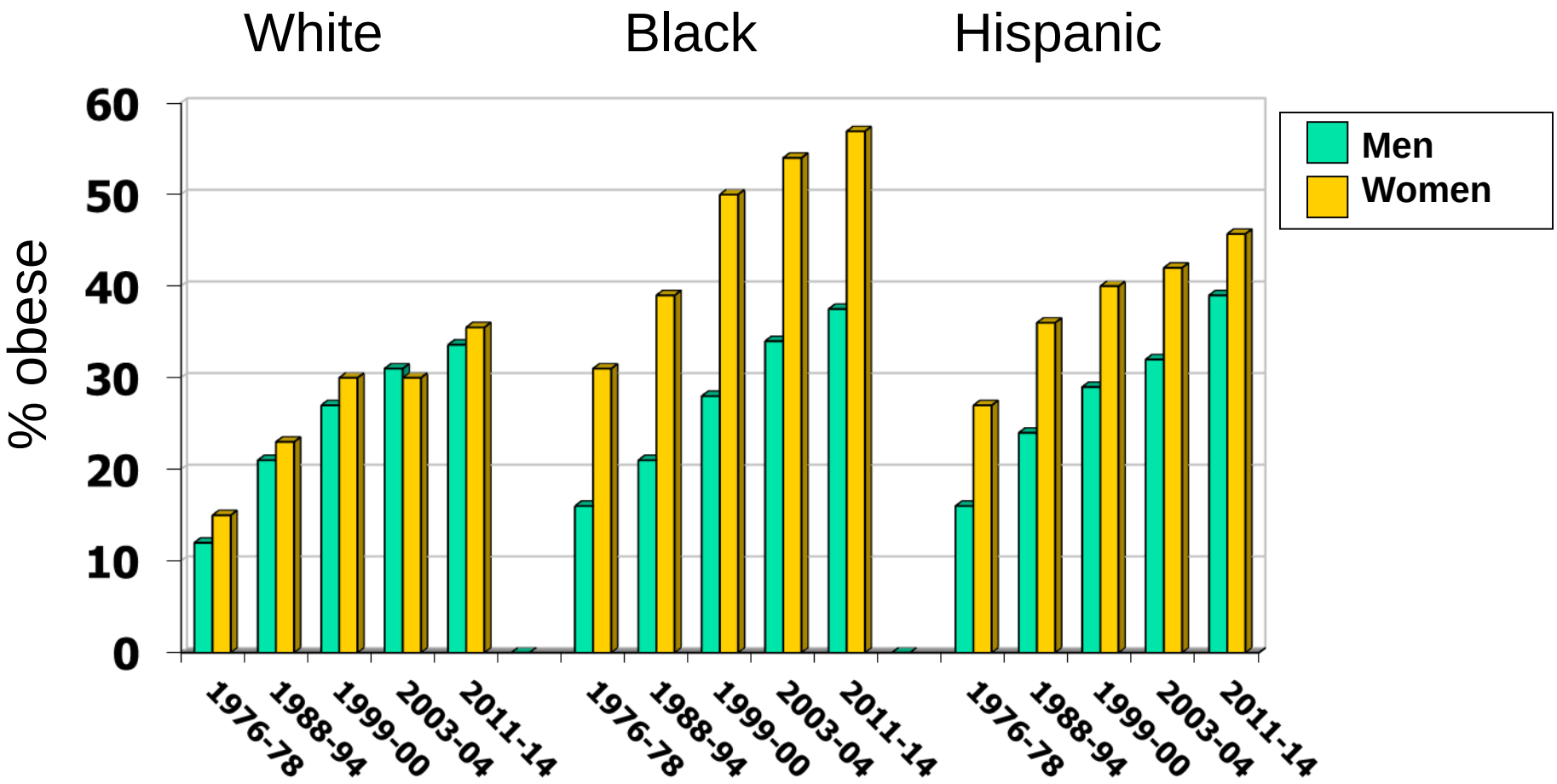
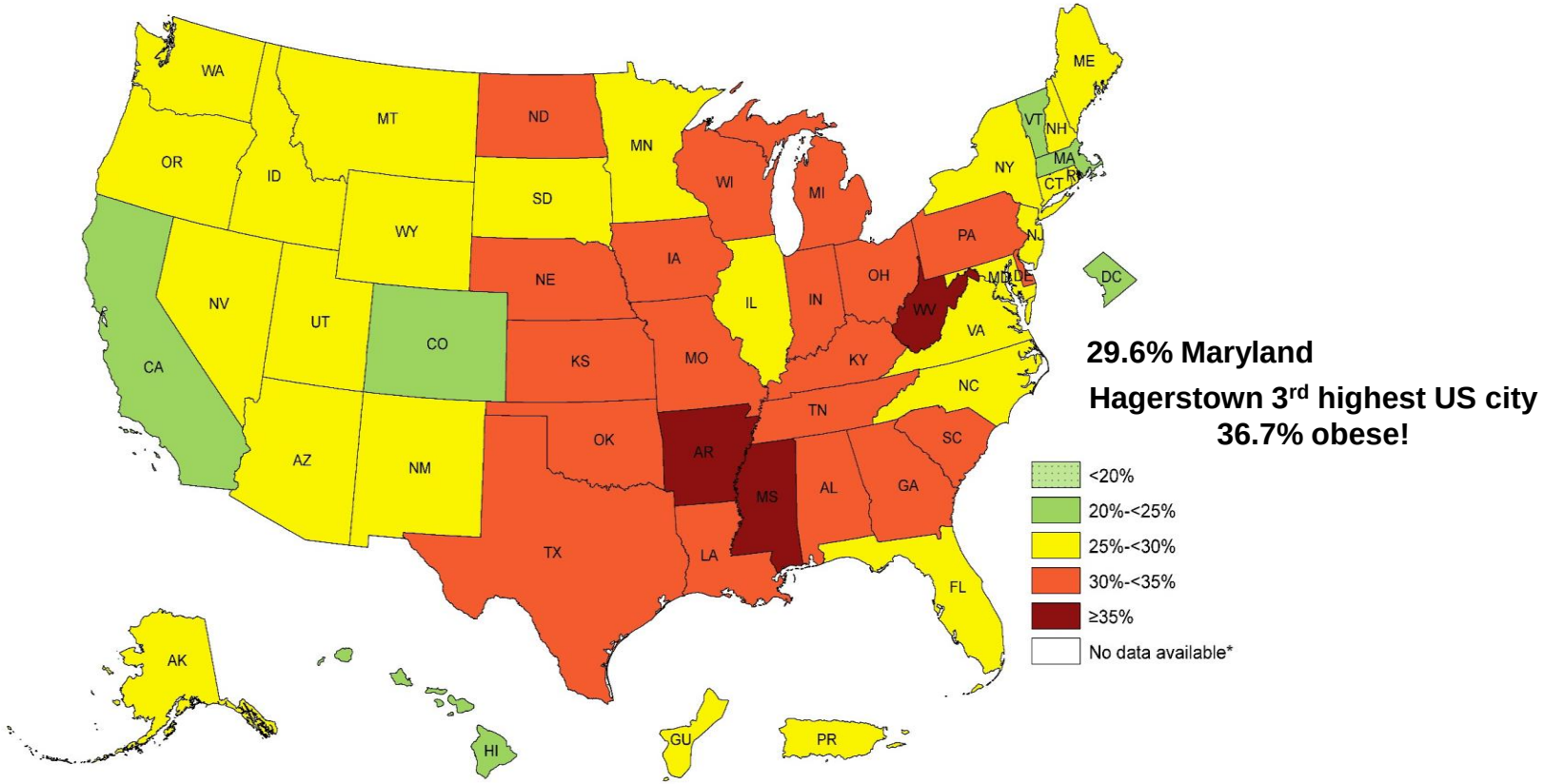


