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Journal

Journal of the National Cancer Institute, 112(2)

ISSN

0027-8874

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Publication Date

2020-02-01

DOI

10.1093/jnci/djz069

Peer reviewed

JNCI J Natl Cancer Inst (2020) 112(2): djz069

doi: 10.1093/jnci/djz069
First published online April 26, 2019
Article

ARTICLE

Insulin Resistance and Cancer-Specific and All-Cause Mortality in Postmenopausal Women: The Women's Health Initiative

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Abstract

Background: Insulin resistance has been proposed as a mediator of the increased cancer incidence and mortality associated with obesity. However, prior studies included limited cancer deaths and had inconsistent findings. Therefore, we evaluated insulin resistance and cancer-specific and all-cause mortality in postmenopausal women participating in the Women's Health Initiative (WHI).
Methods: Eligible were a subsample of 22 837 WHI participants aged 50–79 years enrolled at 40 US clinical centers from 1993 to 1998 who had baseline fasting glucose and insulin levels. Baseline insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA-IR). Cancers were verified by central medical record review and deaths verified by medical record and death certificate review enhanced by National Death Index queries. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer-specific and all-cause mortality. All statistical tests were two-sided.
Results: During a median of 18.9 years of follow-up, 1820 cancer deaths and 7415 total deaths occurred. Higher HOMA-IR quartile was associated with higher cancer-specific mortality (Q4 vs Q1, HR = 1.26, 95% CI = 1.09 to 1.47; $P_{trend} = .003$) and all-cause mortality (Q4 vs Q1, HR = 1.63, 95% CI = 1.51 to 1.76; $P_{trend} < .001$). A sensitivity analysis for diabetes status did not change findings. Among women with body mass index less than 25 kg/m^2, higher HOMA-IR quartile was associated with higher cancer mortality (Fine and Gray, $P = .004$).
Conclusions: High insulin resistance, as measured by HOMA-IR, identifies postmenopausal women at higher risk for cancer-specific and all-cause mortality who could potentially benefit from early intervention.

Obesity affects one in three US adult women (1), whereas diabetes affects nearly one in eight (2). Both conditions have been associated with poor health outcomes, including incident cancer (3,4), death from cancer (5), or death from any cause after cancer diagnosis (6). Insulin resistance has been proposed as one of the underlying mediators of these associations.

The association of insulin and insulin resistance with cancer and all-cause mortality has been examined in other observational studies with mixed results. Of seven studies directly addressing the association of insulin resistance with total cancer-specific mortality, three reported statistically significant associations of some measure of higher insulin resistance with higher cancer-specific mortality (7–9). In contrast, three studies

Received: November 20, 2018; **Revised:** March 9, 2019; **Accepted:** April 16, 2019

Table 1. Insulin resistance and cancer-specific and all-cause mortality

Reference	Cohort	Sample size	Follow-up, y	Deaths		Primary exposure(s)	Pertinent results
				Overall	Cancer		
Pyorala et al. 2000 (12)	Helsinki Policemen Study (Finland)	970*	22	276	81	AUC insulin	Associated with all-cause mortality but not cancer mortality
Ausk et al. 2010 (10)	NHANES 1988–1994 (US)	5511	8.5	673	170	HOMA-IR	Associated with all-cause mortality but not cancer mortality
Loh et al. 2010 (11)	HDDRISC (United Kingdom)	1159*	21.5	233	105	Various measures of the insulin axis, including HOMA-IR	No association between HOMA-IR and cancer mortality
Perseghin et al. 2012 (7)	Cremona study (Italy)	2011	15	495	180	Insulin and HOMA-IR	Associated with all-cause mortality and cancer mortality
Tsujimoto et al. 2017 (9)	NHANES 1999–2010 (US)	9778	6.7	—	144	Hyperinsulinemia	Associated with cancer mortality
Lee et al. 2018 (8)	National health screening program (Korea)	165 849	8.54	1316	653	HOMA-IR, CRP	Associated with all-cause mortality and cancer mortality
Wargny et al. 2018 (13)	TELECOM (France)	3117	28	330	150	Insulin	Associated with cancer mortality but not in women

*Males only. AUC = area under the curve; CRP = C-reactive protein; HDDRISC = Heart Disease and Diabetes Risk Indicators in a Screened Cohort; HOMA-IR = homeostasis model assessment of insulin resistance; NHANES = National Health and Nutrition Examination Survey.

reported no statistically significant association between insulin resistance and cancer mortality (10–12) with a fourth reporting no such association in women (13). In these seven reports, there were a total of 1483 deaths from cancer, with 6 of 7 studies reporting 180 or fewer cancer-specific mortality outcomes (*see* Table 1). The current study objective was to provide definitive assessment of the association between insulin resistance and long-term cancer-specific and all-cause mortality using a larger study population with 1820 cancer-specific and 7415 all-cause mortality outcomes. In addition, analyses stratified by body mass index (BMI) examined interactions among insulin resistance as measured by homeostasis model assessment of insulin resistance (HOMA-IR), BMI, and cancer-specific mortality risk.

The HOMA-IR is a surrogate measure of insulin resistance calculated using fasting plasma insulin and glucose values and is strongly correlated with the more resource-intensive euglycemic hyperinsulinemic clamp method in individuals with and without diabetes (14,15). Although hyperinsulinemia is a manifestation of insulin resistance, HOMA-IR was selected as the primary exposure in this analysis because prior data suggested that it has a stronger association with mortality than serum insulin alone.

