Biomarkers of Lethal Prostate Cancer
Example of Baseline PSA level in midlife

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Risk factors for total prostate cancer

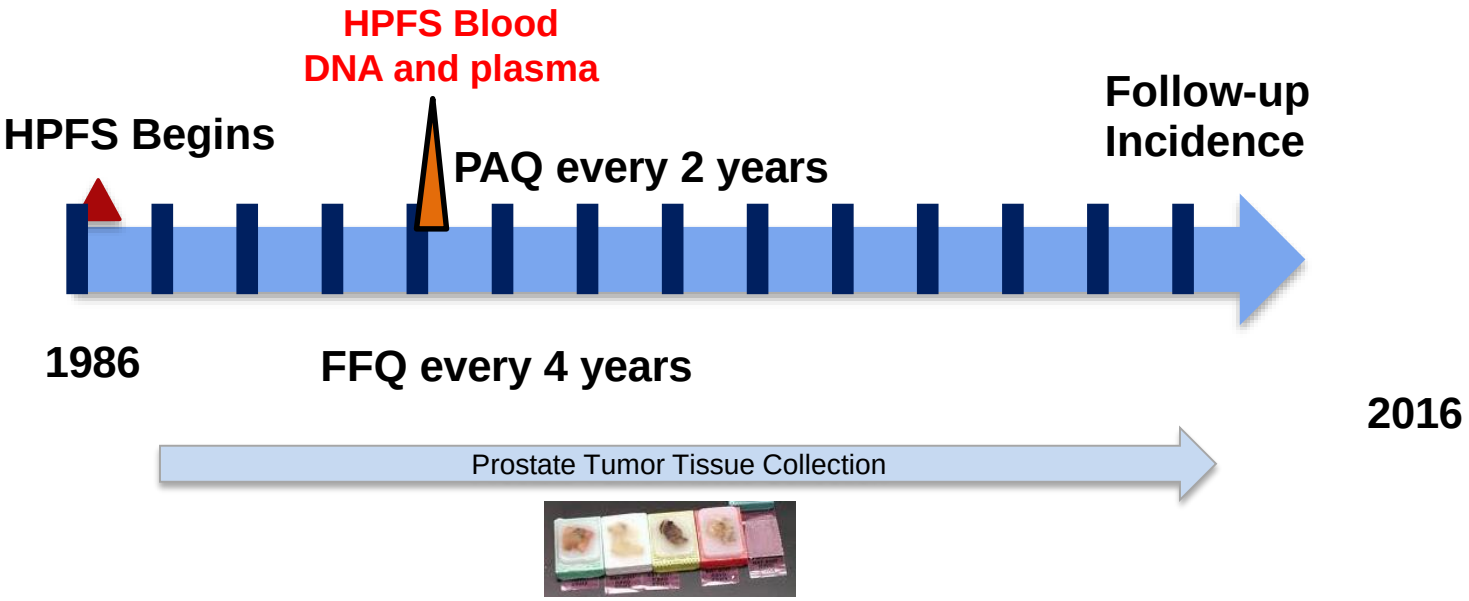
Risk factor	Direction of association	Strength of evidence
Older age	↑↑	Strong
African descent	↑↑	Strong
Family history	↑↑	Strong
Genetic risk loci	↑↑	Strong
Taller height	↑↑	Probable

Risk factors for advanced/fatal prostate cancer

Lifestyle factor	Direction of association	Strength of evidence
Cigarette smoking	↑↑	Strong
Obesity	↑↑	Strong
Taller height	↑↑	Strong
Physical activity	↓↓	Probable
Statins	↓↓	Probable
Lipid levels	↑	Possible
Lycopene/cooked tomatoes	↓↓	Probable
Coffee	↓	Possible
Calcium/Dairy	↑	Possible
Vitamin D	↓	Possible
Circadian rhythm	↑	Possible

Physical activity and advanced prostate cancer in the Health Professionals Follow-up Study

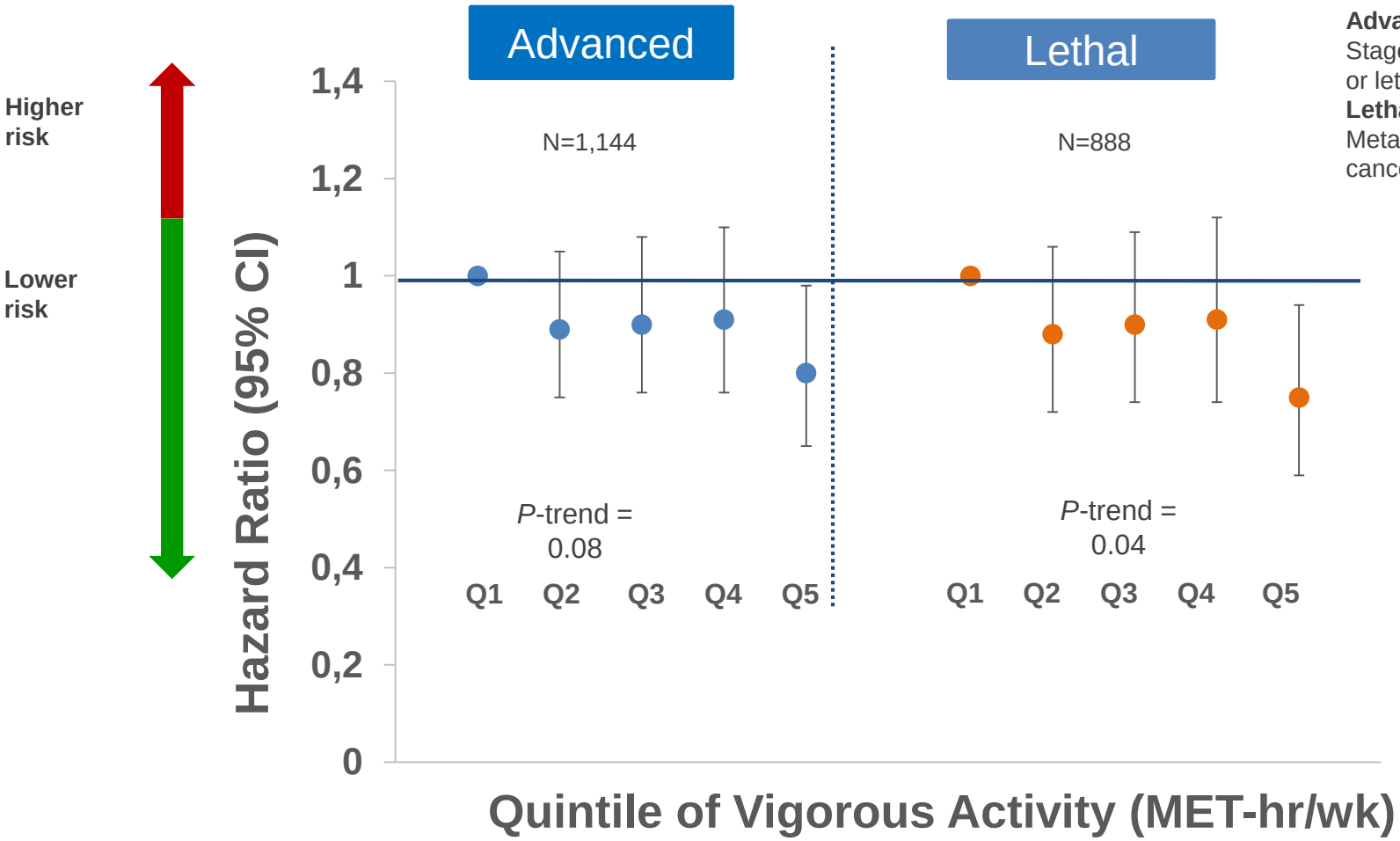
- 51,000 US male health professionals age 40 to 75 years