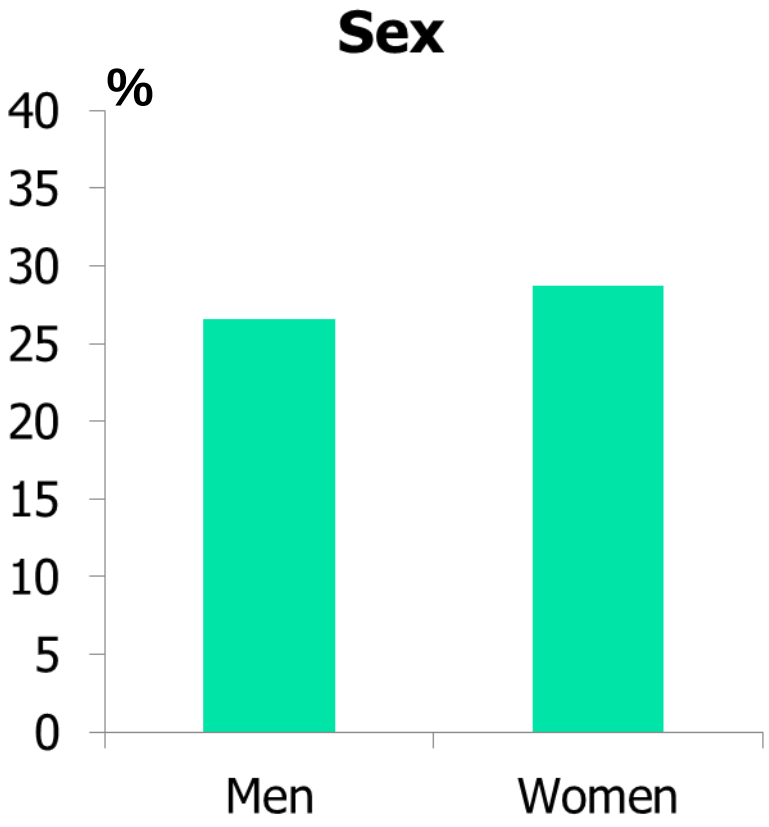
CDC 2003; Ogden 2006, 2015

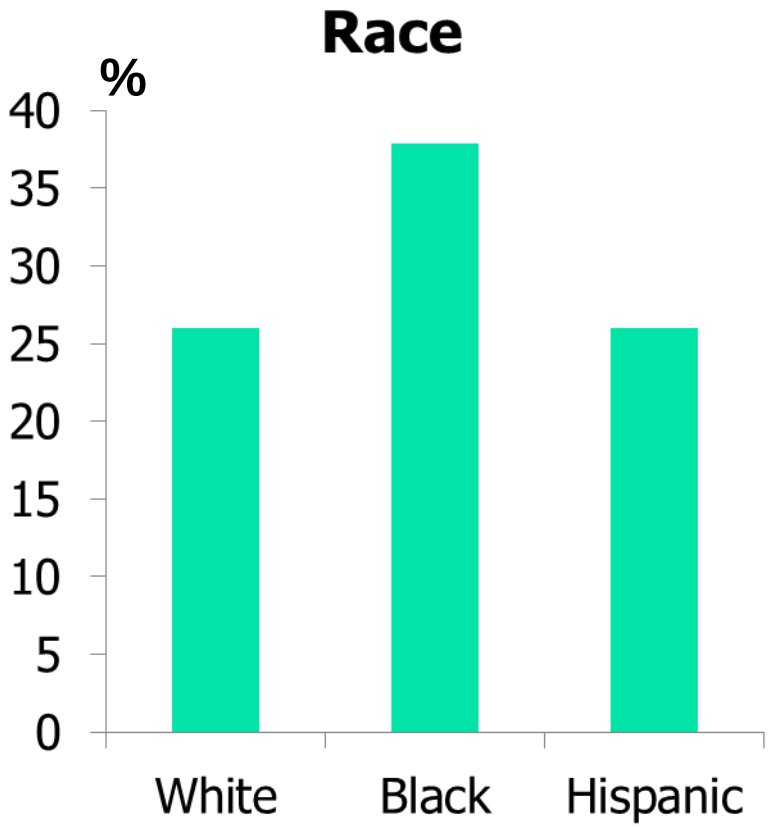
Prevalence of Obesity Among U.S. Adults, 2014



BRFSS 2014

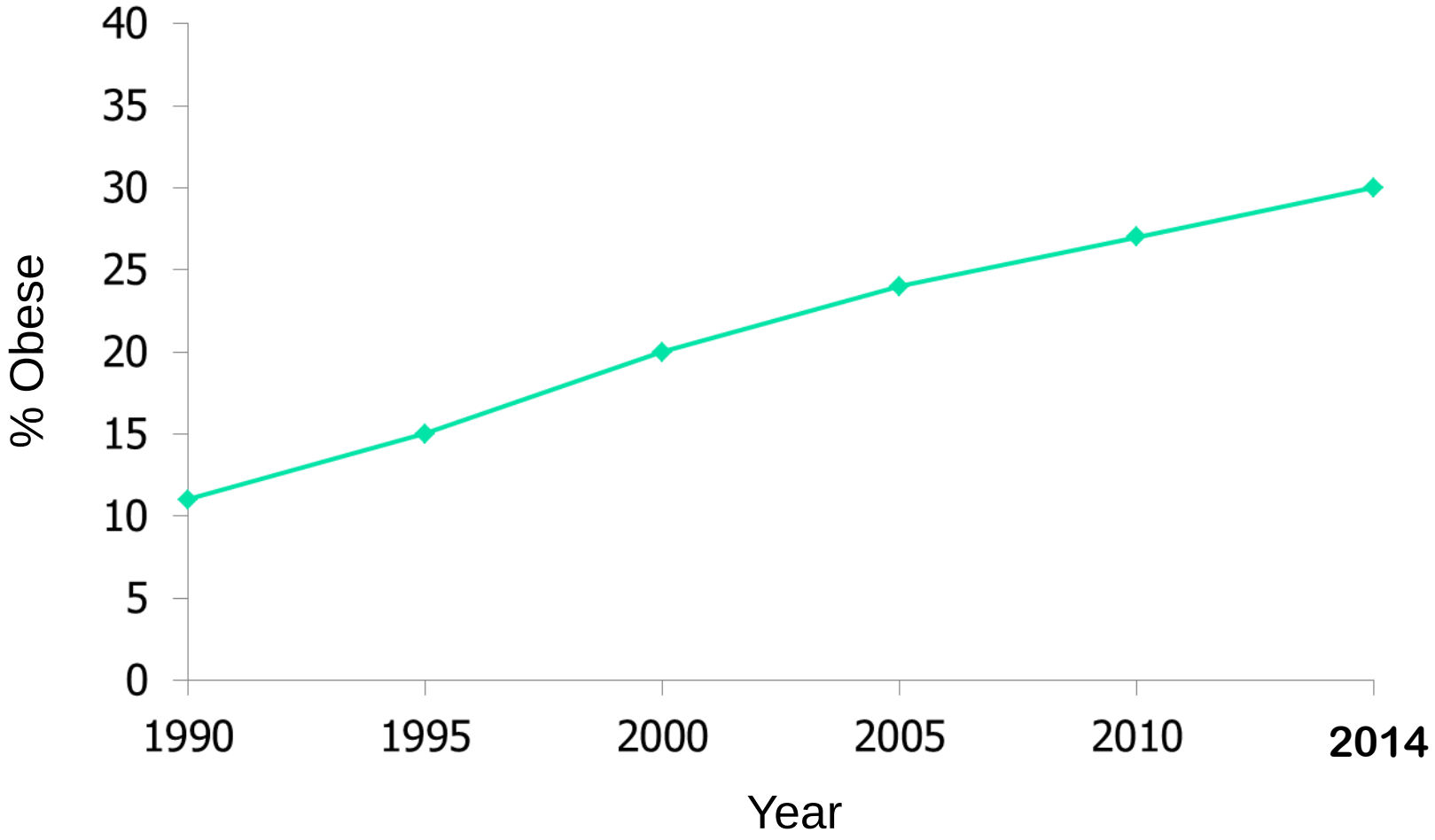
Prevalence of Obesity Among Maryland Adults