Methods

Study Population

Details of the Women's Health Initiative (WHI) studies have been previously described (16). From 1993 through 1998, 161 808 women were enrolled at 40 US clinical centers into one or more of four WHI clinical trials (n = 68 132) evaluating hormone therapy, dietary modification, and calcium plus vitamin D supplementation or an observational study (n = 93 676). Postmenopausal women 50–79 years of age with a predicted minimum 3-year survival were eligible to participate. For the clinical trials, women were excluded if they had prior cancer within 10 years (except non-melanoma skin cancer) or conditions potentially influencing adherence and safety. All WHI clinical trials and the observational study were approved by institutional review boards at the clinical centers, and participants provided written informed consent.

At study entry, information on participant demographics, medical and family histories, and dietary and lifestyle factors were collected by self-administered questionnaires. Weight and height were measured using standardized methods with BMI calculated as weight (kg)/height $(m)^2$. Fasting blood samples were collected from all participants at study entry. To identify women with preexisting treated diabetes, participants were asked at baseline, "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" followed by, "Did you ever take insulin shots?" and "Did you ever take pills for your diabetes to lower your blood sugar?" This method of self-report was previously evaluated for concordance with in-person inventories of participants' medications taken between entry and year 3. Of those who did not report treated diabetes, 99.9% had no oral antidiabetic drugs or insulin in their medication inventory (17).

In the clinical trials component, outcomes were ascertained at 6-month intervals during the intervention period with subsequent updates annually. In the observational study component, outcomes were ascertained annually. All reported cancers were confirmed by centrally trained physician adjudicators via medical record review at the local clinical centers with final adjudication and coding at the WHI Clinical Coordinating Center (18).

After the protocol-specified completion date of March 31, 2005, subsequent outcome assessment required re-consent obtained from 84% of surviving participants for follow-up through 2010 and then 86% of surviving participants for follow-up through September 2016. Cause of death was determined by