- Follow-up for prostate cancer incidence (n=6,411), metastases, mortality (N=878)

Results:

Vigorous activity and advanced/lethal prostate cancer

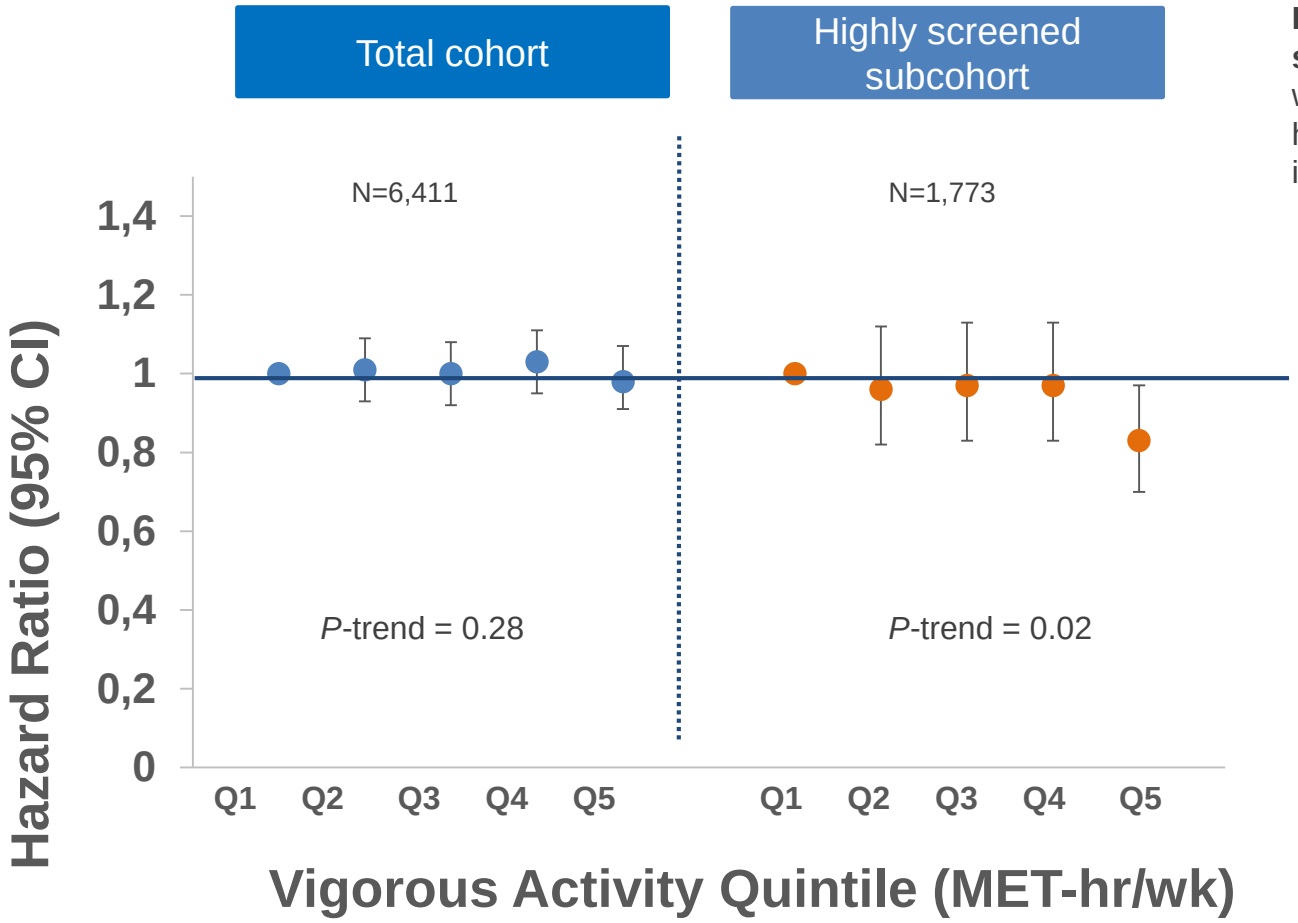


Advanced: Stage T3b, T4, N1, M1 or lethal

Lethal: Metastases or prostate cancer death

Results:

Vigorous activity and overall prostate cancer risk



Highly screened subcohort: Men who reported having a PSA test in 1994 and 1996

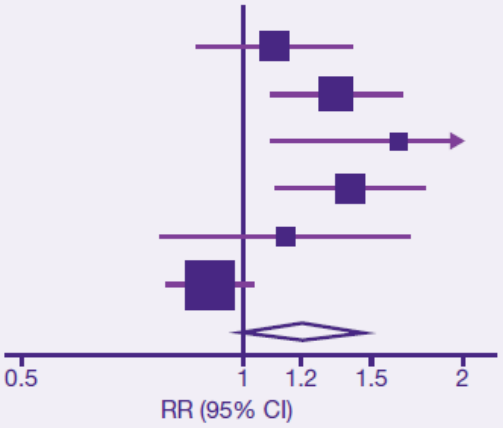
Future directions

- Randomized controlled trials ongoing to look at exercise interventions among men undergoing radiation therapy, active surveillance, CRPC
- Important to understand what type of exercise: walking, aerobic, strength training
- Understanding of importance of exercise for quality of life

Obesity as a prostate cancer risk factor

- Overweight/obesity is a risk factor for advanced prostate cancer
- Among patients, obesity is generally associated with worse outcomes, worse response to ADT, and higher cancer mortality

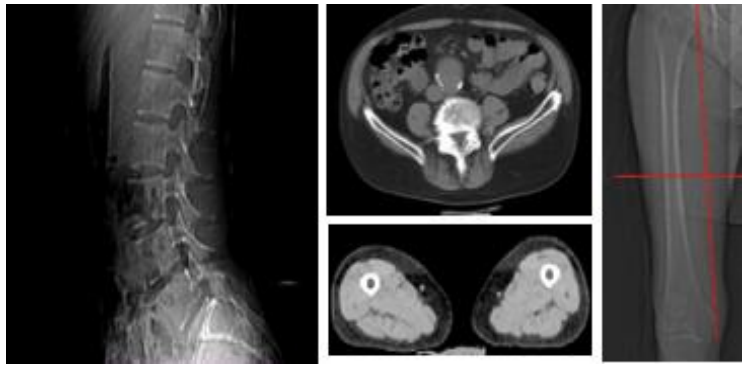
Source	RR (95% CI)
Post diagnosis survival study	
Siddiqui (2006, USA)	1.10 (0.86–1.40)
Efstathiou (2007, USA)	1.34 (1.09–1.65)
Gong (2007, USA)	1.63 (1.09–2.44)
Ma (2008, USA)	1.40 (1.10–1.76)
van Roermund (2009, the Netherlands)	1.14 (0.77–1.69)
Davies (2009, USA)	0.90 (0.78–1.03)
Overall	**1.20 (0.99–1.46)**

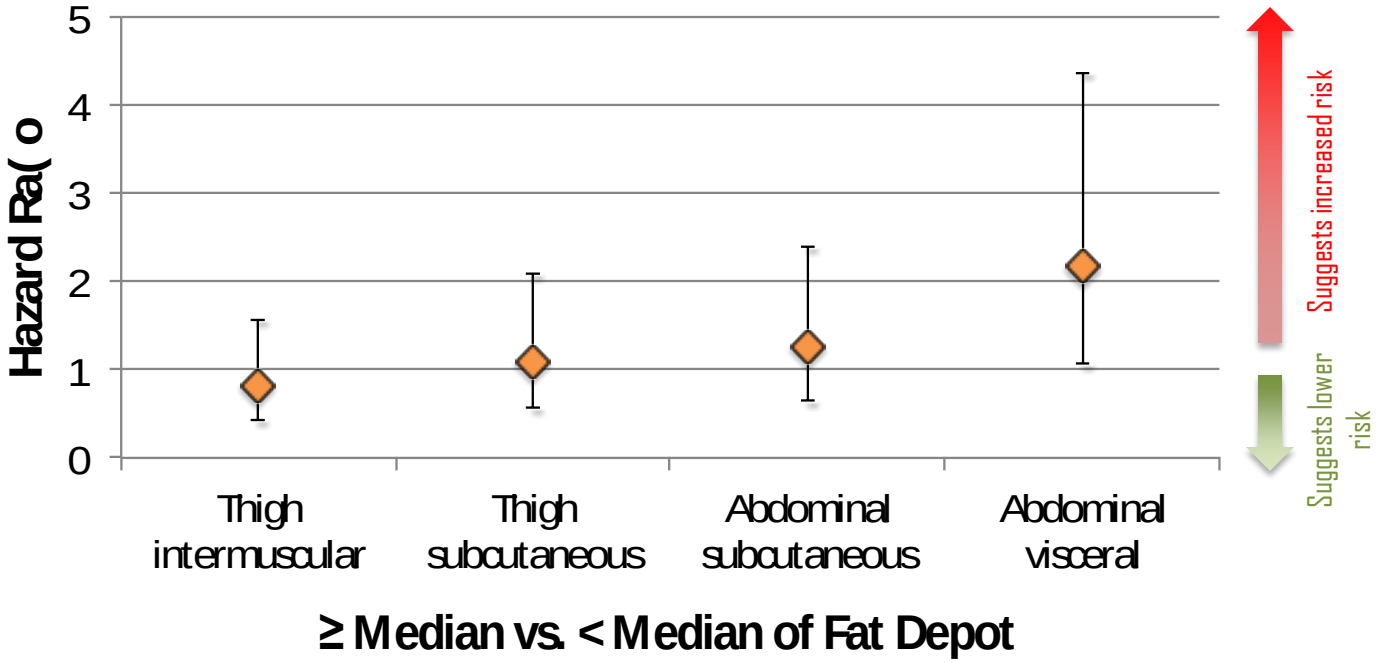


Strong evidence based on 2014 report from the World Institute of Cancer Research/American Institute from Cancer Research