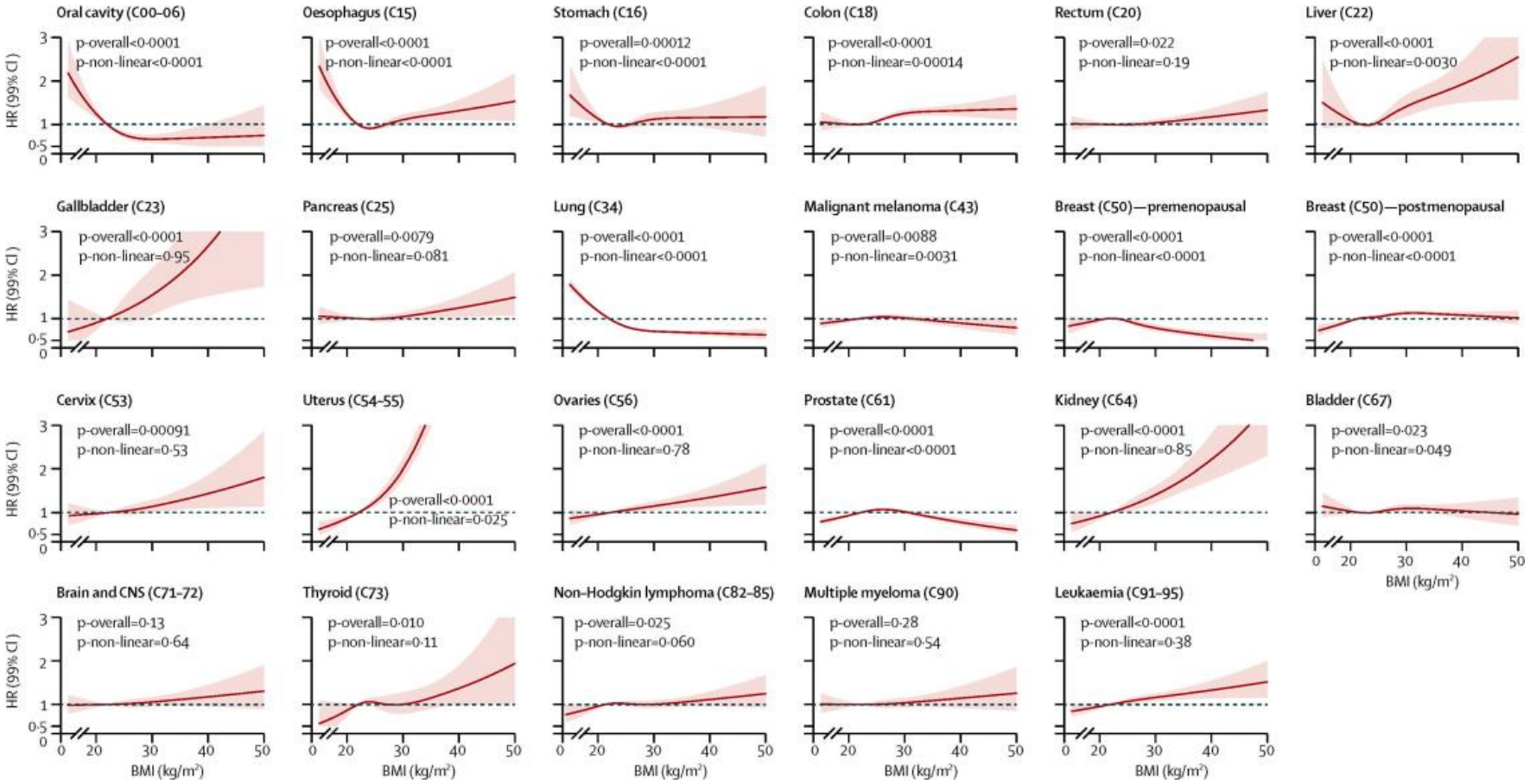
BRFSS 2013, 2015

Trends in Obesity Prevalence Among Maryland Adults, 1990-2014



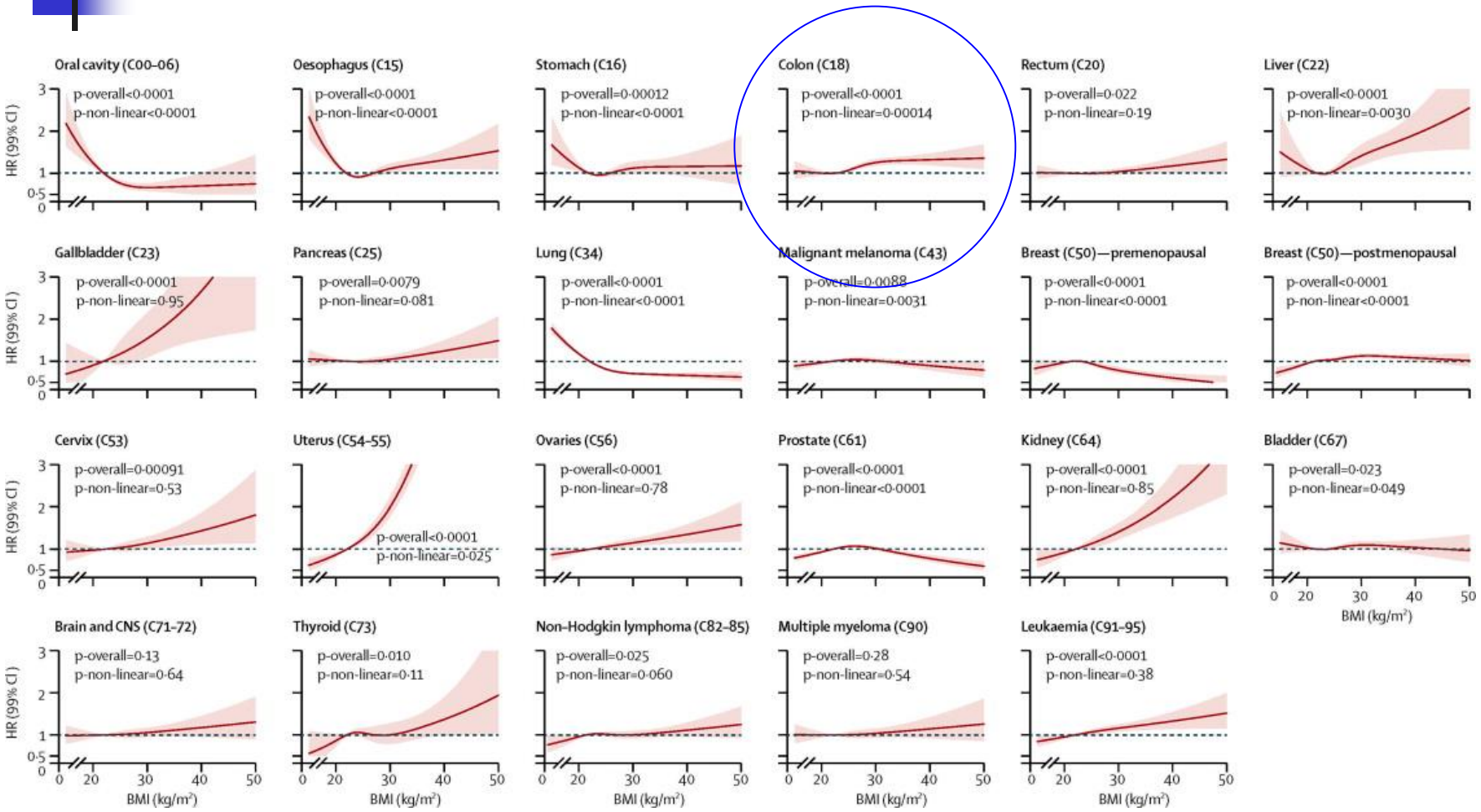
BRFSS 2015

BMI and Cancer Risk



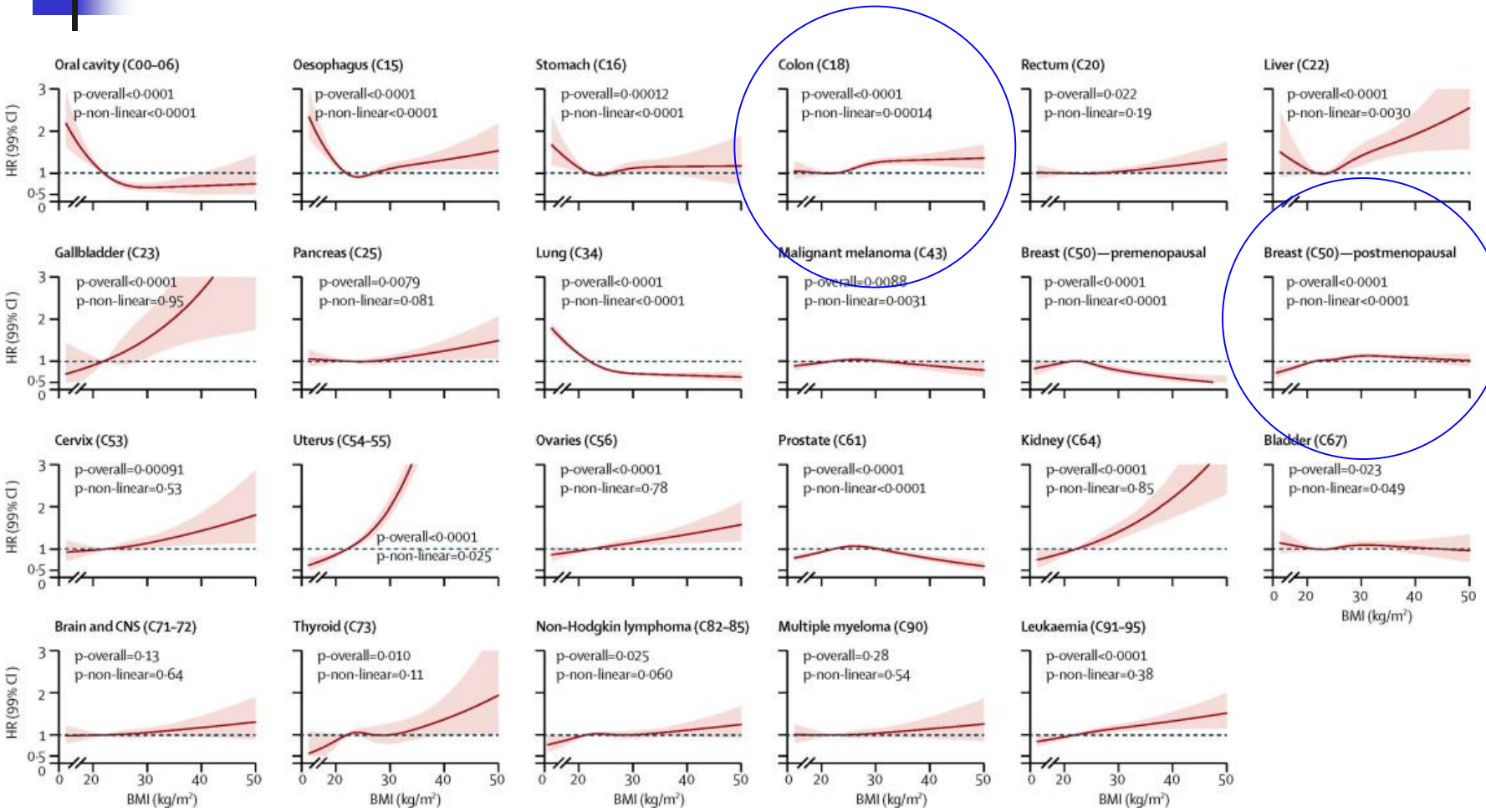
Bhaskaran 2014