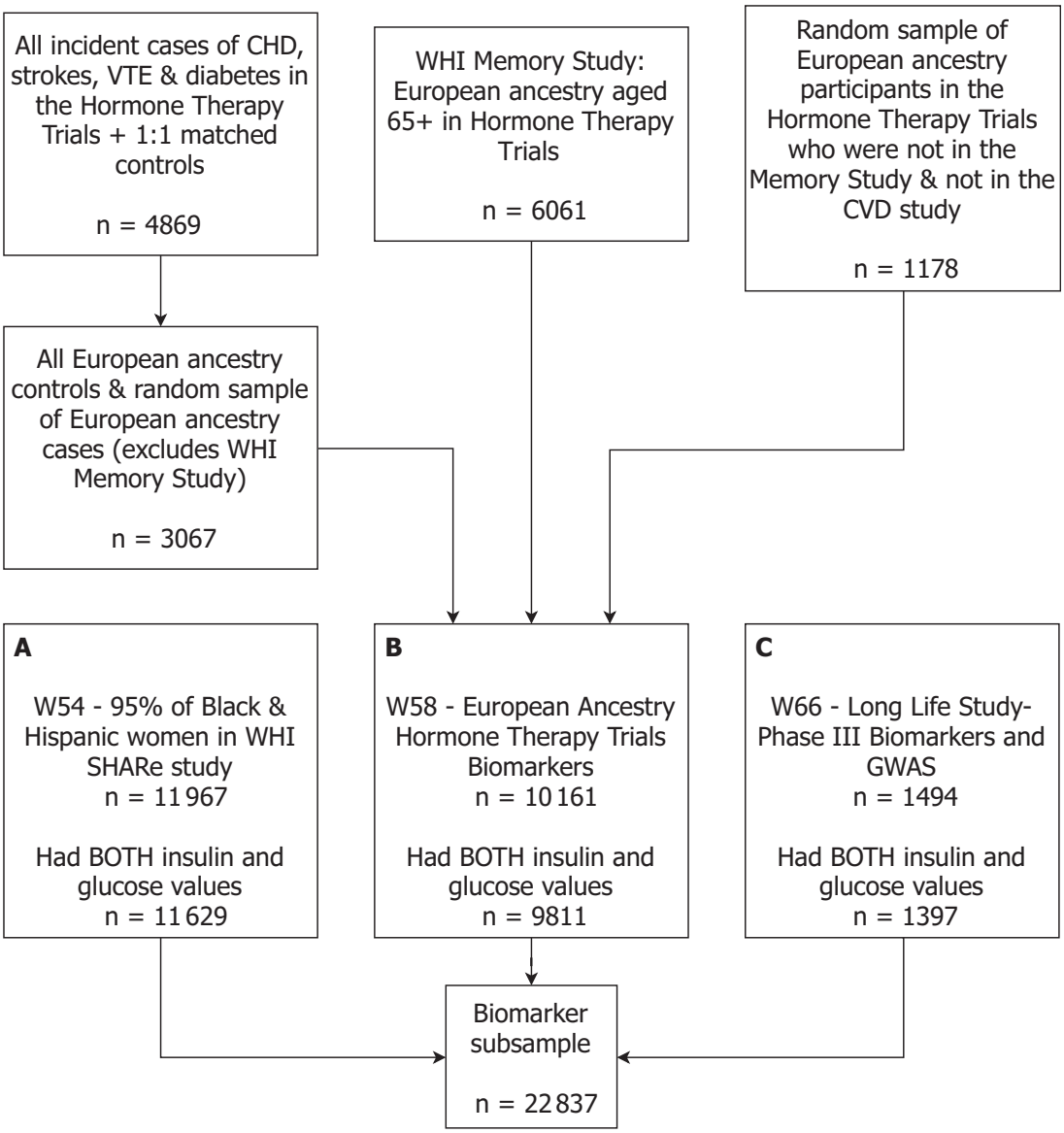

Figure 1. Source of biomarker subsample (N = 22 387). Biomarker studies from ancillary WHI studies, (**A**) W54, (**B**) W58, and (**C**) W66, in which all of the insulin and glucose measures were collected using the same instrumentation and methodology. These tests were identical in terms of test version, test units, test median, test standard deviation, test instrument, and calibration description. CHD = coronary heart disease; CVD = cardiovascular disease; GWAS = genome-wide association study; SHARe = SNP (small nucleotide polymorphism) Health Association Resource; VTE = venous thromboembolism; WHI = Women's Health Initiative.

medical record or death certificate review at the WHI Clinical Coordinating Center. National Death Index (NDI) queries through 2016 provided additional survival information including cause of death regardless of re-consent status. Because of the NDI search, information on deaths was more than 98% complete.

Fasting glucose and insulin levels were measured from baseline blood samples on a subsample of WHI participants (n = 23 622) in several ancillary studies. Eligibility criteria for each ancillary study included specific age and race or ethnicity criteria. For the current analysis, women with fasting glucose and insulin analyzed by the same laboratory methodology were eligible, leaving 22 837 participants. The description of the sources of the analytic sample are identified in Figure 1.

Determination of HOMA-IR

Blood was obtained after at least 12 hours of fasting. Centrifuged aliquots were stored at −70°C within 2 hours of collection, and serum was shipped on dry ice to a central processing facility and stored at −70°C. Serum insulin was measured using the sandwich immunoassay method on a Roche Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN). Serum glucose was measured using the Gluco-quant glucose/hexokinase reagent on the Roche Modular P Chemistry analyzer (Roche Diagnostics). The HOMA-IR, a validated measure of insulin resistance, was calculated using the following equation: [(fasting plasma insulin [microU/mL] × fasting plasma glucose [mmol/L])/22.5] (14).

Table 2. Characteristics by baseline homeostasis model assessment of insulin resistance* quartiles of Women's Health Initiative participants (n = 22 837)

Characteristic	Q1 n = 5791	Q2 n = 5671	Q3 n = 5690	Q4 n = 5685	P†
Age at enrollment, median (IQR), y	65 (58–70)	65 (59–70)	65 (59–69)	63 (58–68)	<.001
Age group at enrollment, no. (%)					<.001
50 to 54 y	779 (13.5)	666 (11.7)	691 (12.1)	734 (12.9)	
55 to 59 y	953 (16.5)	881 (15.5)	953 (16.7)	1097 (19.3)	
60 to 69 y	2431 (42.0)	2592 (45.7)	2667 (46.9)	2718 (47.8)	
70 to 79 y	1628 (28.1)	1532 (27.0)	1379 (24.2)	1136 (20.0)	
Race or ethnicity, no. (%)					<.001
White	3106 (53.6)	2909 (51.3)	2592 (45.6)	2279 (40.1)	
Black	1743 (30.1)	1848 (32.6)	2217 (39.0)	2562 (45.1)	
Hispanic	942 (16.3)	914 (16.1)	881 (15.5)	844 (14.8)	
Education, no. (%)					<.001
High school or less	1366 (23.8)	1493 (26.6)	1636 (29.0)	1859 (33.0)	
>High school/GED	4381 (76.2)	4127 (73.4)	3996 (71.0)	3779 (67.0)	
BMI in kg/m^2, median (IQR‡)	25 (22.5–27.6)	28 (24.8–30.8)	30 (27.2–33.9)	33 (29.5–37.2)	<.001
Smoking status, no. (%)					<.001
Never smoker	2936 (51.4)	2987 (53.5)	2965 (52.9)	2874 (51.4)	
Former smoker	2148 (37.6)	2076 (37.2)	2162 (38.6)	2255 (40.3)	
Current smoker	627 (11.0)	520 (9.3)	478 (8.5)	460 (8.2)	
Alcohol intake, no. (%)					<.001
Never alcohol use	666 (11.6)	734 (13.1)	812 (14.4)	955 (17.0)	
Former alcohol use	1040 (18.1)	1134 (20.2)	1436 (25.5)	1820 (32.4)	
Current alcohol use	4029 (70.3)	3736 (66.7)	3377 (60.0)	2843 (50.6)	
Hypertension ever, no. (%)					<.001
No	4181 (72.7)	3640 (64.7)	3097 (55.1)	2304 (41.2)	
Yes	1568 (27.3)	1986 (35.3)	2528 (44.9)	3286 (58.8)	
High cholesterol requiring pills ever, no. (%)					<.001
No	4883 (89.8)	4488 (84.9)	4391 (82.9)	4263 (80.8)	
Yes	557 (10.2)	796 (15.1)	906 (17.1)	1014 (19.2)	
Cardiovascular disease ever, no. (%)					<.001
No	4701 (86.1)	4537 (85.6)	4418 (83.3)	4124 (77.7)	
Yes	757 (13.9)	765 (14.4)	887 (16.7)	1183 (22.3)	
Cancer ever, no. (%)					.02
No	5461 (95.3)	5308 (94.5)	5330 (94.9)	5269 (94.0)	
Yes	268 (4.7)	306 (5.5)	289 (5.1)	334 (6.0)	
Recreational activity, no. (%)					<.001
None	746 (13.5)	970 (18.1)	1206 (22.4)	1473 (27.3)	
<2 episodes/wk	326 (5.9)	387 (7.2)	474 (8.8)	502 (9.3)	
2–<4 episodes/wk	1118 (20.2)	1128 (21.0)	1184 (21.9)	1222 (22.6)	
≥4 episodes/wk	3346 (60.4)	2888 (53.8)	2531 (46.9)	2200 (40.8)	
Diabetes treated with pills or shots, no. (%)					<.001
No	5750 (99.4)	5577 (98.4)	5411 (95.2)	4339 (76.5)	
Yes	37 (0.6)	90 (1.6)	270 (4.8)	1336 (23.5)	