Visceral obesity and advanced prostate cancer

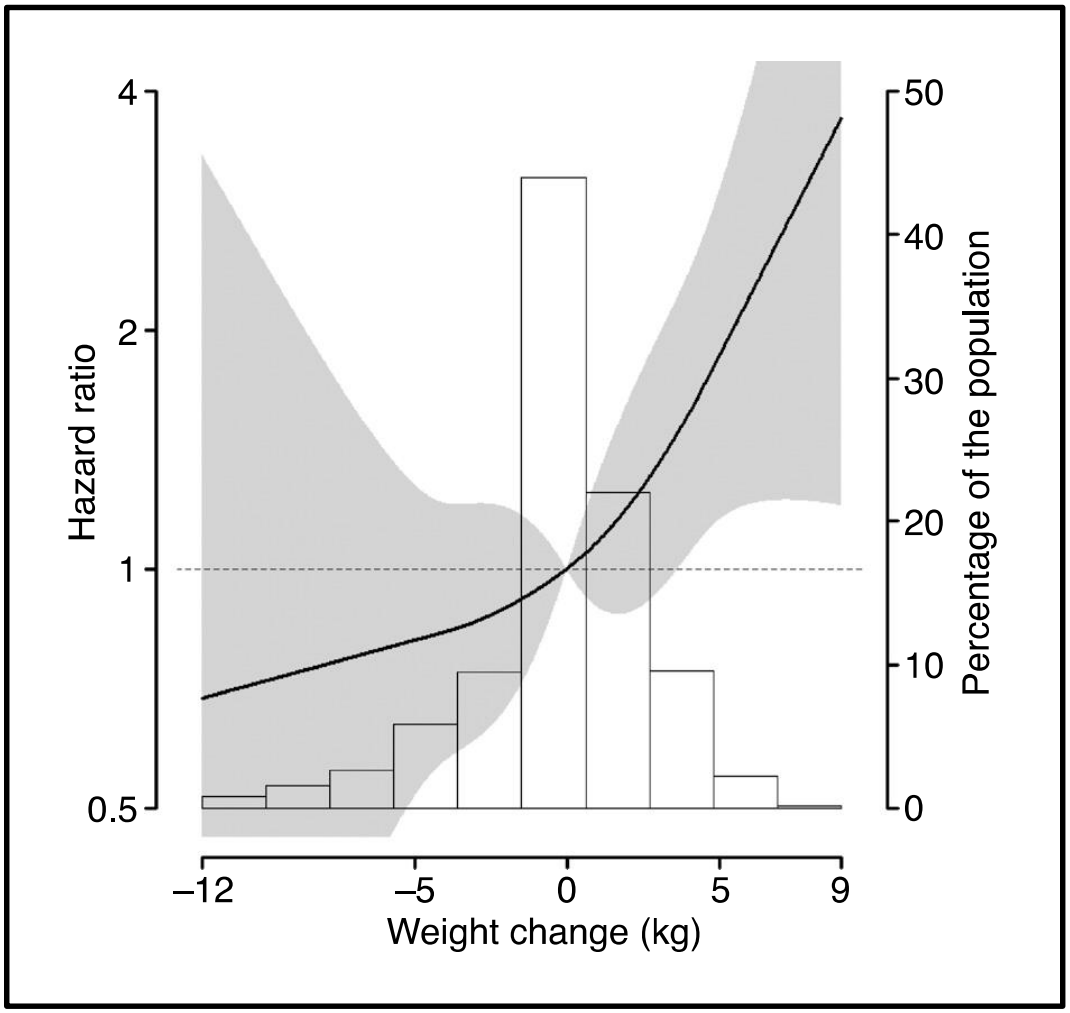
Obesity measures derived from pre-diagnostic CT scans from 1,832 Icelandic older men followed for 12 years





Dickerman et al, in preparation

Weight change and risk of prostate cancer recurrence



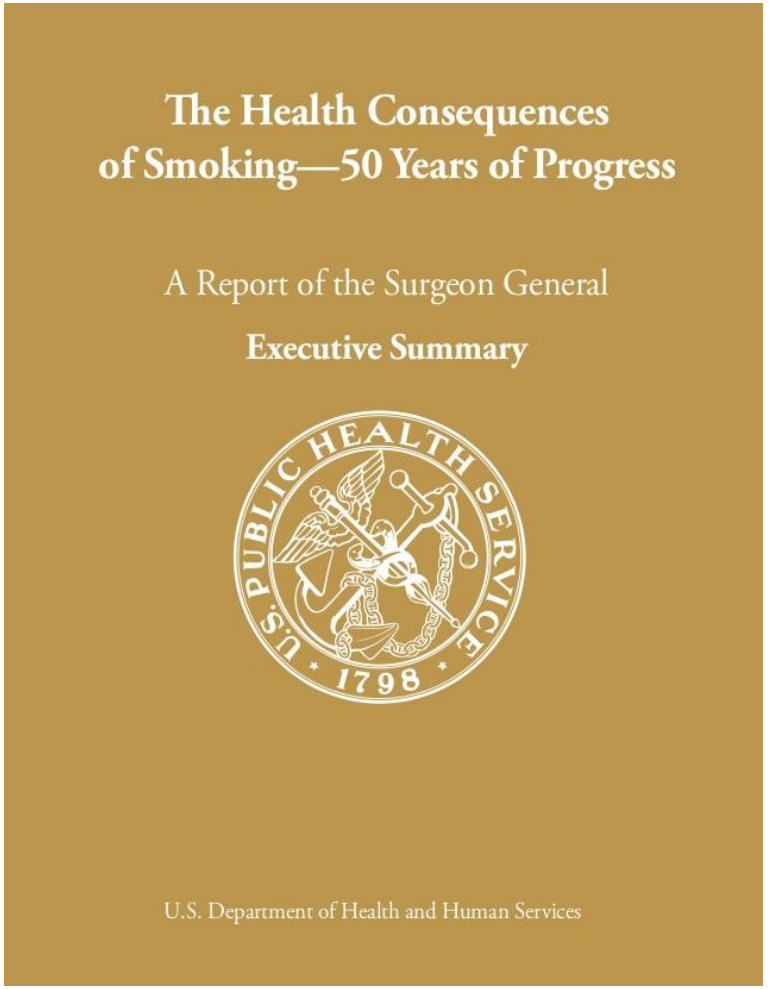
Joshu et al, Cancer Prev Res 2012

Future studies

- Need for an intervention study to investigate whether weight loss is associated with improved cancer outcomes
- Understanding of obesity and its effects on quality of life
- Biomarkers of obesity could be targets for therapeutic interventio
- Weight loss is challenging

Smoking and prostate cancer mortality

Evidence is suggestive of an increased risk of prostate cancer mortality among smokers compared to never smokers



Smokeless tobacco products - Snus

- Moist smokeless tobacco product common in Scandinavia
- Users exposed to high levels of nicotine and other compounds, but without combustion products
- Snus is put forward as a risk-reducing alternative to smoking including by WHO
- Tobacco companies promote use of snus outside of Sweden as healthier alternative to smoking