BMI and Cancer Risk



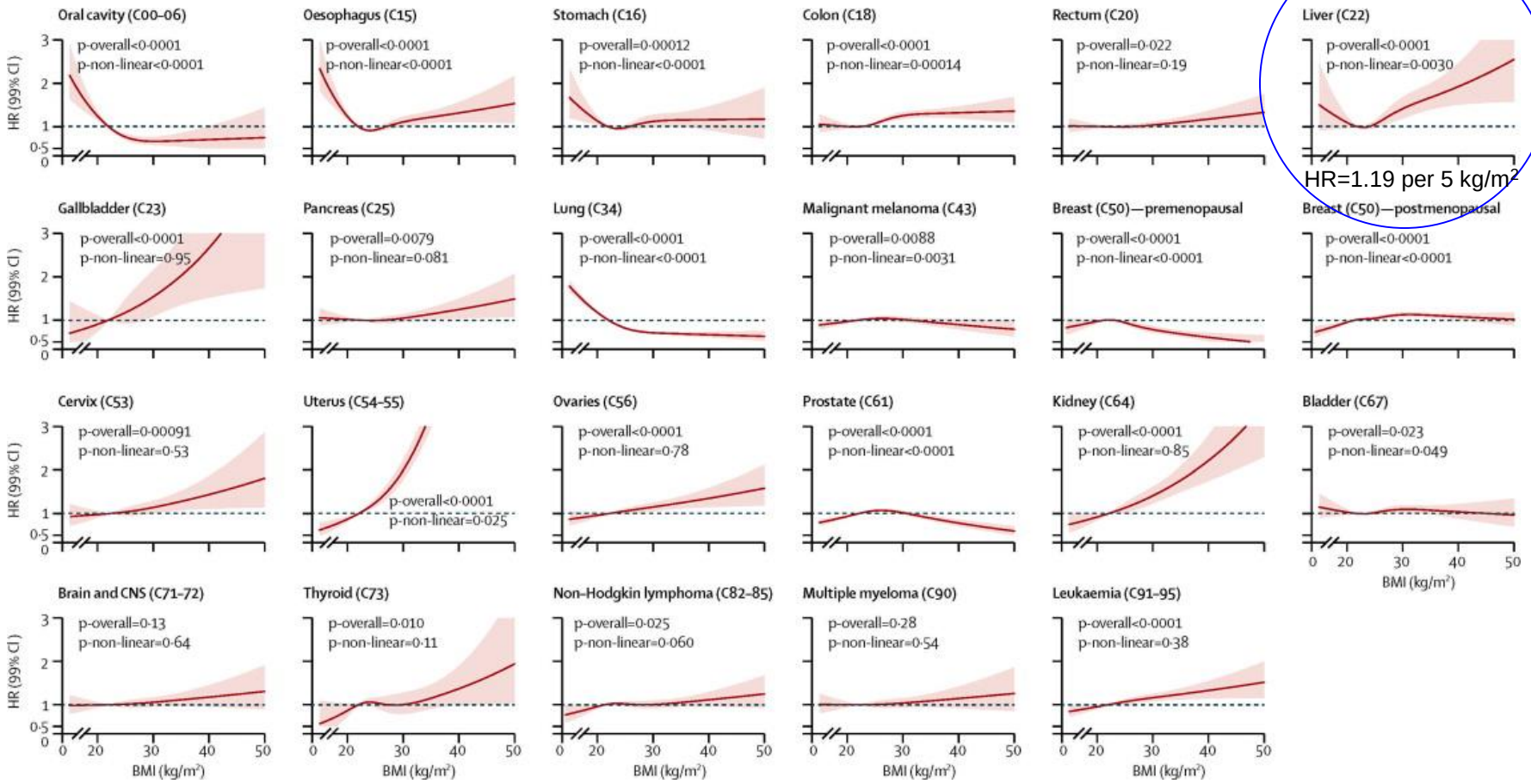
Bhaskaran 2014

BMI and Cancer Risk



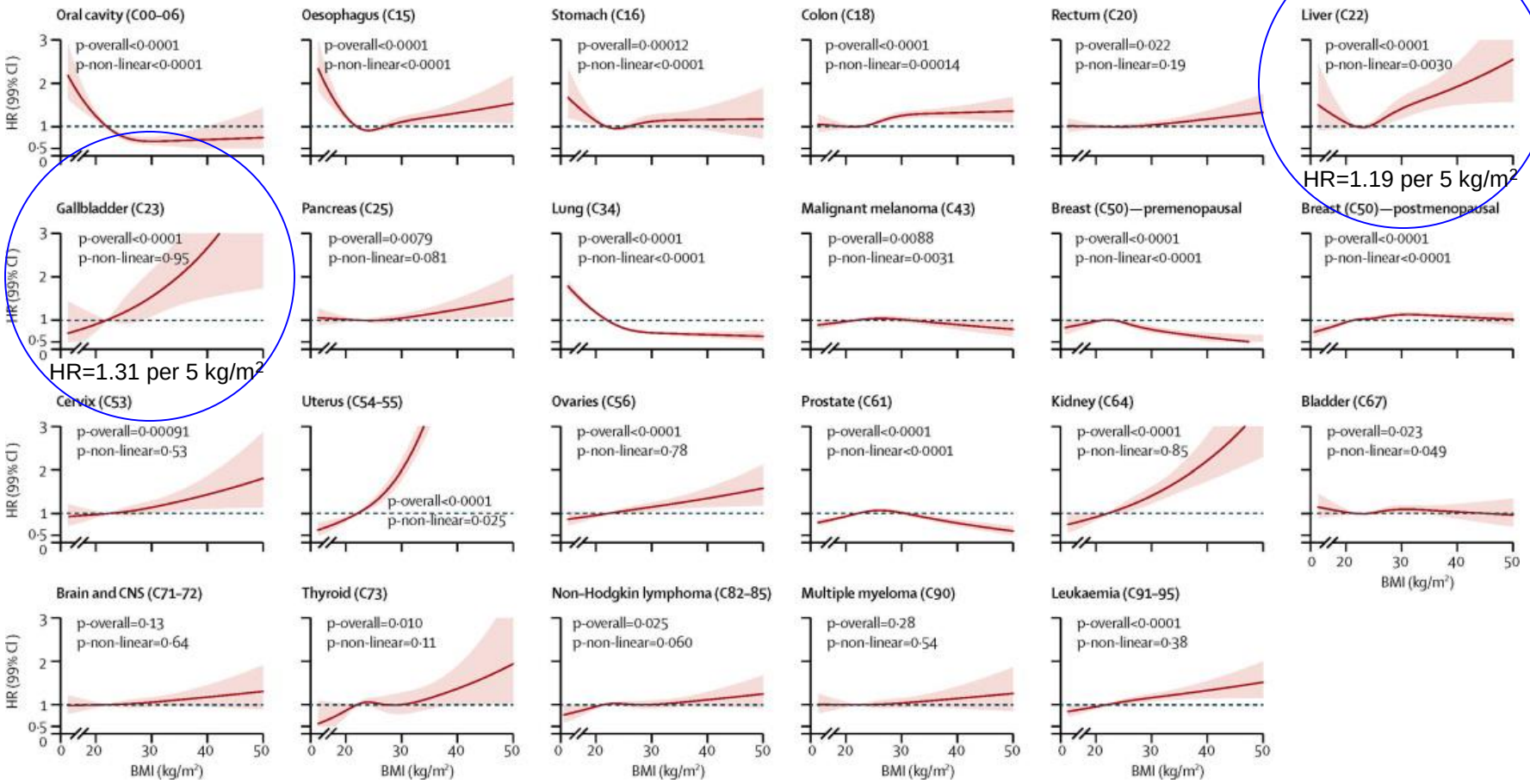
Bhaskaran 2014

BMI and Cancer Risk



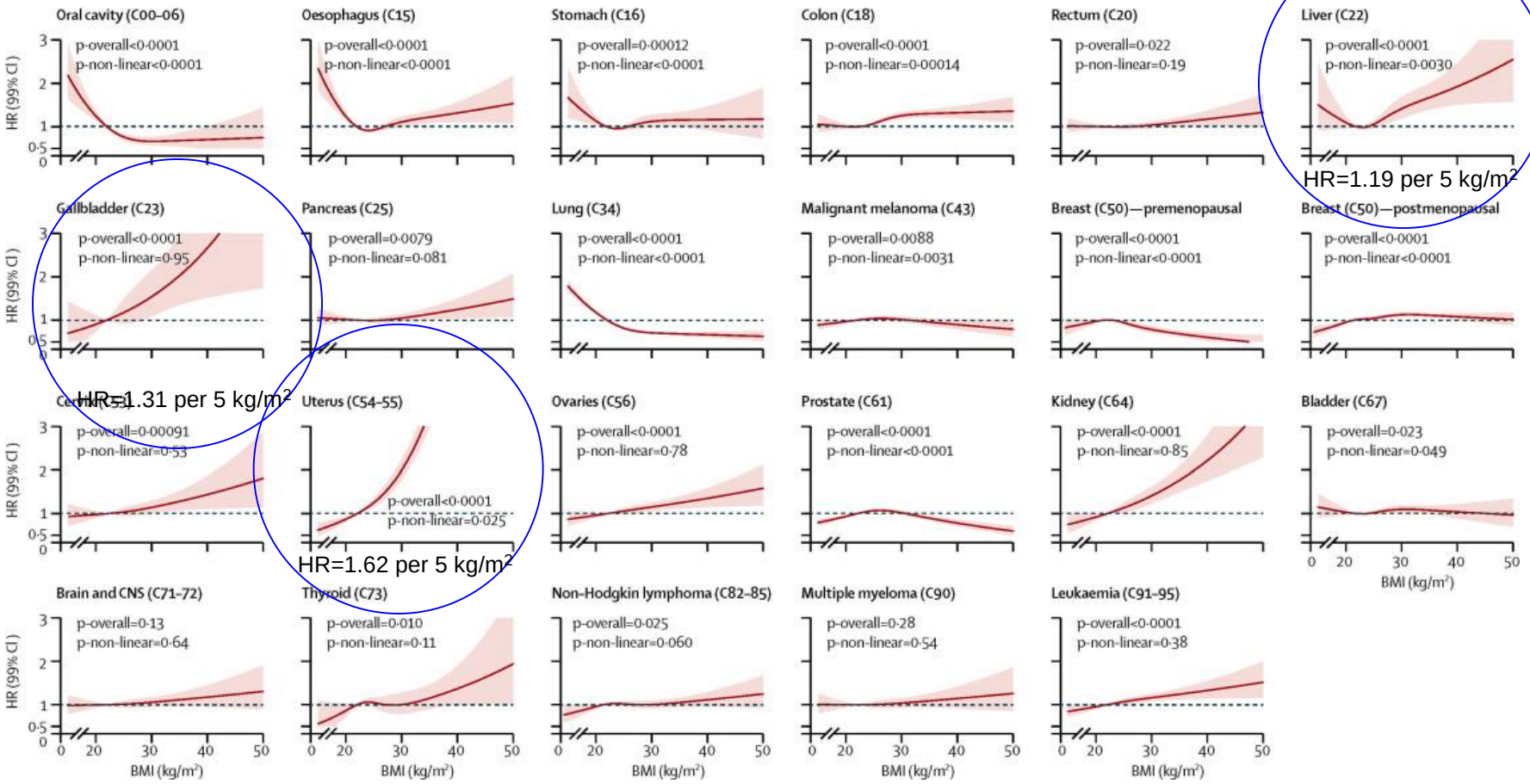
Bhaskaran, 2014

BMI and Cancer Risk