*HOMA-IR is measured as fasting serum insulin (mU/mL) × fasting plasma glucose (mmol/L)/22.5. BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance; IQR = interquartile range; MET = metabolic equivalent.

†Baseline characteristics were examined for eligible participants across quartiles of HOMA-IR using *t* tests for normally distributed continuous data, Wilcoxon rank sum tests for non-normally distributed continuous data, Pearson χ^2 for categorical nominal data, and Jonckheere-Terpstra non-parametric tests for categorical ordinal data.

‡IQR corresponding *P* values are based on nonparametric Kruskal-Wallis test for continuous data.

Statistical Analysis

Associations between HOMA-IR quartiles and cancer-specific and overall mortality were examined using multivariable Cox proportional hazards regression models, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs), and proportionality verified using the Grambsch and Therneau's test (19). Hazard ratios were adjusted for age group and BMI, followed by additional adjustment for other potential baseline covariates as follows: Model 1: race/ethnicity, education, smoking status (never, former, current), and alcohol status (never, former, current); Model 2: race/ethnicity, education, smoking status (never, former, current), alcohol status (never, former, current), recreational activity hours per week, history of cancer, cardiovascular disease, hypertension, and high cholesterol. Primary analyses were conducted in the overall population (n = 22 837), because HOMA-IR has been validated in populations with and without diabetes (14,15). A sensitivity analysis excluded participants with a reported history of treated diabetes or unknown diabetes history (remaining n = 21 077). HOMA-IR associations with cancer-specific mortality were additionally stratified by age group, BMI, and race/ethnicity.

Survival analyses for cancer-specific mortality were plotted using cumulative incidence estimates, with *P* values based on the Fine and Gray method (20). Follow-up time was calculated from the date of enrollment to the date of last follow-up or death through September 2016, whichever came first. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC), with two-sided *P* values less than .05 considered statistically significant. *P* values for interactions were generated using an interaction term in the Cox multivariate model.

Results

Compared with women in the lowest HOMA-IR quartile, those in the highest quartile were younger, were more likely to be black, had lower levels of education, and had higher BMI at baseline (Table 2). Women in the highest HOMA-IR quartile were less physically active and less likely to be current smokers or current alcohol users. They were also more likely than those in the lowest HOMA-IR quartile to report a baseline history of cancer, hypertension, high cholesterol requiring pills, cardiovascular disease, and diabetes requiring pills or shots. From lowest to highest HOMA-IR quartile, 3 (<0.1%), 14 (0.25%), 39 (0.69%), and 504 (8.9%) participants used insulin at baseline. Overall, 9% of participants were current smokers.

Participants were followed for a median of 18.9 years (interquartile range 16.8–19.9 years), during which there were 1820 deaths from cancer and 7415 deaths from any cause (Table 3). Women in the highest HOMA-IR quartile had the highest risk of cancer-specific and all-cause mortality when adjusted for age and BMI (HR = 1.26, 95% CI = 1.09 to 1.47, and HR = 1.63, 95% CI = 1.51 to 1.76, for cancer-specific and all-cause mortality, respectively) and, with additional multivariable adjustment (Figure 2), higher HOMA-IR quartile was associated with higher cancer-specific mortality (P_{trend} = 0.003) and all-cause mortality (P_{trend} <.001). In a sensitivity analysis excluding women with baseline-treated diabetes (n = 1733) or unknown diabetes status (n = 27), higher HOMA-IR quartile remained associated with higher cancer-specific and all-cause mortality (Figure 3). In a sensitivity analysis excluding women with a history of cancer (n = 1197), higher HOMA-IR quartile remained associated with higher cancer-specific and all-cause mortality (Supplementary Table 1, available online), although the association with cancer-specific mortality was no longer statistically significant for Model 2.

Causes of death are listed in Table 3. Lung cancer accounted for 27.5% of cancer deaths. Because lung cancer was the leading cause of cancer death in this population, an analysis was conducted stratifying by smoking status (current vs former/never smokers). Neither group showed an association between higher HOMA-IR quartile and lung cancer mortality (Supplementary Table 2, available online).