Study design – tobacco use and prostate cancer mortality

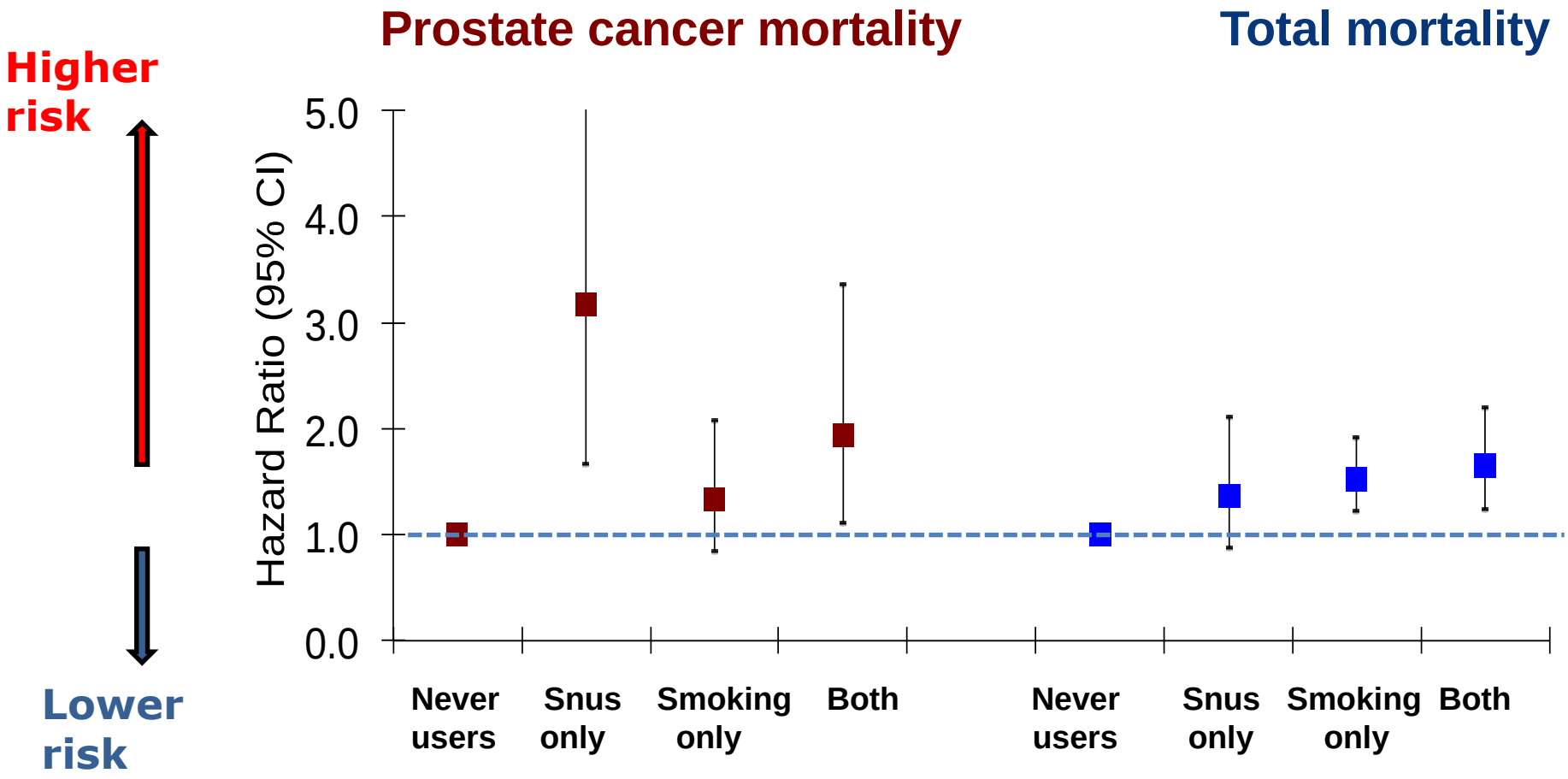

Swedish Constructions Workers Cohort
N=343,000 men aged 40-75 yrs at baseline in 1986

Smoking and snus

50% exclusive smokers
5% exclusive snus
16% used both
29% used neither

9,582 prostate cancer cases
2,489 cancer deaths and 4,750 deaths overall

Smoking and snus use among 9,500 Swedish men with prostate cancer

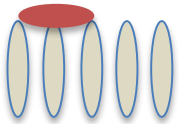


Wilson K., Markt et al, Int J Cancer In press

Potential mechanisms of tobacco link

Nicotine
Nitrosamines
PAH

nicotinic
acetylcholine
receptors (nAChR)