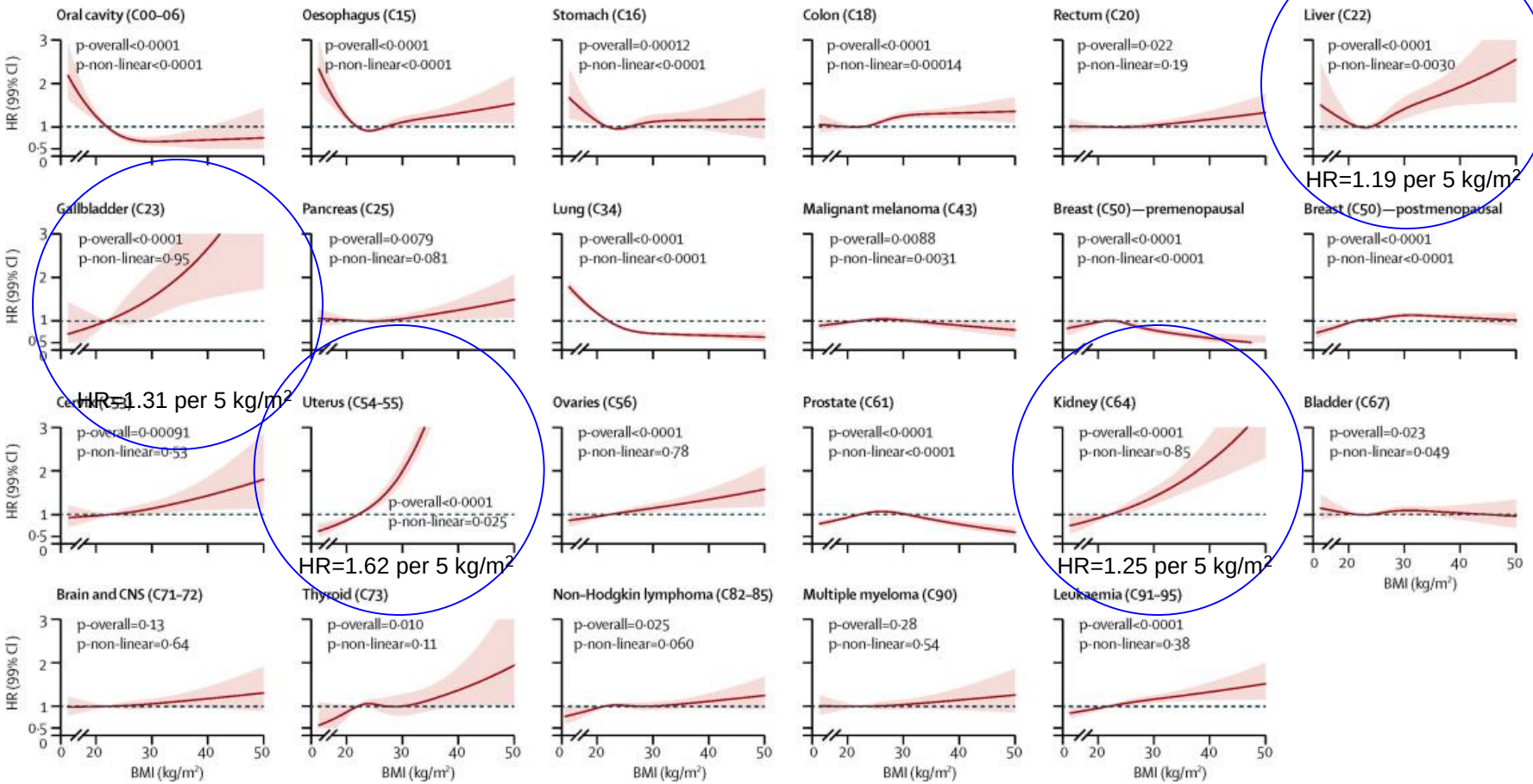
Bhaskaran 2014

BMI and Cancer Risk



Bhaskaran 2014

BMI and Cancer Risk



Bhaskaran 2014

Population Attributable Risk Due to Overweight and Obesity

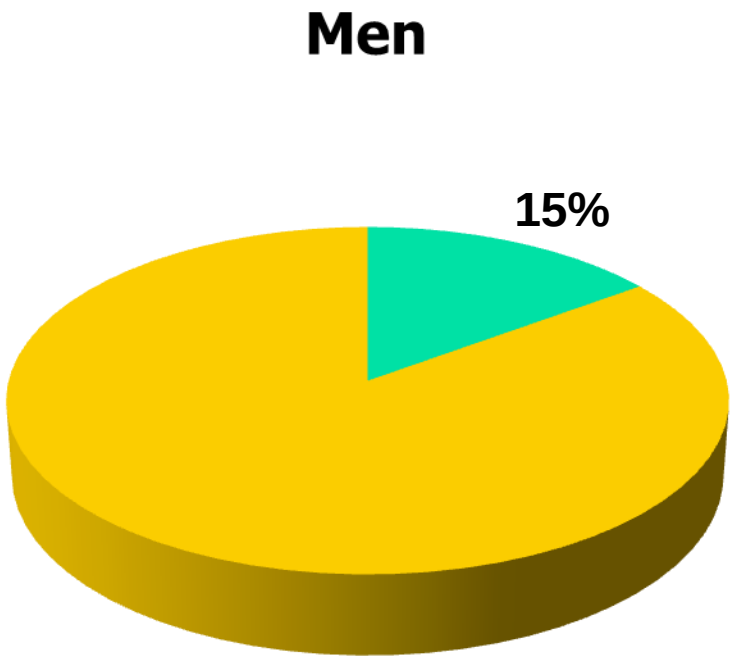
- Relative risk
  - measure of strength of association