In the subgroup of women who were not overweight or obese (BMI <25 kg/m^2), those with elevated HOMA-IR had higher cancer-specific mortality. Comparing lowest to highest HOMA-IR quartile, cancer-specific mortality rates were 1.3% (95% CI = 1.0% to 1.6%) vs 2.0% (95% CI = 1.3% to 3.0%) for 5-year mortality and 3.4% (95% CI = 2.9% to 4.0%) vs 5.2% (95% CI = 3.6% to 7.5%) for 10-year mortality, respectively (Fine and Gray *P* = .004, Supplementary Figure 1); however, the interaction term for BMI and HOMA-IR was not statistically significant ($P_{interaction}$ = .08).

Exclusion of women with diabetes from the analysis did not statistically significantly alter the results (Fine and Gray *P* = .01, $P_{interaction}$ not statistically significant; data not shown). To minimize bias due to occult cancers or other major illnesses that could influence BMI and HOMA-IR, sensitivity analyses were conducted by excluding women with BMI < 18.5 kg/m^2 (n = 120) and women who died during the first year of follow-up (n = 99), with no statistically significant change in results.

In analyses stratified by age, women in older age groups had higher 5-, 10-, and 20-year cancer-specific mortality rates than younger women, but no interaction between age and HOMA-IR was detected ($P_{interaction}$ = .63). In analyses stratified by race/ethnicity, white women had somewhat higher cancer-specific mortality rates than black or Hispanic women, but no interaction between race and HOMA-IR was detected (*P* = .89).

Table 3. Cause of death in 7415 of 22 837 participants

Cause of death	No. (%)
Cancer	
Lung cancer	500 (6.7)
Breast cancer	196 (2.6)
Colorectal cancer	181 (2.4)
Ovarian cancer	102 (1.4)
Unknown cancer site	102 (1.4)
Non-Hodgkin lymphoma	96 (1.3)
Multiple myeloma	89 (1.2)
Leukemia	83 (1.1)
Bladder cancer	41 (0.6)
Liver cancer	41 (0.6)
Stomach cancer	34 (0.5)
Kidney cancer	32 (0.4)
Brain cancer	31 (0.4)
Biliary tract cancer	31 (0.4)
Endometrial cancer	22 (0.3)
Melanoma	22 (0.3)
Esophagus cancer	21 (0.3)
Uterine cancer	20 (0.3)
Other known cancer	176 (9.7)
Total	1820 (24.5)
Cardiovascular disease	
Coronary heart disease	1172 (15.8)
Cerebrovascular	632 (8.5)
Other cardiovascular	708 (9.5)
Unknown cardiovascular	28 (0.4)
Total	2540 (34.3)
Alzheimer's/Dementia	
Total	569 (7.7)
Other	
Chronic obstructive pulmonary disease	292(3.9)
Sepsis	208 (2.8)
Pneumonia	199 (2.7)
Other known cause	1398 (19.4)
Total	2097 (28.2)
Unknown	
Total	389 (5.2)
Total	7415 (100.0)

Discussion

Among 22 837 postmenopausal women in the WHI followed over a median of 18.9 years, increasing quartile of insulin resistance, as measured by HOMA-IR, was associated with increasing risk for cancer-specific and all-cause mortality. The association of HOMA-IR with cancer-specific mortality was mainly seen in women with normal weight (BMI <25 kg/m^2), suggesting that a

