Insulin Resistance and Long-Term Cancer-Specific and All-Cause Mortality: The Women's Health Initiative (WHI)

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Background

- Obesity and diabetes have been associated with increased cancer incidence and mortality[1,2]

- Insulin resistance has been suggested as a potential mechanism[3]
  - Insulin and insulin-like growth factor (IGF) drive signaling pathways that increase cell proliferation and survival
  - Cancer cells express insulin and IGF receptors

[1]Calle et al. N Engl J Med 2003;348:1625-38
[2]Tsilidis et al. BMJ 2015;350:g7606
[3]Pollack. Nat Rev Cancer 2008;8:915-28

Prior observational studies

- Most found an association of hyperinsulinemia or insulin resistance with all-cause mortality, but results for cancer-specific mortality were mixed
- Limited number of cancer deaths (≤180 cancer deaths in 6 of 7 studies), even among studies with >10 years follow-up
- Common lack of laboratory assay standardization
- Not all cancers or causes of death verified by medical record/death certificate review

Ausk et al. Diabetes Care 2010;33:1179-85.
Pyorala et al. Diabetes Care 2000;23:1097-1102
Lee et al. Metabolism 2017;69:87-95
Loh et al. Cancer Causes Control 2010;21:709-18
Perseghin et al. Acta Diabetol 2012;49:421-8
Tsujimoto et al. Int J Cancer 2017;141:102-11
Wargny et al. Diabetes Metab 2018;44:30-37

Study objective

- To evaluate the association between insulin resistance by HOMA-IR* and cancer-specific and all-cause mortality in postmenopausal women with and without diabetes

*HOMA-IR: Homeostasis model assessment of insulin resistance

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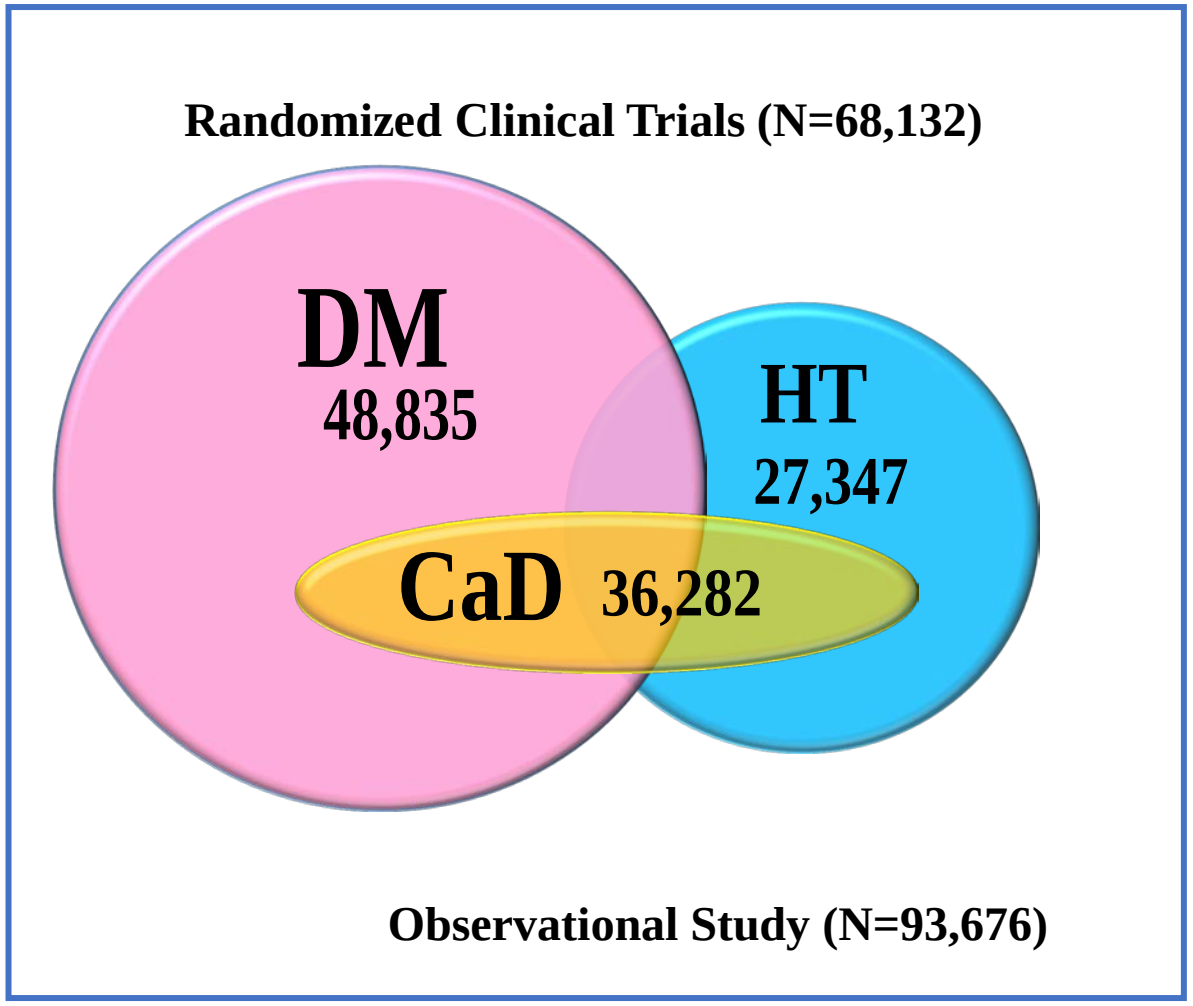