PI3K/mTOR
HIF1-alpha

Angiogenesis
Proliferation

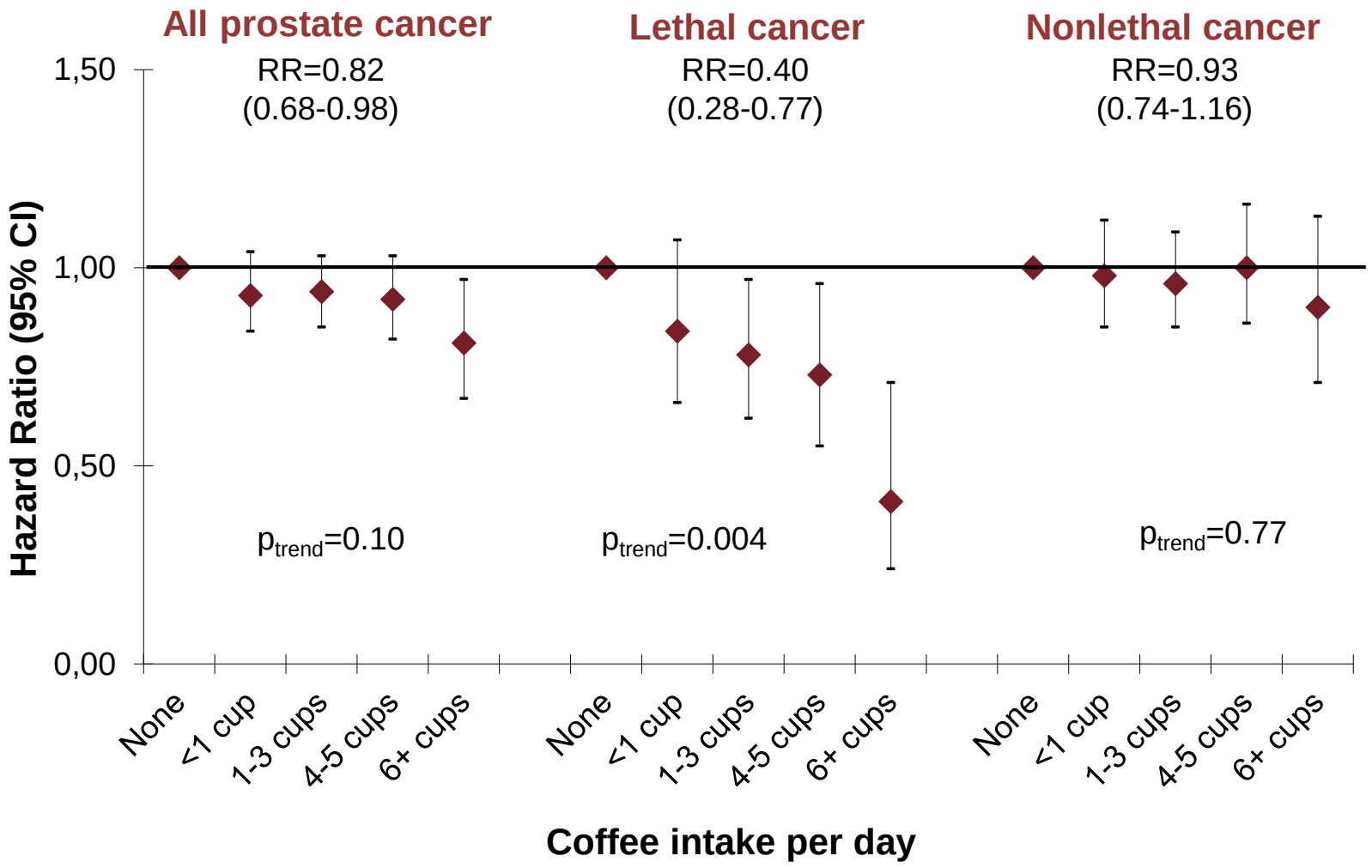
Coffee and prostate cancer risk

Coffee

↓ Insulin ↓ Inflammation ↑ Antioxidants

↓ Prostate cancer progression

Coffee and prostate cancer risk



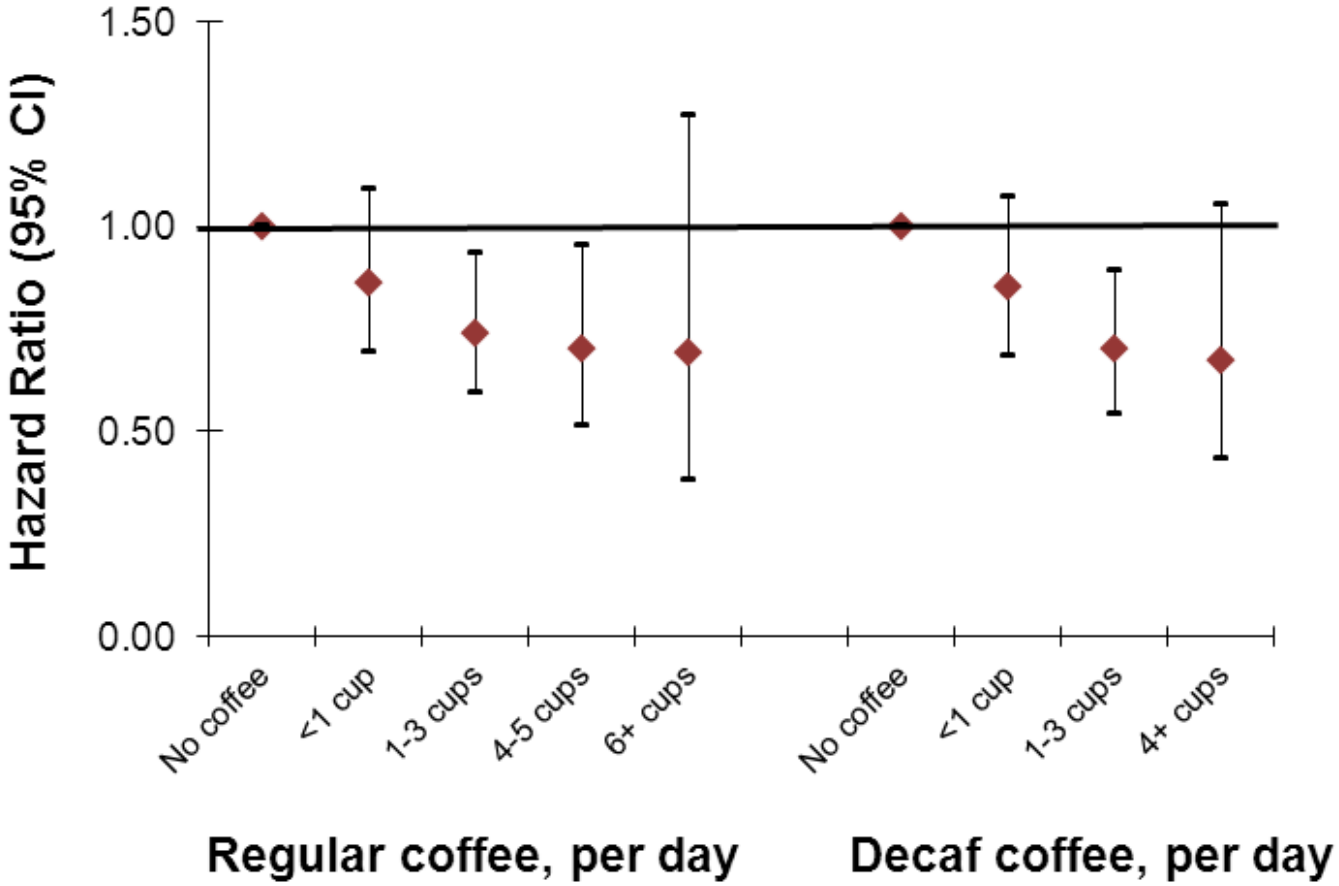
Wilson et al, JNCI 2011

Regular vs. Decaf

Lethal cancer

Regular Coffee
RR=0.56 (0.28-1.11)