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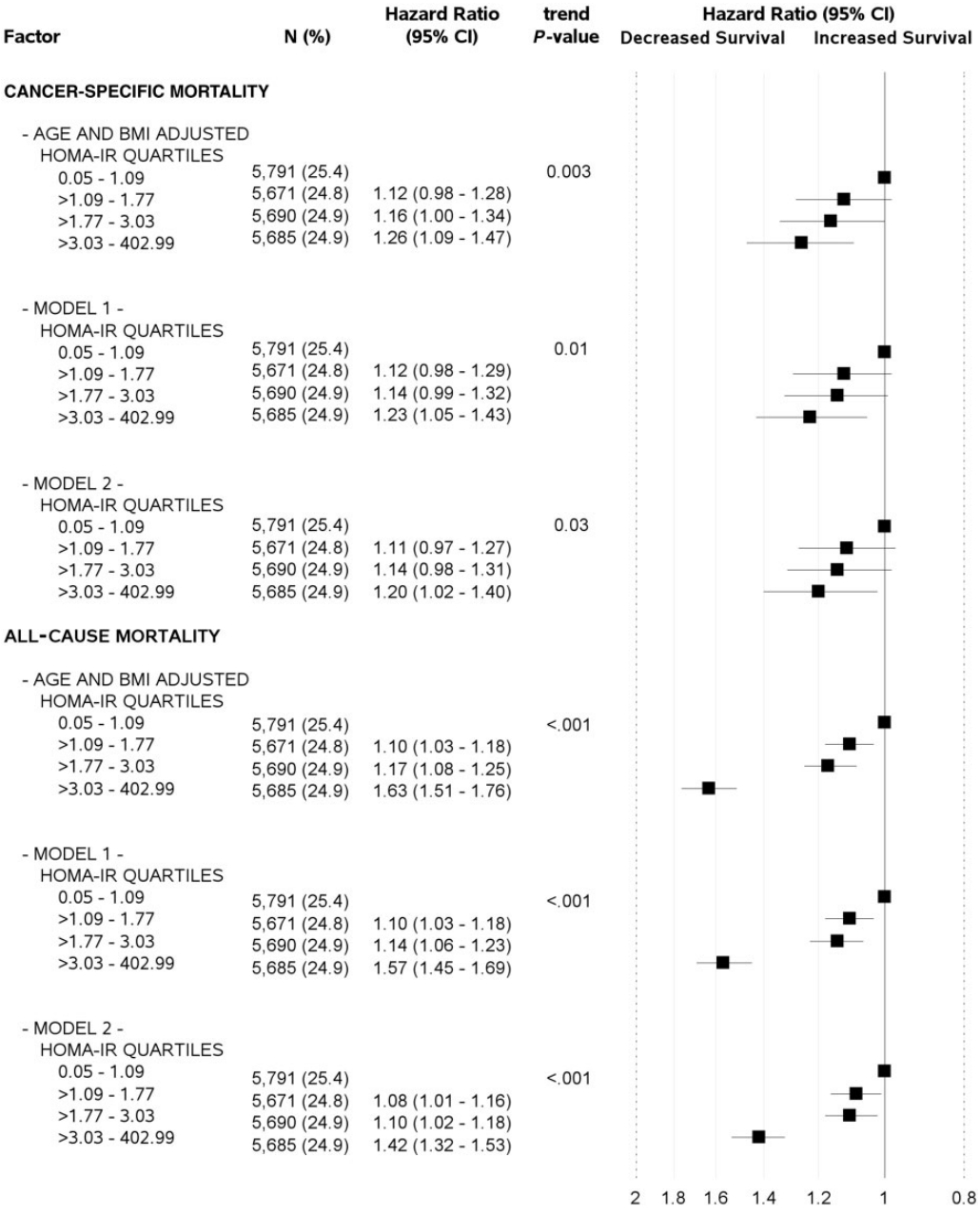

Figure 2. Risk of cancer-specific and all-cause mortality by HOMA-IR quartiles (N = 22 387). HOMA-IR is measured as fasting serum insulin (microU/mL) × fasting plasma glucose (mmol/L)/22.5, 22 837 participants with 18.9 (median) follow-up years since enrollment. Hazard ratio with 95% confidence intervals and *P* values are from Cox proportional hazard models. Model 1 includes adjustment for age, body mass index (BMI), race/ethnicity, education, smoking status (never, former, current), and alcohol status (never, former, current). Model 2 includes adjustment for age, BMI, race/ethnicity, education, smoking status (never, former, current), alcohol status (never, former, current), recreational activity hours per week, history of cancer, cardiovascular disease, hypertension, and high cholesterol. All statistical tests were two-sided. BMI = body mass index; CI = confidence interval; HOMA-IR = homeostasis model assessment of insulin resistance.

subgroup of postmenopausal women, previously considered to be healthy, could be identified to be at substantially higher cancer mortality risk.

Although the influence of insulin resistance on cancer incidence has been receiving increasing attention (21–23), studies examining the long-term influence of insulin resistance on cancer-specific mortality and all-cause mortality have been limited. Our review identified only seven prior studies in this area, as reviewed above, with mixed findings. All four prior studies examining insulin resistance with all-cause mortality found positive associations (7,8,10,12). However, only three (7–9) of seven reports found a statistically significant association for insulin resistance with cancer-specific mortality. The current study, which examined the association of insulin resistance measured by HOMA-IR with all-cause and cancer-specific mortality, included 1820 cancer deaths, a larger number than reported in all prior studies of this question combined (7–13).

In comparing the study designs and participant characteristics of the three prior studies that found an association between insulin resistance and cancer-specific mortality (7–9) to the four studies that did not find such an association (10–13), no consistent differences were identified that could account for the