- Attributable risk
  - takes into account RR and exposure prevalence
  - estimates proportion of cases in population due to an exposure
  - important public health metric

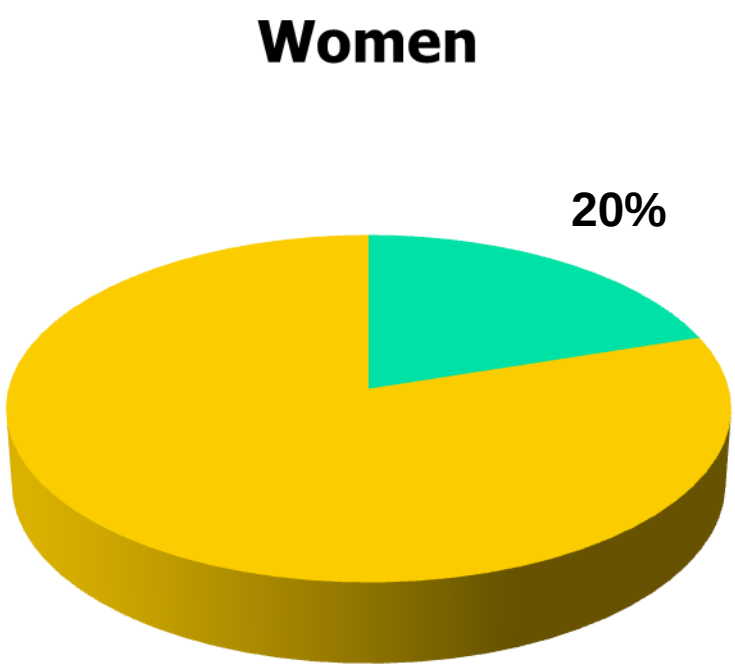
Site	Percent
Colon	11.1
Liver	15.6