Decaf Coffee
RR=0.59 (0.36-0.96)



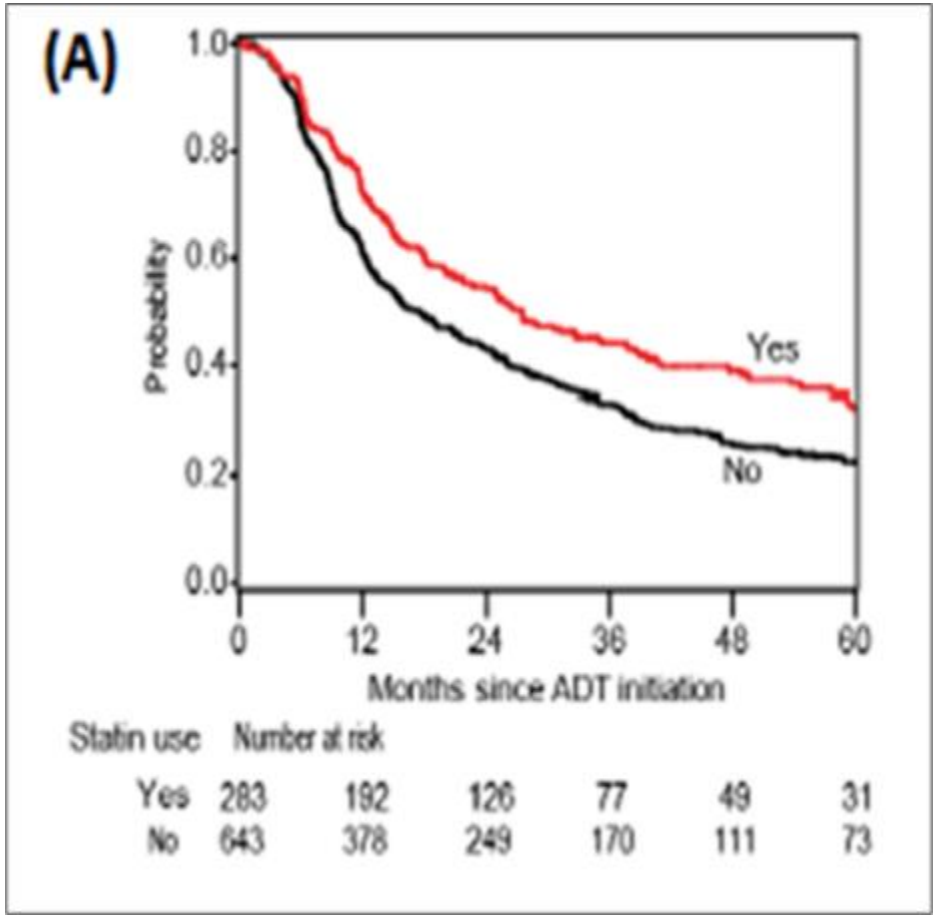
Statins and prostate cancer mortality

Relative risk reduction
25% lower risk cancer death

Pre-dx use?	Relative risk reduction
NO	**18%** lower risk cancer death
YES	**45%** lower risk cancer death

Yu et al, JCO 2014

Statin use and time to progression on ADT



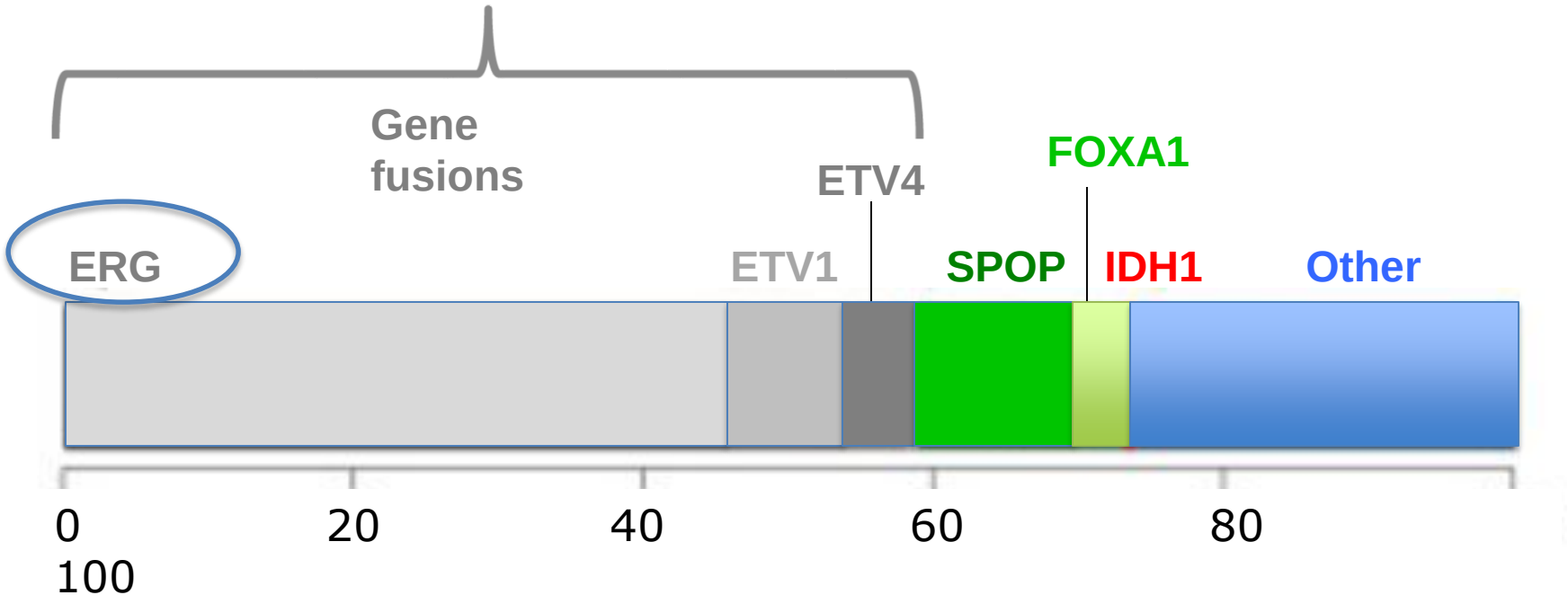
- Statin users at ADT initiation had a significantly longer median TTP on ADT: 27.5 vs. 17.4 months, p=0.0005
- Association remained statistically significant after adjusting for the pre-defined prognostic clinical factors: adjusted HR=0.83, 95% CI: 0.69,0.99

Harshman et al JAMA Onc (in press)

Future Directions

- Intervention study to investigate whether statins after diagnosis are associated with improved cancer outcomes
- Will all men benefit from statins, based on biomarkers?
- What is the right patient population?