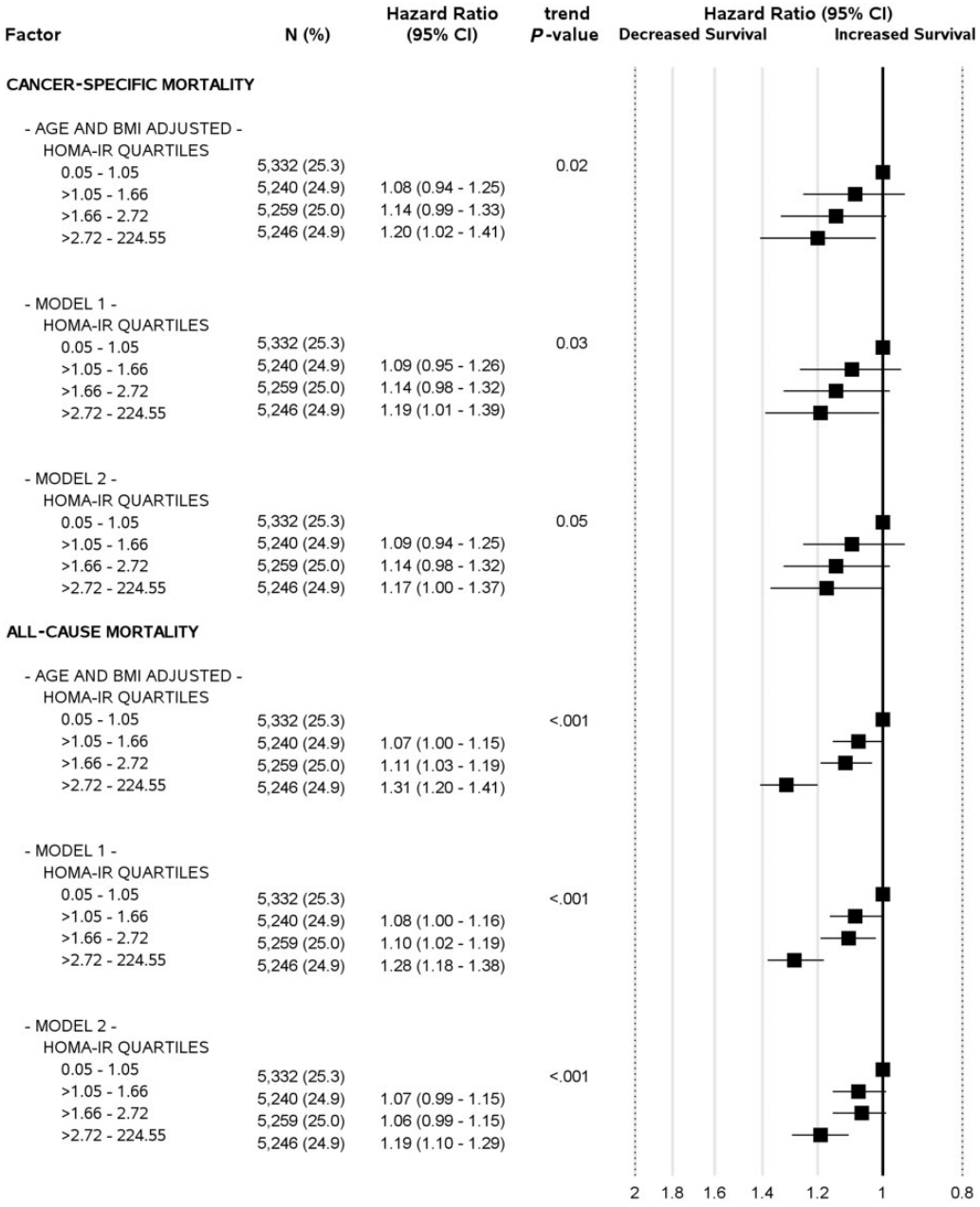

Figure 3. Risk of cancer-specific and all-cause mortality by HOMA-IR quartiles, excluding participants with diabetes at baseline (N = 21 077). HOMA-IR is measured as fasting serum insulin (microU/mL) × fasting plasma glucose (mmol/L)/22.5, 21 077 participants with 18.9 (median) follow-up years since enrollment. Hazard ratio with 95% confidence intervals and *P* values are from Cox proportional hazard models. Model 1 includes adjustment for age, body mass index (BMI), race/ethnicity, education, smoking status (never, former, current), and alcohol status (never, former, current). Model 2 includes adjustment for age, BMI, race/ethnicity, education, smoking status (never, former, current), alcohol status (never, former, current), recreational activity hours per week, history of cancer, cardiovascular disease, hypertension, and high cholesterol. All statistical tests were two-sided. BMI = body mass index; CI = confidence interval; HOMA-IR = homeostasis model assessment of insulin resistance.

discordant outcomes. These studies were fairly heterogeneous, with some examining only men (11,12), only Caucasians (7,11,12), or only Asians (8). Total cancer-specific deaths in these studies ranged from 81 to 653, likely reflecting both smaller sample sizes as well as younger participant age compared with the current study. Only three studies provided information on cancer type, with most common cases as follows: 42 lung cancers (7), 22 prostate cancers (11), and 30 breast cancers (13). The limited number of cancer deaths precludes cross-study comparisons. In the current study, lung cancer was the most common cause of cancer death, accounting for 27.5% of 1820 cancer deaths. Studies to provide reliable information regarding the influence of insulin resistance on specific cancer site mortality will require larger populations combining findings from several cohorts.

Emerging evidence supports an association between insulin resistance and lung cancer incidence. In a nested case-control study, insulin levels were associated with lung cancer risk in current smokers (odds ratio [OR] = 2.06, 95% CI = 1.30 to 3.26) (24). In a case-cohort study of Finnish male smokers, those in the highest HOMA-IR quartile had higher lung cancer risk (HR = 1.83, 95% CI = 0.99 to 3.38) (25). Finally, in a Mendelian

randomization analysis, fasting insulin was associated with lung cancer risk (OR = 1.63, 95% CI = 1.25 to 2.13) (26). In any event, in our cohort of postmenopausal women where only 9% were current smokers, lung cancer as the leading cause of cancer death is noteworthy.

The current study examined cancer mortality related to baseline HOMA-IR, without taking into account the incidence, timing, and prognosis of interval cancer development. However, hyperinsulinemia and insulin resistance have been associated with cancer incidence (23) as well as mortality (26). On a molecular level, the insulin and insulin-like growth factor (IGF) signaling pathways are linked with increased cell proliferation and survival, and cancer cells have been found to overexpress insulin and IGF receptors (27).