Gall bladder	20.3
Breast (postmenopausal)	5.1
Cervix	7.5
Uterus	40.8
Ovaries	7.3
Kidney	16.6
Thyroid	1.9
Leukemia	6.3

Assumes 65% men and 58% women have BMI>25

Bhaskaran 2014

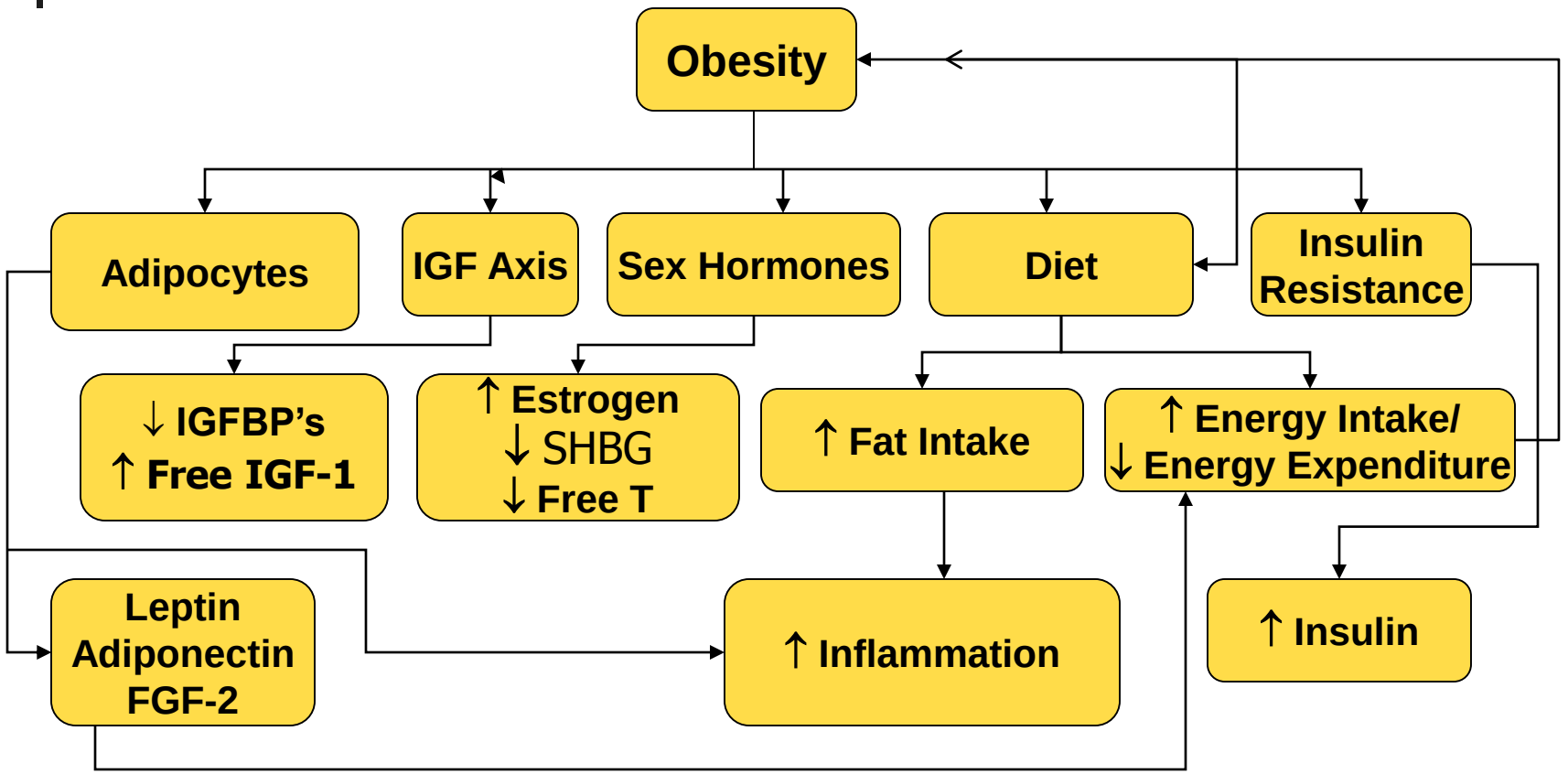
Cancer Diagnoses Attributable to Obesity, US