- Long-term national health study evaluating strategies for preventing common chronic disease in postmenopausal women
- 161,808 women age 50-79 enrolled from 1993-1998 across 40 clinical sites
- 3 overlapping randomized clinical trials and 1 observational study
- Adjudicated outcomes and linkage to National Death Index with follow up through 2015

Anderson et al. Ann Epidemiol 2003;13:S5-17

Biomarkers subsample

	Ancillary Study	In Study	**Analytic Dataset** (insulin & glucose from same date)
W54	Cardiovascular disease biomarkers – SNP Health Association Resource cohort (Black and Hispanic)	11,967	11,629
W58*	Cardiovascular disease biomarkers in Hormone Therapy trials (European Ancestry)	10,161	9,811
W66	Long Life Study Phase III	1,494	1,397
Total		23,622	**22,837**

*W58 included incident coronary heart disease, stroke, venous thromboembolism, and diabetes cases and matching controls.

Study design

- Study population: participants in WHI ancillary studies addressing relevant biomarkers: N = 23,622
  - **Fasting serum insulin and glucose at study entry: N = 22,837**
  - Without reported diabetes at baseline: N = 21,077
- Primary exposure: insulin resistance measured by homeostasis model assessment of insulin resistance (HOMA-IR)
- Primary outcome: cancer-specific and all-cause mortality
- Analyses conducted in the entire population with a sensitivity analysis in women without baseline treated diabetes

Study design

- Determination of HOMA-IR
  - HOMA-IR calculated by [(fasting plasma insulin [mU/L] x fasting plasma glucose [mmol/L])/22.5[1, 2]
  - Serum insulin measured using the sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN) on a Roche Elecsys 2010 analyzer
  - Serum glucose measured using the Gluco-quant glucose/hexokinase reagent (Roche Diagnostics) on the Roche Modular P Chemistry analyzer
- Determination of causes of death
  - Central adjudication at the WHI Clinical Coordinating Center, supplemented by National Death Index queries

[1]Matthews et al. Diabetologia 1985;28:412-19
[2]Bonora et al. Diabetes Care 2000;23:57-63

Statistical analysis

- Associations between HOMA-IR quartiles and cancer-specific and overall mortality examined using multivariate Cox proportional hazards models
- Exploratory analyses examined HOMA-IR associations with cancer-specific mortality in BMI subgroups
- Follow-up time calculated from date of enrollment
- All analyses performed using SAS. Two-sided P-values <0.05 considered statistically significant

Covariates

- Hazard ratios adjusted for age and BMI
- Model 1: age, BMI, demographics (education, race/ethnicity), lifestyle habits (smoking, alcohol use)
- Model 2: age, BMI, demographics, lifestyle habits, comorbidities (history of hypertension, high cholesterol, cardiovascular disease, cancer), energy expenditure

Strengths and limitations

- Strengths
  - Large sample size with 1,820 deaths from cancer and 7,415 deaths from any cause
  - Population with racial/ethnic diversity
  - Complete death information from linkage with National Death Index

- Limitations
  - Subsample was not randomly selected and was not representative of WHI
  - Single measure of relevant exposure and covariates

Conclusions and implications

- Insulin resistance measured by HOMA-IR was associated with increased cancer-specific and all-cause mortality in a large population of postmenopausal women
  - In subgroup analyses, increased cancer-specific mortality by HOMA-IR was found in the population with BMI <25
- These findings identify a population of postmenopausal women at increased risk for cancer-specific and all-cause mortality for whom early interventions could be considered

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