To our review, only two prior studies have examined associations of insulin resistance and cancer-specific mortality by BMI subgroup and provide inconsistent results. In an analysis of National Health and Nutrition Examination Survey (NHANES) data, hyperinsulinemia (defined as fasting insulin level $\geq$10 μU/mL) was statistically significantly associated with higher risk of cancer-specific mortality in nonobese (HR = 2.10, 95% CI = 1.23 to 3.58, P = .007) but not in obese (HR = 2.31, 95% CI = 0.61 to 8.72, P = .22) participants (9). However, the limited number of 144 cancer deaths suggests the finding is not definitive. Another report of NHANES findings from an earlier period with 170 cancer deaths found HOMA-IR associated with all-cause mortality only among persons with normal BMI but reported no association of HOMA-IR with cancer-specific mortality (10). In the current study with 1820 cancer deaths, the association of HOMA-IR with cancer-specific mortality was mainly seen in women who were not overweight or obese. If the current study findings can be confirmed, a subgroup of women previously considered to be healthy could be identified as potential candidates for early intervention strategies such as lifestyle change (28,29) or metformin (30,31). Future studies could explore the potential relationship of these findings to the closely related concept of the "metabolically obese, normal weight" or "metabolically unhealthy, normal weight" state, which has also been associated with increased cancer mortality (32).

Current study findings are consistent with insulin resistance having particular negative consequences for cancer-specific mortality for some lean women who conventionally would be considered to be healthy compared to obese women. The adverse pathophysiologic changes that may be associated with obesity could potentially overwhelm the influence of insulin resistance. One obesity-related contributing pathway follows macrophage infiltration of adipose tissue resulting in inflammatory foci known as crownlike structures (33). The presence of these structures increases circulating pro-angiogenic factors (34), which have been associated with higher breast cancer incidence and spread (33).

To translate the current findings into medical practice, clinicians will require additional information to assist in the interpretation of HOMA-IR values. In the current study, women in the highest HOMA-IR quartile were at highest mortality risk; the highest quartile corresponded to HOMA-IR values greater than 3.03 (or >2.72 in those without diabetes). HOMA-IR values suggestive of insulin resistance have been defined in various ways across studies, with cutoffs ranging from the top tertile or quartile to the 90th or 95th percentile and corresponding HOMA-IR threshold values ranging from 1.7 to 3.8. Furthermore, the distribution of HOMA-IR values differs by age, gender, and race (35,36). To identify and counsel patients with insulin resistance regarding associated risks, clinicians would benefit from knowledge of population-specific HOMA-IR thresholds.

Strengths of the current study include the prospective study design, detailed measure of pertinent variables, the large sample of 22 837 well-characterized postmenopausal women, and long-term 18.9 year follow-up with 7415 all-cause deaths and 1820 cancer deaths. The completeness of the mortality results is assured by serial NDI queries. Also, the study population was more racially diverse than prior cohorts, with a substantial proportion of black participants.

The study has limitations. The observational design precludes causal inference, the number of cancer deaths was insufficient for reliable determination of cancer site associations, and detailed cancer therapy information was not available. There may have been selection bias by the inclusion of women from the ancillary studies with available insulin resistance data. Also, findings are based on a single baseline HOMA-IR determination. However, baseline biological determinations have been associated with subsequent health outcomes 5 to 10 years later. For example, short-term interventions such as only 1 or 2 years of tamoxifen in adjuvant breast cancer trials reduces 10-year breast cancer recurrence risk by 21% and 29%, respectively (37).

In conclusion, insulin resistance, as measured by HOMA-IR, is associated with increased cancer-specific and all-cause mortality in postmenopausal women. These findings identify a previously unrecognized group of women at substantially increased risk for cancer-specific mortality who could potentially benefit from early detection and intervention strategies.

Funding

The WHI program is reported by the National Heart, Lung and Blood Institute, National Institutes of Health, Department of Health and Human Services through contracts N01WH22110, 24152, 32100–2, 32105–6, 32108–9, 32111–13, 32115, 32118–19, 32122, 42107–26, 42129–32, and 44221.

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The WHI Project Office at the US National Heart, Lung, and Blood Institute (NHLBI) had no role in the preparation of this report. A portion of the current findings was included in an oral presentation at the American Association for Cancer Research (AACR) annual meeting on April 17, 2018.

Conflict of interest disclosures: Dr Chlebowski is a consultant for Novartis, AstraZeneca, Amgen, Immunomedics, and Genentech and receives honoraria from Novartis and AstraZeneca. No other author reported conflicts.

Author contributions: KP wrote the analysis proposal and initial draft of the report. KP, RC, and RAN had full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. RAN undertook the statistical analysis. All authors provided critical review of the manuscript for important intellectual content. JW, JEMa, LSP, and RC collected the data and obtained study funding.

Additional contributions: We thank the WHI investigators, staff, and the trial participants for their outstanding dedication and commitment.

Program Office: Jacques Roscoe, Shari Ludlum, Dale Burden, Joan McGowan, Leslie Ford, and Nancy Geller (National Heart, Lung, and Blood Institute, Bethesda, MD)

Clinical Coordinating Center: Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kopperberg (Fred Hutchinson Cancer Research Center, Seattle, WA)

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