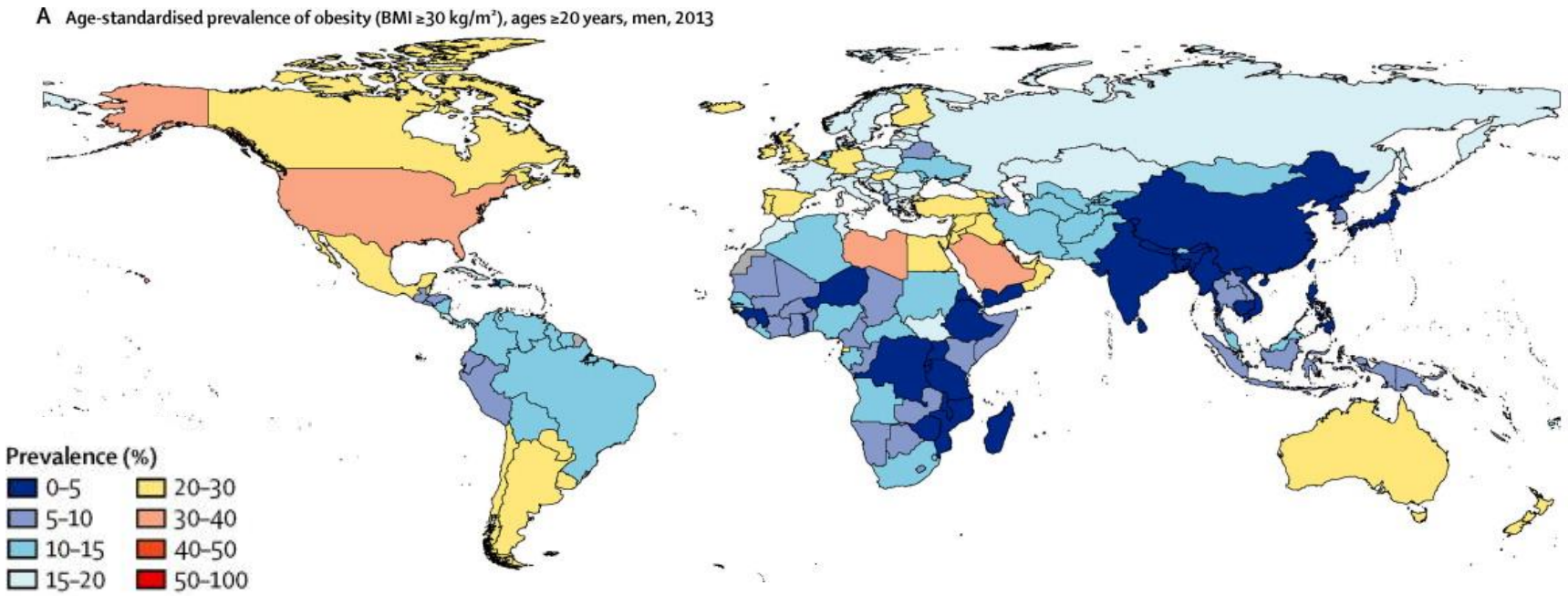
Trust for America's Health and Robert Wood Johnson Foundation 2015

Obesity and Cancer – Possible Mechanisms



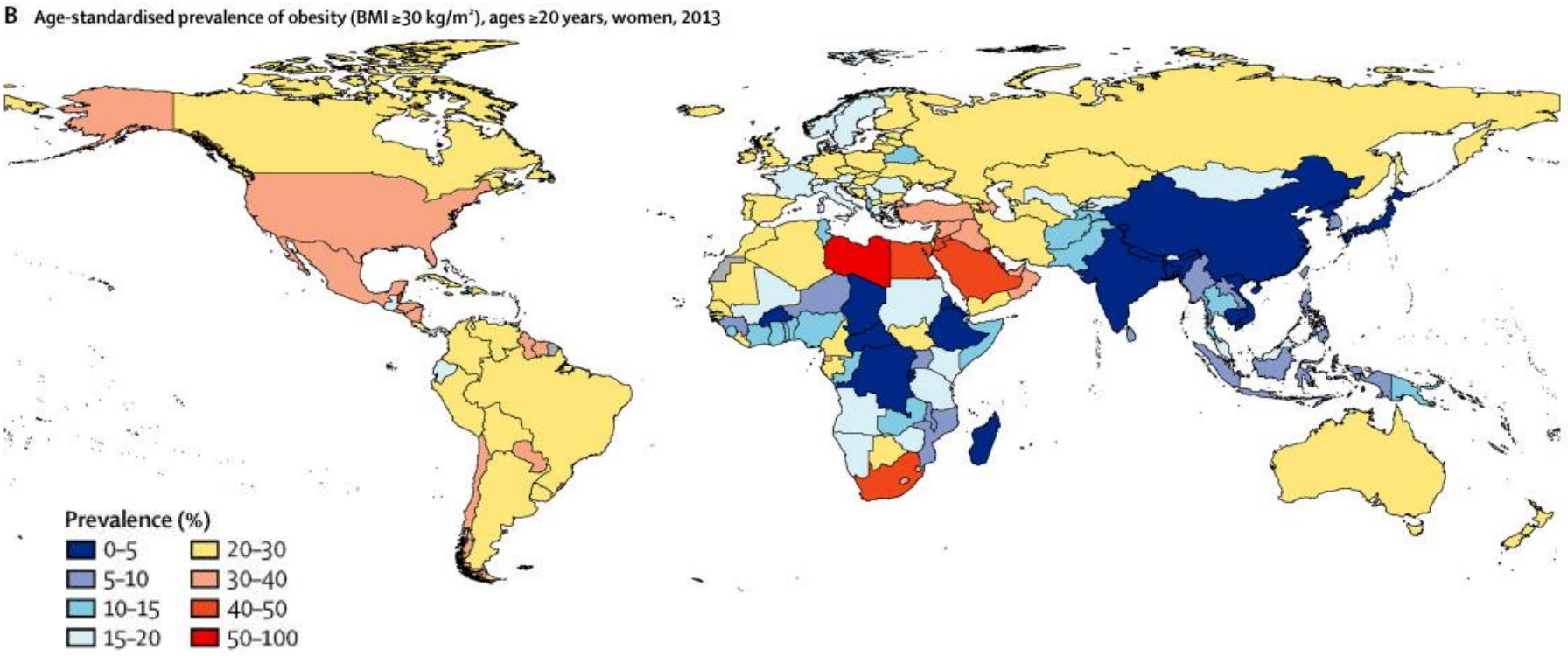
Freedland 2005

Worldwide Obesity Prevalence – Men, 2013



Ng 2014

Worldwide Obesity Prevalence – Women, 2013



Ng 2014

Future Directions

- Research
  - Mechanisms underlying obesity cancer association
  - Interventions to prevent/reduce obesity
- Education
  - Health effects, including cancer, of overweight and obesity
  - Approaches to achieve and maintain healthy weight
- Workplace
  - Encourage physical activity
  - Provide access to healthy food choices
- Public policy
  - School lunch and other food assistance programs
  - Nutrition labeling
  - Title IX
  - Built environment