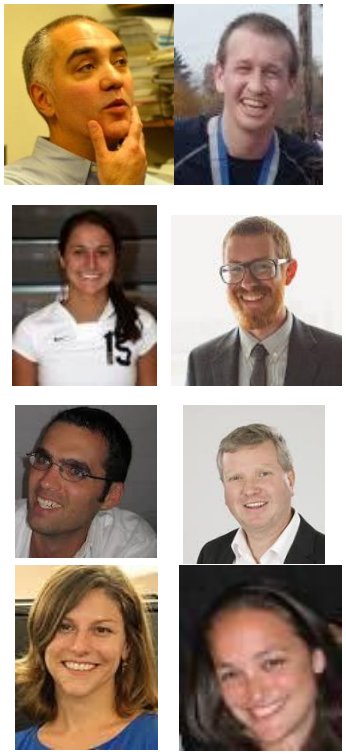
Molecular Subtypes: the Cancer Genome Atlas



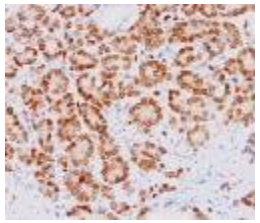
The Cancer Genome Atlas, Cell 2015

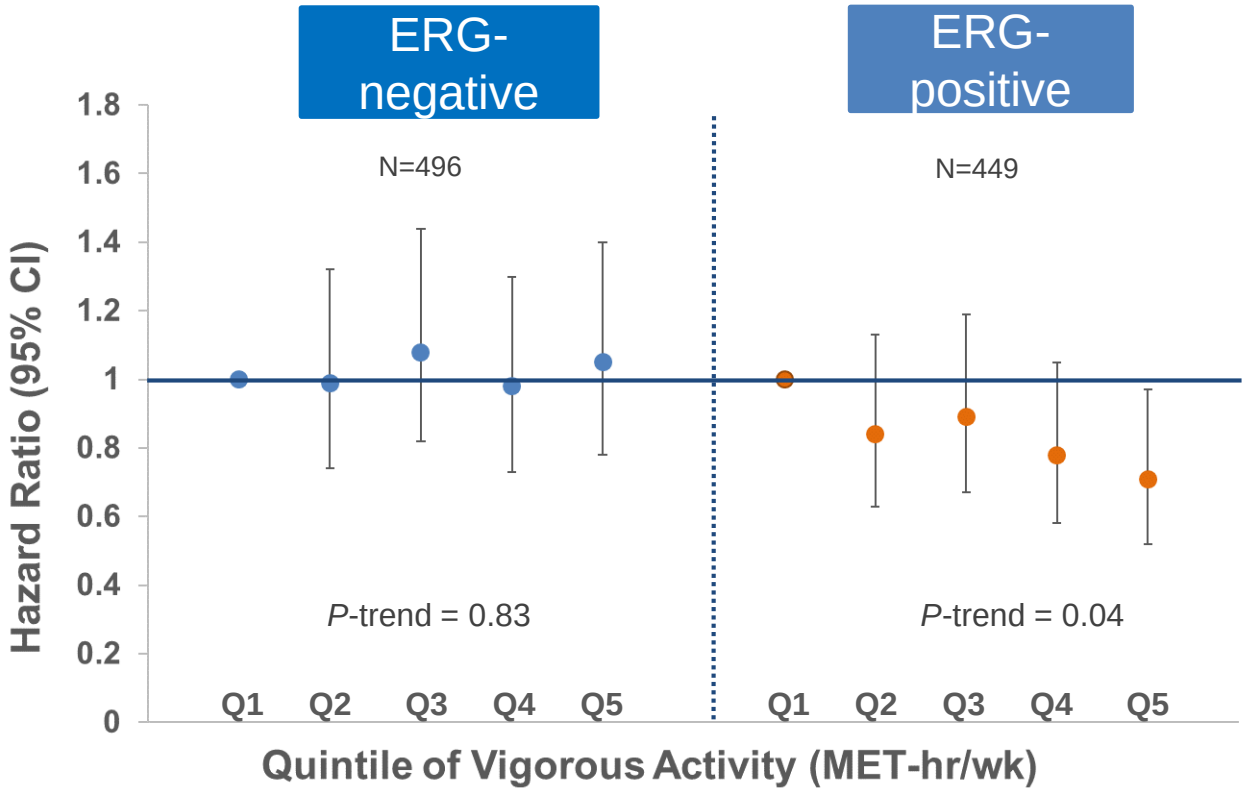
Differences in ERG+ and ERG- cancers

Biomarker	ERG+	ERG-
Insulin receptor/IGF1 receptor	⇧	
Fatty acid synthase	⇧	
PTEN loss	⇧	
Vitamin D receptor	⇧	
MLH1, MSH2, MSH6 (mismatch repair genes)	⇧	
Inflammation		⇧
Atrophic lesions		⇧



Results:
Vigorous activity and ERG-defined prostate cancer





- *P*-heterogeneity = 0.09

Also find associations with ERG-defined prostate cancer for taller height, cooked tomatoes (inverse), free T levels

JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE

Modification of the Association Between Obesity and Lethal Prostate Cancer by *TMPRSS2:ERG*

Andreas Pettersson, Rosina T. Lis, Allison Meisner, Richard Flavin, Edward C. Stack, Michelangelo Fiorentino, Stephen Finn, Rebecca E. Graff, Kathryn L. Penney, Jennifer R. Rider, Elizabeth J. Nuttall, Neil E. Martin, Howard D. Sesso, Michael Pollak, Meir J. Stampfer, Philip W. Kantoff, Edward L. Giovannucci, Massimo Loda, Lorelei A. Mucci