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

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Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Women’s Health Initiative Investigators
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

Pyorala et al. Diabetes Care 2000;23:1097-1102
Lee et al. Metabolism 2017;69:87-95
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
The Women’s Health Initiative

- 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

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

*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 \[
  \frac{(\text{fasting plasma insulin [mU/L]} \times \text{fasting plasma glucose [mmol/L]})}{22.5}\]
  \(^1,^2\)
  • 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
Acknowledgements

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